Technologies for Measuring Cognition in Clinical Trials

Critical Path for Alzheimer’s Disease Consortium
Stephen P. Arnerić, PhD, Executive Director

ISCTM Conference
October 15, 2018
WHY IS DEVELOPING BETTER WAYS TO MEASURE COGNITIVE FUNCTION CRITICAL?

The Brain Health Problem

Dementia is rapidly increasing around the world. By 2050, the number of people with dementia could triple from 47 million to 132 million, overwhelming families, communities, public health care systems, and economies throughout the world (figure from World Alzheimer Report 2015 right). Caring for those with dementia presents profound challenges to families and society, and the growing global burden is vastly underestimated. There is currently no known prevention, cure, or effective treatment for dementia. Research shows that a public health approach to dementia could prevent up to 30 percent of the dementia cases projected around the world in the next two decades (Norton et al. 2014). Yet, very few countries have developed a national dementia plan, and dementia is often assumed a normal part of aging.

https://www.gbhi.org/about/

CRITICAL REASONS

- Unmet need for effective treatments
- Economic burden to Healthcare Systems Worldwide
- A new therapeutic for AD has not been approved in over a decade!
- Any trial in AD is dependent upon the outcome measures used, and must require the necessary sensitivity and specificity - especially true for the “presymptomatic” stage of the disease.
- Need for early detection assessments to detect those “at risk” for cognitive decline.
CRITICAL PATH INSTITUTE

Fifteen global consortia collaborating with 1,450+ scientists and 84 organizations

FOCUS: Data standards; clinical trial simulation tools from actionable data, disease progression models; biomarkers; clinical outcome assessment instruments
CPAD DATABASE UTILIZATION (as of August 2018)

562 Total Applicants from 338 Distinct Institutions

USE BY SECTORS
Academia: 254
Pharmaceutical: 165
Other: 70
Non-profit: 32
Government: 11

USE BY REGION
North America: 57%
Europe: 24%
Asia: 15%
Australia: 2%
South America: 1%
Africa: 1%

Industry
Abbvie; Allergan;
AstraZeneca; Biogen;
Biomarkable; CoreLab;
Daewong; Eisai; GE
Healthcare; IBM; Johnson &
Johnson; Lundbeck; Merck;
NeuroCog; Novartis; Pentara;
Pfizer; Siemens; SAS

Academia & Foundations
Amherst College; Arizona State Univ.; Bill &
Melinda Gates Foundation; CHDI Foundation;
Duke Univ.; Fraunhofer Institute; Goethe
Univ.; Harvard Univ.; Karolinska Institute;
King’s College London; Michael J Fox
Foundation; Rockefeller Univ.; Seoul National
Univ.; Univ. of Oxford; Yale Univ.

Government & Other
NIH; Neurology Today; Gigatrust

29 AD Clinical Trials
6,995 Patients

CPAD DATABASE UTILIZATION (as of August 2018)
VALUE, HISTORY, & FUTURE OF CDISC STANDARDS FOR AD

Value Proposition:

• A reproducible research framework with controlled terminology which accelerates our understanding of AD across trials using a uniform format.

• Improves our ability to detect signals in new compounds; maximizes learnings from successes and failures.

Historical Perspective (CPAD/CDISC partnership):

Version 1.0 (2011) –

• First user guide for AD CDISC standards (did not include biomarkers) focused on key demographic, genetic and clinical outcome assessments (COAs).

Version 2.0 (2016) –

• Added global consensus data standards for key CSF AD biomarkers, vMRI imaging and PET ligands.

Future:

Version 3.0 (~2019) –

• Focus on promising exploratory biomarkers and biometric assessments.
DEMONSTRATED UTILITY OF THE CLINICAL TRIAL SIMULATION TOOL IN MILD-to-MODERATE AD

Balancing power, sample size, and duration, given varying effect magnitudes

- Better power
- ~50% cost savings
- 13 weeks less time
HIPPOCAMPAL VOLUME IMAGING BIOMARKER
QUALIFICATION WITH FDA:
ICV-HV enrichment yields trial size reduction for MCI

~29%, ~37.5%, and ~66% reduction of sample size by enrolling only subjects with baseline ICV-HV <97.7th, <84.1th and <50th percentile, respectively.

The sample size savings estimated by the two models with either LEAP™ or FreeSurfer™ ICV-HV were approximately within 6 to 8% of each other.

Under these assumptions:
- 24-month placebo-controlled parallel group trial.
- Drug effect of 50% reduction in the progression rate.
- Power was calculated as the proportion of trials for which the effect of treatment on progression rate was beneficial with a two-tailed P-value < 0.05
DEFINING DISEASE
Requires a Composite Assessment =

**Signs** + **Symptoms**

### Patient & Physician Reported Outcomes
- Cognition (MMSE, CDR-SB, etc.)
- Behavior (sleep/mood scales – QOL-AD, GDS)
- Motor function (UDPRS)
- Sensation (NRS, etc.)
- Balance & Coordination
- Autonomic

### Observer / Performance Outcomes
- Genetics
- Examination
- Temperature
- Vision
- Forgetfulness
- Infection
- Mobility
- GI/Lung/ Glucose tests
- Kidney function
- EKG
- HR/BP
- EEG/ Sleep/ Fatigue

### Imaging Modalities
- PET
- MRI

**Real World Data**

www.c-path.org/cpad
WHY CONTINUOUS MEASUREMENT IS RELEVANT AND CRITICAL!

Which patient is rapidly declining?

- These data highlight the challenge of infrequent cross-sectional assessments.
- Understanding vector trends (the relevant 90%) in individual continuous performance would be more reflective of true long-term trends in performance/health maintenance, i.e., Aligned with Precision Medicine Objectives!
- GOAL: Validate Digital Assessments as DDTs to identify the “right patients”, enhance Clinical Trial efficiencies, and enable tailored treatment approaches.

Courtesy of Dr. Jeff Kaye

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WE CAN ONLY STUDY AND UNDERSTAND WHAT WE CAN MEASURE & OBSERVE!

PATIENTS & CLINICAL TRIAL SUBJECTS AS ICEBERGS

~10% Observable

>90% Not Measured

www.c-path.org/cpad
DIGITAL DRUG DEVELOPMENT TOOLS

Biometric Monitoring Devices (BMDs) as Regulatory Accepted Clinical Trial Assessments for Specific Contexts-of-Use

**WHY**
- Improve our understanding of real-time changes in FUNCTION during the progression of life in health and disease
- Improve the efficiency of AD clinical trials to accelerate the delivery of novel treatments
- Deliver precision care

**HOW**
- Continuous physiological monitoring with devices (wearables/smart phones, clothing, implants/ingestibles, remote biosensors)

**WHAT**
- Data (signal output) collected from a biosensor that measures a biological response

**KEY COUs**
- Understand disease progression
- Measure treatment responses
- Deliver Precision Care
THE VISION: DEVELOP AN END-TO-END ALZHEIMER DISEASE MODEL

How and when do these factors interact to influence disease progression? ...and treatment response?

Other Relevant Sources of Variability to Evaluate

<table>
<thead>
<tr>
<th>Genetics</th>
<th>Life Events</th>
<th>Co-Morbid Infections</th>
<th>Co-Morbid Disease</th>
<th>Biomarkers</th>
<th>Outcome Assessments</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Protective</td>
<td>• Trauma</td>
<td>[active /latent]</td>
<td>• Depression</td>
<td>• Fluid</td>
<td>• PROs</td>
</tr>
<tr>
<td>• Promoting</td>
<td>• Surgery</td>
<td>• Bacterial</td>
<td>• Diabetes</td>
<td>• PET Imaging</td>
<td>• Digital/ wearables</td>
</tr>
<tr>
<td>• Race/ Ethnicity</td>
<td>• Nutrition</td>
<td>• Viral</td>
<td>• Cardiovascular</td>
<td>• EEG</td>
<td>• IADLs</td>
</tr>
<tr>
<td></td>
<td>• Education</td>
<td>• Parasites</td>
<td>• Cancer</td>
<td>• Evoked responses</td>
<td>• Etc.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Fungal</td>
<td>• Inflammation</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Etc.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
COLLECTING REAL WORLD DATA


RWD = RWE: Careful data standardization, aggregation, and quantitative modeling will be required to transform RWD to RWE.

Real-World Data (RWD) are data relating to patient health status and/or the delivery of health care routinely collected from a variety of sources.

Real-World Evidence (RWE) is evidence derived from RWD through the application of research methods. For regulatory applications, RWE can further be defined as clinical evidence regarding the use and potential benefits or risks of a medical product derived from analysis of RWD.

A FRAMEWORK FOR REGULATORY USE OF REAL-WORLD EVIDENCE, September 2017

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DOMAINS OF FUNCTION: WHERE DO WE FOCUS?

CHALLENGES:

- Data availability
- CDISC Standards Development
- Understanding clinically meaningful relationships for healthcare decision making

BMDs enable a paradigm shift in assessing IADLs

SUBJECTIVE

Current Practice
In Drug Development

Efficacy

“JADLs”
Challenges: Patient-reported, subjective, memory-dependent, non-verifiable, not used in label claims

Safety

OBJECTIVE

Biometric Monitoring Devices
In Drug Development

Efficacy

“IADLs”
Objective, verifiable, patient-independent outcomes for potential use in label claims; ‘Surrogate for QoL’

Safety

Concepts-of-Interest

- Mental Health
- Sleep
- Motor Function
- Cognition
- Mobility/Frailty

Transformed

Quantitative Assessment

- Attention
- Delayed recall
- Speed of Information processing
- Spatial memory
- Executive function; speech
- IADLs

- Sleep onset latency
- Total sleep time
- Wake after sleep onset
- Quality of sleep time (REM vs. non-REM)
- Excessive daytime sleepiness
- Daytime sleep

- Time and distance in/out of home
- Voice
- Dyskinesias, tremor, and chorea
- Motor fluctuations
- ADLs
- Grip strength
- Gait and falls

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MEDICATION ADHERENCE AS A KEY IADL

FDA approves pill with sensor that digitally tracks if patients have ingested their medication

Every Day Cognition:
Medication adherence as a measure of cognitive function

Significantly Worse

‘Drugs don't work in patients who don't take them’

- C. Everett Koop, MD
Former US Surgeon General, 1985

"No covariate can have a bigger impact than not taking the drug." Y. Wang (FDA) at ACDRS meeting, September 2013

Based on ADAS cog: Lower Cognition Group vs Higher Cognition Group
NEUROCOG [VeraSci]

The Brief Assessment of Cognition is a 30-minute test battery developed to assess cognitive performance in schizophrenia (BACS), affective disorders (BAC-A), and a range of other clinical indications (BAC). The pen-and-paper version of the test has been used by academic investigators and pharmaceutical developers to study cognitive outcomes in dozens of clinical trials, including schizophrenia, substance use disorders, and bipolar disorder.

The BAC comprises seven core tests designed to provide a comprehensive view of cognitive function.

<table>
<thead>
<tr>
<th>Cognitive Domain</th>
<th>Task</th>
</tr>
</thead>
<tbody>
<tr>
<td>Verbal Memory &amp; Learning</td>
<td>Verbal Memory</td>
</tr>
<tr>
<td>Working Memory</td>
<td>Digit Sequencing</td>
</tr>
<tr>
<td>Motor Function</td>
<td>Token Motor</td>
</tr>
<tr>
<td>Verbal Fluency</td>
<td>Semantic Fluency</td>
</tr>
<tr>
<td></td>
<td>Letter Fluency</td>
</tr>
<tr>
<td>Speed of Processing</td>
<td>Symbol Coding</td>
</tr>
<tr>
<td>Executive Function</td>
<td>Tower of London</td>
</tr>
</tbody>
</table>
COGSTATE

Tests of Multiple Cognitive Domains

Cogstate Research™ allows the freedom to select a battery of cognitive tests that are most appropriate for your testing protocol. Each test has been designed and validated to assess specific domains including psychomotor function, attention, memory, executive function, verbal learning and social-emotional cognition. The below tests are available as standard; and additional tests, such as the Face Name Associative Memory Exam or pediatric versions of tests, can be added when a Customized Software Configuration is commissioned.

+ Chase Test
+ Continuous Paired Associate Learning Test
+ Detection Test
+ Groton Maze Learning Test
+ Identification Test
+ Set-Shifting Test
+ Social-Emotional Cognition Test
+ Two Back Test

www.c-path.org/cpad
## Memory Loss Biomarkers

May aid in diagnosis of memory loss years before current standard of care

<table>
<thead>
<tr>
<th></th>
<th>Healthy</th>
<th>Early Memory Loss Case 1</th>
<th>Early Memory Loss Case 2</th>
<th>Early Memory Loss Case 3</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>History</strong></td>
<td>Age: 45 None</td>
<td>Age: 41 Memory Memory recall</td>
<td>Age: 63 Forgetfulness</td>
<td>Age: 73 Cognitive impairment Memory Loss</td>
</tr>
<tr>
<td><strong>Peak Alpha Frequency (PAF)</strong></td>
<td>9.5 Hz</td>
<td>8.6 Hz</td>
<td>7.8 Hz</td>
<td>6.6 Hz</td>
</tr>
<tr>
<td><strong>Brain Speed (P300)</strong></td>
<td><img src="image1" alt="Brain Speed" /></td>
<td><img src="image2" alt="Brain Speed" /></td>
<td><img src="image3" alt="Brain Speed" /></td>
<td><img src="image4" alt="Brain Speed" /></td>
</tr>
<tr>
<td><strong>Brain Power (EEG)</strong></td>
<td><img src="image5" alt="Brain Power" /></td>
<td><img src="image6" alt="Brain Power" /></td>
<td><img src="image7" alt="Brain Power" /></td>
<td><img src="image8" alt="Brain Power" /></td>
</tr>
<tr>
<td><strong>Source Localization (EEG)</strong></td>
<td><img src="image9" alt="Source Localization" /></td>
<td><img src="image10" alt="Source Localization" /></td>
<td><img src="image11" alt="Source Localization" /></td>
<td><img src="image12" alt="Source Localization" /></td>
</tr>
</tbody>
</table>
April 2, 2015

NPR

ASU Researchers Explore New Way To Diagnose Neurological Diseases. Interview of Dr. Visar...

March 3, 2015

The New York Times

Parsing Ronald Reagan’s Words For Early Signs Of Alzheimer’s. Contributed to by Dr...
<table>
<thead>
<tr>
<th>TECHNOLOGY ASSESSMENT</th>
<th>USE CASE(S)</th>
<th>ATTRIBUTES</th>
<th>GAP</th>
<th>COMMENTS/LINKS</th>
</tr>
</thead>
</table>
| CogniVue™ (Cerebral Assessment Systems) | Computer-based platform designed expressly for primary-care physicians to measure and monitor brain health to detect the early signs of dementia | • 510K compliant  
• FDA cleared for specific use case  
• Secure data transfer | Not validated for clinical trial assessments | http://cerebralassessmentsystems.com/cognivue/ |
| ImPACT™ (Immediate Post-Concussion Assessment and Cognitive Testing) | A clinician's computerized concussion testing of patients ages 12-99. ImPACT is the most widely used computerized neurocognitive test to help evaluate and manage concussions. | • 510K compliant  
• FDA cleared for specific use case  
• Secure data transfer  
• Extensive research  
• Pursuing additional uses | Not validated for clinical trial assessment of cognition, or use outside traumatic brain injury | ImPACT™ is supported by a database of clinical research, including more than 250 peer-reviewed and 145 independent studies. https://www.impacttest.com/about/ |
| CANTAB™ (Cambridge Cognition) | • CANTAB Recruit is an online trial recruitment platform helping pharmaceutical & biotechnology companies identify qualified clinical trial participants in high-need indications such as Alzheimer’s disease  
• CANTAB Connect offers precise, objective and reliable digital cognitive assessment solutions for pharmaceutical clinical trials in all therapeutic areas from phases I – IV  
• Wearable and smartphone apps for high frequency real-world data collection to improve the understanding of the real-world impact of clinical interventions | • GCP Compliant  
• Analytically validated  
• Time stamped  
• Assessments across various patient populations including: Alzheimer Disease, Parkinson Disease, Depression, Attention Deficit Disorder, Autism Spectrum Disorder, Cognitive Safety, Depression, Down's Syndrome, Epilepsy, Huntington Disease, Mild Cognitive Impairment, Multiple Sclerosis, Schizophrenia, Stroke, Traumatic brain injury | Currently undergoing clinical trial validation assessments for use cases | Assesses: Psychomotor speed, attention, memory, executive function and social function.  
http://www.cambridgecognition.com/products/drug-development  
CANTAB Bibliography |
| AKILI™ | Measurements over time from tracking patients’ conditions to understanding the effect of interventions on brain function.  
• Screening and monitoring products for short measurements configurable to custom tracking needs (hourly, daily, weekly, etc.). Each individual assessment utilizes the technology platform’s proprietary measurement of cognitive control in a format that engages the patient. | • High quality, ultra-frequent, more sensitive cognitive data for use in clinical decision making and clinical trials.  
• GCP compliant  
• Time stamped | Seeking:  
• 510K compliance  
• FDA clearance for specific use cases  
• Large RCT in progress for ADHD therapy  
• Smaller RCTs for other programs to confirm clinical validation | Active programs in ADHD, Parkinson Disease, Depression, Alzheimer Disease, and others.  
http://www.akiliinteractive.com/ |
Selection of and Evidentiary Considerations for Wearable Devices and Their Measurements for Use in Regulatory Decision Making: Recommendations from the ePRO Consortium

Bill Byrom, PhD\(^1\)\(^*,\) Chris Watson, PhD\(^2\), Helen Doll, DPhil\(^3\), Stephen Joel Coons, PhD\(^4\), Sonya Eremenco, MA\(^4\), Rachel Ballinger, PhD\(^5\), Marie Mc Carthy, MBA\(^6\), Mabel Crescioni, DrPh\(^6\), Paul O’Donohoe, MSc\(^6\), Cindy Howry, MS\(^7\), on behalf of the ePRO Consortium

\(^1\)ICON Clinical Research, Marlow, Buckinghamshire, UK; \(^2\)ERT, Nottingham, Nottinghamshire, UK; \(^3\)ICON Clinical Research, Abingdon, Oxfordshire, UK; \(^4\)Critical Path Institute, Tucson, AZ, USA; \(^5\)ICON Clinical Research, Dublin, Ireland; \(^6\)CRF Health, London, UK; \(^7\)assistTek, Scottsdale, AZ, USA
CONSIDERATIONS FOR POSSIBLE ENDPOINTS

Early AD: Draft FDA Guidance
WHERE TO FOCUS DIGITAL COGNITIVE ENDPOINT ASSESSMENT DEVELOPMENT!

<table>
<thead>
<tr>
<th>Stage 1</th>
<th>Stage 2</th>
<th>Stage 3</th>
<th>Stage 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preclinical</td>
<td>Prodromal</td>
<td>Early AD</td>
<td>Mild-mod. AD</td>
</tr>
<tr>
<td>Definition</td>
<td>Asymptomatic</td>
<td>Detectable cognitive changes</td>
<td>Cognitive impairment</td>
</tr>
<tr>
<td></td>
<td>Biomarker evidence of</td>
<td>No functional impairment</td>
<td>Mild functional impairment</td>
</tr>
<tr>
<td></td>
<td>pathology (only)</td>
<td></td>
<td>Overt dementia</td>
</tr>
<tr>
<td>Possible</td>
<td></td>
<td></td>
<td>Cognitive and functional</td>
</tr>
<tr>
<td>endpoints</td>
<td>Biomarker Imaging</td>
<td>Cognitive scale(s) only</td>
<td>impairment</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(biomarker supported dx)</td>
<td></td>
</tr>
<tr>
<td>Clinical</td>
<td>Not required</td>
<td>Clinically meaningful ideal;</td>
<td>Clinically meaningful</td>
</tr>
<tr>
<td>meaningfulness</td>
<td></td>
<td>not required</td>
<td>Clinically meaningful</td>
</tr>
<tr>
<td>Approval type</td>
<td>Accelerated? (conditional)</td>
<td>Accelerated or Regular approval</td>
<td>Regular approval</td>
</tr>
</tbody>
</table>

8.2.3. Efficacy endpoints in Preclinical AD

For the time being there is no "gold standard" for assessment of treatment effect in patients with preclinical AD (see section 9). Cognitive endpoints used in primary and secondary prevention trials have been the diagnosis of dementia (based on cut-off scores), significant cognitive decline and change in cognitive function based on longitudinal performance on certain tests. Novel outcome tools sensitive to small neuropsychological changes in this population are being developed, however they are not yet validated and cannot be endorsed solely as primary endpoints in this population. A time to event analysis could be a complementary measure in order to support the relevance of any chosen outcome, although feasibility issues including length of the trial and number of drop-outs are recognized. The event must be of clear clinical importance such as onset of cognitive impairment (see section 9). Until a biomarker will be qualified as a reliable surrogate measure of treatment effect in absence of a clinically observable change, patients should be followed up for a sufficient time to capture relevant cognitive changes.
“Fit for Purpose”: BEST Biomarker Classes in Perspective

- "Normal" Physiology
  - Susceptibility/Risk
  - Improved Clinical Benefit
  - Surrogate Endpoint

- Pathologic Changes
  - Descriptive Time progression Key factors / events
  - Non-Progression Or Reversal
  - Response

- Altered Physiology
  - Descriptive Threshold of concern
  - Change in Physiology
  - Pharmacodynamic Predictive Safety

- Clinical Disease
  - Diagnostic Monitoring Prognostic
  - Therapeutic Intervention

NCBI NLM NIH. BEST (Biomarkers, EndpointS, and other Tools) Resource. NCBI Bookshelf, 2016
WHAT ARE THE COMMON AND DIFFERENTIATING FEATURES?

NfL Studies:

- Alzheimer Disease
- Chronic Traumatic Encephalopathy (CTE)
- Creutzfeldt-Jakob Disease
- Depression
- Down Syndrome
- Epilepsy
- Frontal Temporal Dementia
- Huntington Disease
- Korsakoff Syndrome
- Lewy Body Dementia
- Mild Cognitive Impairment
- Mixed Dementia
- Multiple Sclerosis*
- Normal Pressure Hydrocephalus
- Parkinson Disease
- Posterior Cortical Atrophy
- Posterior Cortical Atrophy
- Schizophrenia
- Traumatic Brain Injury
- Vascular
- Vascular

http://www.alz.org/dementia/types-of-dementia.asp
BIOMETRIC MONITORING DEVICES: POTENTIAL SURROGATE ENDPOINTS?

BIOMARKER TERMINOLOGY: SPEAKING THE SAME LANGUAGE

Shashi Amur, Ph.D.
Scientific Lead, Biomarker Qualification Program, Office of Translational Sciences, Center for Drug Evaluation and Research, FDA

SURROGATE ENDPOINT
An endpoint that is used in clinical trials as a substitute for a direct measure of how a patient feels, functions, or survives.

Validated Surrogate Endpoint
Supported by a clear mechanistic rationale and clinical data providing strong evidence that an effect on the surrogate predicts a clinical benefit; therefore, such endpoints can be used to support traditional approval without the need for additional efficacy information. Example: Hemoglobin A1C reduction in diabetes clinical trials

Reasonably Likely Surrogate Endpoint
Supported by clear mechanistic and/or epidemiologic rationale but with insufficient clinical data to show that it is a validated surrogate endpoint; such endpoints can be used for accelerated approval for drugs or expedited access for medical devices. Example: Radiographic evidence of tumor shrinkage in some cancer types

Candidate Surrogate Endpoint
A surrogate under evaluation for its ability to predict clinical benefit.
BIOMETRIC MONITORING DEVICES (BMDs)

BMDs have the potential to measure signs related to all domains of function comprising what is viewed as Instrumental Activities of Daily Living (IADL).

- **Physical Function**
  - Mobility
  - Frailty
  - Homeostatic physiology
  - Drug disposition/metabolism

- **Mental Function**
  - Working memory
  - Attention
  - Wakefulness/sleep
  - Long-term memory
  - Mood
  - Pain

- **Social Engagement**
  - Friends/family
  - Social interaction/employment

- **Health Maintenance**
  - Injury & sickness
  - Medication Adherence
  - Surgery
  - Disease

“Quality of Life”
WHAT CAN YOU SEE?

FEB-MAR 2011

Healthy

SEPT-OCT 2012

Diagnosed with Parkinson disease

SEPT-OCT 2013

Treatment with Sinemet

Courtesy of Dr. Jeff Kaye

www.c-path.org/cpad
WE MUST WORK COLLECTIVELY TO BUILD A SUSTAINABLE ECOSYSTEM

CORRESPONDENCE

Biometric monitoring devices for assessing end points in clinical trials developing an ecosystem


Nature Reviews Drug Discovery (online September 22, 2017)

http://rdcu.be/v5bS
BHAG: GLOBAL INTEROPERABLE AD DATA REPOSITORY

Actionable, standardized, anonymized, patient-level data sources:
- Clinical trials
- Observational studies
- Healthy aging cohorts
- eHealth records

Self-Reports/Metadata:
Mood/pain/falls/visitors/sickness

Context:
Weather, type of living environment

mHealth Data
24/7/365 Behavioral Activity:
Computer/phone/mobility activity –
Time in and out of home – sleep
quality - drug adherence

Continuous data collection

Clinical Assessments:
Lab chemistry/imaging
data/biomarker/physical
function/genetics

Demographics:
Age, education, socioeconomic status, etc.

GAAIN as the
ACCESS & COLLABORATION PORTAL

Specific Trial/Study

‘SANDBOX FOR OPEN SCIENCE’
DATA ANALYSIS
& MODELING

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VISION OF FUTURE TECHNOLOGY USE IN CLINICAL TRIALS AND EARLY DISEASE DETECTION

- All patients will involve continuous remote monitoring of physiology/performance
- Data is streamed from the participant to the cloud, and analyzed in real-time for automated change detections
- Earlier and automated identification of changes in IADLS, adverse events, and therapeutic response are SOP
- Algorithm-driven notifications/assessments to participant/health care professional will enable timely changes in health care delivery
ACCELERATE DATA SHARING

• Data sharing – especially from prevention trials [Informed Consent]
• Understanding of what matters most to patients and caregivers
• Data sharing from pilot Biometric Monitoring Device (BMD) studies

A proposed framework

Collaboration for Alzheimer’s Prevention: Principles to guide data and sample sharing in preclinical Alzheimer’s disease trials

Stacie Weninger, Maria C. Carrillo, Billy Dunn, Paul S. Aisen, Randall J. Bateman

INFORMED CONSENT IS CRITICAL

Perspective

Concise informed consent to increase data and biospecimen access may accelerate innovative Alzheimer’s disease treatments

Ann M. Hake, Penny A. Dacks, Stephen P. Arneric, CAMD ICF working group

Eli Lilly and Company, Indianapolis, IN, USA
Alzheimer Drug Discovery Foundation, New York City, NY, USA
Coalition Against Major Diseases (CAMD), Tucson, AZ, USA

www.c-path.org/cpad
IMPAIRED COGNITION & FUNCTION ARE PROMINENT ACROSS NEURODEGENERATIVE DISEASES

- Alzheimer Disease
- Parkinson Disease
- Multiple Sclerosis
- Huntington Disease

SYMPTOMS & SIGNS
- Cognitive impairments; changes in speech
- Gait slowed; walking impairment; gate impairment;
- Sleeping changes; impairment
- Dizziness/vertigo; frailty
- Depression
- Pain

Functional Impact:
- Social life and social participation
- Work/life
- Relationships and family
- Independence
VISION FOR THE FUTURE: CREATE A SECURE INTEROPERABLE DATABASE FOR NEURODEGENERATIVE DISEASES

POTENTIAL QUESTIONS

▪ What are the common features across diseases?
▪ What are the key differentiating features across the diseases? When do they occur?
▪ How do co-morbid diseases affect the rate of progression of each disease?
▪ What resilience factors may exist to slow the progression of disease?
▪ Are their biomarkers that could predict the likelihood of future benefits?
MEMBERS & CONTRIBUTORS

Thank you!

www.c-path.org/

Pharmaceutical Industry
- AbbVie Inc.
- Biogen
- Boehringer Ingelheim Pharmaceuticals, Inc.
- Eisai
- Eli Lilly and Company
- Roche/Genentech
- Johnson & Johnson Pharmaceutical Research & Development, LLC
- Merck, Sharp & Dohme Corp.
- Novartis Pharmaceutical
- Pfizer, Inc.
- Takeda

Government and Regulatory Agencies
- European Medicines Agency (EMA)
- National Institute of Neurological Disorders and Stroke (NINDS)
- National Institute on Aging (NIA)
- U.S. Food and Drug Administration (FDA)
- National Institutes of Health (NIH)

Non-profit Research Organizations
- Alzheimer’s Association
- UsAgainstAlzheimer’s Network
- Alzheimer’s Research UK
- Alzheimer’s Drug Discovery Foundation
- CHDI Foundation

C-Path Staff Advancing CPAD

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www.c-path.org/cpad
VISION OF RWE FOR REGULATORY PURPOSES

Experience Utilizing RWD and RWE for Regulatory Purposes

To date, there has been varying experience utilizing RWD and RWE to inform a range of regulatory use cases. For example, FDA has used both to support a small number of approval decisions in rare diseases or areas of high unmet need (e.g. through the use of historical controls in studies with small patient populations). Following a first-time approval, RWD and RWE have been used on a very limited basis to support label changes such as indication expansions, dosing modifications, or safety revisions. RWD sources are routinely used to monitor the safety of medical products on the market through systems such as Sentinel, which leverages EHRs, claims data, and registries from a diverse group of data partners.

KEY ACHIEVEMENTS FOR CPAD
(previously CAMD: Coalition Against Major Diseases)

Celebrating 10 Years as a Consortium: Rebranded January 2018 to Convey our Focus and Mission

- First integrated database of anonymized, patient level clinical data for AD
- First CDISC Standards
- EMA qualified AD biomarker
- AD clinical trial simulation tool
- FDA letters of support – AD biomarkers