D3.5 Guidelines for use of smart devices as a measure of RWE

116020 - ROADMAP

**Real world Outcomes across
the AD spectrum for better
care: Multi-modal data Access
Platform**

**WP3 – Identification,
mapping and integration
of RWE**

Lead contributor	Martien Kas (15 – Rijksuniversiteit Groningen (RUG))
	Email: m.j.h.kas@rug.nl
Other contributors	Andrew Turner (1– UOXF)
	Dominic Paes (18 – BIOGEN)
	Stephanie Vos (4 – UM)
	Emilio Merlo Pich & Rodrigo Palma dos Reis (23 - TAKEDA
	Iain Simpson, Francine Jury*, Ira Leroi*, Derek Hill and Kirsi Kinnunen (14 -IXICO)

Due date	31/10/2018
Delivery date	28/09/2018
Deliverable type	R
Dissemination level	PU

* Both contributors have appointments at the University of Manchester but contributed through Cygnus study's sponsor, Ixico.

efpia

Description of Work	Version	Date
	V2.0	08/11/2017

Table of contents

Document History

Version	Date	Description
V1.0	28/07/2017	First Draft
V2.0	22/08/2017	Comments
V3.0	19/07/2018	Draft
V4.0	28/09/2018	Final Version

Definitions

- Partners of the ROADMAP Consortium are referred to herein according to the following codes:

    - **UOXF**. The Chancellor, Masters and Scholars of the University of Oxford (United Kingdom)
    - **UM**. Universiteit Maastricht (Netherlands)
    - **IXICO**. IXICO Technologies Ltd (United Kingdom)
    - **RUG**. Rijksuniversiteit Groningen (Netherlands)
    - **BIOGEN**. Biogen Idec Limited (United Kingdom)
    - **TAKEDA**. Takeda Development Centre Europe LTD (United Kingdom)

- **Grant Agreement.** The agreement signed between the beneficiaries and the IMI JU for the undertaking of the ROADMAP project (116020).
- **Project.** The sum of all activities carried out in the framework of the Grant Agreement.
- **Work plan.** Schedule of tasks, deliverables, efforts, dates and responsibilities corresponding to the work to be carried out, as specified in Annex I to the Grant Agreement.
- **Consortium.** The ROADMAP Consortium, comprising the above-mentioned legal entities.
- **Consortium Agreement.** Agreement concluded amongst ROADMAP participants for the implementation of the Grant Agreement. Such an agreement shall not affect the parties' obligations to the Community and/or to one another arising from the Grant Agreement.

Publishable Summary and Introduction

The implementation of digital technologies for neuropsychiatric disorders such as Alzheimer's disease (AD) is rapidly increasing. Advances in quantitative phenotypic assessment, through digital technology, can generate potentially significant improvements in patient-centered care (for example by allowing real life monitoring of treatment efficacy).

In this report, we provide an overview of digital technologies used to assess impairments occurring in AD at different stages of the disease, in particular those in the domains of cognitive abilities, social functioning, functional ability and independence, and sleep-wake patterns and night-time behaviours. Technologies reviewed include tests of cognition like executive function that can be performed on mobile devices, as well as passive functional measurements on systems such as wearables and remotely mounted sensors.

We also mapped several of the ongoing precompetitive major research initiatives that implement these innovations, giving insight into the lessons learned from pilot studies with some of these technologies, in particular by incorporating the opinions from patients and their caregivers about the feasibility and utility of the technology. Several questions remain open and currently only partially addressed, such as the device-agnostic standardization of digital measurements provided by sensors of the same class (e.g., accelerometers), their validation against recognized clinical scales or performance tests already validated for measuring symptom worsening or improvement in AD. Finally, the appreciation of the appropriate value-and-relevance from Regulatory Agencies and National Health Care payers/insurers will be needed to establish the digital technology measurement as an integral part of the future standard of care.

efpia

1. Methods

Based on expert discussions, literature review, and lessons learned from ongoing studies, we provide an overview of digital technologies and ongoing global research efforts used to assess impairments occurring in AD at different stages of the disease. In addition, patient experience, technology appraisal, and regulatory aspects of these novel technologies will be addressed.

2. Results

1. Digital technology to monitor burden in Alzheimer's Disease

This section reviews digital technology to assess cognition and functional measures (e.g., social withdrawal or sleep) of individuals with Alzheimer's disease (AD) at various stages. It describes digital tools specifically designed for these populations (such as those to assess cognition in cognitively impaired or poorly functioning individuals) and technologies such as wearable biosensors that were not designed with an AD population in mind, but have potential application in this population.

Cognition

Age is a major risk factor for neurodegenerative diseases in general, and particularly for dementia and its most prevalent form, Alzheimer's disease (AD). With increasing life expectancy, the annual incidence of AD and its socioeconomic impact are growing. Thus, the issue of screening for dementia and cognitive impairment will become increasingly important. However, currently nearly 50% of dementia cases are not adequately diagnosed (Mukadam et al., 2015). Getting an AD diagnosis typically requires a battery of neurological assessments and traditional pen-and-paper cognitive tests. The trouble is that many people do not seek a medical evaluation of cognitive functioning until they or their loved ones perceive memory decline. By that time, there may already be significant and irreversible brain damage, associated with rapidly progressive cognitive impairment. Increasing knowledge on the pathogenesis of disease allows for the development of interventions aimed at slowing down cognitive decline, or even preventing the onset of dementia. Earlier diagnosis could therefore help clinical trial studies enroll the right participants (i.e. those who are still cognitively healthy but already have AD pathology and are on the verge of cognitive decline). This will allow adequate research of novel pharmacological interventions. For these still non-demented but essentially high-risk individuals there are also proven effective non-pharmacological interventions, focused on lifestyle factors (e.g., preventing physical inactivity, depression and social isolation, improving diet and sleep) or cognitive

efpia

training. Varying levels of evidence have also been shown for efficacy in delaying progression of AD through treatment of comorbidities that increase AD progression risks (e.g., hearing impairment, hypercholesterolemia, diabetes). Early diagnosis may ultimately have a critical impact on the cost-effectiveness of both current and future treatments (Barnett J et al 2014). However, earlier intervention requires tools that facilitate earlier diagnosis so that a neurological workup can be considered. At the moment these tools include an assessment of CSF biomarkers and/or a neuroimaging profiling (either with MRI or PET/SPECT) that have been approved by Regulatory Agencies to support a suspected diagnosis of AD. Although it may be less challenging in the middle-to-late disease stages to make a differential diagnosis of AD based on clinical and cognitive criteria, earlier diagnosis remains a significant challenge. However, since an earlier diagnosis would allow for better long-term patient management including legal, financial and care planning considerations, this challenge is worth pursuing. However, independently from early diagnosis, cognitive test batteries are presently implemented to stage the progression of AD from preclinical to dementia; at first the cognitive tests are used to characterize mild cognitive impairment (MCI), and later to support a diagnosis of either mild or moderate AD. A list of cognitive test batteries commonly used in clinical settings are listed in https://emif-catalogue.eu. For example, the Alzheimer's Association in the USA is dedicated to fuelling the advancement of early detection and diagnosis of dementia and has developed an easy-to-implement process to measure cognition during the Medicare Annual Wellness Visit (Cordell et al 2013). Developed by a group of clinical dementia experts, the recommended process allows primary care physicians to efficiently identify patients with probable cognitive impairment, with the flexibility to choose a cognitive assessment tool that works best in the particular clinical setting.

When a person complains of subjective memory deficit, there is currently no recognized tool for providing an initial assessment in order to determine if a full dementia evaluation is needed. Some providers repeat patient assessments with an alternate tool such as the SLUMS, MoCA or MMSE (Nasreddine Z et al 2005), to confirm initial findings before referral or initiation of a full dementia evaluation in a specialized centre. Recently, a set of features was presented that is thought to increase the likelihood of the presence of preclinical AD in individuals with subjective cognitive decline (Jessen et al. 2014), e.g. the cognitive domain and age at onset of subject complaints, and the presence of concerns.

Many cognitive assessment tools are currently available, from brief evaluations, pen-and-paper tests and computerised testing up to time-consuming, examiner-driven neuropsychological tests (Wilner AN, 2008). However, the crowded field of cognitive tools can make it difficult for physicians to determine which are useful in everyday clinical practice screening. An additional important consideration is whether screening tests can be done remotely, self-administered and scored prior to visiting a physician. The self-administered aspect of a cognitive test may prove beneficial in several ways. Many patients have anxiety about a doctor's visit and having their cognitive abilities assessed by health care workers.

efpia

The ability to self-administer examinations takes away many common stressors for patients who get nervous answering questions or being tested in front of people. Less stressful visits could also be facilitated through open dialogue between patients and physicians, and tests that are taken in the privacy of a patient's home may provide more reliable information (Kaye J et al, 2014). If the test cannot be administered remotely, it might be possible for the clinic's support staff to administer it during a home visit.

Digital technologies offer the promise of remote monitoring of medical conditions in a patient-convenient environment and could be used in both early and longitudinal assessments of cognitive impairment, providing there is a guarantee of exclusive use of the mobile device by the patient (Leurent C and M Ehlers 2015). There have been many initiatives to leverage digital technology for the early diagnosis of probable AD. Many technologies still require further research towards full validation, whereas others are already being used for identifying patients for clinical trials, or for facilitating earlier diagnosis in routine clinical practice. Some of these digital initiatives utilizing computers, tablets or mobile phones are described below, with an emphasis on tools allowing earlier diagnosis and the tracking of disease progression in clinical practice.

CANTAB Mobile (Cambridge Cognition)

Many reliable and well-validated human episodic memory tests exist, which differ in important theoretical and practical aspects. The two most common forms are verbal recall tests or word list learning, and non-verbal tests such as the CANTAB Paired Associates Learning (PAL) test (Sahakian et al. 1988). Verbal tests are very widely used in clinical practice, but their reliance on language may be problematic in some situations, including in patients with difficulties in speaking, reading/hearing, or for whom the test language is not their native language. In contrast, visual memory tests such as the CANTAB PAL offer the advantage of being largely cultural and language neutral, allowing easy use across different countries. Swainson et al. (2001) showed that CANTAB PAL is highly sensitive to the memory impairments that are characteristic of the early prodromal/ MCI phase of AD. PAL shows reasonable sensitivity and specificity; the OPTIMA study, for example, reported a sensitivity of 0.83 and a specificity of 0.82 for the CANTAB PAL in differentiating clinically defined MCI from age-matched healthy controls (Chandler et al. 2008). Scores on the test also show significant correlations with the amount of amyloid pathology present in this population (Scheltens et al. 2014, Nathan P et al. 2017, Reijs et al. 2017).

CANTAB Mobile, delivered via an iPad, is intended to be used as an adjunctive tool to assess memory by testing visuospatial associative learning in patients aged 50 – 90 years. Memory is assessed using the CANTAB PAL test, which is adaptive; testing is stopped once a patient reaches their limit for the number of attempts for their age, gender or level of education. It can be administered by support staff and takes approximately 10 minutes to complete. It also has voiceover guidance in 20 languages (Barnett JH et al. 2016). This application has the potential to rapidly detect early signs of possible AD in patients and to reassure those who

are not at risk. Deteriorating performance can also predict progression from MCI to AD (Chamberlain et al. 2011).

BrainTest (SAGE)

The Self-Administered Gerocognitive Exam (SAGE) (Scharre et al. 2010) has recently been developed into a digital version called BrainTest (Scharre et al. 2017). In the development of SAGE it was felt that one of the most essential elements to its success was self-administration. In addition to enhanced functionality, BrainTest offers the option of timing the assessment, which is not possible with the pen-and-paper version. Additionally, BrainTest is remotely scored in a core-lab model, which removes the need for physicians to learn how to score the test. Physicians are provided the item scores and interpretations, and can explain the results to patients. A self-administered and clinically validated test would not only offer flexibility in an office setting by eliminating the need for a member of staff to administer the test, but would also provide an objective cognitive assessment that can determine if further neurological evaluation is needed. Ultimately, BrainTest combines the advantages of SAGE with an accessible digital format, and offers potential widespread availability. Furthermore, the BrainTest may enable physicians to reach patients who reside in areas where it is difficult to visit their health care provider and are far from specialized cognitive evaluation centers. It is considered an assessment test rather than a diagnostic test, and facilitates further dialogue between patients and physicians.

CogniSense (Quest Diagnostics)

Quest Diagnostics has launched a Digital Tool, CogniSense, to assess dementia. This digital cognitive assessment tool assists physicians in diagnosing, assessing, and managing the care of people with cognitive impairment. CogniSense incorporates a digitized version of the Memory Orientation Assessment Test (MOST) (Clionsky et al. 2010, Clionsky et al. 2017), a protocol in which memory recall techniques, information comprehension tests, and tablet-based clock drawing are used by healthcare practitioners to assess the patients' memory, orientation, sequential memory, and perception of time. Available as an application for the Apple iPad, CogniSense assesses a patient's cognitive health status in 10-15 minutes, and saves the results as a PDF report that is stored digitally in Quest's Care360 cloud portal, from where it is transmitted to supported electronic medical records (EMRs). CogniSense testing is administered and scored electronically, yielding an initial baseline score which, along with subsequent progressive scores, can be stored in Care360. It can be used as a diagnostic and longitudinal assessment tool for cognition. However, its utility may be limited by restrictions to its application to wider geographies and insurance care systems.

COGNIGRAM™ (COGSTATE)

Cognigram™ is a computer-based system designed to measure and monitor cognitive function in neurodegenerative diseases such as AD. Cognigram™ was developed to broadly assess four critical cognitive domains through card playing tasks. Studies using the Cogstate

Brief Battery (CBB) have found it sensitive to cognitive impairment in AD and MCI and to cognitive changes in the preclinical stages of AD. The CBB requires approximately 10 minutes for administration and consists of four cognitive tasks that measure psychomotor function, attention, learning and working memory. The AIBL study assessed the ability of the CBB as a screening tool to assist in the management of cognitive function. The aim was to determine the utility of the CBB in identifying the nature and degree of cognitive impairment in MCI and AD. The AIBL results suggested that the Cogstate learning/working memory composite score from an online test administered in a clinical setting is reduced significantly in MCI and AD, correlates well with measures of disease classification, and is useful in identifying memory impairment related to MCI and AD (Maruff et al. 2013, Lim et al. 2013). An important advantage of this computerized battery is that it is language agnostic and has been validated in several independent cohorts (Koyama et al. 2015). In addition, test performance is related to amyloid levels and hippocampal volume in mild dementia (Lim et al. 2016).

Neurotrack

Neurotrack is developing a simple browser-based application (Imprint™ Eye Tracking Assessment) and screens users for signs of cognitive decline based on their eye movements as they watch images presented on their screens. Assessments of speed, direction and larger patterns of eye movements serve as markers of memory performance. Neurotrack claims it has the ability to detect AD at its earliest stages by assessing recognition memory, a function specific to the brain's hippocampal region, affected relatively early in the course of AD. Traditionally, such tests take about 30 minutes and are available only at a clinic, using expensive equipment including a standard high frame-rate eye tracker camera. Neurotrack's home-based assessment brings scan times down to five minutes, as a result of advances around eye tracking technology, data analytics, machine learning and computer vision for visual paired comparison (VPC) decisional tasks (Bott et al. 2017). VPC tasks have been shown to reliably detect memory dysfunction in humans (Zola et al. 2013).

Neurotrack's app is language agnostic, it doesn't require extensive translation and localization to work for doctors or patients around the world. It also does not require motor skills and utilizes the computer webcam to track eye movements and viewing patterns. Scores from the Imprint™ Eye Tracking Assessment can be used to assess the probability of developing MCI or AD in the 3 years after the assessment. If further validated against imaging measures from positron emission tomography (PET) or magnetic resonance imaging (MRI), or other tests sensitive to early-stage AD, Neurotrack's online test could be a cheap, easy and non-invasive way to detect AD before other, more pronounced, symptoms are evident.

DCTclock (Digital Cognition Technologies, DCT)

The conventional Clock Drawing Test (cCDT) is one of the most widely used tests for screening cognitive impairment and dementia. It has been well accepted among clinicians

efpia

and patients for its ease of use and short administration time (Shulman, 2000). Patients are asked to draw a clock that shows the time to be 11.10, and then copy a pre-drawn clock showing the same time. cCDT demands like drawing and handwriting are complex human activities that entail an intricate blend of cognitive, kinesthetic and perceptual-motor components, including visual perception, memory and reconstruction, visuospatial abilities, on-demand motor planning and execution (praxis), and executive function (Schulman et al 1986). Although there is great interest in the cCDT as a cognitive screening tool, there are multiple cCDT administration and scoring systems with no consensus on which produces the most valid results while remaining user friendly (Ricci et al., 2016).

Digital Cognition Technology's product, called DCTclock, includes a digital pen (Anoto Live Pen) and a microcomputer that transmits the test data from the pen to DCT's servers (Souillard-Mandar et al. 2016, a, b). This research has improved the cCDT. The team behind the latest digital pen study wanted to find a way to automate the test, not only to speed up diagnoses, but to remove doctor subjectivity/inter-rater differences, and potentially help drive earlier diagnoses by using more detailed data markers. The team used data from 2600 tests to build specialized software and create the digital Clock Drawing Test (dCDT). They found it to be far more accurate at delivering a diagnosis than the analogue original, which relies on a doctor's subjective interpretation of the drawings. The company's test of cognitive abilities can be conducted easily and quickly and the results are available immediately. The dCDT was recently compared to the conventional pen-and-paper version of the test in patients diagnosed with early dementia due to AD or amnestic MCI, compared with cognitively healthy controls (Mueller et al. 2017). The study showed that dCDT yielded a higher diagnostic accuracy for discrimination of amnestic MCI patients from healthy controls (78.0%) than the use of the cCDT scoring system (70.0%). Even in those MCI patients with normal cCDT scores, assessment of time-in-air using dCDT yielded a clinically relevant diagnostic accuracy of 79.5%. Pharmaceutical companies are currently using the product in clinical tests and Digital Cognition Technologies expects to offer the service to clinicians in 2018, following further validation.

Savonix Mobile (Savonix)

Savonix has developed a fully mobile, clinically valid digital neuro-cognitive assessment, Savonix Mobile, which takes about 30 minutes to complete. The user is prescribed a code to the app from their physician, and the test can be taken at home, or anywhere, on a tablet or smartphone. The app assesses instant verbal memory, focus, impulse control, spatial memory and emotion identification. Savonix Mobile delivers a set of digitized neurocognitive tests via Android and iOS mobile operating systems, supported by a web-based clinical data dashboard with integrated analytics. Designed with the screen in mind, Savonix was engineered to statistically control for touchscreen effects, and to deliver an age-appropriate test to the individual user that accounts for such effects as device type, screen lag times, and average response time by mechanic (swipe, tap, draw) by age group. Savonix uses 3D technology to more accurately mimic pen-and-paper test conditions with multiple

psychomotor conditions including tapping, choice-based selection, drag and drop, scroll and draw. Key validation data have not yet been published.

Sea Hero Quest

Sea Hero Quest (Jules 2016) is a game designed to help researchers to understand dementia and focuses on the mental processes associated with 3D navigation, one of the first skills lost in dementia (Epstein et al 2017). It was developed by Glitchers, a UK video-game company, in collaboration with University College London, the University of East Anglia, Deutsche Telecom and in association with Alzheimer's Research UK. The game, which is freely available for iOS and Android phones and tablets, involves players tackling several tasks that test spatial awareness; navigating seas mazes, firing flairs to help with orientation and to photograph various sea creatures. Users are requested to (but not obliged to) provide their age, gender and location. One of the developers from UCL, Hugo Spiers, noted that the game can test in one minute around 200 people – the number he would normally test in one year in a laboratory. In the year following the mobile game's launch in 2016, it was downloaded around 2.7M times, with around 80 years of total play time conducted. The team have said this to be equivalent to around 12 000 years of dementia research. The data collected allows research to understand and benchmark how people navigate and develop spatial awareness and how this changes over time. A newer virtual reality version of the game was released in 2017 (Rigg 2017). This allows additional data to be collected, which could facilitate a more immersive and intuitive diagnostic assessment of spatial navigation. The developers envisage that these data will support the development of new diagnostic tests for diseases that cause dementia.

Conclusions regarding cognitive assessment:

Modern digital devices (e.g., smartphones and tablets) offer the opportunity to measure a broad range of memory and visual-constructive abilities that may be used as a fast and easy way to perform screening, and for the early and accurate detection of cognitive impairment in the context of AD.

The advantages of digital or computerized testing include a shorter assessment time, adapted presentation of items to prevent floor and ceiling effects, precise measurement at the millisecond level, automatic scoring (which decreases human scoring error and personnel time), easy portability and fewer examiner effects. Older patients may find that computerized tests are not stressful or difficult to complete, and they can complete them from the comfort of their homes. Language agnostic tools will likely have greater worldwide adoption.

The disadvantages of digital or computerized neuropsychological testing include the need for adequate visual, motor and auditory acuity, which may be problematic in elderly patients and many need more extensive validation for clinical utility. In addition, multiple-choice responses, which are typically elicited in digital or computerized tasks, provide less

qualitative information than patient-generated responses, and include an element of chance. Because of these and other limitations, clinicians should never make a diagnosis of AD based on any one digital or computerized test only.

Social withdrawal and sociability

Studies have indicated that the lack of social affiliation (e.g., small social network, low frequency of participation in social activities and low quality of social relations) or social isolation (i.e., lack of contact with others) has been associated with a rapid decline of cognitive function, and may contribute to the development of dementia in late life (Fratiglioni et al., 2004; Wilson et al., 2007). Furthermore, investigations of the role of the social environment in health promoting behaviour in relation to cognitive performance have shown that an increase in positive social interactions is associated with improved cognition and buffering against stressors (Berkman, 1995; Heinrichs et al, 2003). For that reason, longitudinal and objective monitoring of the level of social affiliation or social isolation will be relevant in view of (preventative) health care in ageing individuals. Smartphone applications have been developed to potentially monitor levels of sociability (e.g., Eskes et al., 2016; Mulder et al., 2018). The feasibility and validity of this technology for people with AD is currently being assessed in a variety of large EU projects within the Innovative Medicine Initiative program, such as the PRISM (Kas et al., in press) and the ROADMAP project.

Functional ability and independence in daily activities

The implementation of digital technologies in assessing the daily functioning of individuals with a diagnosis of MCI or AD is at its infancy, with no technologies so far validated by regulatory authorities or recognized by health care insurance or national institutions. However, while the need for clinical validation remains relevant, some attempts to quantify daily functioning using digital technologies are in place and will be briefly summarized here. In addition, some precompetitive initiatives aimed at assessing the impact on everyday life of the progressive disease have also been launched (e.g., IMI RADAR-AD, Critical Path CAMD).

Daily functioning is still measured by asking patients and/or caregivers to provide ratings on questionnaires, or by getting physicians or other experts to rate clinically relevant functioning on Activities of Daily Living (ADLs) scales (see for example Galaxo et al. 1997). Various ADL scales are used in clinical trials to assess a patient's performance on basic tasks necessary for daily living that are affecting quality of life (QoL). These are often based on informant evaluations, and can have low reliability if self-reported by people with memory deficits or insufficient insight in the patient's daily functioning. Digital technology used for collecting objective data on daily activities could improve the assessment of functional ability in individuals with MCI or AD, perhaps even to identify those at risk of converting to MCI.

To this aim, two different approaches in the use of digital technologies can be recognized: one approach, also defined as pervasive computing, is targeting passive continuous collection of large amounts of data originated by various sensors (Kaye 2017). The other approach is focusing on performance levels on specific tasks that resemble, or simulate, daily activities and that have been shown to correlate with clinically relevant ADLs scores.

Pervasive computing, passive data collection (ORATECH platform)

Pervasive, high-frequency digital data collection from at-home settings for the assessment of daily activities started about 20 years ago in laboratory-like suites, but has only recently shown feasibility on a larger scale in real world conditions. As an example, the Proactive Activity Toolkit (PROACT) from 2004 consisted of 108 radiofrequency identification tags that were attached to various objects in the home. A group of healthy adults were studied whilst they performed a series of daily activities, with the signal of proximity generated by a prototype glove worn by the participants. PROACT accurately identified the act of performing activities in >80% of the participants and in 73% identified the specific activity (Philipose et al. 2004).

More recently, the ORCATECH platform has been used to monitor older adults with and without MCI, using sensors located in the home as well as wearable sensors (Kaye 2017; Kaye et al. 2014). For the Collaborative Aging Research using Technology (CART) Initiative (http://www.ohsu.edu/xd/research/centers-institutes/orcatech/tech/The-CART-Initiative.cfm), environmental sensors placed in the homes of senior citizens continuously monitor gait, mobility, sleep and activity for up to 10 years, developing 'digital signatures for functional decline'. More recently, the ORCATECH team targeted some modern daily activities, such as driving or using a personal computer. In both cases, specific signatures were identified in healthy individuals vs. those with MCI. For example, people with MCI showed a more rapid decline in the use of personal computers, possibly related with a difficulty to navigate a complex interface (Keye et al. 2014). In another study, a group of elderly individuals agreed to fill in a web-based questionnaire about their weekly activities for one year. Those who developed MCI showed progressive delays in submitting their daily contributions and needed more help to complete the questionnaire, compared with individuals whose cognitive profiles on clinical and neuropsychological assessment did not change (Seeyle et al. 2016). A recent study focused on car driving, a key functional or daily living activity for many older adults, which was assessed using an unobtrusive continuous monitoring digital technology in individuals with or without MCI. The driving sensor was found feasible and well accepted by the participants. The results showed that individuals with MCI drove fewer miles and spent less time on the highway per day than cognitively unimpaired participants, and showed less day-to-day fluctuation in their driving habits (Kaye et al. 2017).

Using a passive home-based monitoring system, Urwyler and collaborators (2017) studied ADL in 10 AD patients and 10 age-matched controls over 20 days. The device was made of a

series of boxes that monitored light intensity, temperature, humidity, movement and acceleration, each box being located in critical corners of the house of each subject. The boxed detectors were able to reliably profile some ADL, such as eating, sleeping and grooming. AT the endo of the study, the difference between the erratic behavior of AD patients and healthy volunteers was large, allowing a data-driven recognition of AD vs. healthy with an accuracy of 20%.

Performance assessment, mixed active-passive data collection (iADLs, Altoida)

As an example of the second approach, Altoida proposes a tablet-based augmented reality approach to track the longitudinal worsening of AD by providing an initial standardization of instrumental activities of daily living (iADLs), a marker that was shown to appropriately assess conversion from unimpaired to MCI and from MCI to AD (Tarnanas et al. 2015). The iADLs marker is a set of naturalistic tasks that requires the ability to inhibit being distracted, processing speed, and working memory within an augmented reality- enriched environment. It consists of two modules that simulate more complex ADLs: the first task is an immersive reality day-out task, based on a series of right-or-wrong solutions to a drill, i.e., fire evacuation from a virtual apartment building. In the second task, participants are requested to play a hide-and- seek game, whereby virtual objects are hidden in real locations in their rooms at home, recorded by a smartphone, and later need to be found. Spatial memory and navigation is recorded using the smartphone's sensors. Recently, the Altoida dataset reached thousands of participants, providing an appropriate training set to feed into a learning machine algorithm to classify individuals according to their probability of progressing to the next disease stage. This approach has recently obtained FDA clearance for use in AD.

Performance in a Virtual Reality setting (VRFCAT, NeuroCog)

Another example of measuring performance using digital technology and a virtual reality approach is the Virtual Reality Functional Capacity Assessment Tool (VRFCAT), a web-based task that has been developed to assess the ability to perform daily activities. It consists of a first-person, immersive environment – similar to a video game – to assess 12 objectives across four functional abilities related to ADLs, i.e. taking a bus, completing a recipe, managing currency for household and planning. A technical feasibility and utility trial was conducted in people with schizophrenia and healthy controls, showing a good correlation with the UPSA-B, a standardized assessment that measures functional capacity, mostly focusing on communication and management (Ruse et al. 2014). This technology has been validated in an elderly cohort and is proposed to be implemented in MCI and AD (Allain et al., 2014).

Performance on video-games (Akili Interactive Lab)

Sophisticated video-games have been developed to assess frontal cognitive performance. For example, Akili Interactive Lab, a company that implements a methodology originally

efpia

developed by the University of California, San Francisco (UCSF) to test attention, executive functions and working memory – critical in managing information and communication in everyday life in the current 'digital era'. The Akili video game platform is designed to quantify and improve the ability of individuals to deal with cognitive interference (distractions and interruptions), which impacts the ability to pay attention, plan and make decisions in several demanding daily activities such as driving a car, following a phone conversation when writing or cooking, or, for example, working on a laptop in a noisy environment. Such deficits are particularly present in people with a diagnosis of MCI or AD, and in psychiatric conditions such as attention deficit hyperactivity disorder (ADHD).

The EVO application consists of a 7-minute videogame that runs on tablets or smartphones. The task is to drive at high speed along a winding road while hitting moving targets (by jumping) to gain points and to avoid bullets or other deadly attacks (i.e., task distractors). Psychologically, this creates situations in which two tasks need be performed simultaneously, but at variable speeds. The algorithm assesses the participant's performance and rapidly adapts speed and frequency of distractors to the style (and possible disabilities) of each player, collecting meaningful performance data. A press release in December 2017 indicated that when applied to an MCI population, the EVO was able to identify those with prodromal AD, defined by beta-amyloid loads on PET imaging (Leurent et al., 2016).

Sleep and wake-related activity: passive data collection using actigraphy

Sleep and mobility have recently been receiving attention as potential tools to support research and development in AD. Sleep becomes more fragmented as people age, and sleep-related problems increase in AD, with sleep potentially contributing to the behavioural, functional, and cognitive status of persons with AD, as well as to caregiver burden and health status of the (Trackenberg et al., 2005). Studies have also suggested that poor sleep quality may predict subsequent cognitive decline (Blackwell T, et al. 2014) and that there is a link between sleep and amyloid load and clearance in the brain (Ju et al. 2014). Evidence from animal and human studies further suggests that AD pathology disrupts the sleep-wake cycle, including increased sleep fragmentation and wakefulness (Xie et al. 2013, Lim et al. 2014), and decreased slow-wave sleep (Mander et al. 2015). Converging evidence from animal and human studies suggests that prolonged wakefulness may increase levels of soluble amyloid-beta in the brain, and so may both exacerbate and accelerate the onset of AD pathology (Spira et al. 2013). One night of sleep deprivation in healthy individuals has been shown to result in increased β-amyloid in AD-relevant regions including the hippocampus (Shokri-Kojori et al. 2018), although another recent study in healthy individuals found that partial sleep deprivation (5 or 8 nights with a maximum of 4 hours of sleep; preserved slow-wave sleep) increased CSF orexin, but did not affect CSF biomarkers for amyloid accumulation, neuronal injury or astroglial activation (Olsson et al. 2018). Circadian dysfunction has also been suggested to contribute to the earliest stages of AD pathogenesis (Musiek et al. 2018).

Further research and an increased understanding of these associations could open avenues for new diagnostic and therapeutic approaches.

Polysomnography (PSG), the gold standard for sleep measurement, is expensive and needs to be performed in a specialist facility where sleep may differ from sleep in home settings. Sleep diaries can be used for self-reporting of sleep, but are likely to have limited accuracy, especially in a cognitively impaired population. Digital technology based on wearable biosensors, particularly wrist-worn actigraphy, have the potential to measure sleep in home environments, during clinical trials of AD therapies (McCarthy et al. 2016).

The neuropathological processes leading to the development of AD starts many years before the manifestation of clinical symptoms (Sperling et al. 2014). Identifying individuals during the pre-clinical or early symptomatic phases of AD would provide a critical opportunity for therapeutic intervention. The use of wearable devices for identifying changes in sleep or activity patterns may provide valuable and continuous input into early detection of changes of potential value in clinical trial enrichment and the identification of individuals who might benefit from an approved AD therapy. There is evidence that physical activity is inversely correlated to the risk of dementia in AD and other pathologies (Laurin et al. 2001), and it has been suggested (Rovio et al 2005) that regular physical activity during mid-life could be an important and potentially protective factor for cognitive decline in later years.

Whilst actigraphy has limitations for the measurement of activity over gold standard measures (e.g., gait labs), it is easily deployable in clinical research and practice, including home settings. And because it is capable of measuring both sleep and activity, it is an attractive technology to utilise in clinical trials of experimental treatments for neurodegenerative diseases, including AD (Martin & Hakim 2011, McCarthy et al. 2016). As well as measuring physiological changes in sleep and movement, actigraphy may have the potential to infer symptoms such as apathy (David et al. 2010)[i] or agitation (Khan et al. 2018) in AD populations. Measurement of more specific aspects of movement such as gait, rigidity and tremor are studied less in AD than in neurological diseases such as PD or MS where movement-related symptoms are more central. However, measures able to predict increased risk of falls from wearable technology data collected at home could be relevant to AD as well as movement disorders populations.

Digital tools to measure activity

Actigraphy has been used in clinical research and clinical practice for more than 30 years. Early devices tended to rely on counting steps using mechanical devices, but modern actigraphs usually determine activity by measuring acceleration using Micro-Electro-Mechanical Systems (MEMS), from which activity can then be derived using data analysis algorithms. In some devices the accelerometer data is only stored as total counts (e.g., accelerometer zero crossings) or area under the curve in each specified time interval. These intervals are often termed as "epochs", and can be user selected for the device in a range of
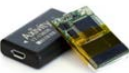
efpia

a few seconds to a few minutes. Sleep patterns can then be determined by identifying periods of low activity from the data using an algorithm. The absence of activity in a short period of time (such as a single epoch) cannot be considered as sleep in its own right; the algorithm needs to classify it in the context of patterns of activity/non-activity within a wider time interval. Conventional algorithms such as Cole-Kripke (Cole et al 1992) do this by generating a weighted average value of activity from the intervals of time around a particular time point. But as discussed below (section 3.3), the use of machine learning, especially when applied to raw rather than epoch data has the potential to improve the specificity and selectivity of the measures.

Improvements in sensor and battery technology, as well as in data analysis, have enabled the development of compact devices that can be worn comfortably for extended periods. The development of wireless technology such as Bluetooth Low Energy (BLE) has opened up the possibility of remote and real-time data collection, although issues with usability and robustness of the technology may limit the utility of this technology in research.

Table 1 shows a summary of available actigraphy devices that are suitable for use in clinical research. These devices can be designed for consumer use (fitness trackers), research studies (devices that have been used to collect data in epidemiological studies such as the UK Biobank) or medical devices cleared by regulators. Some provide simple summary measurements (e.g., total sleep, total activity), while others provide raw accelerometer data that can be post-processed by any algorithm. Although data processing on the device can have benefits around real-time output locally and via a wireless connection, data storage and battery life, raw data collection can support more sophisticated data analysis, including the comparison of different algorithms, and enable potential data reanalysis at a later date with improved algorithms.

Developments in data analysis, particularly the emergence of better algorithms, is having a significant effect on the utility of actigraphy in a range of different settings. In particular, the use of machine learning is making an impact in this area. Approaches have included the use of Fuzzy Logic (Ang et al. 2017), decision trees (Tilmanne et al. 2009) and Deep Learning (Munro et al. 2017). These methods typically can only be applied to raw accelerometer data, and not to compressed summary data (epoch data) from many devices.

efpia

Table 1. Actigraphy devices commonly used in clinical research.

Product		Weight (g)	Raw Data	Battery Life	Memory	Collection Frequency	Wireless	Placement	Cost (euro)	Regulatory status
						Feature				
Withings Activite Pop		37	N	Up to 8 months	Not given	Not given	BLE	Wrist	60-140	Not cleared as a medical device
Axivity AX3		11	Y	30 days @ 12.5Hz; 14 days @ 100Hz	512MB	12.5Hz - 3200Hz	none	Wrist, Back	124	Not cleared as a medical device
GENEActiv		16	Y	45 days @ 10Hz 7 days @100Hz	0.5GB	10-100Hz	none	Wrist, back, hip	180	Not cleared as a medical device
ActiGraph GT9X		149	Y	14 days	4GB	30-100Hz	BLE	Wrist, waist, ankle, thigh	Not given	Class II MD USA CE Mark EU
wGT3X-BT Monitor		19	Y	25 days (30Hz no wireless)	4GB	30-100Hz	BLE	Wrist, waist, ankle, thigh	130	Class II MD USA CE Mark EU
Actiwatch 2		16	N	30 days	1MB	32Hz	none	Wrist	90	Class II MD USA Class I MD EU
Motion-Watch8		9.1	N	Up to 90 days for tri-axial mode or activity+ light	4Mbit	3-11Hz	none	Wrist	Not given	CE Mark (Class I) US FDA cleared (K132764)
Dynaport		55	Y	14 days	>1GB microSD	100Hz	Bluetooth (some versions)	Waist	Not given	Class I MD EU and US
PKG		Not given	N	10 days	Not given	50Hz	none	Wrist	Not given	Class II MD USA CE Mark Europe
ADPM Opal		<25	Y	8-50 hrs	8GB	20-200Hz	Low power radio	Multiple	Not given	

2. Global initiatives on digital data collection in AD

Several European and Global initiatives are underway to incorporate digital technologies into AD medicine. In general, these innovative tools are at the level of validation with respect to feasibility and usability (Table 2).

Table 2. Overview of examples from European and other initiatives that implement digital technologies for the use in AD medicine.

Location	Initiative	Website	Brief description
Denmark	Brain + Care	http://www.brain-plus.com/	Digital platform and app for neurorehabilitation and an innovative meeting of neuroscience, computer games, machine learning, and behavioural psychology.
UK	DPUK	https://www.dementiasplatform.uk/about	Support the Deep and Frequent Phenotyping (DFP) study to collect data from digital interfaces.
UK	Anglia Ruskin University	https://www.anglia.ac.uk/business-employers/support-for-innovation/independence-project	Independence Project: interactive digital daily planner for people with early-stage dementia that runs on a tablet computer. The aim is to help them to continue to live at home for as long as possible.
EU	Human Brain Project	https://www.humanbrainproject.eu/en/medicine/medical-informatics-platform/	The Medical Informatics Platform acts as a bridge between brain-science research, clinical research and patient care, providing the collaborative infrastructure and tools to improve our knowledge of the human brain and define biological signature of diseases, towards better diagnosis and improved treatments. As part of the platform, we develop a set of tools to manage the data acquisition, treatment and analysis.
EU	IMI PRISM	http://www.prism-project.eu	PRISM aims at the identification of quantitative biological parameters to generate biologically meaningful patient clusters irrespective of their initial clinical diagnosis. In a proof of concept study, AD and schizophrenia patient assessments are being performed in the domains of social withdrawal, sensory processing, working memory and attention. For the assessment of social withdrawal, among other tests, the BeHapp smartphone application is being used (Eskes et al., 2016; Mulder et al., 2018).
EU	IMI RADAR-AD	http://ec.europa.eu/research/participants/portal/desktop/en/opportunities/h2020/topics/imi2-2017-12-01.html http://www.imi.europa.eu/projects-results/project-factsheets?keywords=RADAR-AD&status=All&call=All&programmes=All&disease_areas=All&products=All&tools=All	Development and validation of technology-enabled, quantitative and sensitive measures of functional decline in people with early-stage Alzheimer's disease (RADAR-AD) This project is part of the Remote Assessment of Disease and Relapse Programme (RADAR-CNS). Measuring functional and activity-based parameters remotely and continuously via unobtrusive on-body sensors, smartphones or home-based detectors has the potential to revolutionise our ability to characterise the disease and its trajectories.
EU + Israel	SHARE	www.share-project.org	Survey of Health, Ageing and Retirement in Europe: multidisciplinary and cross-national panel database of micro data on health, socio-economic status and social and family networks of more than 120,000 individuals aged 50 or older
EU, Norway, Switzerland, Canada	Ambient Assisted Living (AAL)	www.aal-europe.eu	Localization systems specialized for persons with high risk of getting lost, with the goal of improving the quality of life of these people and their families.
EU	CORAL & ECHAlliance	www.coral-europe.eu www.echalliance.com	Jointly organised promotion of collaboration of Regional Ecosystems & Impact Investing in Smart Health for Dementia Support at Home
EU	SMART4MD	http://dex-ic.com/smart4md_en	application that is specifically targeted to patients with mild dementia Designed to: • Increase patients adherence to their treatment, • Reduce the progression of their illness • Generate data to be sent to their carers and doctors
EU	IMI EPAD	http://www.imi.europa.eu/projects-results/success-stories-projects/epad-revolutionising-clinical-trials-dementia	The European Prevention of Alzheimer's Dementia (EPAD) is aimed to profile 24,000 people to identify a Europe-wide cohort of 1500 high risk individuals that will be invited to participate in a technology-enabled trial to test new treatments for the prevention of AD.
USA	CAMD	https://c-path.org/programs/camd/	Not yet launched. The focus will be on regulatory issues related to digital biomarkers.
USA	NIH	https://grants.nih.gov/grants/guide/rfa-files/RFA-AG-	The NIH is funding a clinical trials network and coordinating center for mobile cognitive trials

		18-012.html	
USA	ADNI-3	https://clinicaltrials.gov/ct2/show/NCT02854033	ADNI-3 is an imaging and biomarker longitudinal study, is directly comparing an at-home computerized cognitive self-test measure vs. standard paper and pencil tests as well as pathological markers of AD progression in a sample of 1200 participants ranging from normal to MCI to mild AD dementia.
USA	Critical Path Institute (C-Path)	https://c-path.org/	Developing an interest in extending to digital data. 1st Online Data Repository of the Critical Path For Alzheimer's Disease (CPAD) Database. Developing an interest in extending to digital data. 1st Online Data Repository of the Critical Path For Alzheimer's Disease (CPAD) Database. This database is linked to GAAIN (the Global Alzheimer's Association Interactive Network)
Ireland & USA	GBHI Driving Dataset	https://www.gbhi.org/	Alzheimer's Disease Prediction Service (ADPS): a computational biomarker. Focus will be on driving behaviour data, collected through IT devices. BOSCH is co-sponsoring this pilot with 250 specialized devices. Driving data will be collected through the two pilot sites: Dublin, Ireland and Thessaloniki, Greece.

3. Lessons learned from the use of digital technologies and biosensors in clinical research

Although, as discussed throughout this report, there are substantial benefits to be gained from deploying digital technologies to support the management of neurodegenerative diseases such as AD, there are also challenges that need to be addressed. A strength of the approach is that is typically involves direct engagement with patients, but if patient experience is not properly considered, it risks issues such as patient mistrust and dissatisfaction, resulting in non-adherence and problems in data collection and interpretation. Although some aspects of patient experience can be considered analytically, through techniques such as risk and task analysis, an empirical approach involving testing with users and iterations based on their feedback is absolutely vital. Capturing and sharing lessons learned is critical in moving the approach forward effectively. In ROADMAP both active and passive applications of digital technology have been considered and participant feedback has been sought. The rest of this section reviews the lessons learned from the use of biosensors, principally for passive data collection, in which data is collected from sensors built into a device worn by the patient, rather than by them interacting with a device such as a smartphone or tablet. In particular, the experience using wrist worn actigraphy devices in a study of patients presenting at memory clinics in the North of England, and their study partners (Cygnus project, sponsored by IXICO with PI Pro. Ira Leroi) is described.

Cygnus is an Innovate UK-funded, collaborative project between IXICO, Northern Health Science Alliance Ltd and Greater Manchester Mental Health NHS Foundation Trust, aimed at exploring the opportunities and challenges offered by real world data collection in the management of dementia. The study included the collection and analysis of standardised longitudinal real world data including outcomes from a large sample of symptomatic patients presenting with memory concerns and their carers. Figure 1 shows an overview of the data study design for Cygnus.

In addition, work on passive remote behavioural monitoring using the BEHAPP smartphone app is ongoing (Mulder et al., 2018) and lessons learned have been added to deliverable report 3.4 as part of a pilot study in AD patients in the ROADMAP project, and will be extended in collaboration with other IMI projects, such as the PRISM project. It is anticipated there will be some overlap in learnings, but for the smartphone work there will also be some new outcomes to consider.

Section 1.4 above introduced the potential value of actigraphy to measure sleep and activity in people with AD, in clinical trials, or to support diagnosis and management in healthcare practice. Operational use of these devices in clinical trials of experimental medicines is, however, at an early stage, and there are important differences between approaches. For example, there are consumer devices, research devices and medical devices[1]. Furthermore, some devices can be synced in "real time", such as via Bluetooth or smartphones, while others store data for later extraction at a central facility. In addition, some devices inform the subject of their sleep and activity, providing information on estimated sleep quality, the amount of deep sleep, heart rate, the number of steps taken, etc., while others do not provide any such information during data collection.

IXICO has conducted a number of pilot studies and deployed biosensor measures into commercial drug trials. These have allowed the exploration of issues and trade-offs around device and data handling and data analysis. Experiences from this work are summarized below.

3.1 Feasibility

There are a number of practical challenges to collecting data from elderly individuals, including those with cognitive impairments and neurodegenerative diseases. From its experience using wearable actigraphy sensors in ongoing studies, including studying sleep and activity in around 100 elderly participants, IXICO has identified the following issues.

Selection of Devices

An increasing range of devices incorporating biosensors are available, including:

- Devices such as the Global Kinetics Corporation Personal KinetiGraph™ (PKG™) and the Empatica Embrace, both cleared as medical devices with approved endpoint measures
- Devices such as Actigraph GT9X Link which are cleared as medical devices and provide raw data that can be analysed offline using a range of algorithms
- Devices such as the Axivity AX3 that are designed for clinical research and have demonstrated analytical validity in a range of published studies, but are not cleared as medical devices
- Consumer devices such as the Fitbit Alta which provide step count data and measures of sleep and activity. These devices are typically designed for a healthy population for which they may give adequate results to encourage healthier lifestyles, but their validity for use in clinical research and specific patient populations is uncertain.
- Advanced biosensor systems incorporating several sensors in a small flexible package that can be attached to a subject using an adhesive layer.

---

[1] The term medical device is used to mean a device that is cleared or approved as a medical device by one of the relevant regulators, and has a relevant indication for us.
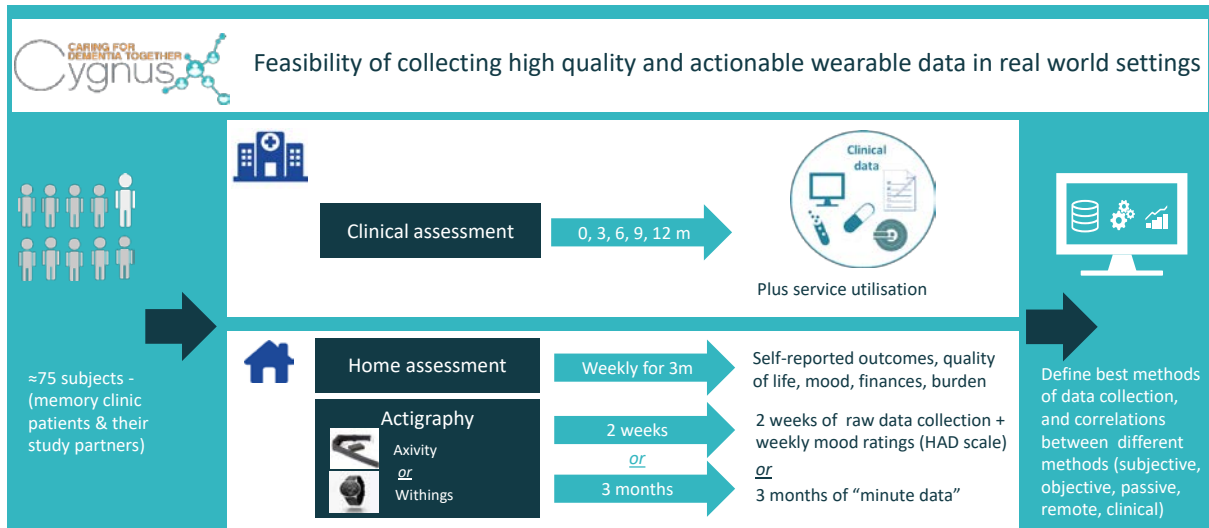
Figure 1: Overview of the Cygnus Study evaluating feasibility of biosensor & mobile technologies for collecting high quality and actionable data in real world settings

The MC10 Biostamp system includes a 3-axis accelerometer, a gyroscope, and a single electrode measure of electro-potential (that can perform ECG, EMG and EEG). Vital Connect's VitalPatch measures heart rate, respiration rate, skin temperature, activity and posture from a small, disposable stick-on sensor.

The choice of device is study-specific and depends on a range of factors including the data to be collected, sample size, patient group, etc. Given that within a majority of drug trials being conducted at present, the biosensors are providing exploratory measures, alongside standard clinical endpoints, site and patient burden are important considerations and clearance as a medical device not necessary – provided that analytical validity of the measurements can be established. Concerns can be mitigated by carefully planning the set-up, distribution and return of devices. Although it might be feasible to have a single site perform the device set-up, this can be impractical in large multi-site studies, with the sites's other study support activities. It has therefore been our experience that devices that are simple, comfortable to wear and easy to use, and that can be passively set up, without significant site burden, are the ideal way forward in many situations, at least until improved reliability of the technology and increased experience of the clinical sites in deploying biosensor-based outcome measures.

Acceptability of devices

Devices that are worn passively, and do not require either charging or manual syncing, can be reliably used to study clinical populations in real-life settings, including in people with MCI (Falck et

al. 2017, Wams et al. 2017) and AD (Leger et al. 2017, Weissová et al. 2016). Any need to remove a device to charge it increases the risk that it will not be replaced or will be wrongly replaced on the body. Comfort is also a factor for devices to be worn continuously – large or bulky devices may affect sleep or cause embarrassment in daytime use. People are increasingly having access to technology that allows the use of app-based activity monitors, however, concerns around data security limit the use of technology available on smartphones and tablets, as does a lack of confidence or willingness to use this technology. Younger or otherwise technically apt relatives often act as enablers, but without continuous support the devices can be put aside or used sporadically. In the IXICO studies, participants using app-based devices enjoyed receiving feedback that they could use to support lifestyle modification (e.g., to increase physical activity). Participants who used a passive device often reported that they would have preferred feedback and being able to self-monitor activity. This is likely to be increasingly the case for studies that require longer wear times and the lack of feedback to the participant may result in a loss of motivation to continue to where the device. Equally if any feedback from the device direct to the participant might be considered to motivate the participant in a way that is beneficial to the study outcomes, such as increasing medication adherence or activity, then there is a risk that regulatory may insist on it being part of the label for the approved medication that might then increase the burden in supporting the therapy in clinical practice.

In the Cygnus study and other studies supported by IXICO we have found good acceptability for simple passive devices such as the AX3, for periods of up to 21 days. Moreover, non-wear time was limited, and only a few issues with skin rash and discomfort were reported.

Ethics aspects

Including wrist-worn actigraphy measurements in protocols for studies targeting AD and cognitively impaired populations and obtaining consent is not problematic from a research ethics point of view. In one study using consumer devices, research ethics approval was obtained for a process by which participants consented to create an account on a consumable biosensor website, and to give consent for the project to access their data through the applicable API. Ethical concerns were raised that suitable insurance was needed to cover potential study-related injuries or losses. Finally, confidentiality regarding the data storage and management should be implemented within the standards required by the Law and the ethical standard.

Device handling

Distributing devices to study sites is analogous to distribution of other devices already commonly used in studies, with a need to ensure robust ways of documenting device reference numbers against subject identifiers. Providing devices for study staff at individual sites to try out themselves has proved beneficial in terms of getting staff comfortable with distributing devices to participants.

Data management

GCP data management is challenging for biosensors that synchronize remotely, especially consumer grade devices that may upgrade their firmware at arbitrary times, and that may send data to a "cloud" storage performing further data analysis. An unbroken audit trail and a careful record of software versions used in this process can be challenging to achieve. The more pragmatic approach is to use a "store and return" model, whereby the participant is provided with a device that they wear until the battery runs out or its memory is full (can typically be around 2 weeks) and then returns it. Data upload from returned devices can be performed on a closed computer system, validated in accordance with normal industry practice. Longitudinal measurements of longer than about two weeks can be made by providing the participants with different devices to wear at each time point (e.g., baseline, 6 months, 12 months), with each device set up for two weeks of data collection.

Adverse events

When distributing devices that are designed to measure sleep and/or activity, it is important to emphasize that these devices should be worn continuously, remain on at night and also be worn in shower/bath or during other "wet activities". Wearing a device with a strap can cause skin rashes over time in some individuals, and such rashes or bruising may occur in frail elderly people due to, for example, looseness of skin around the wrist, which causes them to fasten the strap more tightly. This can increasingly trap soap, perfume and other irritants under the strap and device, resulting in skin reactions. It is important to ensure that study participants are clearly told to remove the device and contact the study team if they get a rash. It is also important to ensure that the strap is made of material that is unlikely to cause skin reactions. Adhering to guidelines on adverse event reporting is critical and providing guidance for study teams in dealing with skin reactions advisable.

Validation of digital measurements vs. current standard: sleep/wake activity

Validity of measurements from wrist-worn actigraphy can be assessed using sleep and activity questionnaires. It can, however, be challenging to get reliable questionnaire responses from elderly and cognitively impaired participants.

 IXICO has undertaken two validity assessments:

1. Actigraphy sensors worn while participant is undergoing overnight PSG and then at home, for a following period of time alongside completing and activity log.
2. Review of activity data for plausibility by study partner.

    In the IXICO sponsored study, Cygnus, study partners were questioned about the validity of data collected by participants using the consumer wearable initially used in that study (Withings Activité Pop). This approach showed instances when data collection was

unreliable, for example, not picking up walking in participants using a walking frame; detecting knitting was detected as "running a marathon", and not recording sleep activity accurately.

While both studies are ongoing, initial findings suggest:

1. Established algorithms for quantifying sleep agree poorly with PSG in the elderly population. This appears to be primarily because they record periods of "quiet wakefulness", which are common in the elderly population, as sleep. Hence devices, including consumer devices, using algorithms of these types significantly over-estimate sleep efficiency in the target population.

2. Older people with memory loss may suffer from REM sleep disorders where a period of sleep paralysis is absent making it difficult for deep sleep to be recognized. Sleep efficiency in these participants may therefore be under-estimated.

3. Consumer devices are not good at measuring activity in elderly participants, perhaps because they were designed with young and fit customers in mind. Devices to include monitoring of heart rate may improve the recognition of mild/moderate/strenuous activity in this population.

4. It is important to distinguish activity in a confined area from more ambulatory activity, which may help distinguish behaviours such as agitation, wandering and repetitive actions from purposeful physical activity.

3.2. Data analysis

As mentioned in Section 1.4, accelerometer data is processed using algorithms to provide measures for sleep and activity, and with the development and accessibility of machine learning approaches, there is considerable scope of improvement of data analysis.

3.2.1. Application of deep learning to actigraphy data

An algorithm was developed to quantify sleep efficiency in a group of elderly participants (n=30), including healthy ageing individuals, some with cognitive impairment, and some with Parkinson's disease. The data collection included Polysomnography (PSG) while the participants were also wearing wrist actigraphs.

An Artificial Intelligence approach often referred to as "deep learning" was used. A convolution neural network (CNN) was trained on this dataset, with each 30 seconds of binary PSG (sleep vs. awake) data used as the gold standard, and the actigraphy data +/- 3 minutes of this applied as input. The CNN determined the required weightings on the input data, to predict the binary PSG score. The algorithm was then evaluated on unseen participants. A leave one out approach was used to train the algorithm multiple times and in each case apply the algorithm trained on (n-1) participants on the nth subject to characterize performance. Figure 2 compares the quantification of sleep efficiency using the novel algorithm referred to as Deep Learning Sleep (DLS) with two
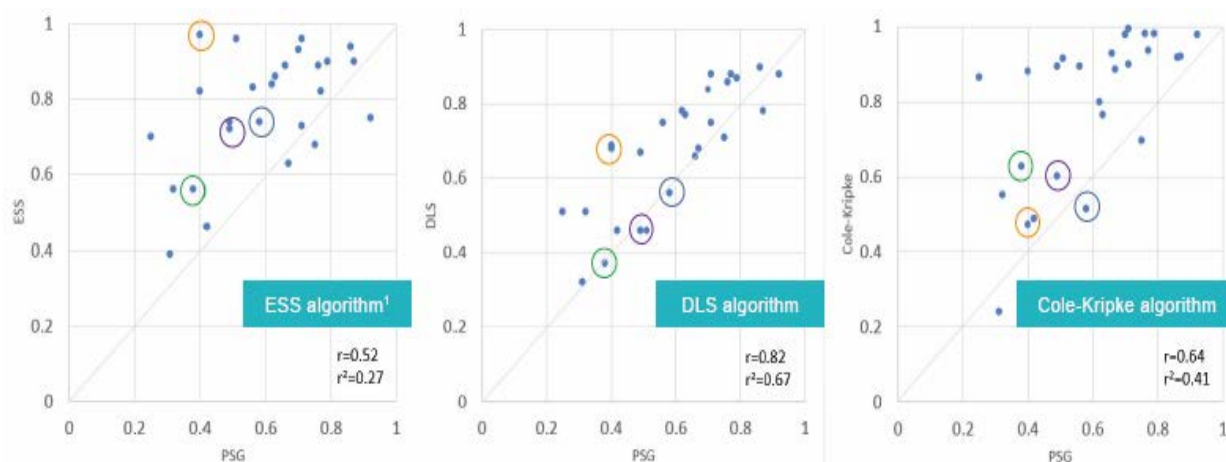
Figure 2: A comparison actigraphy-based measures of sleep efficiency for 3 different algorithms with polysomnography. Data presented at MDS 2017 (Vancouver) and Alzheimer's Association Research Round Table, June 2017

conventional algorithms (Cole-Kripke and ESS),. The vertical axis shows sleep efficiency measured by actigraphy with one of the three algorithms, while the horizontal axis shows the PSG measure of sleep efficiency. Even with this modest sample size, the deep learning approach demonstrates improved correlation (0.84) with PSG, compared to the more traditional methods (Cole-Kripke: 0.61; ESS: 0.57).

3.2.2 Data quality management

IXICO reports experience with two types of wrist-worn actigraphy technologies: Withings Activate pop and the Axivity AX3. The former is an example of a consumer device, and the second a research device.

The consumer device was the favoured product when evaluated in patient and carer focus groups, because it looks like a traditional analogue watch, and does not look "medical" or like a "probation tag". There were, however, significant data quality issues with this device on ~30 participants. For example, many in this population struggled to maintain synchronization through their smart phone, even though this synchronization was automatic. This may be due to the age of the phones/tablets and certain versions of operating systems. Furthermore, there were challenges with getting complete data transfer from the consumer device servers to IXICO servers through the API provided by the manufacturer. We reported these issues to the manufacturer, who are seeking to address them. In addition, the sparse nature of the 60-second epoch or "minute data" from the Withings device limited its applicability. Finally, it was not possible to control full provenance of data in terms of firmware and software versions on the device and servers. We therefore chose to cease using this device, due to the low volume of usable data.

Experience with the research devices, which required a "store and return" model, was that usable data was >90%. Participants tended to wear the device as instructed for two weeks and then return

it. The greatest challenge seemed to be the reuse of devices, as the battery life on reused devices reduced, shortening the data collection period to less than the full two weeks. Battery life on the AX3 devices could be extended by reducing the kHz of signal required for reliable data analysis.

Quality checking of data implemented by IXICO involves visual checking of the incoming data, which for a raw data device (the research grade device) can identify periods where the device appears not to be worn, or any spikes in the data that look atypical of normal wearing. Such periods can be excluded form subsequent analysis. QC approaches could be automated after further experience with data from these devices. In our experience it was less easy to spot artefacts in 60-second epoch data from the consumer devices.

3.2.3. Data reliability

Test re-test experiments were conducted on 17 participants undergoing a PSG assessment in a sleep lab, while wearing two identical raw actigraphy data devices (Axivity AX3). The data from both devices could be analyzed, and the agreement between each device and the PSG assessment was assessed by calculating a measure of between-device variability. This was again done for the three different algorithms: Cole-Kirpke (Cole et al. 1992), ESS (Borazio et al. 2014), and IXICO's own algorithm trained using deep learning (DLS).

Algorithm	Sleep efficiency variability
Cole-Kripke	3.1%
ESS	6.6%
DLS	5.2%

4. Shaping the environment for digital technology in AD

Patient Experience and Technology appraisal – Learnings from the Cygnus Study

As discussed in section 2.2, one of the objectives of the Cygnus study, in addition to collecting biosensor data was to look at some of the user issues in taking this approach.

As expected, the use of home computers/laptops, tablets and smartphones varied considerably, with less than 50% of persons with dementia using a laptop or tablet frequently. Smartphone use was significantly higher, nearing 80% of responders being frequent users. Usage levels for study partners were higher for all types of devices.

When asked about their confidence in using the technology, 29% of people with dementia felt confident compared to 65% of study partners. Commonly reported concerns for both groups included scams/fraud, sharing personal data, banking and online security. However, users of

technology felt that training and reassurance about data security would help alleviate these concerns.

In terms of device usage, good tolerability was found with the majority of participants reporting no concerns about wearing a device and finding the device to be comfortable to wear both during the day and at night during sleep. Participants reported no issues with people questioning them about the device and were keen to explain what it was and demonstrate the app to friends and family. However, one participant stated that the AX3 device was mistaken for a "probation tag".

For the Withings device, users reported that in general it motivated them to be more active, although on occasions technical issues prevented participants from seeing activity. Participants wearing the AX3 device, which provided no feedback, reported that they did not feel they were more active by wearing the device, but thought that feedback would be a desirable feature and might have given them more motivation. Neither device was considered to have encouraged participants to change their sleep patterns.

50% of participants said they would consider wearing a device in the future for their own health and well-being. Nevertheless, interestingly, all said that they would be happy to wear such a device if prescribed by a doctor.

Most complaints were about the lack of accuracy of the watches when participants actively monitored their own activity by other approaches and compared this to the data output from the Withings device.

All participants reported that they would be happy to share data, although some said that they would prefer this to be done anonymously.

Shaping the regulatory path

Regulatory requirements

The regulatory requirements for digital biosensors can be divided between those required for use in clinical trials of new treatments, and those required for technologies that might also be used alongside marketed drugs.

For clinical trial use, the biosensor should be deployed in a trial in a way that meets the requirements of Good Clinical Practice (GCP), and 21 CFR part 11, which means that the biosensor is deployed in a way that meets the requirements of audit trail, user authentication and validation of the computer systems involved. For clinical trial use, if they are to be used as primary or secondary endpoints, it is also important to characterize the clinical validity of the endpoints or biomarkers derived from the biosensor. Devices that send data from a smartphone to a cloud server can be problematic for clinical trial use if the software on these devices is not properly controlled. Regulators might be concerned that any change in measurement might result from

change in software rather than change in the subject. Validation of distributed digital technologies that regularly upgrade their software, as is common in consumer devices, remains challenging, as there is no documentation of "change control" that results from such uncontrolled software changes. Furthermore, regulators sometimes recommend that a sensor used in clinical trial applications is a cleared or approved medical device (see below). And even when a medical device is not recommended, it is clear that the FDA Center for Drug Evaluation and Research (CDER) would take advice from the Center for Devices and Radiological Health (CDRH) on matters to do with biosensors. At public meetings, CDER officials have suggested that the description of the way that biosensors are used, might be best described in a protocol annex, which would be reviewed by CDRH for analytical validity of the device. CDRH now has a regulatory science team looking at these devices that has considerable expertise and will wish to ensure that the way that the device is being used in the clinical trial is supported by suitable data from the correct patient population. This applies whether a cleared medical device is being used or not, though of course the situation is more straightforward if a cleared medical device is used in accordance with the indication for its use of a medical device.

For use alongside a marketed drug, the medical device regulations directly apply. The two key regulators in this sector, the US (through the FDA CDRH) and the EU (through the medical device directive now being replaced by the medical device regulations) have traditionally had a rather different regulatory approach to digital technologies. But medical device regulations for technologies that are heavily dependent on software are evolving rapidly, and, there is also an increasing level of harmonization between the major regulators, through the International Medical Device Regulators Task Force (imdrf.org). FDA has issued some IMDRF guidance directly as an FDA guidance, and the European EMR states that IMDRF guidance should be taken into account.

The new regulations and guidance documents therefore offer greater clarity about the regulatory path for digital technologies, and there is some convergence. Conceptually, it is sometimes helpful
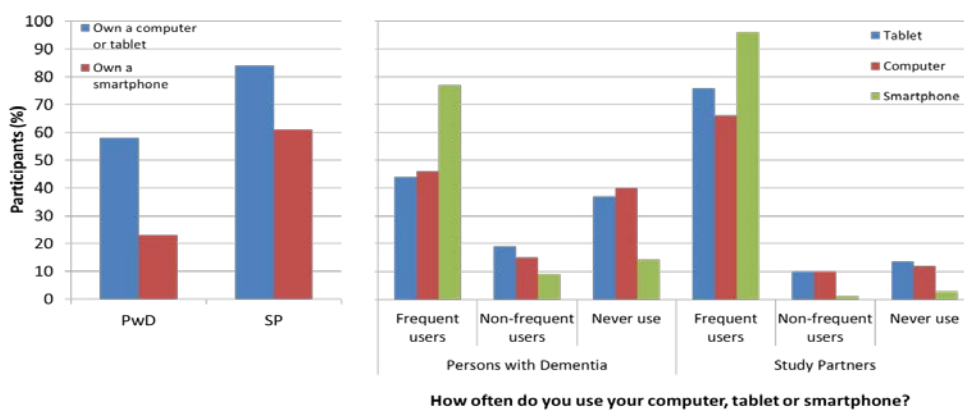

Figure 3: Frequency of use of mobile digital technology by people with dementia and their study partners. Questionnaire data from the Cygnus study

to separate the sensor collecting data, from the software that performs the analysis of the data. The diagram below, taken from the FDA pre-cert programme[2] for digital technologies illustrates this concept – the software performing the analysis can be considered "Software as a Medical Device" (SaMD). In these cases, the sensor itself might have a predicate device, and novel software could follow the guidance recommended by the Software as a Medical Device Guidance generated by IMDRF and adopted as a guidance by the FDA in Nov 2017[3].
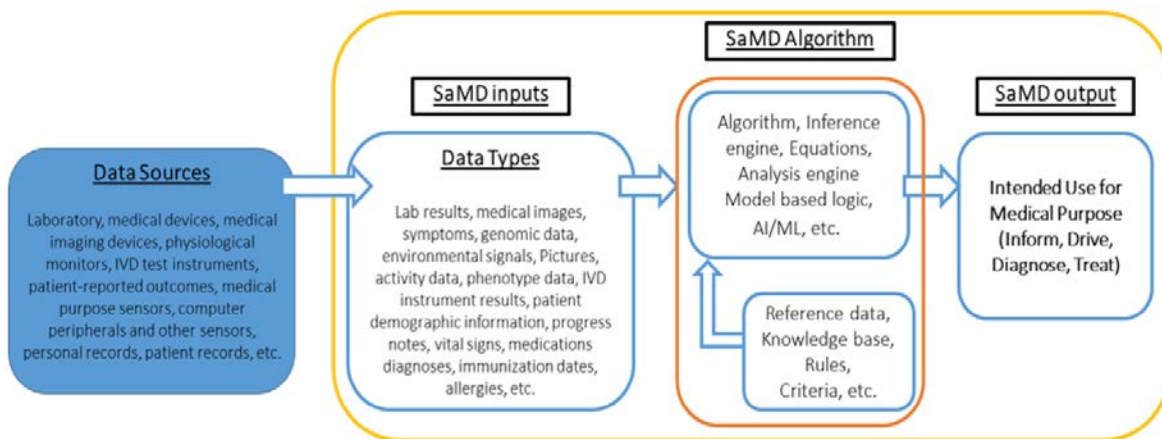
The benefit of considering the data source to be a separate device from the analysis software is analogous to the way medical imaging is considered by regulators (where the scanner, and an analysis workstation are considered two separate devices). Importantly, the SaMD guidance specifically discusses sophisticated algorithms including those using Artificial Intelligence and Machine Learning (see figure).

The FDA approach is distinguished from the EMA approach in that the FDA covers both clinical trial and medical device applications.

Role of the partner/family

The support study partners provide to the participants has proved to be invaluable in providing reassurance ensuring the device is synchronized to the app. .In many cases the study partner wore a device alongside the patient. Study partners could also report back where the participant's watch-recorded activity did not match the activity they observed. Where a participant was wearing the AX3 device, such feedback was not provided, as this is a passive device and study partners would not be aware of any data discrepancies.

---

[2] https://www.fda.gov/downloads/MedicalDevices/DigitalHealth/DigitalHealthPreCertProgram/UCM611103.pdf
[3] https://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM524904.pdf

Social and ethical implications

Digital sensing technologies promise to provide measures for early diagnosis, monitoring of disease progression, and to assist the care of individuals with AD or other dementias by, for example, promoting independence and autonomy or providing new mechanisms to manage care (Maresova and Klimova, 2015).

The design and implementation of such technologies impacts and reconfigures the relationships between persons with AD, family members, carers, and healthcare providers. Ethical and sociological reflection addresses how this takes place and how it can be managed responsibly. For instance, how should technologies 'fit' into private spaces and care settings in ways that achieve promised benefits without disrupting or undermining established care practices?

Issues posed by monitoring technologies revolve around key concepts such as autonomy, dignity, privacy, benefit, and equity (Meiland et al., 2017), and discussions are often structured in terms of (1) balancing the privacy and autonomy of individuals against improvements in individual safety and risk reduction; (2) the tension between the need for informed consent to implement particular technologies and deterioration of an individual's condition undermining the ongoing basis of that consent (Alzheimer Europe, 2010; Meiland et al., 2017).

For example, Bartlett et al. (2017) highlight the role monitoring technologies could play in enhancing individual agency by providing evidence that augments accounts given by persons with AD. That is, supporting them as authors of "coherent and trustworthy accounts" and "truth-bearers" through technological interactions that "supplement a person's memory and ability to narrate biographical information" (2017). Relatedly, Cheek et al. (2005) suggested a series of ways that monitoring technologies can empower the elderly, including facilitating increased engagement with their care (for example, through feedback from monitoring devices), as well as reduced social isolation for the individual (from knowledge of being monitored) and greater reassurance for distant family members (through being able to monitor their elderly relatives).

Crucially, Bartlett et al. (2017) also emphasise the ambiguous role of technologies, and their potential to disempower individuals. They suggest alternative scenarios in which the agency of persons with dementia is reduced through deference to the apparent objectivity of accounts provided by sensing and monitoring technologies. Similarly other authors note that monitoring may constitute unwanted surveillance that diminishes dignity and constrains behaviour. Such negative consequences typically stem from concerns with the passive and pervasive nature of monitoring. For example, that individuals fear repercussions for engaging in disapproved behaviours, or that individuals alter their behaviour because of the perception of surveillance (Alzheimer Europe, 2010; Dorsten et al. 2009). In a focus group study at long-term care facilities, Dorsten et al. found that "all stakeholder groups agreed that there should be sensitive boundaries around the implementation of technology in the daily lives of residents" (2009, p. 31) (See also (Alzheimer Europe, 2010; Cheek et

al. 2005).) The ways this can be operationalized to mitigate the surveillance concerns raised by monitoring technologies, also noted by Dorsten et al., include assurances about the security and governance of data being collected, and mechanisms for giving persons with AD or their family members control over data use.

Monitoring technologies create new socio-technical relationships that must support and not diminish the exercise of individuals' "agency, personhood and citizenship" (Bartlett et al. 2017). More instrumentally, further concerns exist around possible stigmatizing effects of the presence of monitoring technologies. For example, adoption of particular monitoring technologies may be taken as an admission of dependence; or equally, elderly persons and their families may feel pressure to adopt monitoring technologies in order to retain independence (Alzheimer Europe, 2010; Kang et al., 2010). This has led to suggestions that devices themselves should be unobtrusive (Kang et al., 2010) and therefore "discreditable" (Goffman, 1963). Additionally Cheek et al. highlight the need for device design to be sensitive to the technological confidence of older people and their "functional limitations, associated with age" (2005, p. 336), to ensure concordance and avoid individuals resisting, refusing or removing devices (Mahoney and Mahoney, 2010).

As well as impacts on the individuals being monitored, it is also important to account for how carers' roles are reconfigured by the introduction of new technologies (Saborowski and Kollak, 2015), including how established care practices may be altered and what knowledge and skills are presupposed by new configurations. A key concern noted by many authors is that monitoring technologies may negatively affect care by disrupting existing practices. For example, sensing technologies may be used as a substitute (of better or worse quality) for personal care, leading to reduced contact time and social interaction between carers and individuals being monitored (Demiris et al. 2006; Hoenig et al. 2003; Kang et al. 2010). Carers may also raise concerns about their own autonomy and privacy in relation to monitoring technologies in the care environment (Alzheimer Europe, 2010). Additionally, monitoring technologies may create new kinds of work for carers, such as work to maintain the devices themselves, or to ensure the reliability, security and confidentiality of the data they generate (Dorsten et al. 2009). These latter two examples represent shifts in practice that must be evaluated by taking a holistic view of the interrelations between individuals, carers, new technologies and the care environment. As Saborowski et al. note, in a discussion of assistive technologies generally, "a systematic view of all the interactions would allow the services to be configured in context and would take some of the tension out of the perceived competition between staff and technology" (2015, p. 139).

More broadly, ethical and sociological reflection also includes the political and economic consequences of developing and implementing monitoring technologies. For instance, the resources required to equip an environment with monitoring technologies raises questions about who will be able access to these technologies (Cheek et al. 2005; Meiland et al. 2017). Additionally, Cheek et al. observe a logic of efficiency driving technology development, such that "in times of

nursing shortage assistance from smart home appliances and technology would lessen the burden on home care providers. Less time spent on home visits would promote better resource utilisation and time management" (Cheek et al. 2005, p. 337), or elsewhere Hoenig et al. similarly note "the potential humanitarian and financial benefits of reducing dependence on personal assistance" (2003, p. 330).

The design and implementation of monitoring technologies is characterized by ambiguity about whether the reconfigurations of care practices that those technologies bring about enhance or diminish individual identity, care quality and access to care. To address this, frameworks and guidelines have been developed for thinking through the ethical and social issues presented by assistive technologies for people with dementia and their carers (Alzheimer Europe, 2010; Mahoney et al. 2007). Responsible innovation requires awareness and anticipation of the different roles that technologies might play, and how they may transform social relations in more or less positive ways. The development of monitoring technologies raises empirical questions about the extent to which these issues are felt by stakeholders and how to mitigate possible negative effects. Existing ethical debates about consent, privacy, autonomy and dignity should be evaluated in light of the distinctive features of novel technologies, such as the fact that monitoring is passive and pervasive, devices may be wearable, and are used in populations with cognitive impairment.

Finally, there is also the consideration that increasing the precision of knowledge of an AD individual's disease progression and the impact of this progression on cognition, ADL and social isolation without being able to couple this knowledge with an effective (or even potentially disease-modifying) intervention, may be a form of increasing patient and caregiver anxiety. It is therefore vital that the evolution in digital tools for AD patient support is matched, even if partially, with successful evolution in the realm of therapeutic intervention

5. Conclusion and next steps

• Cognitive testing is central to and well established in AD

• However, traditional cognitive tests were not designed to pick up early disease signs.

• Digital measures of cognition bring some significant advantages but there are also issues around methodology and uptake of technology in elderly populations that need to be addressed.

• There is hence a need to develop more sensitive tests to identify dementia and to predict its onset possibly through the integration of different measures including biomarkers from CSF assays and/or neuroimaging (MRI or PET/SPECT) and cognitive tests. This would mostly likely involve continuous data collection.

• The use of smart phones and wearable devices to collect continuous data in real world settings offers enormous potential both in clinical research and in healthcare practice. Challenges that affect technology uptake and data quality are being identified in early studies and approaches to address these developed.

• Overall, the development of new digital tools should enable direct measurement of activities of daily living in the real world for the benefit of clinical trials and healthcare practice. Collecting such data may improve trial efficiency and better align trial endpoints with actual disease impact. This will eventually support the development and reimbursement of new medications in a more cost effective and reliable way.

• Great adoption of digital technologies will also lead to improved cost effectiveness in healthcare practice and provide better and more patient centric support to those affected by the disease.

6. References

Adam P. Spira, Alyssa A. Gamaldo, Yang An, Mark N. Wu, Eleanor M. Simonsick, Murat Bilgel, Yun Zhou, Dean F. Wong, Luigi Ferrucci, , and Susan M. Resnick; Self-Reported Sleep and β-Amyloid Deposition in Community-Dwelling Older Adults, JAMA Neurol. 2013 December 1; 70(12): 1537–1543.

Akili Press Release: http://www.businesswire.com/news/home/20161209005095/en/Akili-Pfizer-Present-Positive-Data-Digital-Biomarker

Allain, P. et al. Detecting everyday action deficits in Alzheimer's disease using a nonimmersive virtual reality kitchen. J. Int. Neuropsychol. Soc. 20, 468–477 (2014).

Alzheimer Europe, 2010. The ethical issues linked to the use of assistive technology in dementia care. Alzheimer Europe, Luxembourg.

Ang C.K., W.Y. Tey, P.L. Kiew, and M. Fauz, An Artificial Intelligent Approach Using Fuzzy Logic for Sleep Quality Measurement., Journal of Mechanical Engineering Vol SI 4(2) , 31-47 2017

Anguera JA, Brandes-Aitken AN, Antovich AD, Rolle CE, Desai SS, Marco EJ (2017) A pilot study to determine the feasibility of enhancing cognitive abilities in children with sensory processing dysfunction. PLoS ONE 12(4): e0172616.

Atkins AS, Stroescu I, Spagnola NB, Davis VG, Patterson TD, Narasimhan M, Harvey PD, Keefe RS. Assessment of Age-Related Differences in Functional Capacity Using the Virtual Reality Functional Capacity Assessment Tool (VRFCAT).J Prev Alzheimers Dis.2015, 2(2):121-127.

Bartlett, R., Balmer, A., Brannelly, P., 2017. Digital technologies as truth-bearers in health care. Nurs Philos 18, n/a-n/a. doi:10.1111/nup.12161

Barnett JH, Lewis L and Blackwell AD. Early intervention in Alzheimer's disease: a health economic study of the effects of diagnostic timing. BMC Neurology 2014, 14:101-110

Barnett JH, Blackwell AD, Sahakian BJ et al The paired associates learning (PAL) test: 30 years of cantab translational neuroscience from laboratory to bedside in dementia research. Current Topics in Behaioural Neuroscience 2016, 28: 449-474

Berkman LF. The role of social relations in health promotion. Psychosom Med. 1995;57(3):245–254.

Borazio et al (2014) Towards benchmarked sleep detection with wrist-worn sensing units, Borazio M, Berlin E, Kücükyildiz N, Scholl P, Van Laerhoven K. 2014 IEEE International Conference on Healthcare Informatics (ICHI), 2014;125-134

Bott NT, Lange A, Rentz D et al Web camera based eye tracking to assess visual memory on a visual paired comparison task. Frontiers in Neuroscience June 2017

Bryce A Mander, Shawn M Marks, Jacob W Vogel, Vikram Rao, Brandon Lu, Jared M Saletin; β-amyloid disrupts human NREM slow waves and related hippocampus-dependent memory consolidation related hippocampus-dependent memory consolidation, Nature Neuroscience (2015) 18, 1051–1057

Chamberlain SR, Blackwell AD, Nathan PJ et al Differential cognitive deterioration dementia: a two year longitudinal study. J Alzheimers Dis 2011, 24:125–136

Chandler J, Marsico M, Harper-Mozley L et al Cognitive assessment: Discriminationmpairment and detection of decline in Alzheimer's disease and mild cognitive impairment.Alzheimer's Dement 2008, 4:T551–T552Clionsky M, Clionsky E. Development and Validation of the Memory Orientation Screening Test (MOST™): A Better Screening Test for Dementia. Am J Alzheimers Dis Other Demen. 2010, 25(8): 650-656.

Cheek, P., Nikpour, L., Nowlin, H.D., 2005. Aging well with smart technology. Nursing administration quarterly 29, 329–338.

Clionsky M, Clionsky E. Psychometric equivalence of a paper-based and computerized (iPad) version of the Memory Orientation Screening Test (MOST), The Clinical Neuropsychologist, 2017 in press.

Clionsky M, Clionsky E. Development and Validation of the Memory Orientation Screening Test (MOST™): A Better Screening Test for Dementia. Am J Alzheimers Dis Other Demen. 2010 Dec;25(8);650-6.

Clionsky M, Clionsky E. Psychometric equivalence of a paper-based and computerized (iPad) version of the Memory Orientation Screening Test (MOST), The Clinical Neuropsychologist, in press.

Cole et al (1992) Automatic sleep/wake identification from wrist activity, Cole RJ, Kripke DF, Gruen W, Mullaney DJ, Gillin JC. Sleep 1992;12(5):461-469.

Cordell CB, Borson S, Boustani M et al. "Alzheimer's Association Recommendations for Operationalizing the Detection of Cognitive Impairment During the Medicare Annual Wellness Visit in a Primary Care Setting. Alzheimer's & Dementia. 2013; 9(2):141-150.

Demiris, G., Skubic, M., Rantz, M., Keller, J., Aud, M., Hensel, B., He, Z., 2006. Smart home sensors for the elderly: a model for participatory formative evaluation. human-computer interaction 6, 7.

Dorsten, A.-M., Sifford, K.S., Bharucha, A., Mecca, L.P., Wactlar, H., 2009. Ethical Perspectives on Emerging Assistive Technologies: Insights from Focus Groups with Stakeholders in Long-Term Care Facilities. Journal of Empirical Research on Human Research Ethics 4, 25–36. doi:10.1525/jer.2009.4.1.25

Douglas W. Scharre, Shu-Ing Chang, Maria Kataki, Haikady Nagaraja Self Administered Gerocognitive Examination (SAGE) score changes over time in worried well, Mild Cognitive Impairment (MCI), dementia converter, and Alzheimer patients J Alzheimer's & Dementia 2010 Jul;vol 6,issue 4,P369-370. doi:10.1016/j.jalz.2010.05.1238

EMA (2016). Draft guideline on the clinical investigation of medicines for the treatment of Alzheimer's disease and other dementias (EMA/CHMP/539931/2014, 28 January 2016) www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2016/02/WC500200830.pdf

Epstein, R.A., Patai, E.Z., Julian, J,B., Spiers, H. J. , 2017. The cognitive map in humans: spatial navigation and beyond. Nature Neuroscience Vol 20, 1504–1513

Eskes P, Spruit M, Brinkkemper S, Vorstman J, Kas MJ. The sociability score: App-based social profiling from a healthcare perspective. Computers in Human Behavior, 2016, 59, 39-48

FDA (2018). Early Alzheimer's Disease: Developing Drugs for Treatment: Guidance for Industry www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm596728.pd

Fratiglioni L, Paillard-Borg S, Winblad B. An active and socially integrated lifestyle in late life might protect against dementia. Lancet Neurol. 2004;3(6):343–353.

Galasko D, Bennett D, Sano M, Ernesto C, Thomas R, Grundman M, Ferris S. An Inventory to Assess Activities of Daily Living for Clinical Trials in Alzheimer's Disease. Alzheimer Dis Assoc Disord. 1997;11 Suppl 2:S33-9.

Gazzaley A., Rosen L. The distracted mind: ancient brains in an High/Tech world. MIT press, 2016.

Goffman, E., 1963. Stigma: Notes on the Management of Spoiled Identity. Penguin Books Ltd, Harmondsworth.

Heinrichs M, Baumgartner T, Kirschbaum C, Ehlert U. Social support and oxytocin interact to suppress cortisol and subjective responses to psychosocial stress. Biol Psychiatry. 2003;54:1389–1398.

Hoenig, H., Taylor, D.H., Sloan, F.A., 2003. Does Assistive Technology Substitute for Personal Assistance Among the Disabled Elderly? Am J Public Health 93, 330–337. doi:10.2105/AJPH.93.2.330

Jessen F, Amariglio RE, van Boxtel M, Breteler M, Ceccaldi M, Chételat G, Dubois B, Dufouil C, Ellis KA, van der Flier WM, Glodzik L, van Harten AC, de Leon MJ, McHugh P, Mielke MM, Molinuevo JL, Mosconi L, Osorio RS, Perrotin A, Petersen RC, Rabin LA, Rami L, Reisberg B, Rentz DM, Sachdev PS, de la Sayette V, Saykin AJ, Scheltens P, Shulman MB, Slavin MJ, Sperling RA, Stewart R, Uspenskaya O, Vellas B, Visser PJ, Wagner M; Subjective Cognitive Decline Initiative (SCD-I) Working Group. A conceptual framework for research on subjective cognitive decline in preclinical Alzheimer's disease, Alzheimers Dement. 2014 Nov;10(6):844-52.

Jules, M. 2016. Gaming for dementia research: a quest to save the brain The Lancet Neurology , Volume 15 , Issue 13, 1313

Kang, H.G., Mahoney, D.F., Hoenig, H., Hirth, V.A., Bonato, P., Hajjar, I., Lipsitz, L.A., for the Center for Integration of Medicine and Innovative Technology Working Group on Advanced Approaches to Physiologic Monitoring for the Aged, 2010. In Situ Monitoring of Health in Older Adults: Technologies and Issues. Journal of the American Geriatrics Society 58, 1579–1586.

Kas MJ, Penninx B, Sommer B, Serretti A, Arango C, Marston H. A quantitative approach to neuropsychiatry: The why and the how. Neurosci Biobehav Rev. 2017 Dec 12. pii: S0149-7634(17)30534-1. doi: 10.1016/j.neubiorev.2017.12.008.

Kaye J. Making Pervasive Computing Technology Pervasive for Health & Wellness in Aging. Public Policy & Aging Report, 2017.

Kaye J, Mattek N, Dodge HH, Campbell I, Hayes T, Austin D, Hatt W, Wild K, Jimison H, Pavel M. Unobtrusive measurement of daily computer use to detect mild cognitive impairment. Alzheimer's & Dementia, 10 (1): 10-17, 2014.

Kaye J, Matteka N, Dodge H et al Unobtrusive measurement of daily computer use to detect mild cognitive impairment. Alzheimer's & Dementia, 2014, 10: 10–17

Koyama AK, Hagan KA,· Okereke OI et al Evaluation of a Self-Administered Computerized Cognitive Battery in an Older Population. Neuroepidemiology 2015;45: 264-272

Laurin D, Verreault R, Lindsay J, MacPherson K, Rockwood K.. Physical Activity and Risk of Cognitive Impairment and Dementia in Elderly Persons, Arch Neurol. 2001;58(3):498-504

Leurent C, Ehlers MD. Digital technologies for cognitive assessment to accelerate drug development in Alzheimer's disease. Clin Pharmacol Ther. 2015, 98(5):475-6. doi: 10.1002/cpt.212. Epub 2015 Sep 8.

Leurent C, Ehlers MD. Digital technologies for cognitive assessment to accelerate drug development in Alzheimer's disease. Clin Pharmacol Ther. 2015, 98(5):475-6. doi: 10.1002/cpt.212. Epub 2015 Sep 8.

Leurent C, Pickering E, Goodman J, Duvvuri S, He P, Martucci E, et al. A Randomized, Double-Blind, Placeo Controlled Trial to Study Difference in Cognitive Learning Associated with Repeated Self administration of Remote Computer Tablet-based Application Assessing Dual Task Performance Based on Amyloid Status in Healthy Elderly Volunteers. Clinical Trials in Alzheimer's Disease, 9th conference; San Diego, CA, USA: J Prev Alz Dis; 2016. 281.

Lim, Y. Jaeger Y, Harrington J et al . Three-Month Stability of the CogState Brief Battery in Healthy Older Adults, Mild Cognitive Impairment, and Alzheimer's Disease: Results from the Australian Imaging, Biomarkers, and Lifestyle-Rate of Change Substudy (AIBL-ROCS). Arch Clin Neuropsychol. 2013, 28(4):320-330

Lim Y, Villemagne VL, Laws S et al, Performance on the Cogstate Brief Battery is related to amyloid levels and hippocampal volume in very mild dementia. Journal of Molecular Neuroscience 2016, 60 (3): 362–370

Mahoney, D.F., Purtilo, R.B., Webbe, F.M., Alwan, M., Bharucha, A.J., Adlam, T.D., Jimison, H.B., Turner, B., Becker, S.A., 2007. In-home monitoring of persons with dementia: Ethical guidelines for technology research and development. Alzheimer's & Dementia 3, 217–226. doi:10.1016/j.jalz.2007.04.388

Mahoney, E.L., Mahoney, D.F., 2010. Acceptance of Wearable Technology by People With Alzheimer's Disease: Issues and Accommodations. Am J Alzheimers Dis Other Demen 25, 527–531.

Maresova, P., Klimova, B., 2015. Supporting Technologies for Old People with Dementia: A Review. IFAC-PapersOnLine, 13th IFAC and IEEE Conference on Programmable Devices and Embedded Systems 48, 129–134.

Martin JL and Hakim A, Wrist actigraphy, Chest. 2011 Jun;139(6):1514-1527

Maruff P, Ying Lim, Darby D et al Clinical utility of the cogstate brief battery in identifying cognitive impairment in mild cognitive impairment and Alzheimer's disease. BMC Pharmacology and Toxicology 2013, 1:30

Mc Carthy, W. Muehlhausen, P. Schüler, The Case for Using Actigraphy Generated Sleep and Activity Endpoints in Alzheimer's Disease Clinical Trials, J Prev Alz Dis 2016;3(3):173-17

Meiland, F., Innes, A., Mountain, G., Robinson, L., van der Roest, H., García-Casal, J.A., Gove, D., Thyrian, J.R., Evans, S., Dröes, R.-M., Kelly, F., Kurz, A., Casey, D., Szcześniak, D., Dening, T., Craven, M.P., Span, M., Felzmann, H., Tsolaki, M., Franco-Martin, M., 2017. Technologies to Support Community-Dwelling Persons With Dementia: A Position Paper on Issues Regarding Development, Usability, Effectiveness and Cost-Effectiveness, Deployment, and Ethics. JMIR Rehabilitation and Assistive Technologies 4, e1. Mukadam, N., Cooper, C., Kherani, N. and Livingston, G. A systematic review of interventions to detect dementia or cognitive impairment. Int. J. Geriatr. Psychiatry 2015, 30: 32–45.

Miranda M Lim, Jason R Gerstner & David M Holtzman, The sleep–wake cycle and Alzheimer's disease: what do we know?, Neurodegener. Dis. Manag. (2014) 4(5), 351–362

Mulder T, Jagesar RR, Klingenberg AM, P Mifsud Bonnici J, Kas MJ. New European privacy regulation: Assessing the impact for digital medicine innovations. Eur Psychiatry. 2018 Aug 16;54:57-58.

Munro J., R. Wolz, D. Hill, Y. DAUVILLIERS. Validation of actigraphy-derived sleep metrics in Parkinson's disease (PD) patients and elderly controls, taking into account clinical and physiological status [abstract]. Mov Disord. 2017; 32 (suppl 2).

Musiek et al. Circadian Rest-Activity Pattern Changes in Aging and Preclinical Alzheimer Disease. JAMA Neurol. 2018 Jan 29

Nasreddine, Z, Phillips N,.Bédirian, V et al "The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment". Journal of the American Geriatrics Society. 2005, 53 (4): 695–699.

Philipose, M.; Fishkin, K.P.; Perkowitz, M. Inferring activities from interactions with objects. IEEE Pervasive Comput. 2004, 3, 50–57.

Reijs BLR, Ramakers IHGB, Köhler S, Teunissen CE, Koel-Simmelink M, Nathan PJ, Tsolaki M, Wahlund LO, Waldemar G, Hausner L, Vandenberghe R, Johannsen P, Blackwell A, Vanderstichele H, Verhey F, Visser PJ, Memory Correlates of Alzheimer's Disease Cerebrospinal Fluid Markers: A Longitudinal Cohort Study, J Alzheimers Dis. 2017;60(3):1119-1128.

Renaud David, Alice Rivet, Philippe H. Robert, Veronique Mailland, Leah Friedman, Jamie M. Zeitzer, Jerome Yesavage, Ambulatory actigraphy correlates with apathy in mild Alzheimer's disease, Dementia 2010;9(4):509-516

Ricci, M., Pigliautile, M., D'Ambrosio, V., Ercolani, S., et al. (2016). The clock drawing test as a screening tool in mild cognitive impairment and very mild dementia: a new brief method of scoring and normative data in the elderly. Neurol. Sci. 37, 867–873

Rigg, J., 2017 'Sea Hero Quest' hides dementia research inside a VR game' https://www.engadget.com/2017/08/30/sea-hero-quest-vr/?guccounter=1, retrieved July 13, 2018

Rovio S, Kåreholt I, Helkala EL, Viitanen M, Winblad B, Tuomilehto J, Soininen H, Nissinen A, Kivipelto, 2005. Leisure-time physical activity at midlife and the risk of dementia and Alzheimer's disease. Lancet Neurol. 2005 Nov;4(11):705-1. DOI: https://doi.org/10.1016/S1474-4422(05)70198-8

Ruse SA, Harvey PD, Davis VG, Atkins AS, Fox KH, Keefe RSE. Virtual reality functional capacity assessment in schizophrenia: Preliminary data regarding feasibility and correlations with cognitive and functional capacity performance. Schizophr Res Cogn. 2014;1:e21–6.

Saborowski, M., Kollak, I., 2015. "How do you care for technology?" – Care professionals' experiences with assistive technology in care of the elderly. Technological Forecasting and Social Change, Science, Technology and the "Grand Challenge" of Ageing 93, 133–140. doi:10.1016/j.techfore.2014.05.006

Sahakian BJ, Morris RG, Evenden JL, et al A comparative study of visuospatial memory and learning in Alzheimer-type dementia and Parkinson's disease. Brain 1988, 111: Pt 3:695–718

SCarlet RoAD trial, a study of gantenerumab in patients with prodromal AD. Jour Prev AD 2014, 1:231–232

Scharre DW, Chang S-I, Maria Kataki, Haikady Nagaraja Self Administered Gerocognitive Examination (SAGE) score changes over time in worried well, Mild Cognitive Impairment (MCI), dementia converter, and Alzheimer patients J Alzheimer's & Dementia 2010 Jul;vol 6,issue 4,P369-370. doi:10.1016/j.jalz.2010.05.1238

Scharre DW, Chang S-I, Nagaraja H et al Digitally translated Self-Administered Gerocognitive Examination (eSAGE): relationship with its validated paper version, neuropsychological evaluations, and clinical assessments Alzheimer's Research & Therapy 2017, 9: 44-57

Scheltens P, Boada M, Dorflinger E et al Baseline patient characteristics from the Phase 3

Shulman, K. I., Shedletsky, R., and Silver, I. L. (1986). The challenge of time: clock-drawing and cognitive function in the elderly. Int. J. Geriatr. Psychiatry 1, 135–140

Seelye A., N. Mattek, D. B. Howieson, D. Austin, K. Wild, H. H. Dodge, and J. A. Kaye, "Embedded online questionnaire measures are sensitive to identifying mild cognitive impairment," Alzheimer Dis. Assoc. Disord., 30 (2): 152–159, 2016.

Seelye A, Mattek N, Sharma N, Witter P, Brenner A, Wild K, Dodge H, Kaye J. Passive Assessment of Routine Driving with Unobtrusive Sensors: A New Approach for Identifying and Monitoring Functional Level in Normal Aging and Mild Cognitive Impairment. J Alzheimers Dis. (in press) doi: 10.3233/JAD-170116, Jul 19 2017.

Shulman, K. I. (2000). Clock-drawing: is it the ideal cognitive screening test? Int. J. Geriatr. Psychiatry 15, 548–561.

Souillard-Mandar W, Davis R, Rudin C et al Learning classification models of cognitive conditions from subtle behaviors in the digital Clock Drawing Test 2016b, Machine Learning 3, Issue 3: 393-441

Souillard-Mandar W, Davis R, Rudin C et al Using the digital clock drawing test and machine learning to improve accuracy of cognitive screening. Alzheimer's and Dementia, 2016, 12, Issue 7, Supplement; 363–P364

Sperling et al., The evolution of preclinical Alzheimer's disease: Implications for prevention trials, Neuron. 2014 November 5; 84(3): 608–622.

Swainson R, Hodges JR, Galton CJ et al Early detection and differential diagnosis of Alzheimer's disease and depression with neuropsychological tasks. Dement Geriatr CognDisord 2001, 12: 265–280

Tilmanne, J., Urbain, J., Kothare, M. V., Wouwer, A. V. And Kothare, S. V., Algorithms for sleep–wake identification using actigraphy: a comparative study and new results. (2009) Journal of Sleep Research, 18: 85–98

van Schooten KS, Pijnappels M, Rispens SM, Elders PJM, Lips P, Daffertshofer A, et al. (2016) Daily-Life Gait Quality as Predictor of Falls in Older People: A 1-Year Prospective Cohort Study. PLoS ONE 11(7): e0158623. doi:10.1371/journal.pone.0158623

Urwyler P, Stucki R, Rampa L, Müri R, Mosimann UP, Nef T. Cognitive impairment categorized in community-dwelling older adults with and without dementia using in-home sensors that recognise activities of daily living. Scientific Reports volume 7, Article number: 42084 (2017).

Wilner AN. Assessment Tools for Mild Cognitive Impairment and Alzheimer's Disease. Neurology Reviews. 2008, 16(9):5

Wilson RS, Krueger KR, Arnold SE, Schneider JA, Kelly JF, Barnes LL, et al. Loneliness and risk of Alzheimer disease. Arch Gen Psychiatry. 2007;64(2):234–240.

Xie L, Kang H, Xu Q, Chen MJ, Liao Y, Thiyagarajan M, O'Donnell J, Christensen DJ, Nicholson C, Iliff JJ, Takano T, Deane R, Nedergaard M., Sleep Drives Metabolite Clearance from the Adult Brain, Science. 2013 October 18; 342(6156):

Zola SM, Manzanares CM., Clopton P et al A behavioral task predicts conversion to mild cognitive impairment and Alzheimer's disease. Am. J. Alzheimer Dis. Dement. 2013, 28, 179–184.