DELIVERABLE

D1.2 THE PILOT STANDARD OPERATING PROTOCOL

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Deliverable Summary

The purpose of this document is to stablish the Standard Operating Protocol for the TV-ASSISTDEM project. It details the methodology of the protocol. *SOP has been drawn up, with full collaboration of consortium members and a final version has been sent to the Ethic´s Committee for their approval.*

Evaluation of the Efficacy of a TV-based Assistive Integrated Service to Support European adults living with Dementia (TV-AssistDem)

Randomized controlled trial inside of the “Assistive Active Living (AAL) 2016 project” TV-based Assistive Integrated Service to Support European adults living with Dementia.

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1. Background

Population ageing within Europe has major social and economic consequences. Although many older people are able to support themselves and continue to make important contributions to society, the burden of non-communicable disease and disability increases with age, exerting pressures on health services and support systems for older people. One of the most devastating conditions that predominantly affects older people is dementia (1) . Dementia is not exclusively a condition of older people, but its prevalence increases sharply with age. It is an umbrella term describing a set of symptoms that occurs when various diseases or conditions affect the brain, the most common cause of dementia being Alzheimer's disease (AD). Alzheimer's disease was found to be the second most feared condition (after cancer) in a representative sample of 2678 adults in France, Germany, Spain and the US (2). The symptoms that comprise dementia can vary greatly, with people often experiencing memory loss but also problems in communication and attention as well as anxiety and depression (3). Treatment options currently remain centred on symptomatic treatment, the main class of drugs prescribed to people with mild to moderate AD dementia being cholinesterase inhibitors.

There are currently about 10.5 million people in Europe with dementia, costing around €275 billion annually. Given that the number of people with dementia in Europe is expected to rise to 13.4 million by 2030, the challenge of dementia is likely to remain formidable (4). Healthcare policies are therefore focused on extending the ability of older people to continue to live independently, as one way of meeting these challenges. This entails maintaining the quality of life (QoL) of people with dementia, as well working to reduce the costs of their care. The negative impact that people with dementia can experience in regards to their QoL is well established and helps explain why people with dementia are increasingly voicing their desire to get on with life and to be provided with the support they need to do so (5–9).

Living with dementia in the early stages can be burdensome for both those affected as well as their relatives (10,11). Caring for persons with dementia can compromise the informal carer's own well-being and health due to a feeling of being overloaded in the caregiving role (12). The central role the informal carers play for people with dementia lifts the importance of the well-

being of the informal carers themselves, and provision of support to the informal carers is therefore essential (13).

The importance of including quality of life as a measure of outcome in dementia trials has been identified by the World Federation of Biological Psychiatry's Old Age Taskforce (14). The quality of life is multifactorial; therefore, in addition to "the perception of the individual of his position in life in the context of the value system, and in relation to its objectives, standards and concerns" (15), the quality of life also includes physical and mental health , social relations, participation in activities. Therefore, in the case of people with dementia it cannot be determined solely by changes in cognition or other symptoms.

In the scientific literature, there are few systematic reviews focused on the effectiveness of interventions in the quality of life of people with dementia. In a recent review, evidence was found that non-pharmacological interventions aimed at patients and their caregivers improved the quality of life of people with dementia living in their home. Meanwhile, in another systematic review, pharmacological interventions did not improve the quality of life and well-being of these people (14).

Other studies have focused on the use of assistive technologies that improve the quality of life in elderly people in general (16). These technologies are computers, sensors, telemedicine, mobile applications of medication management, that is, ICTs in general. Regarding the quality of life of people with dementia, this review identified three ICT studies, which show that these technologies not only improve the quality of life of the patient with dementia, but also of their caregivers.

It is also important to keep in mind that most of the studies included in these reviews had a small sample size, did not include quality of life as a main outcome measure, or did not include valid quality of life scales. Therefore, there is no clear literature on the use of ICTs in people with dementia to improve the quality of life of patients, with the need to perform randomized controlled clinical trials in large samples.

Recently, the results of a randomized controlled pilot study called "A technology platform for the Assisted living of Dementia elderly Individuals and their carers" (ALADDIN) (17) have been published. The authors demonstrated that the use of ALADDIN improved the ability of the

caregiver when caring for a person with dementia by improving the quality of life, as well as reducing the anguish and burden of the caregiver.

The World Health Organization (WHO) defines medication adherence as "the extent to which a person's medication taking behaviour corresponds with agreed recommendations from a health care provider"(18).

Patient adherence to prescribed medication is probably the most important therapeutic factor and a crucial determinant of medication effectiveness and safety(19,20). The literature revealed poor cognitive function as a risk factor of medication non-adherence (21). Prevalence of medication non-adherence in patients with cognitive impairments is variable, depending of the method used to assess the adherence (20). Frequencies of adherence in these CI populations were worse when compared to cognitively intact populations. Interestingly, when an informal caregiver was ensuring adherence, the objective adherence rates were similar in cognitively intact and impaired populations (21).

Assessing medication adherence is important not only for obvious reasons, but also because in many cases, documentation of a patient's inability to manage their medications is the only evidence of functional impairment, and makes the difference between a patient's diagnosis being mild cognitive impairments (MCI) versus dementia (20). A number of ways of assessing adherence have been developed. These can generally be described as direct methods or indirect methods. Direct methods are examinations of blood, urine or other bodily fluids for the presence of the medicine or a metabolite. Indirect methods do not measure the presence of the medicine but use methods such as self-report from patients, pill counts, prescription reordering, pharmacy refill records, electronic medicine monitoring and therapeutic effect to form an assessment of adherence. Although self-reporting has the problem of over-estimating adherence, is the most simple and inexpensive method of measuring adherence, is quick and easy to administer and Self-reporting methods which are validated can feasibly be used in clinical settings(22).

There are several interventions aimed at improving adherence to treatment found in the literature 1) Technical adherence intervention: for example on dosage and packaging, are usually directed at simplifying the medication regimen. Most adherence interventions in this domain are aimed either at reducing the number of doses per day. Simplification of regimen by unit-of-use packaging also seems to improve adherence. 2) Behavioural interventions: the most common behavioural interventions provide patients with memory aids and reminders, whether by mail, telephone, computer, or by home visits. Other classes of interventions consist of

monitoring, by means of calendars or diaries, and providing feedback, support or rewards. 3) Educational interventions: education is a cognitive didactic approach that includes teaching and providing knowledge. There are different ways to educate patients: individual versus group education, face to face contact, audio-visually, in writing, by telephone, by e-mail or via home visits. 4) Social support interventions; 5) Complex or multi-faceted interventions: comprehensive interventions, combining cognitive, behavioural and affective components, were more effective than single-focus ones. Affective components concern the provider-patient relationship and refer to issues such as empathy, attentiveness, care, concern or support(23).

The development of simple interventions seems the most promising, preferably within a multidisciplinary setting of medical, pharmaceutical, social and technical science and, not in the least, by incorporating patients' perspectives. Patients are the experts when trying to establish what constitutes a simple intervention, e.g. as being not too intrusive or invasive nor time-consuming or costly (24).

Strategies to address adherence include the use of alternate dosage forms such as transdermal patches, once daily oral dosage forms, multi-compartment devices and medication reminder aids, all of which are easily implemented in routine clinical practice (20).

The NICE-SCIE Guideline on Supporting people with Dementia and their carers recommends that people with mild-to-moderate dementia of all types should be given the opportunity to participate in a structured group cognitive stimulation programme. This should be commissioned and provided by a range of health and social care staff with appropriate training and supervision, and offered irrespective of any drug prescribed for the treatment of cognitive symptoms of dementia (25). Evidences suggest that persons with MCI maintain cognitive plasticity and they can be an ideal target population for cognitive intervention(26).

The potential benefits of non-specific stimulation of cognitive functioning for people with dementia have long been recognised. These interventions typically involve engaging the person with dementia in a range of general activities and discussions, are commonly conducted in groups and are aimed at general enhancement of cognitive and social functioning (27), its objective is a general improvement of cognitive and social functions (28).

Cognitive stimulation therapy (CST), which involves people with dementia participating in mentally simulating games and other activities in groups, is beneficial for cognition and quality of life as well as being good value for money (29).

An individual cognitive stimulation therapy may be introduced as a useful component of individually tailored home care packages, which may also help maintain people with dementia in their home situation for longer. A further potential benefit of developing a home-based cognitive intervention would be increasing the accessibility of the intervention for people unable to get to groups due to health/mobility problems, lack of groups in the local area, or preference not to participate in group activities (30).

Reminiscence is the volitional or nonvolitional act or process of recollecting memories of one's self in the past. It may involve the recall of particular or generic episodes that may or may not have been previously forgotten, this recollection from autobiographical memory may be private or shared with others (31). Reminiscence is a common, effective and purposeful psychosocial intervention used with individuals with dementia which permits intrapersonal self-evaluation and fosters interpersonal relationships and self-esteem, while additionally reinforcing one's own sense of competence and wellbeing (32), maintaining or improving mood, cognitive functioning, life satisfaction in the elderly, in addition to this, increased use of remote memory in older adults improves general cognitive function (33). Individual reminiscence involving life review or personalised specific memory triggers in a life-story book showed some psychosocial benefits for people with dementia (34). The literature document a variety of creative methods for stimulating reminiscence, including the use of sensitizing questions, historical material and music(31).

Information and communication technologies can help to providing opportunities for remote sessions to reach distant clients (35).

2. Hypothesis

The research hypothesis is that use of the TV-AssistDem platform over 18 months can result in an improvement in quality of life of people with mild cognitive impairments and mild dementia and their caregivers.

The statistical null hypothesis is that the use of the TV-AssistDem platform produces no change in quality of life of people with mild cognitive impairments and mild dementia and their caregivers over 18 months.

3. Objectives

Primary objective:

To test the effectiveness of a TV-based Assistive Integrated Service to Support European adults living with Mild Dementia to improve quality of life in people with mild cognitive impairments or mild dementia and their caregivers .

Secondary objectives:

- To monitor the mental well-being of carers, measured by the Zarit Caregiver Burden Interview (ZBI-12) and by the EuroQoL-5D-5L scale.
- To test the treatment adherence evolution across the study, measured by pills count and Morisky Green test.
- To reduce functional decline of patients during the follow-up by 10%, measured by the Lawton Instrumental Activities of Daily Living (IADL).
- To test the economic and financial benefits of using the TV-ASSISTDEM platform, measured by the Client Service Receipt Inventory (CSRI).
    a) To reduce costs wasted on unused medicine by 50%.
    b) To reduce costs associated with patients failing to attend appointments by 75%.
    c) To reduce costs associated with readmission of patients to hospital (for resurgent conditions due to lack of treatment adherence) by 30%.

To provide overall efficiency savings to the healthcare system of 10% of dementia budget.

4. Methods

4.1. Participants

240 participant dyads in two European countries (Spain and Romania). The participant dyads will comprise the person with MCI or mild dementia and their informal carers, defined as the person who is unwaged for this role and who spends the most time with the participant and whom the participant declares that he/she is his/her informal carer, for care or support of care, and who does not take part in a formal network of organized care (36).

4.1.1. Inclusion criteria

A participant will be eligible for inclusion in this trial only if all of the following criteria apply:

- Participants score 24-28 points on Mini-Mental State Examination (MMSE)
- Cognitive impairment must have been present for more than six months

- Participants +55 years of age
- Participants are home-care recipients
- Participants have an informal carer
- Those participants who take prescribed medication are in charge of their own medication use
- Participant with treatment for a chronic condition during study period
- The place where the participant is normally resident has enough wireless or phone network connectivity to enable them to use Tv-AssistDem platform on a daily basis
- Participant agree to be part of the study by giving signed written consent

4.1.2. Exclusion criteria

A participant will not be eligible for inclusion in this trial if any of the following criteria apply

- Participants have a terminal illness with <3 years expected survival
- Participants score above 11 on the Geriatric Depression Scale (GDS-15)
- Participants have specific conditions reducing their physical ability to use the application to a point that makes their participation in the project impossible, as evaluated by the responsible investigator (the nature of the conditions should be recorded in such cases).

4.2. Sample size

The main outcome measure is the total score of the QoL-AD. This score is based on 34 points / items (from 1 to 4) on a discrete analogue visual scale. According to recent studies (37,38), the standard deviation of the total score of the QoL-AD is 7.

For a minimum important clinical difference of 2.77 on the total QoL-AD score, with a standard deviation of 7, the effect size is 0.39. To compare two groups (Intervention and Control) using a two-sample, two-sided t-test with a 5% statistical significance level, the minimum number of evaluable PWDs required in each group is 100 (200 overall), to give a power of 80%. Given that it is a follow-up study, we must bear in mind that there will be losses along this one, therefore we will recalculate the sample size to take into account an expected percentage of losses of 20%, the number of subjects needed for each group will be 120 subjects (240 in total).

4.3. Design

This study is a multicentre randomised control trial (RCT).

4.4. Setting

This study will be performed in two European countries, Spain and Romania. The participant centres will be:

- Spain: **Health Research Institute of Malaga (IBIMA**; www.ibima.eu) is a multidisciplinary public institution dedicated to biomedical research around the Servicio Andaluz de Salud in Malaga (Regional University Hospitals and Hospital Virgen de la Victoria and primary care centres: Distrito Sanitario Malaga-Guadalhorce, Distrito Sanitario Costa del Sol, Distrito Sanitario Malaga Este-Axarquia) and biotech groups at the University of Malaga.
- Romania: **Home care Association (Asociatia Ingrijire Acasa – AIA**, Romania) is a NGO, founded in 2014, but its team has experience of over 7 years in home care. AIA provides social and medical care at home for over 800 people, most of them elderly, temporarily or permanently incapacitated and unable to take care of themselves. From wound care to treatment administration and physical recovery, AIA provides its services in a large region in Romania, having a team of approx. 25 people (doctors, medical nurses, nurses, kynetotherapists)

4.5. Outcomes measures

4.5.1. Outcomes in patients

Primary Outcome: *Health Related Quality of Life (HRQL)* measures by QoL-AD and EuroQoL-5D-5L questionnaires.

Quality of Life AD (QoL-AD)

HRQoL of person with MCI or mild dementia , will be measured using the total score on the QoL-AD (39–41). Person with MCI or mild dementia may lose cognitive function during the course of the study to the extent that they are unable to complete the QoL-AD assessment themselves. For this reason, the informal carer of the person with MCI or mild dementia will also complete the QoL-AD, in parallel and on behalf of the person with MCI or mild dementia, from the start of the study. The instrument has been specifically designed to measure QoL in individuals with dementia from the perspective both of the person with MCI or mild dementia and the informal carer.

It is a 13-item measure, which includes assessments of the person with MCI or mild dementia's relationships with friends and family, financial situation, physical condition, mood, and an overall assessment of life quality. Informal carers complete the measure as a questionnaire about the QoL of the person they care for, while the person with MCI or mild dementia completes it in interview format about their own QoL.

QoL-AD will be assessed via interview with person with MCI or mild dementia and via self-completion with informal carers at baseline and then at 6, 12 and 18 months.

EuroQoL 5 Dimension (EQ5D)

The EQ5D (42,43) will also be used to evaluate Quality of Life due to its recognition as standardised, generic cost utility analysis instrument.

The EQ5D is a self-completion questionnaire that consists of five questions, covering mobility, hygiene, activities, pain and anxiety, plus a scale where the participant rates their health state on a scale of 0-100. Person with MCI or mild dementia will complete the EQ5D at baseline, 12 and 18 months. EQ5D has been shown to correlate well with QoL-AD, indicating that using the two measures are compatible for use side-by-side (44).

Secondary outcomes:

Adherence to prescribed medication: ***doses/pills count***

Adherence to prescribed medication in the intervention and control group will be assessed by comparing the person with MCI or mild dementia's documented prescription for medications with the number of pills taken (or if medication is not in pill form, pill equivalents) in the 30 days previous to the assessment day. This assessment will be undertaken at baseline and then at 6, 12 and 18 months. Person with MCI or mild dementia- informal carer dyads will be asked to bring to the clinic any documentation relating to their prescription history for all medications and all the pills (or pill equivalents) and empty medication packaging they have remaining from the previous 30 days, so that the researcher can undertake the medication count.

The dose/pill count is the number of pills or doses taken divided by the number of pills or doses prescribed, multiplied by 100 (expressed as a percentage) (45,46). According to Haynes et al (45) recommendations, a good adherence is considered when the result of counting is between 80% (a twenty percent of doses/pills missed) and 110% (the patient inhales ten percent more doses/pills) of dose/pill prescribed (47).

Drugs that will be taken into account to evaluate adherence will be anti-dementia drugs and other chronic diseases' treatment that influence the evolution of dementia (e.g., drugs for cardiovascular diseases, antidiabetics, anticoagulants, antihypertensive and antidepressants).

Adherence to prescribed medication: **Morisky Green test**

This method, which is validated for various chronic diseases, was originally developed by Morisky, Green and Levine to assess medication compliance in patients with hypertension (48). Since the test was introduced it has been used in the assessment of therapeutic compliance in different diseases. This test have been validated in Spanish population (49).

It consists of 4 contrast questions with dichotomous yes / no response, reflecting the patient's behavior regarding compliance. They are intended to assess whether the patient adopts correct attitudes regarding treatment for their disease; it is assumed that if the attitudes are incorrect the patient is non-compliant.

Cognitive function measure by the **Mini-Mental State Examination** (MMSE) will be used to assess the cognitive function of person with MCI or mild dementia (50–52). It is also used to estimate the severity and progression of cognitive impairment and to follow the course of cognitive changes in an individual over time; thus making it an effective way to document an individual's response to treatment. Administration of the test takes between 5 and 10 minutes and examines functions including registration, attention and calculation, recall, language, ability to follow simple commands and orientation. Any score greater than or equal to 24 points (out of 30) indicates a normal cognition. Below this, scores can indicate severe (≤9 points), moderate (10–18 points) or mild (19–23 points) cognitive impairment.

To be included in the trial, individuals must score between 20 and 26 points on the scale. The MMSE will be filled by the participants in the intervention and control group at the baseline and at 6, 12 and 18 months.

Depression: The **Geriatric Depression Scale** (GDS-15) (53,54) will be used as an exclusion criteria, screening for depression. If participants score above 11, they will be excluded from the trial. Person with MCI or mild dementia will also self-complete the GDS-15 at 6, 12 and 18 months.

Questions are answered "yes" or "no." A five-category response set is not utilized in order to ensure that that the scale is simple enough to be used when testing ill or moderately cognitively impaired individuals, for whom a more complex set of answers may be confusion, or lead to

inaccurate recording of responses. The GDS is commonly used as a routine part of a comprehensive geriatric assessment. One point is assigned to each answer and the cumulative score is rated on a scoring grid. The grid sets a range of 0-4 as "normal", 5-8 as "mildly depressed", 9-11 as “moderate depressed” and 12-15 as "severely depressed".

Functional decline. **Lawton Instrumental Activities of Daily Living** (IADL) (55) scale will be used to evaluate functional decline for person with MCI or mild dementia . The IADL is an interview format scale of eight items covering instrumental activities, such as shopping and preparing food, which are required for independent living. Because these instrumental functions are usually lost before more basic ADL functions (such as bathing, eating, and using the toilet), assessment of IADLs may identify incipient decline in an older people who might otherwise appear capable and healthy.

The Lawton IADL questionnaire will be administered via interview with person with MCI or mild dementia at baseline, 6, 12 and 18 months.

Service Utilisation. The **Client Service Receipt Inventory** (CSRI) (56,57) scale will be used to evaluate the service utilization. This scale is an internationally usable method for gathering data on service utilisation and other relevant domain to the economic analysis of mental health care.

The CSRI has five sections: Background client information, such as study identification number, age, gender and other socio-demographic information. It may also include past admissions/discharges from hospital or participation in special programs depending on the study and information available. Accommodation and living situation, which can identify housing tenure or facility type and region (some geographic areas are more costly to live in than others). More about this topic can be found here. Employment history, earnings and benefits, which may assist with calculations of cost of, lost employment due to poor health. A record of services that may be used usually grouped into subsections such as hospital care, primary care, community-based specialist or generic health care, social care etc. Questions on prescribed medication can be included here. Information about support from unpaid carers.

It was originally designed to be administered to the service user or their carer face to face with a trained interviewer, the CSRI has been successfully administered via post for the service user to complete by themselves, and in a telephone interview. However, an interview is generally the preferred method to ensure as much relevant information as possible is obtained.

Usability test. Usability Evaluation focuses on how well users can learn and use a product to achieve their goals. It will be performed based on the **System Usability Scale** (SUS) (58,59). The System Usability Scale (SUS) is a simple, ten-item scale giving a global view of subjective assessments of usability.

SUS is a Likert scale, the respondent indicates the degree of agreement or disagreement with the statement on a 5 (or 7) point scale with a scores range of 0 to 100. The SUS scale is generally used after the respondent has had an opportunity to use the system being evaluated, but before any debriefing or discussion takes place. Respondents should be asked to record their immediate response to each item, rather than thinking about items for a long time.

Independent variables-covariables:

Socio-Demographic data: Age, Gender, Education, whether participant lives alone, Marital status.

Medical history: Family antecedents: Alzheimer's disease, Parkinson's disease, other dementing illness; Comorbidity: cardiovascular (hypertension, cardiac insufficiency, myocardial infarction, ischemic cardiopathy, arrhythmia, peripheral vascular disease), metabolic/endocrine (diabetes, thyroid disease, hyperglycaemia), gastrointestinal, psychiatric (depression, anxiety), neurologic, respiratory; Current Treatment; A specific question whether the person have been diagnosed with dementia or not including supplementary questions such as what type of dementia, if they have undergone an MRI scan and if they are using any pharmacological treatment.

User behavior. In the intervention group, the following data will be collected from the platform: Date and time of any interaction with TV-AssistDem platform; Length of interaction; Functions used during interaction

4.5.2. Outcomes in carers

Carer Burden. The **Zarit Caregiver Burden Interview** (ZBI-12)(60,61) will be used to evaluate informal carers' burden . The ZBI-12 is a 12 item scale with each answer chosen from a 5-point Likert scale. It is a shortened version of the original scale was developed specifically for informal carers of person with MCI or mild dementia and covers issues such as carer stress and the degree to which caring is effecting their health and social life. It will be administered via interview with the informal carer at baseline, and then at 6, 12 and 18 months.

Health Related Quality of Life (HRQL) measures by **EuroQoL-5D-5L** questionnaire a standardised generic instrument. The carers will complete this test at baseline, 12 and 18 months.

Independent variables-covariables:

Socio-Demographic data: Age, Gender, Education, whether participant lives alone, Marital status.

5. Intervention

Intervention will consist in a remote assistance through a device connected to the television, through this platform the participant will get information and interact.

Participants will receive two weekly calls during the three months after the beginning of the use of the platform to encourage them in the use of the platform and to solve all problems related to its use.

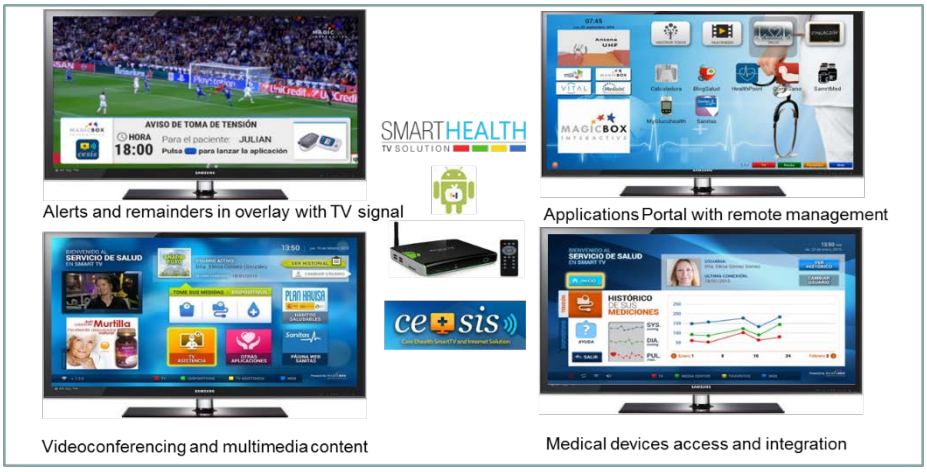
Investigational product:

The product consists of an Android software and hardware TV (a Digital TV STB with Android technology) designed to provide tele-care and tele-medicine services at home using the TV. The platform functionalities will include:

- Integration with home biometric devices such as glucometer, blood pressure, oximeter, weight scale, body mass index meter…
- Videoconference + Tele-care for remote assistance, health monitoring and remote support, as well as distance-learning and social network.
- Connection with public and private e-health service providers
- Integration with 2nd screen (tablets and smartphones)
- Other applications for chronic diseases support and prevention, including on-screen alarms (such as pillbox reminder while watching TV).
- Medical questionnaires, to be filled by end-users/patients, relatives or caregivers
- Questionnaires for end-users, relatives or caregivers.
- Second screen framework, for interaction with smartphones and tablets

The system consists of:

- Set Top Box based on ARM chipsets with Android operating system and a digital TV tuner (optional, including HDMI pass-through) compatible with DVB-T/T2 (European version).
- An specific version of firmware
- Several software modules implementing the different functionalities (videoconferencing, medical devices integration, reminders etc.)
- Basic User Interface, in order to access to the main features and functionalities



Platform utilities:

This platform will have the following utilities:

Calendar: Will be a calendar tailored to each person that will include medical appointments, important dates for the person (e.g. family birthdays), festivities.

Reminders: medication and medical appointments: reminder messages will appear on the screen while the patient watches the television, the patient should check when the medication is taken. The check data will be recorded for further analysis. The caregiver / patient dyad will add to the platform the information necessary to create the reminders (e.g. medication: dose, time; medical appointment: date, time, place).

Videoconference: The patient will be able to videoconference with researches (from a remote station), with the main caregiver (from an application that will be installed on his mobile device or PC), these communications may be bidirectional.

Vital signs tracking and health data transmission: through measurement devices with the possibility of data transmission by Bluetooth. A reminder will appear on the television when the patient has to perform the measurement. The patient can access a video demonstration of how to perform the measurement if he needs it. The information of the type of measurement and of the periodicity will be entered on the platform by the patient / caregiver dyad.

Cognitive stimulation and serious games: platform will include a cognitive stimulation application that will be design specifically for this study. This application will contain activities to work on different cognitive abilities (short and long term memory, attention, orientation, language, executive functions). Each cognitive function will be stimulated by a group of tasks. There will be different levels of difficulty to be able to individualize the treatment, and to adapt it to the participants' results.

Reminiscences: Through the platform of the study will provide the tools to build a book of life of the person, in which the personalized form may include photos, music and videos.

6. Recruitment

Participants will be recruited by the research team in Spain and Romania. Participants will not receive financial reimbursement for taking part in the trial.

Participants will be identified from people with cognitive impairment that has been present for more than six months and who meet all the study eligibility criteria. The participants can be under primary care services as well as secondary care services, such as those who are being followed up in memory clinics, outpatient clinics, day hospitals or other components of specialist mental health, geriatric medicine and neurology services. Participants will also be identified from patient databases such as those integrated in the network. The clinicians involved in identifying the participants will be physicians (primary care, psychiatry, neurology, and geriatrics), neuropsychologists and dementia nurses. The identification process by the clinician will consist of screening, using information gathered from medical notes, clinic records and/or clinical consultations, for initial eligibility based on inclusion criteria.

Participants will be invited to participate in the study after a brief explanation by telephone and they will receive an appointment in the health centre. At this first appointment (Visit 0) patients will receive detailed information about study through an Information Sheet (Annexes 2 and 3). In order to ensure reporting meets the CONSORT guidelines requirements (62,63), the following information will be recorded for any for any participant who is a potential recruit but is never subsequently randomised (including those who decline to take part despite meeting eligibility criteria):

- Age
- Gender
- Eligibility criteria (including reason for screen failure, if applicable)
- Other reason for withdrawal/non-continuation to randomisation

6.1. Consent

A key condition for the conduct of ethical research is that participants have been informed of and understand the purpose of the study and of possible harm which might arise as a result of participation, that they have given informed consent and that appropriate measures have been taken to minimize the likelihood of harm occurring.

Consent must be obtained from person with MCI or mild dementia participating in the trial and the individuals who act as their informal carer.

Consent will only be considered valid if it has been given by a person with the necessary capacity and provided voluntarily (not obtained under duress), based on the provision of relevant information (e.g., full details of what is involved, including possible risks and benefits). To this

end, participants will be provided with the information they need to make an informed decision via a Participant Information Sheet. Participants will be given a cooling off period of at least 24 hours between informally agreeing to participate and being invited to formally consent in a meeting with research team.

A standard Consent Form and Participant Information Sheet will be provided in English for all clinical partners, detailing the list of items to be consented. Each clinical partner will be responsible for ensuring that the consent process they apply locally meets all necessary standards, including translation to local language. (Annexes 4 and 5).

Consent process for people with MCI or mild dementia

Consent is understood in this context as a 'process' rather than an 'event'. Investigators will therefore actively seek reaffirmed consent on all the occasions they seek data from person with MCI or mild dementia. Investigators will use a two-stage test for capacity at recruitment stage and at each subsequent occasion before a participant takes part in a trial procedure or set of trial procedures. Supporting documents supplied to all clinical partners will include a form guiding investigators through this process. The process involves explaining the trial and then carrying out the 2-stage test for capacity. Any investigator gaining consent must demonstrably be qualified to assess the person with MCI or mild dementia's capacity to consent.

The first stage of the two-stage process is to be sure that the person with MCI or mild dementia is aware of the conditions of participation in the study when giving the initial informed consent. The second stage is to follow up for each visit that the person with MCI or mild dementia is still aware of the conditions of participating taking into consideration the progression of dementia by follow-up questions. This is assessed by the personnel and decided by the PI of the respective study site.

If a person with MCI or mild dementia lose capacity to continue participation in the study due to progression of dementia, the legal representative of the person with MCI or mild dementia can decide to withdraw the consent on behalf of the person with MCI or mild dementia. If the legal representative does take over the consent process from the person with MCI or mild dementia, this must be recorded on the trial database by the investigator concerned.

Consent process for informal carers

Investigators must gain consent from informal carers at the start of the trial using the prescribed consent process but do not need to regain consent on each occasion of a trial procedure. However, if a new individual becomes the informal carer of the person with MCI or mild dementia during the trial period, consent must be obtained from that person before they can become involved in the trial.

6.2. Randomisation

The randomization will be made using the block randomization technique. The blocks consist of 4 patients, two subjects per group [Intervention (I) and control (C)]: (IICC); (CCII); (CICI); (ICIC); (ICCI); (CIIC). The blocks will be marked with a number from 1 to 54 and they will be chosen at random to create the allocation sequence using a sequence of random numbers generated by the Microsoft Excel program with the function fx:RAND(). The assignment to this group will be made by contacting the person responsible for random sequence by phone. Because the patients are from various health centres, the randomization and the presence of the intervention and control subjects in all the health centres will be guaranteed.

After randomisation all the study data will be recorded and the adherence will be measured in both groups.

7. Follow up

7.1. Control Group

Visit 1: It will take place 6 months after the inclusion. It will involve the measure of adherence and other variable changes.

Visit 2: It will take place 12 months after the inclusion. It will involve the measure of adherence and other variable changes.

Visit 3: It will take place after 18 months follow up. All the study data will be recorded including treatment adherence.

There will be a pre-adherence visit before each follow-up visit except for the inclusion one. The reason for the pre-adherence visit is to ask the patient to bring a new container that will be marked with the date in which it is opened in order to count doses/pills through the month. This is done because most of the devices that patients use last 30 days. The pre-adherence visit could be done by telephone to guarantee the follow-up.

7.2. Intervention Group

After the inclusion, the first part of the intervention (group session) will be carried out in each health centre and the intervention group will receive appointments for:

Visit 1: It will take place 6 months after the intervention. It will involve the measure of adherence and other variable changes, information about the use of platform and they will be asked to complete a brief user satisfaction.

Visit 2: It will take place 12 months after the intervention. It will involve the measure of adherence, other variable changes and information about the use of platform and they will be asked to complete a brief user satisfaction.

Visit 3: It will take place after 18 months follow-up. All the study data will be recorded and encouragement about inhalation techniques and information about the use of platform and they will be asked to complete a brief user satisfaction.

There was a pre-adherence visit prior to all visits as explained previously. Adherence will be measured at each visit to control its evolution during the follow-up period.

Each clinical partner will assign one central contact to deliver technical support to intervention group participants regarding the use of the platform. These contacts will function as the first port of call for technical support, helping users in their own language. MagicBox will provide initial training for the central technical support contacts, as well as continuing support to overcome any technical issues.

Before recruitment of participants begins, the central technical support contacts will agree between them the protocol for training participants in the use of the platform so as to deliver training across the trial sites in as uniform way as possible, thereby minimizing any bias from this aspect of the trial design. That protocol will be shared on the project management website.

8. Statistical Analysis

Data collected for the study will be analysed to measure and assess the TV-AssistDem platform impact on treatment adherence for the persons with MCI or mild dementia as the primary comparison. In addition, functional status (IADL) for person with MCI or mild dementia, HRQoL, health care appointment and admissions records and carer burden will be analysed as secondary comparisons. The analysis will be made following an intention-to-treat procedure.

Descriptive statistical analysis and arms comparison

All variables collected will be summarized by group and overall, and also by site. The purpose of this is to provide experts in the field with an indication of the profile of the persons with MCI or mild dementia so that they can judge whether they are typical of what would be expected. Among the statistical summary statistics considered for presentation for continuous measures in summary tables will be the mean, median, minima and maxima, lower and upper quartiles, and standard deviation. Categorical variables will be summarized using counts and percentages. The 95% confidence interval will be applied.

As persons with MCI or mild dementia will be assigned to the intervention and control using random allocation it is known in advance that any differences between these groups at baseline will be because of chance and so a comparison of the groups using statistical significance tests will be carried out at baseline (the Chi-Square test or the ANOVA).

The flow of persons with MCI or mild dementia will be shown schematically with counts and percentages in a CONSORT diagram.

Dropout effect

A comparison will be made between all study variables at baseline and final visit using the Chi-Square test or the ANOVA to test the impact of losses on sample structure. The analysis will be made in the total sample and in each arm of study.

Intervention Efficacy

The between-group and between-visits comparison for the primary outcome will be explored using the Chi-Square Test, to test the primary outcome evolution across the study.

The Relative Risk Reduction (RRR: how much the risk is reduced in the experimental group compared to a control group), the Absolute Risk Reduction (ARR: the absolute difference in outcome rates between the control and treatment groups) and the Number Needed to Treat (NNT: the number of people who must be treated to result in benefit in one person. It is the inverse of absolute risk reduction) will be calculated. The 95% confidence interval will be applied.

Quality of life related factor

Univariate analysis will be conducted to explore the relationship between the primary outcome (quality of life) and all of the independent variables at the end of the study. The chi-square test or analysis of variance (ANOVA) will be used.

Finally a logistic regression model will be performed for the primary outcome, considering the intervention as the predictive variable and the rest of the independent measures as the possible modifying factors. We will use a 5% significance level (a = 0.05).

Secondary outcomes analysis

Inferences for the secondary outcomes will be made using an analysis of variance (ANOVA) or Chi-Square test. Each group will be analysed separately.

User-Behaviour analysis

Data on a various platform usage variables will be collected for the intervention group of person with MCI or mild dementia. Regression analysis will be used to assess the relationship between the primary and secondary outcome variables and the usage variables in order to indicate which aspects of the computer platform use most affected the outcomes.

A user-behaviour analysis will be performed in order to assess how users interact with the platform and how their behaviour affects its efficacy. Specifically, we will assess and analyse the frequency of access to the TV-AssistDem platform, the length of this interaction, and the quality of the inputs provided. These data will be correlated with users' reminder schedules to explore difference between proactive and reactive use of the platform and will be followed up over time to understand how increasing familiarity with the platform affects user behaviour. Also, the data will be used to improve the TV-AssistDem platform, if necessary, to optimize user interaction.

We will analyse the data from the TV-AssistDem itself, and from the feedback received during interviews that will be scheduled with 5% of randomly selected users after 12 months of using the platform. Interviews will be held by staff of the clinical partners in face-to-face meetings with end users. Usability tests will be performed based on the System Usability Scale (SUS). The results of the usability tests will be analysed using statistical methods to quantify the error rate, effectiveness and learning curve of the TV-AssistDem platform. To do that, during the intervention group will be asked to perform specific tasks with the applications and different interaction parameters will be measured such as number of taps, reaction time, time-to-target, time of accomplish, etc.

Economic analysis

A cost-effectiveness and/or cost-utility analysis from a Health Service perspective (financer perspective) will be performed. The time horizon is two years and will include only direct costs. This refers to direct health costs (medication and healthcare use of services including outpatients visits and hospital admissions and emergencies visits). The QUALYs will be calculated to estimate the benefit calculating the utility improvement measure by EuroQoL5D.

Missing data

Procedures can sometimes be considered when using statistical methods that fail in the presence of any missing values, or when in the case of multiple-predictor statistical models all the data for an individual would be omitted because of a missing value in one of the predictors. For analyses involving multiple regression analysis, a multiple imputation approach will be considered and used if statistically sound, depending on the proportion and pattern of missing values.

Methods to ensure validity and quality of data

Accurate and reliable data collection will be assured by verification and cross-check of the case report form (CRF) against the investigator´s records (source document verification). Source document verification will be conducted for 5% of data in subjects.

A comprehensive validation check program utilizing front-end checks in the CRF will verify these data. Discrepancies and queries will be generated accordingly in the CRF for online resolution by the investigator at the site. In addition, the CRF data will be reviewed on an ongoing basis for medical and scientific plausibility.

9. Adverse Events

According to the ICH GCP E2 and E6 Guidelines (64), the definitions of adverse events (AEs) and serious adverse events (SAEs) are:

Adverse event (AE)

Any untoward medical occurrence in a patient or clinical investigation participant administered an investigational product and which does not necessarily have a causal relationship with this treatment. An adverse event (AE) can therefore be any unfavourable and unintended sign

(including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational product, whether or not related to the investigational product.

Even though adverse event is a term traditionally used within a medical context, it can also be used for conditions of a psychosocial nature, e.g. stress and affected mental health associated with the use of an investigational product, whether or not related to the investigational product. An example of this could be increased carer burden for the informal caregiver.

Serious adverse event (SAE)

Any untoward medical occurrence whether or not related to the investigational product that meets one of the six criteria:

- Results in death
- Is life-threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is an important medical event requiring medical or surgical intervention to prevent serious outcome

In the occurrence of an adverse event, the investigator and his or her team are responsible for detecting, recording, reporting and taking appropriate actions in according to the requirements of the local institutional review board (IRB) and the appropriate regulatory body (ies) with health- and social care in respective country of the study.

General requirements

The principal investigator may delegate the detecting, recording and reporting of adverse events to other qualified medical personnel, e.g., co-investigators.

The investigator should be familiar with any information produced by MagicBox about risks entailed in using Tv-AssistDem platform.

The investigator should review the protocol about the requirements of recording and reporting of AEs for the trial.

The investigator should assess and report any AEs and SAEs from the point at which the product is administered until the end of the study period.

The investigator is not required to actively detect AEs or SAEs in participants who have completed the study. However, if the investigator learns of any SAEs at any time after a participant has been discharged from the study, and he or she considers the event to be related to the investigational product, the investigator should promptly report the event as a SAE.

Each partner organization will appoint a local lead person regarding AEs and SAEs (henceforth 'local lead'). In addition, a person will be appointed as the overall lead at trial level regarding AEs and SAEs (henceforth 'overall lead').

Detection and follow-up of AEs and SAEs

The investigator will actively assess and inquire about the occurrence of AEs/SAEs at every contact during the study.

The investigator will also encourage the participants/family members/medical care providers to report any untoward medical condition or incidence of hospitalization to the investigator or any study site staff.

The investigator or other study site staff should be alerted to events documented in the participants' medical records or consultation notes that may be an AE or SAE. Active regular review of medical records should be implemented whenever possible.

All ongoing AEs will be continually monitored and followed up at subsequent study visits by the investigator until the AE has stabilized or has been resolved.

The investigator will also follow up with the participant regarding the SAE until the event has resolved, stabilized or if the event is otherwise explained.

Recording and reporting of an AE

The adverse events will be documented on the CRF and, in addition, flagged up to the local lead. The following types of information about the AE are required:

- Description of adverse event (a diagnosis is preferred)
- Start date and end date
- Severity of the event

- Relationship to the investigational product
- Countermeasures
- Outcomes
- Serious/non-serious

The investigator should try to establish a diagnosis of the event based on the signs and symptoms and/or other clinical information. If making a diagnosis is not possible, the investigator will record sign and/or symptom as an event.

The investigator should follow the definition of the severity of adverse events in the protocol when recording AEs.

The investigator is required to assess the causal relationship between the investigational product and the event.

The investigator should ensure sufficient source data documentation for supporting the data related to the AE recording on CRFs.

Recording and reporting of an SAE

All the above procedures for recording and reporting of AEs apply to that of SAEs.

If an investigator becomes aware of any SAE that occurs during the study, whether related to trial treatment or not, they must report it to the local lead, who, in turn, must report it to the overall lead. This reporting must be done within 24 hours of the investigator first becoming aware of the SAE.

The SAE will be documented on the SAE reporting form contained in the individual CRF. The investigator will document all available information regarding the SAE on the SAE reporting forms within the CRF. The investigator should not wait to receive all the information to fully document the event before reporting the SAE. The initial SAE report should minimally include the following information or information otherwise specified in the protocol/study procedure manual:

- Participant's study number
- Participant's initials

- Time and date of first starting the trial treatment
- Time and date of occurrence of the event
- A brief description of the event and countermeasures taken
- Investigator's opinion of the relationship with the investigational product

The follow-up SAE report should be sent to relevant lead people as soon as the follow-up information is available. The study site staff should follow the timeline for sending follow-up reports to these lead people.

The investigator is responsible for complying with the local IRB requirements in relation to the reporting of SAEs to the IRB.

The overall lead will send external SAE reports to each investigator participating in trial testing of the same investigational product. The investigator should acknowledge receipt of the external SAE reports to the overall lead. The external SAE reports should be submitted to the IRB in accordance with the local IRB requirements.

When submitting SAE reports to the IRB, the study site staff should ensure clear documentation of each specific report sent to the IRB.

The investigator is obliged to comply with any applicable regulatory requirements related to the reporting of safety events to the regulatory body.

If there is any further action required by the local IRB or regulatory body after reviewing the safety reports, the investigator should inform the sponsor.

A summary of all adverse events should be reported to the IRB on the regular progress report to the IRB.

10. Study Limitations

The first limitation will be the selection bias resulting from the missing data. To diminish this bias, several strategies will be applied: an increase of 20% in the sample size (expected losses), three phone calls on different days and at different times for unreachable patients and additional appointments for the patients who did not attend the clinic visits (three different appointments). Despite this, the dropout will be inevitable. For this contingency, a comparison

will be made between all study variables at baseline and final visit to test the impact of losses on sample structure and a multiple imputation approach will be considered.

Another important aspect to consider is the protocol and the intervention standardization. To solve this the dynamic will be structured in an exhaustive way and professionals trained will perform the intervention. Furthermore, a manual for the researchers will be designed where we the working plan, the different parts of the intervention, the protocol scheme to know what they have to measure each time and the details to assess each variable included in the study will be explain. In this way, the procedure can be replicated elsewhere.

Other aspect is the Hawthorne effect along the study (ie, tendency of subjects participating in a research study to change their behaviour). Although this could affect overall estimates the adherence, the implications might be less important in comparing results of different measurements tools (unless, of course, the effect is differentially captured by each measurement tool); furthermore, it is difficult to perceive that any potential Hawthorne effect would be maintained over the many months of study.

11. Ethics

Institutional Review Board (IRB)/Independent Ethics Committee (IEC)/Multicentre Ethics Committee (MEC) review and reports

This study will be conducted in compliance with the protocol, the ethical principles that have their origin in the Declaration of Helsinki, the International Conference on Harmonization (ICH) consolidated Guideline E6 for Good Clinical Practice (GCP) (CPMP/ICH/135/95), and applicable regulatory requirement(s) including the following:

- European Commission Directive (2001/20/EC Apr 2001) and/or;
- European Commission Directive (2005/28/EC Apr 2005) and/or;
- Other applicable local regulations

Approval will be sought from an Institutional Review Board (IRB)/Independent Ethics Committee (IEC)/Multicentre Ethics Committee (MEC), appropriate to the regulations for that country, for the trial protocol, informed consent forms and other relevant documents e.g. advertisements and GP information letter.

Substantial amendments that require review by the IRB/IEC/MEC will not be implemented until the IRB/IEC/MEC grants a favourable opinion for the study. All correspondence with the IRB/IEC/MEC will be retained in the Trial Master File/Investigator Site File.

If required by the IRB/IEC/MEC, an annual progress report (APR) will be submitted relevant board within the timescale for that country, and annually until the trial is declared ended (or as appropriate to the regulations for that country).

It will be the Chief Investigator's responsibility (for that country) to produce the annual reports as required. The Chief Investigator will notify the IRB/IEC/MEC of the end of the study if the study is ended prematurely, the Chief Investigator will notify the IRB/IEC/MEC, including the reasons for the premature termination.

The Chief Investigator will submit a final report with the results, including any publications/abstracts, to the IRB/IEC/MEC within one year after the end of the study.

Peer review

This trial protocol was reviewed by the funder, The European Commission (EC) and internal departments of each partner of the trial consortium.

Public and patient involvement

There has been public and patient involvement since the conception of this study. Focus groups have been held in the countries of each recruiting site of the project consortium to help finalize the specific requirements that come with the symptoms and progression of the condition. Their input has helped to tailor the application to the needs of those with mild dementia. Short reports were written after each focus group to record the participants present and the progress of customization. These focus groups were attended by patients, informal carers and healthcare professionals, and they worked together to suggest features which would be important in the design of the application, as well as feedback on the usability of it. This ensured that the application to be used in the study, was relevant and usable to those with mild dementia.

Regulatory compliance

The application in this study is not defined as a medical device under directive 93/42/EEC therefore Clinical Trial Authority is not needed.

Protocol compliance

Sponsor and Investigator will conduct this clinical investigation in accordance with the Good Clinical Practice and all applicable regulatory requirements including transpositions into national law.

Prospective, planned deviations or waivers to the protocol are not allowed under the regulations on Clinical Trials and must not be used e.g. it is not acceptable to enrol a participant if they do not meet the eligibility criteria or restrictions specified in the trial protocol.

Accidental protocol deviations can happen at any time and must be adequately documented on the relevant forms and reported to the Chief Investigator and sponsor immediately.

Deviations from the protocol which are found to frequently recur are not acceptable, will require immediate action and could potentially be classified as a serious breach.

In medical emergencies, sponsor does not require confirmation for protocol deviations, but Investigator will notify sponsor immediately and will notify the IRB/IEC/MEC according to local requirements. Investigator, or designee, will record deviations with an explanation for the deviation. Investigator will report to sponsor who will analyse them and assess their significance.

Notification of Serious Breaches to GCP and/or the protocol

A “serious breach” is a breach which is likely to effect to a significant degree –

(a) the safety or physical or mental integrity of the subjects of the trial; or

(b) the scientific value of the trial

The sponsor will be notified immediately of any case where the above definition applies during the trial conduct phase. The sponsor of a clinical trial will notify the IRB/IEC/MEC in writing of any serious breach of:

(a) the conditions and principles of GCP in connection with that trial; or

(b) the protocol relating to that trial, as amended from time to time, within the timescales as appropriate for that country of becoming aware of that breach

Data protection and patient confidentiality

All data and information collected during this study will be considered confidential by the sponsor in accordance with the European Union Directive 95/46/EC (Data Protection Directive of 1995). All investigators and trial site staff must comply with the requirements of this directive

with regards to the collection, storage, processing and disclosure of personal information and will uphold the core principles. The Investigators will ensure that the trial sites comply with the participant confidentiality provisions and privacy laws of each EU member state in which they are domiciled, local regulations, and institutional requirements

Participants will own and centralize all of their health information within the application. Participants consent to who has access to their information and what information can be viewed. The application creates an audit trail and makes this visible to participants, so they can see who viewed their record, what parts they viewed and from where they viewed it and report any unauthorized access.

The Investigator must ensure that the participant's anonymity is maintained. On the Case Report Forms (CRFs) or other documents submitted to the sponsor or lead clinical site, participants will be identified by a unique identifier. Documents that are not for submission to the sponsor or lead clinical site, (e.g., signed Informed Consent Forms [ICFs]) must be kept in strict confidence by the Investigator.

All data used in the analysis and summary of this study will be anonymous, and without reference to specific study participant names. Access to study participant files will be limited to authorized personnel of the sponsor, the Investigator, and research staff. Authorized regulatory personnel have the right to inspect and copy all records pertinent to this study, but all efforts must be made to remove participants' personal data.

Certain questions in the instruments used in the study might be considered sensitive to reveal, such as QoL-AD (e.g., relationship with family members; financial situation, etc). Confidentiality is maintained by asking such parts of the interview separately to the person with MCI or mild dementia and informal carer respectively. Further, both person with MCI or mild dementia and informal carers are asked if there is anything in particular they want to share with the clinical test leader or if there is specific information not to be shared with the other.

Financial and other competing interests for the chief investigator, PIs at each site and committee members for the overall trial management

This project has received funding from the European Active and Assisted Living Programme (AAL Programme): TV-AssistDem (AAL-2016-024).

None of the investigators, nor members of the consortium have any conflicting financial or competing interests.

Amendments

Changes made to the research after review body (ies) approval are amendments. These may be substantial or non-substantial. Any amendments to the study protocol required as the study progresses will be communicated by the sponsor.

Amendments undergo the same review and approval process as the original protocol via the IRB/IEC/MEC and regulatory authorities. Protocol amendments are implemented after it has been approved by the IRB/IEC/MEC and regulatory authorities, where applicable, unless immediate implementation of the change is necessary for participant safety. In this case, the situation must be documented and reported to the IRB/IEC/MEC and regulatory authorities within five working days. The sponsor will assure the timely submission of amendments to regulatory authorities. Amendments will be tracked in the protocol appendix and the version of the protocol will be updated.

Non-substantial Amendments

The sponsor may make a non-substantial amendment at any time during a trial. Non-substantial amendments should be made by via the IRB/IEC/MEC and regulatory authorities reporting procedures for that country. The form will be filled by the CI and authorized by the sponsor.

Examples of Non-substantial Amendments

- minor changes to the protocol or other study documentation, e.g. correcting errors, updating contact points, minor clarifications;
- updates of the investigator's brochure (unless there is a change to the risk/benefit assessment for the trial);
- changes to the chief investigator's research team changes to the research team at particular trial sites (other than appointment of a new principal investigator in a CTIMP);
- changes in funding arrangements; changes in the documentation used by the research team for recording study data;

- changes in the logistical arrangements for storing or transporting data; inclusion of new sites and investigators in studies other than CTIMPs;
- extension of the study beyond the period specified in the application form

Substantial Amendments

If the sponsor wishes to make a substantial amendment to the protocol or the documents that supported the original application, the sponsor must submit a valid notice of amendment via the IRB/IEC/MEC and regulatory authorities as appropriate for the regulations of that country. The IRB/IEC/MEC will provide a response regarding the amendment within the timescales as appropriate for that country of receipt of the notice. It is the sponsor's responsibility to decide whether an amendment is substantial or non-substantial for the purposes of submission.

If applicable, other specialist review bodies (e.g. CAG) need to be notified about substantial amendments in case the amendment affects their opinion of the study.

Amendments also need to be notified to R&D departments (if appropriate) of participating sites to assess whether the amendment affects the permission for that site. Note that some amendments that may be considered to be non-substantial for the purposes of IRB/IEC may still need to be notified to NHS R&D (e.g. a change to the funding arrangements).

Examples of Substantial amendments

- changes to the design or methodology of the study, or to background information affecting its scientific value;
- changes to the procedures undertaken by participants;
- any change relating to the safety or physical or mental integrity of participants, or to the risk/benefit assessment for the study;
- significant changes to study documentation such as participant information sheets, consent forms, questionnaires, letters of invitation, letters to GPs or other clinicians, information sheets for relatives or informal carers;
- a change of sponsor(s) or sponsor's legal representative; appointment of a new chief investigator a change to the insurance or indemnity arrangements for the study;

- inclusion of a new trial site (not listed in the original application) in a CTIMP; appointment of a new principal investigator at a trial site in a CTIMP;
- temporary halt of a study to protect participants from harm, and the planned restart of a study following a temporary halt; a change to the definition of the end of the study;
- any other significant change to the protocol or the terms of the REC application

Post-trial care

After the study has ended, participants will be asked to return the Set Top Box and will continue with standard practice. Participants will be made aware of this at the beginning of the study and within the Participant Information Sheet (PIS).

Access to the final trial dataset

The final dataset will be available to the statistician for data analysis. Each country involved in the study will perform an independent analysis on the data for that country, before an analysis for all countries is performed together. The chief investigator and members of the steering group will have access to the full dataset. This will ensure that results are not disclosed prior to publication. Site investigators will not have access to full dataset.

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