Alzheimer's & Dementia: Translational Research & Clinical Interventions 4 (2018) 234-242

Perspective

Digital technologies as biomarkers, clinical outcomes assessment, and recruitment tools in Alzheimer's disease clinical trials

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Abstract Digital technology is transforming the development of drugs for Alzheimer's disease and was the topic of the Alzheimer's Association's Research Roundtable on its May 23–24, 2017 meeting. Research indicates that wearable devices and unobtrusive passive sensors that enable the collection of frequent or continuous, objective, and multidimensional data during daily activities may capture subtle changes in cognition and functional capacity long before the onset of dementia. The potential to exploit these technologies to improve clinical trials as both recruitment and retention tools as well as for potential end points was discussed. The implications for the collection and use of large amounts of data, lessons learned from other related disease areas, ethical concerns raised by these new technologies, and regulatory issues were also covered in the meeting. Finally, the challenges and opportunities of these new technologies for future use were discussed.

Keywords: Alzheimer's disease; Digital technology; Cognition; Function; Clinical trials; Biomarkers

1. Introduction

Recent advances across a range of digital technologies, including wearable devices, unobtrusive sensors, and passive data collection applications, along with improved computational power and analytic approaches have the potential to provide a more nuanced and comprehensive understanding of the presentation and progression of Alzheimer's disease (AD) and other neurodegenerative diseases. Moreover, the potential ability of digital technologies to detect subtle changes in cognition and function across the disease spectrum may improve the sensitivity and specificity of diagnosis, help identify appropriate participants for clinical

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https://doi.org/10.1016/j.trci.2018.04.003

trials, and improve the assessment of therapeutic responses. Digital technologies may also enhance the care and safety of patients by promoting aging in place and facilitating the development of precision medicine approaches to therapy. Yet, digital technologies also introduce many challenges ranging across scientific, clinical, technological, business, ethical, and regulatory domains.

On May 23rd and 24th, 2017, the Alzheimer's Association Research Roundtable convened a meeting of researchers from academia, the pharmaceutical industry, and health agencies, along with digital technology and data analytics experts, representatives of patient advocacy organizations, and a patient and caregiver to discuss how digital biomarkers are transforming clinical trials in other disease areas and emerging efforts to apply lessons learned in these areas to the AD clinical trial space.

2. Transforming clinical trials with new technologies

Interest in developing novel technological approaches to aid in the clinical diagnosis and assessment of AD cognitive and functional progression in response to treatment has grown in recent years as interventional trials have moved into earlier stages of disease. Current testing paradigms have proved to be poor at identifying meaningful ecologically valid changes in individuals with early stage disease. For example, high variability in scores of existing cognitive tests at baseline and over the course of a trial has produced false signals in phase 2 studies that contributed to costly failures in phase 3 [1]. Other problems with existing tools include the questionable accuracy of self- [2] and clinician-reported measures, substantial variability among individuals administering tests, and appropriateness for diverse groups of patients.

To address these well-known issues, a range of validated digital technologies are being applied to clinical trials. Electronic or direct data capture represents an interim step on the path toward digital biomarkers. Digitized forms have been shown to improve data quality and enhance guidance during the administration of a test by proactively responding to errors, calculating results automatically, managing branching rules, checking for consistency of responses, and responding immediately to missing data. They also enable the management of translations and the integration of audio and video data capture into assessments. The end result of using electronic or direct data capture is an increase in both accuracy and precision, both of which are necessary to detect anything other than large effect sizes.

Meanwhile, new tools that provide sensitive, frequent or continuous, objective, and multidimensional measurement of changes in function or behavior are being incorporated into clinical trials in multiple disease areas. For example, daily activity assessments with accelerometers were used as a primary end point in a study testing the ability of nitrates to enhance activity tolerance in patients with heart failure [3]. In AD, ankle-mounted wearable accelerometers have also been used to measure changes in everyday motion behavior even in the absence of major behavioral impairments [4]. High-frequency, in-home monitoring data have also been shown to distinguish individuals with mild cognitive impairment from those with normal cognition [5,6], suggesting that such data could reduce sample sizes needed for clinical trials and thus reduce exposure of participants to potentially harmful drugs [7]. To evaluate personalized/precision medicine approaches in clinical trials, digital tools with continuous measurements may also enable detection of individualized behavioral profiles, susceptibility to placebo responses, or be used as run-in data to reduce regression to the mean effects.

A range of sensors, software, and smart phone applications ("apps") can provide passive remote monitoring across a range of settings including the home, community, automobiles, and health-care settings to name a few. These sensors can measure behaviors (e.g., in sleep, mood, physical activity, social activity, and eating behaviors) from which we may be able to infer cognitive and functional status and changes therein. Platforms consisting of a network of diverse sensors may be needed to effectively measure and identify biomarkers of change; and interfacing these devices with other data streams such as electronic medical records will be needed to facilitate communication and sharing of data. However, as the number and range of devices increases, it will be important to maintain a focus on outcomes that are clinically meaningful. For some outcomes such as sleep, a single sensor may be sufficient; whereas for other outcomes affected by subtle cognitive decline, multiple sensors may be needed. Redundancy will be initially necessary to validate novel devices and analyses, and clear data and metadata annotation will also be essential, particularly at early stages of development.

To investigate the transition from current practice to real-time, continuous, home-based, objective, unobtrusive, ambient measures, researchers at the Oregon Center for Aging and Technology developed a platform of sensors and devices to capture data in the home or in simulated home environments [8,9]. This technology-agnostic platform uses pervasive computing wireless technologies and data analytics to assess a range of functional and behavioral activities, including time and location of sleep, patterns of movement around the home, taking of medications, use of a phone or computer, opening and closing of doors and refrigerators, and driving. The platform has been deployed in free-standing single-family homes and retirement communities and has been incorporated into several observational and clinical studies. Data from these studies are being used to identify behavioral biomarkers that can be used to phenotype populations and stratify potential participants in clinical trials by identifying persons who are progressing more rapidly.

Another platform, EmPowerYu, uses a variety of sensors to detect motion within a fixed space, appliances being turned on and off, doors being opened and closed, and entry or exit from a room to build a multidimensional understanding of

individual patients. The platform incorporates time/sequence tracking with an inference engine and machine-learning approach to assess gait, pacing, night wandering, repetitive activities, medication compliance, and other parameters.

Assessing cognition with these digital devices goes beyond inferring cognitive decline from behavioral and functional changes, given that many of these devices capture metadata that may capture subtle cognitive changes. For example, in the Oregon Center for Aging and Technology Life Laboratory study, Seelye et al [10] showed that computer mouse movement patterns were more variable, less efficient, and had longer pauses between movements among people with mild cognitive impairment compared with those with normal cognition. Digital devices can also preserve the integrity of traditional neuropsychological measures while at the same time expanding those tests beyond a single score to capture responses across multiple domains. For example, the Framingham Health Study uses what they call the "Boston Process Approach," which focuses on the path to the final response and allows them to derive value from incorrect responses. On the Trails B test or Clock Drawing Test, a digital pen maintains the integrity of the paper and pencil test while also tracking when a pen is lifted from the paper, which may indicate altered cognitive processes [11].

Because speech patterns may also be early markers of cognitive decline [12], computerized analysis of recorded speech provides rich data related to cognition and may thus be used to develop cognitive biomarkers. For example, in Parkinson's disease (PD), computerized analyses of syntax changes in spontaneous discourse were used to discriminate patients and controls with 75% accuracy [13]. Semantic coherence also degrades in neurodegenerative disease [14]. The Framingham Health Study is conducting deep speech pattern analysis with funding from the Defense Advanced Research Projects Agency using digital recordings obtained during the administration of neuropsychological tests.

3. Screening

Technology companies are now developing screening approaches such as gaming approaches to subtle cognitive changes. For example, Akili Interactive Labs is developing the video game platform EVO as a screening tool and potential biomarker for amyloid positivity. EVO requires multitasking by combining a perceptual discrimination task (targeting) with a concurrent visuomotor tracking task (navigating). Developed by neuroscientists at the University of California, San Francisco, the prototype of EVO, NeuroRacer, can detect age-related loss in cognitive performance that can potentially be remediated with training [15]. A study done in collaboration with Pfizer demonstrated that in healthy elderly adults, this positive training effect correlated with amyloid status, that is, amyloid-positive individuals showed an improvement in reaction time, but their ability to react while multitasking did not change; whereas amyloid-negative individuals showed improved ability to react while multitasking [16].

Another technology company, Altoida Inc., has developed a test using an augmented reality paradigm. Preliminary data indicate that this test can predict if someone will convert to AD dementia 6 years in advance with 94% accuracy. The 10-minute Altoida Neuro Motor Index (NMI) test works with an iPhone app, presenting tasks with varying difficulty levels to assess spatial memory, prospective memory, executive function, and psychomotor processing speed. NMI correlates with other biomarkers of AD and is a better predictor than individual biomarkers, although a combination of AD biomarkers (fluorodeoxyglucose-positron emission tomography, magnetic resonance imaging, electroencephalography/event related potentials, and cerebrospinal fluid phosphorylated tau protein/amyloid β 42) outperforms NMI [17]. Altoida is now collaborating with the Global Brain Health Institute, following a 10,000-patient cohort longitudinally for 10 years to gather real-world evidence about the utility of NMI digital phenotyping. The test will also be a part of the cognitive battery used by PharmaCog, a precompetitive drug development partnership in Europe [18].

4. Improving patient engagement, recruitment, and compliance

Digital technologies, including social media and online platforms, can enhance the patient and caregiver experience, help patients learn about and manage their health, and engage them as active participants in drug development and other treatment protocols. Tools that facilitate early identification of cognitive impairment might also encourage people to enroll in trials earlier. Improving subject recruitment, retention, and compliance is essential to the goal of developing effective treatments for AD [19,20]. For early disease intervention or prevention studies, identifying potential participants in the early stages of cognitive impairment with digital tools could substantially reduce trial duration, costs, and improve outcomes.

Nonetheless, there remain substantial challenges to the use of digital technologies as recruitment tools and to maximize compliance in clinical trials. Complex tools may require technology, motor, or cognitive skills that some trial participants do not possess, thus requiring the use of different tools for different populations. Some types of tools may be inappropriate for certain populations; for example, ingestible sensors could be unacceptable in patients with paranoia or psychosis. Providing a positive user experience and integrating tools into the patient journey will likely increase compliance. For example, tools with a game-like interface can gather relevant data while also reducing anxiety and social isolation in dementia patients. Utilization and compliance can also be optimized by integration of these applications and devices into the workflow of physicians and health-care systems and by incorporating data visualization components that provide caregivers with useful information.

5. Digital biomarkers as secondary end points in clinical trials: Lessons from other disease areas

Digital biomarkers are already being used as secondary end points in clinical trials for neurological disorders such as PD, multiple sclerosis (MS), and schizophrenia. These efforts were fueled in 2015 when Apple announced the release of smartphone applications for medical research using their ResearchKit platform [21], enticing over 70,000 people in the first 7 months to sign up to participate in studies.

One of these apps (mPower) was developed by Sage Bionetworks as a mobile app that uses sensors to collect data regarding activity, mobility, tremors, and voice changes as users carryout structured motor tasks. Using a 20-second voice recording, the app extracts features for analysis, including jitter, changes in prosody, and fundamental frequency, showing distinct changes before and after medication. When combined with accelerometry data acquired during tapping and walking tasks, the app creates an individualized digital fingerprint that can be used as a personalized classifier regarding, for example, the effects of L-dopa on performance. Early analyses suggest that mPower assessments can detect treatment response and predict disease severity and that they correlate with motor scores on the standard PD clinical assessment, Movement Disorder Society Unified Parkinson's Disease Rating Scale, mPower has been incorporated as an exploratory outcome measure into the Safety of Urate Elevation in Parkinson's Disease Phase III clinical trial, which is testing an inosine that may lower the risk of PD and slow disease progression. The mPower app will use five standard mPower metrics to explore changes in motor and cognitive function among participants and will also survey digital engagement at baseline, monitor medication use, and collect serial self-assessments of motor function, apathy, and quality of life.

Digital biomarkers have also been proposed in the MS field. The Multiple Sclerosis Performance Test (MSPT) is a computer tablet–based tool designed to assess cognitive, motor, and visual symptoms, as well as quality of life in individuals with MS [22]. The tool is self-administered following brief patient training on the use of the test and requires about 20 minutes for patients to complete (1) a Processing Speed Test based on the paper-and-pencil Symbol Digit Modalities Test to assess cognitive function; (2) a contrast sensitivity test to assess visual acuity; (3) a manual dexterity test with a peg board, based on the 9-hole peg test, to assess upper extremity function; and (4) a walking speed test with a Bluetooth remote to assess lower extremity function. The Processing Speed Test has been shown to correlate very highly with the Symbol Digit Modalities Test [23]. Importantly, it can be fully integrated into a clinical office, enabling the collection of cognitive data on every patient without the need for personnel trained to administer the Symbol Digit Modalities Test.

Developers believe that by integrating clinical care with clinical research, the MSPT has the potential to transform clinical research. Instructions are auditory, while visual stimuli include symbols, numbers, and letters, simplifying translation into other languages. Data collected by this device can be integrated with electronic medical records. Compared with traditional clinical assessments, where the provider manually acquires and records data, the MSPT allows the provider to spend more time with the patient interpreting the data and developing a treatment plan.

Individuals with schizophrenia display a constellation of mood, cognitive, and behavioral symptoms that disproportionately contribute to disability. Cognition in schizophrenia has emerged as an important drug target because cognitive impairment accounts for more disability in real-world functioning than any other aspect of the illness, including psychosis [24,25]. Standardized performance-based assessments that regulators will accept for clinical trials include the MATRICS Consensus Cognitive Battery, the Brief Assessment of Cognition, and computerized test batteries such as CogState or Cambridge Neuropsychological Test Automated Battery [26]. The paper-and-pencil Brief Assessment of Cognition has been adapted as a digital version, which allows standardized presentation of task instructions and stimuli, audio recording of responses, and automatized scoring and data management, all of which should reduce error variance. A validation study showed good sensitivity and correlations with the original Brief Assessment of Cognition instruments.

A co-primary functional capacity outcome measure is also typically required in schizophrenia clinical trials. Standard functional measures may comprise interview- or performance-based assessment, both of which require skilled raters. Performance-based assessments also may be limited by practice effects, lack of alternate forms, and outdated content, whereas interview-based assessments may require an informant. The test most frequently used to assess functional capacity in schizophrenia is the University of California at San Diego performance-based skills assessment. A Virtual Reality Functional Capacity Assessment Tool (VRFCAT) was developed by NeuroCog Trials, Inc., as a performance-based measure that could be self- or clinician-administered on a tablet or personal computer, integrated into the clinical setting, delivered remotely, and adapted for different cultural and geographic populations. The VRFCAT provides an interactive environment where users navigate their way through a series of scenes and tasks in a kitchen, grocery store, and on a bus. These tasks test their visuospatial ability; executive function; verbal, visual, and working memory; and attention. A validation study indicated that the VRFCAT had similar sensitivity as the MATRICS Consensus Cognitive Battery with good test-retest reliability, minimal practice effects, and availability of alternate forms. It also compared favorably with the University of California at San Diego performance-based skills assessment [27]. The VRFCAT is currently being used in phase 2 trials for schizophrenia and major depressive disorder.

6. Deriving insights from complex data

Collecting data from closed ecosystems limits their ability to inform new insights about disease mechanisms and progression, which is typical for digital tools in development. Indeed, collecting data from multiple types of digital markers (genomics, transcriptomics, proteomics, protein-protein interactions, signaling cascades, in vitro phenotype, electrophysiology, medical imaging, phenotype, and epidemiology) could more precisely define phenotypes, clarify disease mechanisms, and conquer vast spatial and temporal scale differences, which ultimately could produce new and better biomarkers, including predictive biomarkers, improve clinical trials, and facilitate personalized medicine. However, using open ecosystems to develop models or tools present many challenges.

To address these concerns, Sage Bionetworks, a nonprofit organization based in Seattle, has been building an open ecosystem that currently comprises the mPower app discussed earlier and other digital data-gathering tools designed to improve management of and treatment development for disease conditions such as melanoma, asthma, heart disease, and MS. Sage recently launched the PD Digital Biomarker DREAM challenge [28], in which they will provide researchers around the world with raw sensor time series data recorded during the performance of prespecified tasks, asking challenge participants to extract features and apply standard machine-learning algorithms to predict disease phenotype.

Also in the PD space, IBM has partnered with Pfizer on the BlueSky Project, which will collect real-time continuous data from patients' wearable sensors to quantify on/off periods, quality of life, activities of daily living, sleep quality and architecture, and cognition. The goal is to create a digital health assistant and improve clinical trials for PD using passive and unobtrusive tools. In initial studies, participants fitted with 14 wearable devices carryout tasks from the Movement Disorder Society Unified Parkinson's Disease Rating Scale Part 3 and scripted activities of daily living [29]. Data from these disparate streams are cleaned, time-aligned, transformed into a unified format, and collected in a customized database based on Systematized Nomenclature of Medicine Clinical Terms. The system uses classifiers based on machine learning that can decompose complex human movements (such as in activities of daily living) into a sequence of simpler movement primitives (e.g., supination and pronation of the hand). The movement primitives can then be rated in ways that are analogous to the human-based scoring in the Movement Disorder Society Unified Parkinson's Disease Rating Scale.

7. Ethical concerns

The massive amounts of data collected actively and passively by wearable and home-based sensors and apps, online assessment tools and platforms, electronic medical records, and online technologies that collect metadata such as browser history and typing speed may be useful in understanding disease progression and response to intervention. Yet, although their potential is great, all these technologies present ethical challenges that can cause setbacks when used in clinical trials, potentially increasing the time and cost of development. For example, a data breach within the British Columbia Health Ministry in 2012 compromised patient privacy, leading to a freeze on release of medical research data, which affected 20 clinical studies [30]. While there are technologies available to mask data, they risk upsetting the delicate balance between the benefits of open data and the hazards of exploitation.

Ethical issues including privacy and data sharing policies, informed consent, disclosure, conflicts of interest, and ownership of data should be considered during the development of new technology. Although there are technologies to anonymize data, privacy remains one of the biggest concerns for users. Nonetheless, most people want their data to be shared. For example, Lars Omberg of Sage Bionetworks reported that in the Parkinson's mPower study, 75% of participants were willing to share their data. Participants expressed substantial willingness to share data collected during structured activities but were less willing to share passive data. Yet, some persons with AD or other conditions that may have less visible signs and symptoms expressed concern about how data sharing might impact their daily life, for example, will neighbors find out, will friends be lost, will they lose ability to drive, and so on [31]. Caregivers as well may have concerns about monitoring. They may want the ability to turn off a device at certain times and may also want to know more about what is being recorded, what impact it could have on the study, and how the information will be used, for example, whether it will be sold for a profit. These concerns reflect a lack of clarity regarding ownership of the data. Do the data belong to the participants or the researchers? Rhoda Au of the Framingham Study suggested that participants own the data and give researchers the privilege of using it, as well as the responsibility to push data into the research community while still protecting participant's personal health information. However, recent stories in the lay press have raised substantial concerns about the data industry selling personal information for commercial purposes. These stories emphasize how valuable data are. Within the medical device world, venture capitalists that may be funding development of a device need to have confidence that their intellectual property position is strong. Au suggested that multisector solutions will be needed to enable sharing of precompetitive data, which companies can then use to come up with proprietary products. It is incumbent on developers to clarify these privacy and ownership issues before asking for consent.

The process of informed consent, traditionally used in the context of medical interventions and research, is crucial to ensure end-users fully understand the risks and the benefits of digital biomarkers. In this context, two key challenges

emerge: (1) the routinization of consent; and (2) obtaining consent from persons who are cognitively impaired or may become cognitively impaired over the period of data collection.

Consenting to the use of a large range of digital products, from brain training applications to online cognitive screening tools, often involves lengthy and overly dense text and little meaningful choice [32], when an informed consent process is present at all [33]. The complexity of these types of informed consent processes makes them inaccessible to target end-users and threatens the "informed" aspect of informed consent [34]. Obtaining informed consent with regard to data collection from wearables and other passive and active sensors can be particularly challenging. To address this issue and in an effort to make informed consent more accessible, investigators at Sage developed a self-administered electronic informed consent process and conducted a study to assess the efficacy of this tool [35]. They found a wide disparity in comprehension of core research concepts among participants as well as misunderstandings about data privacy, confidentiality, and study procedures, highlighting the need for continued efforts in this area.

The process of informed consent warrants special considerations when data are being collected from persons with cognitive impairment. At this time, the relationship between cognitive decline in dementia and capacity to consent is not well defined [36]. There is an emerging consensus that whenever possible, the person with dementia should be fully engaged in the informed consent process [37]. A recent study aimed at assessing informed consent capacity in persons with mild to moderate AD found that nearly three quarters of participants had the capacity to understand the informed consent process [38]. Difficulties arise when surrogate consent must be obtained, as it can be challenging for the surrogate decision-maker to balance the patient's autonomy against safety and caregiver burden [39]. Julie Robillard from the University of British Columbia noted that as technologies are increasingly developed with meaningful end-user input, the hope is that they will be better aligned with the needs and values of people with dementia and their caregivers, which will in turn improve acceptance and facilitate the informed consent process.

Developers also have the ethical responsibility to ensure claims made about a device are accurate. Robillard et al [32] examined scientific and ethical features of 16 English-language online tests for AD. An expert panel determined that the overall quality ranged from very poor to poor, with very poor to poor ratings for appropriateness to achieve the goal of the test, scientific validity and reliability, and grounding in peer-reviewed literature. The human-computer interaction ranged from poor to good, whereas ratings for a range of ethics items were low, including poor to very poor ratings for introductory items, process of informed consent, disclosure of measures for privacy and confidentiality, interpretation of results and advice for follow-up, and disclosure of conflicts of interest. In a subsequent study, Robillard et al are analyzing the user experience when taking a computerized cognitive screening test in the clinical setting. Preliminary results have identified several major challenges including wide variability in familiarity with computers, the need for human intervention, attention to the emotional impact of the technology, and a tendency for people to make negative assumptions about their performance even in the absence of a return of results process.

Robillard suggested five pillars of an ethical framework for technology development to ensure the technology leaves a positive impact on users and balances benefits and challenges: (1) inclusive participatory design; (2) emotional alignment; (3) adoption modeling of data use; (4) standards assessment, for example, for consent; and (5) training and education. Screening technologies that may provide earlier identification of disease also raise concerns about re-identification and potential impact on employment and insurance. An appropriate regulatory framework similar to the Genetic Information Nondiscrimination Act may be needed to protect participant privacy in this regard.

8. Regulatory issues

The regulatory path for digital medical devices is unclear but moving forward, learning from imaging with regard to large data volumes, distributed collection, use of sophisticated algorithms, good clinical practice guidelines, and device heterogeneity. To attract the interest of the pharma industry, Roundtable participants noted that developers must do their due diligence with regard to regulatory approval. This can mean following design control methods outlined in 21 Code of Federal Regulations 820.30, producing a design history file, and ensuring that devices are compliant with the Health Insurance Portability and Accountability Act and cyber secure. Richard Chapman of Biogen warned that fear of the pain of regulation may drive companies to develop a lower risk device instead of a device that could have more significant medical impact. For example, if a device is linked to the development of a drug and will be used in a clinical trial to show efficacy of drug under an investigational new drug application, the drug company will likely consider many issues, and if the device is under enforcement discretion, there may be insufficient documentation to satisfy the requirements of the drug company. Device developers may need to demonstrate to the drug company that the device meets the company's quality standards, does what it is supposed to do, and was initially developed for the intended use in the trial and in the population that will be enrolled in the trial. When used in a clinical trial or for a treatment decision, devices thus must reach a higher bar than they would for prescreening, recruitment, or other uses.

The US Food and Drug Administration and European Medicines Agency handle devices differently; however, recent changes in the United States should lead to better alignment, and the two agencies have established a working

group to attempt to harmonize regulations. The Food and Drug Administration's Center for Devices and Radiological Health established a new branch within the Division of Neurological and Physical Medicine Devices—the Neurodiagnostic and Neurosurgical Devices Branch—to make sure they have the appropriate staffing to protect the population while still promoting innovation using a risk-based approach, wherein low- or no-risk products can be approved on the basis of valid scientific evidence alone, with no need for randomized clinical trials, and products with low to moderate risk can be approved relatively quickly. Developers are encouraged to contact regulatory agencies early to gain a clear understanding of the regulatory landscape and thus speed development.

Because innovation cycles for digital technologies move quickly, traditional regulatory paradigms for software are inadequate. Regulators recognize this and have become more aggressive in helping to get trials up and running. They may, for example, consider a company's history of software verification and validation. They emphasize the importance of identifying end points that are meaningful to patients with real-world assessments and to look beyond questions of safety and effectiveness by assessing the user interface and user comprehension. Clinician input is also needed to confirm patients' diagnoses. In this regard, Europe was recognized as far ahead of the United States in terms of establishing and maintaining a clinical database. Other important factors that regulators cited included the need to build trust with community and harmonize tools internationally. To ensure that ethical issues are addressed, the Food and Drug Administration uses a consulting ethicist and includes persons with dementia on advisory committees for devices intended for that population.

The issue of voice or video recording of clinical outcomes assessments has caused intensive public debate at the European Union. New European Clinical trials guidance regulation will be adopted in 2019 by the European Union where the issue of privacy will be clearly evaluated for each clinical trial [40]. Alzheimer's disease is of enormous importance in the aging population worldwide, and development of accurate methods to access personal risk of developing the disorder reflects the mounting demand for health care. The clinical relevance of biomarkers for Alzheimer's disease must be considered in the wider context of ethics, genetic counseling, public education, cost, patient access, and ease of use [41].

9. Moving forward to advance AD treatments: Opportunities and challenges

Roundtable participants described upcoming studies designed to integrate digital devices into the AD clinical research space. For example, a natural history study funded by The National Institute of Aging and Merck was recently launched using the Oregon Center for Aging and Technology platform to detect changes throughout the continuum of AD. This study, EVALUATE-AD (Ecologically Valid, Ambient, Longitudinal, and Unbiased Assessment of Treatment Efficacy in AD), will use a dyad approach, assessing changes in individuals with early AD or late mild cognitive impairment as well as in their caregivers. The goal is to establish digital biomarkers that are sensitive to clinical change associated with conventional AD treatments.

At the Cleveland Clinic, investigators are applying lessons learned from the development of the MSPT, by developing a self-administered cognitive testing tool designed to be integrated into the primary care workflow as a low cost and sensitive screening method for preclinical AD. The Cleveland Clinic Computerized Cognitive Battery (C4B) combines tests of visual memory, processing speed, sequencing, and switching. The visual memory test challenges both verbal and spatial memory. Similar to the MSPT, all stimuli involve numbers, symbols, common nameable objects, or letters. Auditory instructions can be easily translated. A validation study is planned, which will compare results from neuroimaging and cerebrospinal fluid measures in at-risk primary care patients aged 60 years or older who perform below expectations on cognitive testing. The goal is to identify a cost-effective means of flagging individuals with AD pathology.

Other recent technological innovations are also being explored for their potential to transform AD clinical trials. These range from platforms to cross-correlate devices or to bridge functional measures with health economics data to the use of artificial intelligence approaches in drug development and care management, and deep learning approaches that could enable the training of sensors to generate end points.

Achieving these goals will require confronting many challenges:

- There are no empirical data to show that devices could get answers more quickly in phase 2 studies, although simulations suggest that there is a tradeoff between sample size and follow-up, and theoretically, more data points acquired more frequently should produce more precise measures.
- What are now considered the "gold standard" cognitive tests, such as the Mini–Mental State Examination and Alzheimer's Disease Assessment Scale-cognitive subscale, were created with the goal of differentiating overt disease from healthy elders. New tools to characterize disease in early, preclinical stages will need novel metrics, not simply improvements to these older tests.
- Obtaining normative data in older people is difficult because many older people have comorbid conditions, and using samples of super-healthy elders may not be representative of the overall population. Smart home laboratory environments have been useful in the development of digital tools to understand how wearable and unobtrusive sensors can gather valuable behavioral data, but people perform differently in their natural

environment, raising questions about the normative data that may have been gathered in the laboratory environment.
- Collecting and analyzing massive amounts of data may be impractical, given currently available technologies and the resources available, suggesting that it may be better to start with more generalized behaviors and activities that can be easily sensed.
- When collecting data from patients, timing is crucial because people have good days and bad days and different cycle times. Integrating affect into data collection may help in this regard.
- Gaining acceptance from primary care physicians is crucial, so it will be important to integrate devices into primary care without interfering with workflow. Tools that enable better patient management and financial incentives, such as increased reimbursement following the identification of dementia patients, may also lead to better physician acceptance.
- Usability testing of these devices and applications with representative sample of users is also critical.

Showing that these tools can enhance care in a meaningful way remains particularly difficult given that there is currently no disease-modifying drug. However, the field should prepare for the day when such drugs are available by educating physicians about the meaning of outcomes from devices and when they may signal the need for more comprehensive testing or a change in management strategies. To this end, the Alzheimer's Association is working to develop national clinical practice guidelines that will include care plans that would follow a positive screen.

Even in the absence of effective molecules, digital technologies may add value to clinical studies by enabling investigators to extract insight from small signals. For example, if these tools are shown to be more sensitive to earlier stage disease, it may be feasible to design smaller studies testing multiple mechanisms to help determine which molecules should be developed further.

10. Conclusions

While it may be unrealistic to think that digital tools in their current state will be useful as outcome measures in registration trials in the near future. However, Roundtable participants urged drug developers to start to embed these tools in clinical trials in parallel with other measures as a means of moving the field forward. Bridging data to other existing less sensitive readouts, for example, early indicators of functional improvements bridged to more traditional assessments, may provide enough signal to warrant testing a drug in earlier disease stages. Objective data acquired using these technologies may also be more reliable than self-report in helping understand the placebo response and for use as run-in data in a clinical trial.

Broad interest in digital tools suggests that they will occupy an increasing role in drug development and patient care over the coming years. Recognizing that there are substantial consequences to misuse of technology, Michael Gold of AbbVie urged Roundtable participants to proceed carefully and thoughtfully to maintain credibility and trust with the patient community.

Acknowledgments

The authors thank Meredith McNeil for logistical planning of the Research Roundtable meeting as well as additional contributing speakers and panelists: Alexandra Atkins, Ph.D., Rhoda Au, Ph.D., Richard Chapman, E. Ray Dorsey, M.D., M.B.A., Colin Foster, M.Sc., Derek Hill, Ph.D., Jeffrey Kaye, M.D., Yoshiko Komuro, Ph.D., Eddie Martucci, Ph.D., Laura McIntosh, Ph.D., David Miller, M.D., Larsson Omberg, Ph.D., Spyros Papapetropoulos, M.D, Ph.D., Carlos Pena, M.D., Timothy Peters-Strickland, M.D., Christopher Randolph, Ph.D., Stephen Rao, Ph.D., Jeff Shuren, M.D., and Stacie Weninger, Ph.D.

The authors particularly want to thank Geri & Jim Taylor, Patient and Care Partner from the Alzheimer's Association Early Stage Advisory Group for their participation in the Research Roundtable meeting.

The views of M.B.T. expressed in this review are the personal views of the author and should not be construed as being made on behalf of or reflecting the position of the EMA or one of its committees or working parties or any of the national agencies.

RESEARCH IN CONTEXT

1. Systematic review: This review summarizes the presentations made at the May 2017 Research Roundtable meeting on the new digital technology that is being applied to Alzheimer's disease drug development. Each presenter reviewed the recent literature in their specific topic areas within the context of digital technology being applied to Alzheimer's disease.
2. Interpretation: The information covered in this article summarizes viewpoints of industry drug developers, academic colleagues, and government representatives on the potential value and challenges of adopting new digital technology for Alzheimer's disease clinical research.
3. Future directions: A section on challenges and future directions for the utility of digital technology in Alzheimer's research is discussed.

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