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Perspective

Use of nonintrusive sensor-based information and communication technology for real-world evidence for clinical trials in dementia

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Abstract Cognitive function is an important end point of treatments in dementia clinical trials. Measuring cognitive function by standardized tests, however, is biased toward highly constrained environments (such as hospitals) in selected samples. Patient-powered real-world evidence using information and communication technology devices, including environmental and wearable sensors, may help to overcome these limitations. This position paper describes current and novel information and communication technology devices and algorithms to monitor behavior and function in people with prodromal and manifest stages of dementia continuously, and discusses clinical, technological, ethical, regulatory, and user-centered requirements for collecting real-world evidence in future randomized controlled trials. Challenges of data safety, quality, and privacy and regulatory requirements need to be addressed by future smart sensor technologies. When these requirements are satisfied, these technologies will provide access to truly user relevant outcomes and broader cohorts of participants than currently sampled in clinical trials.

1. Introduction

A recent systematic review based on 125 individual trials concluded that in randomized controlled trials (RCTs) on disease-modifying drugs for dementia, "[c]ognition should be measured by the Mini–Mental State Examination or the Alzheimer's Disease Assessment Scale–Cognitive subscale (ADAS-Cog)" [1]. However, future trials may benefit from a more innovative approach. Established cognitive tests in prodromal and clinically manifest stages of neurodegenerative dementing disorders, such as Alzheimer's disease (AD), have been criticized for their limited sensitivity and specificity, particularly with respect to the effects of interventions on cognitive function over placebo [2,3]. Outcomes need to capture the full range of clinically relevant phenomena, including the fluctuation of cognitive disability and decline in noninstrumental and instrumental activities of daily living related to general functioning and autonomy at home as well as in the community and consider the impact of an intervention on the everyday life of people with cognitive decline and caregivers. In addition, standard

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RCTs may be biased to selected cohorts of participants by excluding people who cannot receive neuropsychological tests due to language or motor barriers. Therefore, current RCTs on dementia using only paper and pencil clinical and neuropsychological scales may not entirely reveal the effect of an intervention on cognitive challenges of daily living for the population of people with dementia at large [4], see Panel 1.

Recognizing these limitations, major stakeholders, such as the Alzheimer's Association, regulatory authorities, the pharmaceutical industry, and the European Research Council, have invoked more research on procedures collecting real-world evidence (RWE) in people with dementia (see Panel 2). This evidence implies the continuous acquisition of quantitative information on subjects' cognitive status and daily living abilities outside hospitals or point-of-care settings by information and communication technology (ICT) solutions such as wearable sensors and distributed (environmental, home) sensing; these data are elaborated and visualized by smart algorithms. In some cases, these technologies may also be able to deliver interventions to support everyday activities in people with dementia. The use of ICT for capturing RWE data and for delivering interventions cannot always fully be separated, as delivering situation-aware support requires assessment of current behavior and context as well. For sake of brevity, the current perspective article focuses on the derivation of RWE data from pervasive ICT devices irrespective of an eventual additional function as a support device.

ICT solutions allow the collection of short- (e.g., short episodes in paradigmatic situations allowing the measurement of cognitive performance during activities of daily living), medium- (e.g., RCTs lasting several months), and long-term (e.g., observational study lasting years) RWE tracking the trajectories of a person's everyday behavior and activities at home (see Fig. 1 for a schematic depiction of the interaction between these factors). Over a long period, RWE can be used to estimate the onset of functional decline due to the underlying cognitive dysfunction induced by natural disease progression. Over medium-term follow-up, RWE can serve as an end point for the evaluation of targeted interventions.

The association between RWE measures and cognitive status is obtained by data mining, machine learning, cognitive computing, and statistical learning [8,9]. In the validation process of RWE measures, a major issue is the control of quality, validity, fidelity, and reliability. Other issues are users' and family consent of the level of privacy and intrusion into the daily life of people with dementia,

Panel 1
Two types of biases in randomized controlled trials

In-trial bias: sources of bias within the randomized controlled trials.

- Widely studied
- Selection bias considered as a within trial problem (see [5], http://handbook.cochrane.org/front_page.htm), where systematic differences between baseline characteristics of the groups that are compared may drive biased assessment of intervention effects.

Per-trial bias: the randomized controlled trials as a source of bias.

- By its design, randomized controlled trials may preclude a relevant segment of the population from participation in clinical intervention research based on comorbidity, social status, education, and age.
- Research into this source of bias is more limited; examples are:
  - A study on rehydration of children with gastrointestinal infection pointed to the importance of the setting of the trial [6].
  - A study on cancer treatment [7] pointed out: "If, however, the patients in a clinical trial are not representative of the entire patient population because of patient and physician selection biases, the generalizability of the results to the entire patient population may be compromised."

Panel 2
Real-world evidence definition and dimensions

Definition: Real-world evidence (RWE) "entails data collection and analysis about the use, benefits and risks of medicines that fall outside the bounds of the classic Randomized Clinical Trial, including use of data that is routinely collected in the daily practice of medicine, and thus reflective of the heterogeneous patients seen in real world practice settings." (http://catalyst.phrma.org/real-world-evidence-not-just-big-data).

RWE data categories according to the Network of Excellence in Health Innovation (http://www.nehi.net/writable/publication_files/file/rwe_issue_brief_final.pdf)

- Claims data derived from insurance reimbursements
- Clinical trials data derived from the outcomes of randomized clinical trials
- Clinical setting data derived from patient medical records and patient care
- Pharmacy data derived from prescription orders and fulfillments
- Patient-powered data derived directly from the patient experience

Real-world evidence on the political agenda: The National Institutes of Health in the United States has inaugurated the Precision Medicine Initiative and a series of Open Data initiatives. On April 14, 2016, the European Parliament voted in favor of the EU Data Protection Regulation stating that by default all patient health data may be opted in for research by default.

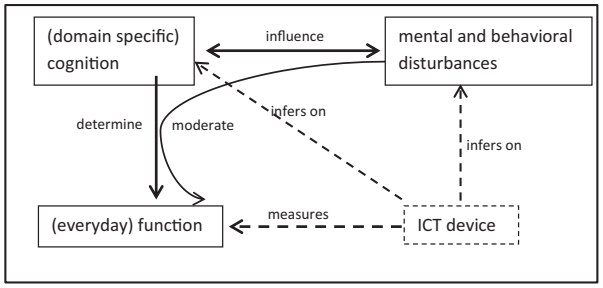

Fig. 1. Cognition, function, and mental disturbances. Abbreviation: ICT, information and communication technology.

family members, and visitors, especially using video or audio recordings from patients' home or resident homes obtained outside of dedicated testing situations. Of note, video or audio assessment of a persons' behavior at his or her home can also be considered a technology solution to capture RWE. However, such data when obtained outside of dedicated testing situations rise issues of user privacy and therefore would be regarded highly intrusive by many people. Consistently, previous studies typically used such approach only in structured and constrained conditions, such as monitoring defined episodes of between patients or patients with caregiver interactions [10–12] or measuring cognitive function in memory clinics during performance of defined cognitive tasks [13].

In this position paper we:

- summarize the available mature and promising future ICT sensors and procedures for early detection of onset and changes in functioning (i.e., activities of daily living), autonomy, (i.e., instrumental activities of daily living) and underlying cognitive functions.
- address the main technological issues to be considered for the practical use of ICT sensors and procedures in dementia.
- address the main ethical, acceptance, and regulatory issues to be considered for the practical use of ICT sensors and procedures in the planning of future RCTs and observational longitudinal studies in dementia.
- suggest how to validate and combine ICT with current standard approaches based on clinical and neuropsychological scales.

The article contents represent a selective (nonsystematic) literature review and evidence-based consensus on this matter among the authors, representing domain experts of neuroscience, clinical research, computer science, and ethics.

2. Available and forthcoming ICT technologies for RWE in dementia research

2.1. Examples of sensor-based patient-powered RWE in dementia research

In Panel 3, four examples illustrate how emerging everyday ICT-sensing systems can continuously collect RWE on cognitive and functional status of senior people. We propose the following dimensions to characterize their main features and outcome:

- Target: Specific cognitive or functional status
- Analysis interval: Short-term (real-time) epoch (e.g., instantaneous disorientation), medium (e.g., last week's/month's activity trajectory) or long-term epoch (e.g., activity trajectory over years)
- Location: a specific locale (e.g., indoor or outdoor settings)
- Sensing technology: mobile devices (e.g., wearables such as bracelet-type sensors, carried smartphone), or sensors integrated into the subject's living environment (e.g., camera, environmental sensors)

To explore the full scope of current use of ICT for functional outcomes in dementia (including prodromal stages), we additionally performed a search of clinical databases (accessed in November 2017) using the string ((dementia [MeSH term](MeSH = Medical subject headings) OR (neurocognitive disorder) [MeSH term] OR (mild cognitive impairment)[MeSH term]) AND (sensor OR actigraphy [MeSH term] OR wearable) in PubMed, and the string ((dementia OR (neurocognitive disorder) OR (mild cognitive impairment)) AND (sensor OR actigraphy OR wearable) in ClinicalTrials.gov, the WHO-Register International Clinical Trials Registry Platform and The Cochrane Central Register of Controlled Trials (http://onlinelibrary.wiley.com/cochranelibrary/search). This search resulted in 233 studies retrieved from PubMed, 46 studies from ClinicalTrials.gov, six additional studies from the International Clinical Trials Registry Platform database, and 42 studies from the Central Register of Controlled Trials. Most studies did not fit the scope of this article, as they addressed sleep abnormalities or intervention effects on sleep (mainly related to "actigraphy"). Several studies addressed conditions not related to dementia, did not involve any RWE or addressed biosensors to detect changes in biofluids or electroencephalography (mainly related to "sensors"). Several studies addressed the detection of apathy, delirium, or agitation as an outcome.

Those studies of interest are listed in Table 1. Together with the examples in Panel 3, this current evidence illustrates the use of ICT devices for dementia detection. Particularly, gait and walking features serve as valuable additional source of context information to enhance function detection in prodromal and early stages of dementia.

2.2. Changing perspective

2.2.1. The application view

Table 1 and the examples in Panel 3 indicate novel ICT-based RWE procedures, combined with appropriate analysis strategies, that are able to produce relevant statements about the clinical and functional status of people with cognitive impairments. From the application viewpoint, there are three major uses of patient-powered RWE: (1) use of

Panel 3
Examples of real-world evidence studies in dementia

Example 1 (wearable, indoor, short-term, clinical): A study by Kirste et al. [14] reported an effect of Alzheimer's disease on accelerometric motion protocols of unconstrained everyday behavior, before this effect manifested itself in established behavior rating scales. In this study, Wearable Inertial Measurement Systems (WIMS) were used to obtain accelerometric recordings of motion intensity in each partner of 23 dyads in their private home during 24 consecutive hours. One partner in each dyad was diagnosed with Alzheimer's disease (AD), without manifest behavioral symptoms according to the Cohen-Mansfield Agitation Inventory [15] rating by proxy. They introduced a novel accelerometric motion score, based on applying functional principal component analysis [16] to the frequency spectrum of the motion intensity signal, to capture a model of the average activity structure among all study participants. The accelerometric motion score reached 91% cross-validated accuracy (.96 sensitivity and .87 specificity) to separate the healthy partners from their AD patients based on the accelerometric motion score on 46 target subjects (23 AD, 23 healthy). In addition, sensitivity (as well as the area under the curve) was superior when benchmarked by the Cohen-Mansfield Agitation Inventory. WIMS-based analysis was thus able to establish a link between clinical diagnosis and measurable behavior in clinical dementia stages.

Example 2 (wearable, outdoor, short-term, functional): A study by Koldrack et al. [17] presented first results on a study that aimed at detecting disorientation in dementia patients during wayfinding tasks. While the detection of manifest wayfinding errors—that is, choice of wrong route with respect to target—is straightforward based on global positioning system traces, the detection of disorientation before it leads to erroneous actions is difficult. In this study, detailed data on fine-grained motor behavior in urban wayfinding was recorded using WIMS and global positioning system for 13 people with dementia. A set of energy- and kinematics-based features was developed with the objective to achieve real-time detection of episodes of disorientation in the WIMS data stream. Machine learning using a cross-validated compound feature set based on WIMS was able to detect effects of spatial disorientation (area under the curve .74), even without correcting for knowledge where behavior change can be expected due to transition points such as road crossings.

Complementary to wearables, sensing devices that do not require any instrumentation of the user also provide potentially relevant data:

Example 3 (video, indoor, long-term clinical + short-term functional): A study by Konig et al. [18] analyzed the performance of everyday activities (such as "prepare medication" or "use phone") on image processing algorithms applied to video recordings of these activities. The researchers used an Event Monitoring System to automatically extract information about patient's performance (e.g., feet position, number of steps, and the activities carried out). Extracted features were used as input for a Naïve Bayes classifier to classify the participants in two dimensions: (1) degree of autonomy (good, intermediate, and poor) as a functional end point; and (2) cognitive status (AD dementia, mild cognitive impairment, and healthy). The Event Monitoring System reached highly accurate autonomy and cognitive group classification benchmarked by established clinical instruments. Such system, due to its use of video data and an experimental environment, is applicable as an objective measure of functional level in clinical trials, but not likely to be used as home assessment.

Example 4 (dense, indoor, long-term clinical): A study by Lazarou et al. [19] investigated the use of a prototype dense sensing system for homes to obtain continuous state monitoring of older people with dementia. The sensing technology of the proposed system included wearable and integrated sensors to monitor sleep, object motion, presence, and utility usage. These sensors were deployed at four different home installations of people with cognitive impairment. Sensor data combined with clinical observations were used to introduce individually targeted psychosocial interventions that led to improvement in physical condition and sleep quality. This was a proof of concept study that addressed not the feasibility of a broader use of such technology but showed potential effectivity that justifies further research toward feasibility and efficiency of such systems.

sensor-derived features of everyday activities (e.g., finding one's way outdoors or cooking a meal) as end points in clinical trials; (2) use of ICT devices to detect long-term trajectories of everyday function and underlying cognitive status, but also of challenging behavior or behavioral impairment (e.g., depression, anxiety, apathy, agitation, and sleep disturbances); and (3) long-term observation of high-frequency behavioral features (naturally occurring or prompted by an ICT device) to assess trajectories of everyday function and underlying cognitive and behavioral changes.

With respect to (1), the use of standard actigraphy is well established. However, Table 1 and Panel 3 illustrate that wearable sensing devices beyond actigraphy are able to provide additional relevant end points in future RCTs.

With respect to (2), few studies so far have used ubiquitous and unobtrusive ICT solutions to monitor long-term behavior; one example is the determination of factors that influence time out of home in older adults using up to 1 year of in-house sensor-based monitoring [47]. If monitored over long periods of time, a sensor intended to control lighting

Table 1
ICT studies relating to dementia outcomes from the clinical database search

Project	Project objectives	Main characteristics of project
PubMed		
Yuce et al. [20]	Geofencing system for people with dementia	Fixed restriction system for people with dementia, no assessment of function or cognition
van Alphen et al., and James et al. [21,22]	Assessment of daily activities in people with dementia	Aims at determining an aggregated measure of overall activity, no assessment of function or cognition
Cavallo et al. [23]	Ambient assisted living environment to support people with Alzheimer's disease dementia	System to support people with dementia, no assessment of function or cognition
Nijhof et al. [24]	Home monitoring system for people with dementia	This system includes no intelligence in the technology device but provides access to the patient's behavior for a caregiver through direct observation.
David et al., and Kuhlmei et al. [25,26]	Apathy detection	Assess a certain behavior to guide intervention; this approach supports the feasibility of function detection by wearable sensors
Etcher et al. [27]	Aggression detection	
Greene et al. [28]	Automated detection of timed up and go test performance	Predictor of cognitive decline, linked to a certain test situation; serves as useful context factor for detecting functional decline.
Hsu et al., Gietzelt et al., and Gietzelt et al. [29–31]	Detection of gait and balance parameters by wearable sensors, use for detecting cognitive changes	These parameters can enter in constructing context factors for detecting functional decline.
Schwenk et al., Gietzelt et al., and Schwenk et al. [32–34]	Wearable sensors for fall prediction in geriatric frail people	Target gait and walk changes as predictors of the physical risk of falls in frail people. Demonstrate the feasibility of wearable sensor application even in multimorbid senior people, but do not address cognitive or functional end points.
Akl et al., Suzuki et al., Hayes et al., Suzuki et al., and Jekel et al.[35–39]	Fixed indoor instrumentation to detect signs of cognitive impairment in instrumental activities of daily living	This approach requires instrumentation of the living environment by fixed sensors, eventually confounding user's need of privacy. These studies showed that detection of cognitive changes is possible in principle even from relatively coarse assessments of behaviors, such as arrival times at rooms. The studies used a purely data driven approach and reported no prediction accuracies.
Stucki, 2014#37991 [40]	Web-based nonintrusive ambient system to classify activities of daily living	This study supports the notion that function measures are accessible to sensor-based assessment, but has only been applied in healthy young individuals, allowing no inference on its use for detection changes in function due to dementia.
Lopez-de-Ipina et al. [41]	Reports features from automated speech detection based on video data of patients with Alzheimer's disease and healthy controls	Highly invasive method, so far only applicable in experimental settings. As perspective, language is a promising future domain to be included in detection system, provided user privacy can be protected.
Eby et al. [42]	Monitoring driving behavior by ambient sensors	Very sensitive topic for users, but promising in applications for healthy older people and the transition to cognitive impairment. Legal requirements for the use of such systems are widely unclear.
Mahoney and Mahoney [43]	Identifies key features necessary to consider when making products to be worn by persons with cognitive impairment	This study serves as valuable resource for the needs assessment of senior people with cognitive decline.
Kirste et al., and Bankole et al. [14,44]	Wearable sensors to detect agitation and dementia features	This study provides an accelerometric motion score related to cognitive decline.

(*Continued*)

Table 1
ICT studies relating to dementia outcomes from the clinical database search (*Continued*)

Project	Project objectives	Main characteristics of project
Clinicaltrials.gov		
NCT02496312, NCT03272230, NCT03293537, NCT01384344	Wearable and fixed sensors to detect apathy	Assess a certain behavior to guide intervention; this approach supports the feasibility of function detection using different environmental and/or wearable sensors, including monitoring of motion as well as of physiological signals such as heart rate or skin conductance. These studies did not target the end point of cognitive function and navigation at a prodromal stage of dementia.
NCT03297268	Wearable and fixed sensors to detect agitation	
NCT02258386, NCT02465307	Wearable and fixed sensors to detect delirium	
NCT03120741	Daily activity and environmental sensing techniques based on wandering behavior indoors, changes in times being in bed, and using electric devices at home to establish behavioral models of early dementia patients and cognitive healthy function	Primary outcomes are risk behaviors (such as forgetting to turn water and gas off) and behavioral disturbances (such as repetitive behaviors, and wandering during the night). The approach did not address prodromal or early functional impairments.
NCT02290912	Wearable devices to detect effects of a large number of life style interventions in middle-aged individuals	Target not further specified, aims at healthy middle-aged individuals.
ICTRP		
JPRN-UMIN000023764	To develop machine learning algorithm to provide objective measures for depression, bipolar disorder, and dementia using facial expression, body movement, voice, and daily activity data	Data-driven approach targeting a broad range of different conditions, involving intrusive data types such as video data and audiotapes of spoken language
TCTR20160916001	Effect of cognition-specific computer training versus nonspecific computer training on the cognitive function and health-related quality of life in mild cognitive impairment	No use of ambient or wearable sensor systems for function detection.
JPRN-UMIN000029785	ICT interactive system providing light, sound, odor, and somatic stimuli to people with dementia	Technology devices provide certain stimuli, fixed devices, no function detection
ISRCTN25427954	Questionnaires about living with dementia, and about willingness to use a wearable device that collects data about activity and sleep over two or 12 weeks	Need and acceptance assessment; provides access to user needs and values.
CENTRAL		
Schwenk et al. [45]	Use of wearable sensors to monitor the effect of gait training in people with MCI	Supports the relevance of gait parameters in MCI, does not address functional or cognitive outcomes.
Kaye et al. [46]	Spoken work counts as MCI biomarker	Needs transcripts of audiotapes of spoken language. Underscores the relevance of language domain, but provides no means for protecting user privacy.

Abbreviations: CENTRAL, Central Register of Controlled Trials; ICT, information and communication technology; ICTRP, International Clinical Trials Registry Platform; MCI, mild cognitive impairment.

in a home automation application can at the same time provide observation on behavior patterns of the inhabitants. Similar outcomes can be derived from the pattern of use of cooking devices or other electronic markers of daily activity. Other dimensions for long-term assessment of change are the pattern (not contents for privacy reasons) of social communication via electronic devices [48], or levels of physical activity [49].

Finally, with respect to (3), high-frequency behavior detection, for example, elicited by use of electronic devices for performing everyday activities, entertainment or playing games, is not yet part of long-term observations of behavior and cognition. Electronic devices have increasingly become part of the natural environment of most people, including senior people. Therefore, intra-individual change in the use of electronic devices, either driven by the user or regularly elicited by the device itself (for example through serious games), provides potential access to a rich source of high-frequency real-time behavioral data associated with everyday function and underlying cognitive and mental status. Examples for future applications are the use of navigation systems that adapt to the user's cognitive abilities, such as those explored in previous studies [50,51]. Over time, the growing demand of assistance from such systems would provide RWE inputs to assess a long-term trajectory of functional and underlying cognitive decline. A similar

trajectory can be derived from the pattern of solving problems in a computerized serious game [52] from a user followed over years.

2.2.2. The user's perspective

A classification of RWE devices and procedures from the user's perspective in dementia research is the distinction between active and passive systems. Active systems require direct user's input to the system such as a computerized serious game with defined psychometric properties that can probe a user's cognitive capabilities. Regular use of such a system draws a trajectory of cognitive performance or prompts activities of users in everyday situations ("leave home for a walk", "use communication device with family member") and monitors the ensuing activities. In contrast, passive systems monitor the naturalistically occurring everyday behavior with as little interference as possible. Active sensing is sometimes referred to as "participatory sensing", as it requires user participation and is easier to control in terms of privacy. Passive sensing is sometimes referred to as "opportunistic sensing" as the devices take initiative to seek, record, and process data [53]. A passive system to monitor long-term trajectories of everyday activities in an older person would represent the closest approximation to RWE, albeit active systems may have the advantages of being more easily applicable to models of cognitive capabilities under scrutiny and having reduced noise due to a priori defined behavior categories. The use of such active systems for RWE has found little application so far with few exceptions, most of which, however, were still located in highly controlled environments [54–56]. One small study (13 cases) found a high content validity of a cognitive game outside a controlled environment, using the Montreal Cognitive Assessment as a reference marker of global cognition [57]. This finding serves as an example of a hybrid system, an active assistive device that becomes embedded in a real-word environment.

2.3. Future work: From data-driven to model-driven analysis

Most of the investigations presented in Section 2.1 focus on data-driven analysis strategies. These strategies aim at directly estimating the target value (e.g., a diagnostic label, a clinical score, and the current activity) from the sensor data by applying a variety of classification or regression methods; they are directed toward key outcomes that require anomaly detection, prediction, diagnostic classification, or decision-making derived from features in sensor data streams (see Fig. 2 for a schematic depiction of the inferences required to derive estimates of behavior or function from sensor data and related instantaneous or aggregated [intrinsic] targets). Although many of the sensors used in patient-powered RWE observe effects of human behavior, the data-driven analysis approach has no explicit model of behavior—for example, no model of the causal connection between the different actions that make up a complex activity and typical action sequences and the context factors that influence when persons execute which actions.

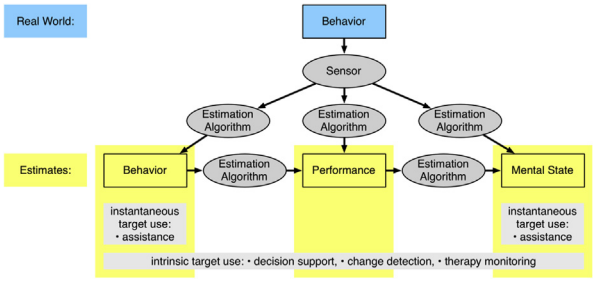

Fig. 2. Fundamental estimation targets in sensor-based analysis of everyday behavior.

However, everyday behavior is highly variable. This high variance appears as "noise" from the viewpoint of analysis strategy and thus restricts the accuracy of purely data driven approaches to infer an individual's activities and underlying cognitive abilities from sensor data. In contrast to data-driven analyses, model-driven concepts use knowledge about the causal structure of behavior and the effect of cognitive state on the possible sequence of activities. Such knowledge, for instance, encodes that for washing hands, the water tap needs to be turned on and that failure to do so may indicate a lapse of memory. Previous studies [58,59] indicated that model-driven methods may indeed improve accuracy in the detection of human actions. For example, in [60] a Bayesian causal model represented the steps involved in handwashing for a person with dementia, and these steps were modeled as being conditionally dependent on the person's overall stage of dementia. As persons interacted with the system, the model inferred their stage of dementia from the sequence of actions in the task. If they required assistance at most steps, for example, the system inferred that they suffered from severe cognitive deficits. If they only required occasional prompts, the system inferred mild cognitive deficits.

The main outcome of medium-term RWE procedures in senior people is the effects of an intervention on cognition and/or cognitive fluctuation within an RCT, while that of long-term studies is the detection of smooth transitions from normal cognition to mild cognitive impairment and then dementia. These procedures are expected to benefit from the model-based consideration of context factors [47], and a prior knowledge on personal characteristics, such as habitual pattern of device use or a priori level of navigation ability.

3. Requirements for RWE obtained by sensor technology

ICT-based procedures for RWE studies on intervention effects in dementia research have to capture relevant clinical features validly to be useful, fulfill minimum standards of

data fidelity and robustness, ensure user privacy and data safety, and need to incorporate user needs.

3.1. Clinical requirements

A significant clinical requirement of ICT systems capturing patient-powered RWE is the ability to detect smooth transitions in everyday function and underlying cognitive abilities. As an additional source of complexity, the trajectory of prodromal dementing disorders, particularly with respect to behavioral and mental disturbances, can fluctuate. Therefore, ICT-based features should be adaptive and take into account variability. Implementation of ICT end points should ensure the compatibility of the devices with the guidelines of regulatory agencies on the measurements accepted in standard clinical care settings and clinical trials for drug development. This scenario implies several conditions to be established to develop health-care products in the longer term: (1) ethical and functional requirements from patients, caregivers, patients' advocates, regulatory medicines agencies, and payers of health services; (2) the maturation and large-scale production of ICT digital monitoring in relation to those requirements by synergies between ICT and pharma industries, small-medium enterprises, and academic researchers; (3) standards for remote assessment technology, data exchange and sharing, and analytical methodology for the classification of RWE.

Today, available ICT sensors in routine applications such as actigraphy allow coarse-grained, short-term assessments of motion features that have been associated with global measures of activity, circadian rhythms, sleep disturbances, apathy, and global cognitive status (Panel 3). To date, such information is potentially useful for identifying at-risk cases and monitoring disease progression and intervention effects. Future ICT sensors should be able to capture more comprehensive and fine-grained features of activities of daily living and functioning. Cognitive models for functioning detection (described in Section 2.3) need to consider relevant confounding variables and outcomes, such as intrinsic traits (e.g., resilience or propensity to manage physical and psychological stress and disease, sensory deficits), intrinsic states (e.g., motor capacity, cognitive capacity, psychological and physical stress), and extrinsic factors (e.g., built environment, social network or climate conditions). The outcomes and confounds to be captured by ICT-based sensors can be ordered according to their relevance for the patient and his/her caregiver as well as by their accessibility for sensor-based assessment. This leads to a prioritization of variables to be included in future RWE trials in dementia that can be further expanded with advances in technology. In perspective, adaptive ICT-based RWE devices may be able to learn user characteristics and increasingly take them into account when inferring behavior and functioning from sensor data, eventually requiring expert based recalibration of cognitive model parameters during long-term use of such a device.

3.2. How do we ensure clinical validity of ICT sensor measurements?

A particular challenge is the validation of sensor modalities by ensuring they reflect relevant clinical features and allow interpretation of variability in sensor data trajectories in terms of change of functioning and underlying cognitive status.

Sensor data as RWE end points can serve three major clinical use cases: (1) diagnostic, for early detection or prediction of cognitive decline and dementia; (2) monitoring, for capturing the impact of natural disease progression on daily activities and underlying cognitive functions; and (3) testing intervention effect on the trajectory of cognitive decline and function.

Actigraphy studies have provided some insights into associations between sensor-based motion features and underlying cognitive and mental states. Using established scales, the validity of actigraphic measures for detecting sleep disturbances, agitation, apathy, or global cognitive decline has begun to be established mainly in cross-sectional analysis (Table 1). What is required in view of the outlined key use cases is establishing sensor-based rates of change in major domains including cognition, sleep, apathy, and agitation.

With respect to established biomarkers of underlying pathologies, such as cerebrospinal fluid amyloid, tau protein, APOE genotype, or medial temporal lobe atrophy, ICT-based sensor data may serve the purpose of meaningful phenotype enhancement. Sensor-based signals of imminent or ongoing cognitive or functional decline would identify those people who will benefit from in-depth diagnosis using clinical instruments and established biomarkers.

There is a major limitation in the clinical assessment of cognitive functions in older adults. Standard clinical and neuropsychological pencil and paper tests typically used for the detection of change in cognitive functions and activities of the daily life (e.g., Mini–Mental State Examination score, Alzheimer's Disease Assessment Scale–Cognitive subscale, clinical deterioration scale, and so forth) have limited sensitivity. In addition, the institutional use of these tests can enhance the beneficial effects of the placebo conditions when local clinicians are particularly esteemed, patients generally have limited access to healthcare, and raters and patients think that they will receive special benefits in the case of an improvement of the subjects' clinical status or cognitive functions at follow-up [61].

Keeping in mind these considerations, the reference gold standard for the validation of the new ICT sensor measurements of clinical status and cognitive functions should include not only conventional paper and pencil scales and tests but will also need to consider standardized and unsupervised process-based computerized batteries testing cognitive functions in patients' homes allowing as well to capture test taking behavior and type of errors [62,63]. Currently available examples for such potential benchmark tests for use outside of specialized settings are summarized in Panel 4.

Panel 4
Standardized and unsupervised computerized batteries testing cognitive functions for potential application inside and outside of specialized clinical settings

Cambridge Neuropsychological Test Automated Battery (CANTAB, www.cambridgecognition.com/cantab):

CANTAB has enabled researchers to highlight significant deficits affecting broad cognitive domains in schizophrenia (e.g., working memory, decision-making, attention, executive functions, and visual memory suggestive of frontostriatal dysfunctions) and dementia (e.g., especially paired Associates Learning, PAL) test [64]. Furthermore, CANTAB may ensure a reliable and reproducible administration, which allows testing various aspects of executive functions that are expected to underpin activities of daily living in Alzheimer's disease patients suffering from prodromal or mild dementia stages. It also predicted the level of dependence of the patients from caregivers [65]. CANTAB has been originally designed to be used by clinicians and researchers but has the potential to be self-administered with the support of a caregiver. Indeed, there is evidence of the feasibility and reliability of unsupervised self-administration of the computerized battery for testing mild cognitive impairment in older primary care patients [66].

Novel Assessment of Nutrition and Ageing toolkit (NANA, http://www.newdynamics.group.shef.ac.uk/nana.html):

NANA aims at tracking cognitive function and other health and behavioral domains in seniors [67]. NANA was designed to be self-administered at subject's home with the only support of a caregiver. The NANA cognitive tasks are sensitive to cognitive processing speed, which is related to other cognitive functions [68] and several relevant well-being outcomes across aging [69].

Computerized battery for cognitive assessment (Cogstate, https://cogstate.com):

Cogstate measures the speed of processing, visual attention, and visual learning and memory. Cogstate has been shown to be effective to probe cognitive decline in seniors with no retest-related increases in scores after 1 month [70–72].

Automatic Speech Analysis for the assessment of cognitive disorders (Delta, https://ki-elements.de):

Delta is a purely speech-based tool empowered by artificial intelligence and computational linguistics technologies to assess different neurocognitive domains such as language, learning, but also affective states such as apathy. It has been shown to provide as accurate results as manual annotations and extract additional qualitative semantic features (i.e., word frequencies) or quantitative acoustic features (i.e., pause lengths) from a patients' recorded performance [73].

3.3. Data robustness, quality requirements, and ICT standards

The literature defines several general dimensions of data quality valid for clinical research as well [74], including accuracy, completeness, timeliness, and validity. Each of these aspects needs to be targeted to ensure high-quality standards. Unfortunately, information about data quality is scarce in most of the studies on ICT-based RWE procedures. The result of a PubMed Central search for ("data quality"[All Fields] OR "data validity"[All Fields] OR "data robustness"[All Fields]) AND ("wearable sensors"[All Fields] OR "actigraphy"[All Fields] OR "actigraphy"[MeSH Terms]) AND ("remote sensing"[All Fields] OR "remote health monitoring"[All Fields] OR "remote monitoring"[All Fields]) revealed that most studies addressed data safety (e.g., encryption or privacy), but not quality (see Supplementary Material for details).

Approaches for semi-automatic verification of data quality derived from ICT-based RWE procedures are the subject of active research. Specific problems of data quality for wearable sensors may, for instance, arise from poor device placement [75] and lack of a gold standard. In addition, a low signal-to-noise ratio may blur signal structure. Moreover, data sets generated from ICT solutions for RWE collection are complex, heterogeneous, and large, posing additional challenges of big data quality assurance [76].

Quality requirements for ICT-based RWE procedures not only address the data themselves but also target the processes of data collection and data use, which are often neglected [74]. Dobkin [77] provides a list of technical features that address the particular requirements of data collection for RWE. Among others, these requirements include reliability of sensors and data transmission.

Consolidating heterogeneous data sources and preparing the collected data for further analysis are typically the first delicate steps during data analysis [78]. There is currently no consensus among stakeholders (i.e., academics, patients' advocates, industrials, regulatory agencies, payers, and so forth) concerning valid, automatic, or manual procedures for validating the quality of data (i.e., sensor data completeness, artifact detection and rejection, and so forth) and extraction of markers of daily activities and cognitive functions during the phases of ICT-based RWE studies in dementia research, which span over the entire data lifecycle [79] from data collection to publication.

Today, validation procedures for data collection (e.g., semi-automatic checks for sensor data completeness) and data analysis [80] (e.g., semi-automatic generation of

analysis reports) are being developed on demand during all steps of the data lifecycle whenever a problem occurs in a trial [81]; a top-down strategy to ensure of data quality for ICT-based RWE is still missing.

Other research domains such as bioinformatics have successfully demonstrated the positive impact of data openness on reproducibility [82]. Similarly, open standards for sensors, data, models, ICT platforms for the storage and visualization of the data, and analysis workflows have to be established to sustainably address issues of data handling and analysis in the context of ICT-based studies in dementia research. The publication of data models, algorithms, and analysis scripts allows other researchers to understand, reuse, revise, and advance all steps of the entire data lifecycle. As a result, this increases the reliability and validity of ICT-based studies. However, small and medium enterprises and industrial partners of those ICT-based studies may want to exploit own formats, platforms, and the commercial value of the procedures validated with clinical studies, so the temporal and modality terms of the open access of procedures and findings should be defined in the calls by private and public sponsors of RWE research. For example, an intercontinental public-private alliance may promote a shared solution for a global federation and interoperability of the most relevant international ICT platforms for biomedical applications with a focus on aging and dementia (Panel 5).

3.4. Privacy and data safety

Data privacy is a key ethical concern with ICT which collects personal information. To date, important privacy issues have been raised for a range of existing ICTs aimed at measuring aspects of memory and cognition or tracking health variables, such as online memory tests [83], and mobile applications for health tracking [84,85].

Studies on the attitudes of older adults, family members, and caregivers toward tracking devices show that these stakeholders weight the potential benefits, and safety benefits in particular, of these devices against the risks to loose privacy. Their acceptance of that technology depends on the users' values and priorities [86,87]. For example, privacy concerns have been shown to be negatively correlated with the intention to adopt mobile health technologies [88]. Generally, the most important concerns related to privacy are the transfer of personal data, lack of awareness about how personal information is used, and storage of the information [89].

In light of the potential harms of privacy breaches, technology developers and clinical trialists alike should consider the moral complexity of using tracking or sensing devices in potentially vulnerable populations who may experience challenges in providing informed consent [90]. For a large proportion of existing ICTs available on the consumer market, the consenting process is problematic, involving overly

Panel 5
Examples of international ICT platforms for biomedical applications that may be interoperated with a focus on aging and dementia

An important goal of a future public-private transcontinental alliances may be the development and testing of an ICT digital platform combining ready to use wearable technologies, such as smartphones and smart-watches, with mature smart-home sensors to measure a valid and meaningful combination of real-world evidence from unrestricted activities of daily living to detect subtle functional deficits. Ideally, this future digital platform may result from the integration of standards and interoperability of available ICT platforms for data and resource sharing for biomedical applications. The following initiatives are mentioned just as an example:

- Remote Assessment of Disease and Relapse-CNS to collect and share real-world evidence in mental disorders (http://www.radar-cns.org).
- The European Medical Information Framework (http://www.emif.eu) to access the data sets required to evaluate functional domains in AD patients.
- ROADMAP (http://roadmap-alzheimer.org) to obtain input from regulators and payers.
- ELIXIR (https://www.elixir-europe.org) to bring together life science resources from across Europe including databases, software tools, training materials, cloud storage, and supercomputers.
- Human Brain Project to search real patient data to understand similarities and differences among brain diseases (https://www.humanbrainproject.eu).
- AgedBrainSYSBio (http://www.agedbrainsysbio.eu) to integrate numerous European initiatives addressing the scientific and societal challenges of neurodegenerative diseases and aging.
- SENSECog (http://www.sense-cog.eu) to understand the combined impact of age-related hearing and vision impairment, and dementia, and translate this knowledge into clinical applications for the mental well-being of EU citizens.
- Critical Path Institute's Coalition Against Major Diseases (https://c-path.org) to create new tools and methods that can be applied to increase the efficiency of the development process of new treatments for AD and related neurodegenerative disorders with impaired cognition and function.

lengthy and complex text, and fails to provide meaningful information and choice. As a result, most consumers do not read terms of agreement or privacy policies of ICT-based resources, which leads to the routinization of consent, where the act of agreeing to the use of a technology becomes unreflective and uninformed [91]. Moving forward, it will be imperative to exercise transparency in the provision of RWE ICT solutions and to carefully consider, with the help of the dementia community, how to best preserve end-users' autonomy while ensuring safety [92]. Following the concept of citizen science, ownership of ICT-based sensor data obtained outside of the framework of clinical trials require a regulatory approach where the data remain with the user or patient, and technical solutions are provided to allow the user to opt-out of any reuse proposed to them. Linked with this approach, calls of public sponsors for new ICT platforms for RWE collection may ask a regulated access to ICT and portlet algorithms by a formal procedure to speed the validation process. After the end of the project and a reasonable period of embargo, external researchers may present a formal research project to the technological and scientific committee of the granted consortium, which in turn provides technological solutions to allow data owners to opt-out of any data use.

3.5. Usability, adoption, and user values

Patient engagement approaches such as user-centered design can help inform technology usability and adoption as well as ethical concerns regarding autonomy and ability to consent to technology use. User-centered design based on peer research methodology requires the creation of structures that enable patients, caregivers, and other stakeholders to act as co-researchers rather than only as research objects or informants [93]. As stated by Span et al. [94]: "most researchers acknowledge the importance of involvement of people with dementia in the development but they differed in how they involved people with dementia. […] People with dementia played mainly the role of study objects and informants […] rather than being co-designer". One key issue "concerns the negotiation of power between researchers" [95]. This negotiation requires a moderated process of communication between stakeholders.

Adoption of a technology depends critically on its acceptance by main users [96]. The co-design of a technological innovation with future users is one operational approach to ensure future acceptance. In addition, technical characteristics of the system will influence its acceptance by the users (summarized in Table 2). The basis of these dimensions is still narrow as only few user-centered studies on acceptance have been conducted so far. One highly innovative approach toward acceptance of an ICT solution takes identities and mood of user into consideration for user interaction. This integrates with strong patient engagement at the development stage of the technology.

A growing body of literature suggests that identity and a sense of self persists in people through late stages of dementia [97,98] and their capacity to experience prolonged states of emotion [99]. Therefore, the notion of emotion, identity, socio-cultural civility, and normative behavior should be considered in the design of ICT solutions that monitor a participant's behavior continuously in his/her environment, both from the perspective of the patient and caregivers. When developing technology for older adults, it is critical to consider that each person comes from a different cultural and socioeconomic background, has a different sense of self and identity, and has different emotional responses. A technological solution that triggers discomfort due to an emotional misalignment with how the user perceives oneself will most likely be rejected. For instance, a person with dementia who perceives herself not as a patient but as still functional and independent will most likely not adopt a technology that conflicts with this self-image by supervising her behavior. One approach is to tailor the monitoring function provided by the technology, and the framing of the presentation of that technology to the individual's identity, self, needs, and emotional states. For this, extensive user needs analysis and user profiling as well as the extraction of affective identities and features of the user for adapted customization are essential steps in future development of ICT technologies. This in turn implies a deep level of engagement from end-users throughout the elaboration process.

Table 2
Important device characteristics for user acceptance in a routine care setting, integrating and extending recommendations from [43,103]

Device characteristics	Effects on acceptance
Wearability	Place and comfort of wearing the device, discrete and not stigmatizing
Additional hardware features	Aesthetically appealing, water proof, safe (getting off possible)
Energy efficiency	Energy efficient device needs lower frequency of recharging and leads to less off-time
Data read out	Simple, self-explanatory automated data read out increases usability and acceptance, reduces error rate, immediate output, sensitive to change in the type, and intensity of patient activity
Data privacy	Clear data access regulation
Data safety	No unauthorized access possible
Perceived benefit	Device use brings direct benefit, such as patient safety, autonomy
Additional functional features	For example, wrist worn sensor system functions as a watch, provides alarm and reminding features.
Connotation of device use	Device is not classified as dementia product, but as a device for active living.

For the design of ICT-based sensor devices to monitor older adults with dementia in daily (instrumental) activities, it has been suggested to modify the look and accessibility of the monitoring findings to conform with the current identity of the user and his/her emotional state [100]. This in turn has ethical and outcome implications that require careful consideration.

4. Integrating ICT technology in RWE type clinical research

4.1. Regulatory challenges

Classical RCTs are subject to strict legal provisions. In contrast, any stakeholder may conduct an RWE trial using ICT data with no more regulation than adherence to patient data confidentiality. The lack of regulation will cast doubt on RWE results on novel interventions from the point of views of regulators and payers of public health services. Stakeholder interests may drive collection and analysis of data and interpretation of outcomes. Therefore, the anticipated growth of RWE trials using ICT calls for the implementation of a framework that maximizes data fidelity and receives an approval by regulators and payers. ICT sensors lend themselves to continuously monitor data recording quality and surveillance of analysis strategy. From a regulatory standpoint, the US Department of Health and Human Services released a report emphasizing that laws protecting health information, such as the Health Insurance Portability and Accountability Act of 1996, do not apply to health information submitted on mobile apps, social media, or the Internet. As such, concerted international efforts will be required to develop responsive policies that address what McCarthy has identified as "large gaps in policies around access, security and privacy" of ICT-based solutions [101]. This comprises rules for the control of data use by other stakeholders (such as employers or health insurances), the policies for managing synchronized data dictionaries and terminologies, and interoperability standards. Different to products for the consumer market, RWE monitoring ICT devices that should serve to measure primary end points in clinical trials would likely have to undergo medical device certification, albeit this is not yet clearly defined by regulatory authorities.

4.2. Complement classical RCTs

As far back as the 11th century, the Arab philosopher Ibn al-Haytham, known to the West as Alhazen, noted that "experimental data and reproducibility of its results" characterize sound scientific methodology. Accordingly, RCTs serve as the gold standard of clinical intervention research. The introduction of RWE trials using ICT outcomes may challenge this paradigm in dementia research; the advantage of the RWE is its ability to cover the complexity of the individuals at stake, but it brings with itself the limited ability to reproduce findings typically acquired under constrained conditions where reproducibility is a key criterion of an experiment. On this basis, current results of RWE trials have tended to generate rather than confirm a hypothesis on a potential effect of an intervention. Traditional RCT outcomes have a long-standing record of standards and reference values based on decades of literature and data. This is not yet the case for RWE studies. Therefore, the next step in RWE studies will be to calibrate their outcomes using standard RCT end points, such as cognitive scales or biomarkers, as established reference tests. Only after this step has been conducted, confirmatory RWE studies will become possible. This process has begun with guidance emerging from regulatory agencies (https://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM513027.pdf).

RWE studies in dementia research provide the unique opportunity of obtaining daily measurements, possibly reflecting fluctuations of cognitive abilities and functioning and trajectories of the disease progression over a long term (i.e., years). On the other hand, the quality of RWE should be carefully considered due to the obvious limitations associated with lack of control on the participants' mental status and environmental conditions (e.g., intake of psychostimulants or substances inducing bad performances) during the data collection. Therefore, the results of an RWE trial should ideally be considered complementary with results from an RCT on the same or a similar intervention, where differences in outcomes would be informative with respect to the generalizability of the RCT findings. In addition, the characteristics of a cohort participating in an RWE trial may serve as comparator for the characteristics of a RCT addressing the same or similar intervention, as it has been suggested in the domain of chronic pain intervention [102].

5. Summary

We have identified basic requirements for the design and use of presently available ICT-assisted procedures measuring RWE to estimate functioning/autonomy (i.e., instrumental and noninstrumental activities of daily living) and underlying global cognitive status in patients with prodromal and manifest stages of dementia in RCTs and longitudinal observational studies, as well as for enrichment of the standard clinic-based experimental settings. ICT procedures can assess these outcomes in the community and homes of a large number of participants. The data collection may be set on a day-to-day basis for very long periods (e.g., years), in a near continuous manner, with the advantage of probing variability in functioning and global cognitive status and trajectories of disease progression on those relevant variables. Indeed, those ICT solutions have the potential to enhance clinical care and research in dementia by detecting the onset

of cognitive decline and its concrete effects on functioning and autonomy.

In perspective, such technology offers three major application scenarios: (1) early identification of cognitive decline and reduction in functioning and autonomy as a possible manifestation of prodromal stages of dementing disorders; (2) long-term monitoring of natural disease progression; and (3) enhancing intervention RCTs in real-world settings that is urgently needed in face of the insufficient effectiveness of unimodal treatments on long-term functional decline and quality of life of people with dementia or prodromal stages.

From an engineering perspective, the requirements of such technologies push the boundaries of currently available algorithmic and hardware solutions and provide an innovation engine for future health-care technologies. From the perspective of the humanities, such technologies require careful assessment of legal and ethical consequences and the development of shared decision-making and data protection procedures that respect stakeholder needs and values, from patients to payers of public health services. At the intersection of technology and the humanities lies the critical issue of technology adoption. This adoption requires deeply integrated user engagement in the development and deployment process, which brings with it ethical, industrial, and social considerations related to participation in research.

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Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.jalz.2018.05.003.

RESEARCH IN CONTEXT

1. Systematic review: The authors reviewed the literature based on PubMed, ISI Web of Knowledge and meeting abstracts and presentations. We used a qualitative approach of document analysis to screen literature for key statements. These relevant citations are appropriately cited.
2. Interpretation: The literature on patient powered real world evidence for dementia indicated a gap between technological concepts and their implementation in a clinical research context. Our research suggests that the emerging technologies can monitor continuously participant behavior reflecting patient relevant functional outcomes.
3. Future directions: We propose technologies and regulatory frameworks to capture patient relevant outcomes and access broader clinical cohorts than sampled in current clinical trials.

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