REALIZING THE VISION OF DIGITALLY ENABLED, PATIENT-CENTRIC CLINICAL TRIALS

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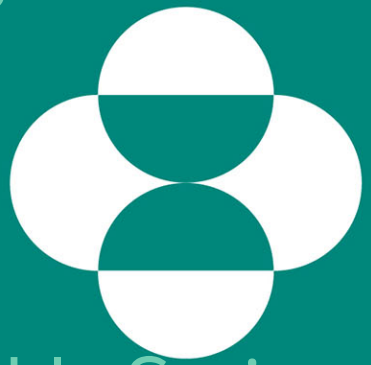
Merck & Co, Inc., Kenilworth, NJ, USA



INVENTING
FOR LIFE

IPAC-RS Digital Devices Roundtable Series

What is a Digital Biomarker and why is it important?

The “Traditional” Clinical Trial Paradigm is Lacking

Site Centricity

Participant burden

Geographical limitations

Data loss between visits

Lack of real-time feedback

Adherence

Lack of adherence

Data inaccuracies

Lack of real-time data

Endpoints

May not be meaningful to patients

May be categorical or subjective

Variability and sensitivity

Operational Inefficiencies

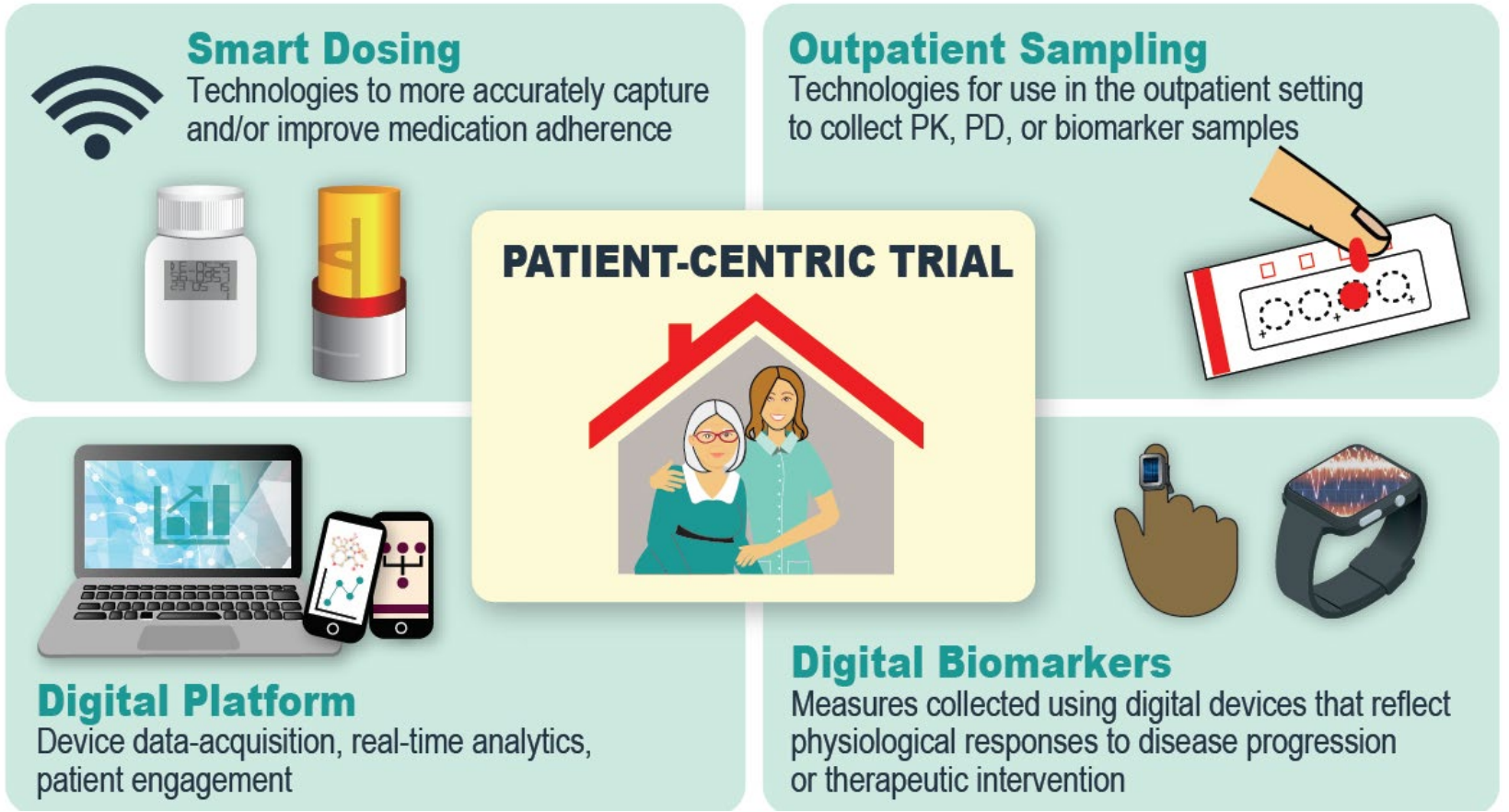
Transcriptional errors

Laborious data acquisition

Cost of visits

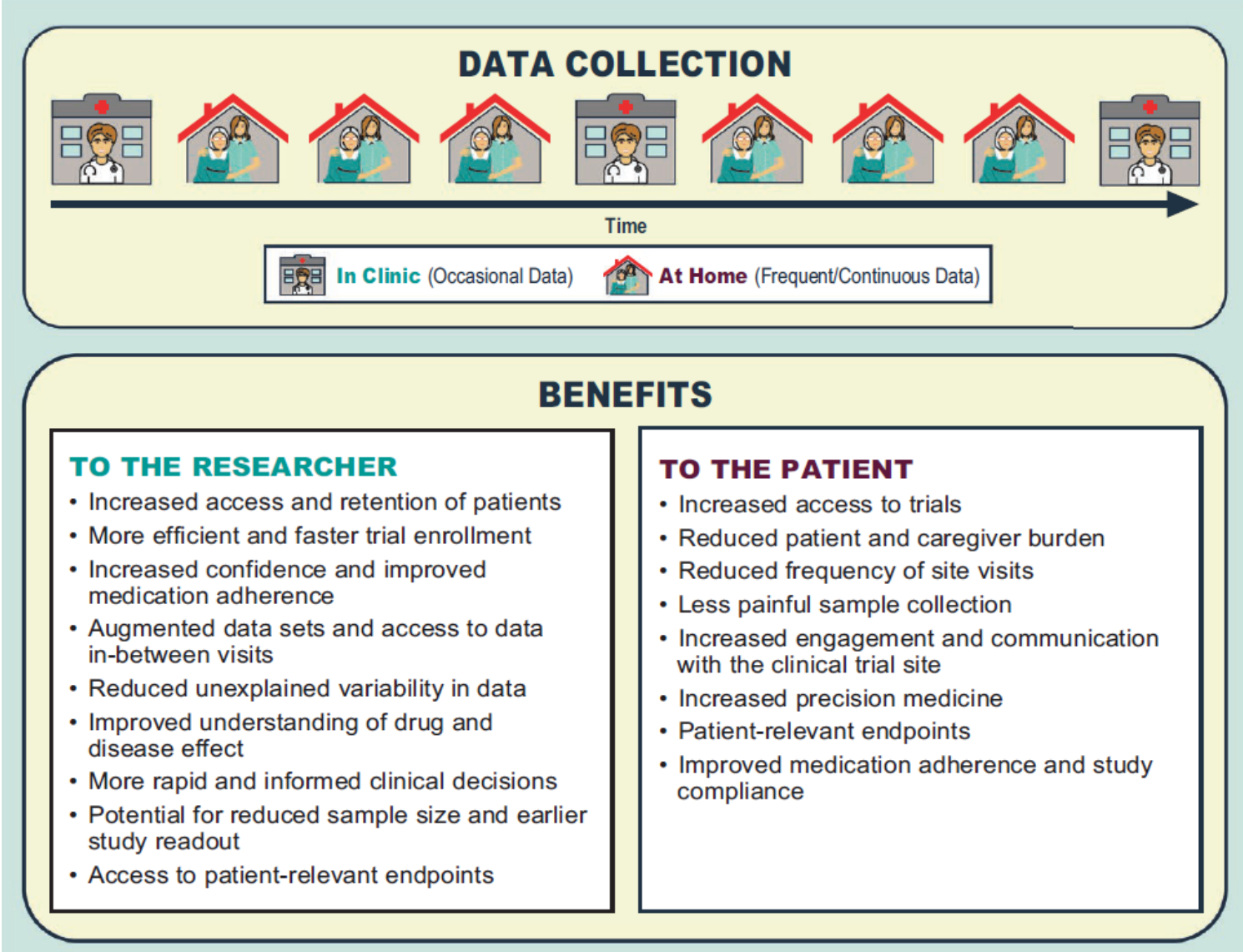
Digitally-Enabled Clinical Trials

Our aim is to deploy innovative, digital technologies in clinical trials to reduce patient burden, collect higher quality data, enrich clinical datasets, and enable rapid and informed clinical decisions.



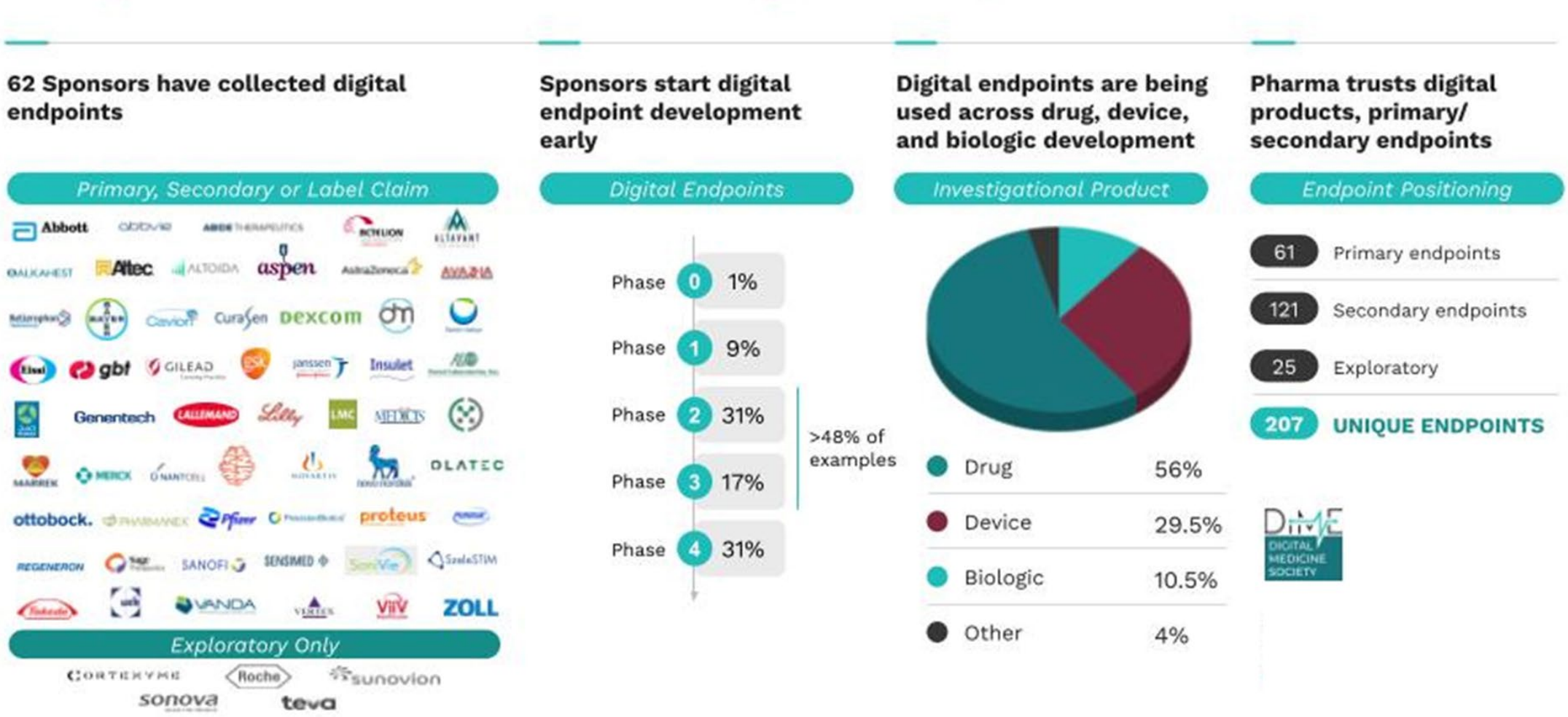
Dockendorf et al., *Clinical and Translational Science* (2020)

Potential Benefits of Digitally-Enabled Clinical Trials



Dockendorf et al., *Clinical and Translational Science* (2020)

Digital Endpoints Are a Reality Across the Industry



Source: https://www.dimesociety.org/index.php/knowledge-center/library-of-digital-endpoints (*last updated June 27, 2021*)

The Shifting Regulatory Environment

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

26 April 2019
EMA/CHMP/SAWP/178058/2019
Committee for Medicinal Products for Human Use (CHMP)

Qualification opinion on stride velocity 95th centile as a secondary endpoint in Duchenne Muscular Dystrophy measured by a valid and suitable wearable device*

Figure 1. Main components (A), the wearable device and system attached to ankle (B) and to the wrist (C)

EMA Regulatory Science to 2025

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

1 June 2020
EMA/219860/2020
Human Medicines Division

Questions and answers: Qualification of digital technology-based methodologies to support approval of medicinal products
Status as of June 2020

FDA U.S Food and Drug Administration

DIGITAL HEALTH INNOVATION ACTION PLAN

Digital Health Center of Excellence

Public

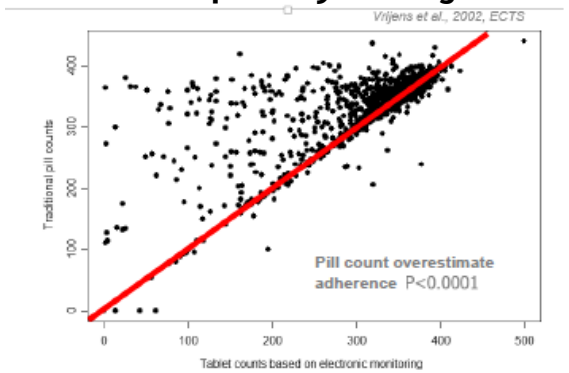
The Challenge of Nonadherence

Nonadherence is Underestimated by Pill Count[1]

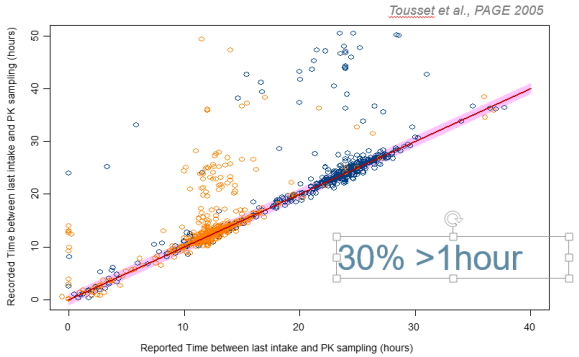
TABLE 1. Medication Nonadherence in AstraZeneca Psychiatry Studies, 2001 to 2011

Indication	No. Subjects Receiving Active Treatment	Name of Drug Under Study	ClinicalTrials.gov Identifier (NCT no)	Subjects With Any PK Sample BLQ (%)	Subjects With > Half of PK Samples BLQ (%)	Subjects With all PK Samples BLQ (%)	Nonadherence Calculated From Pill Counts (%)
MDD	39	AZD2066*	NCT01145755	12.8	12.8	2.6	NC
MDD	91	AZD7268†	NCT01020799	28.6	16.5	12.1	2.9
MDD	100	AZD5077† (quetiapine)	NCT00326144	26.0‖	26.0‖	26.0‖	2.2
GAD	169	AZD7325‡	NCT00807937	33.0	22.5	16.0	2.8
GAD	309	AZD7325‡	NCT00808249	33.7	21.7	13.6	5.1
CIAS	313	AZD3480§	NCT00528905	34.8	20.1	15.0	4.6
MDD	331	AZD5077† (quetiapine)	NCT00320268	23.3‖	23.3‖	23.3‖	0.0
GAD	413	AZD5077† (quetiapine)	NCT00329264	39.2‖	39.2‖	39.2‖	NC

Bias in quantity of drug taken[2]

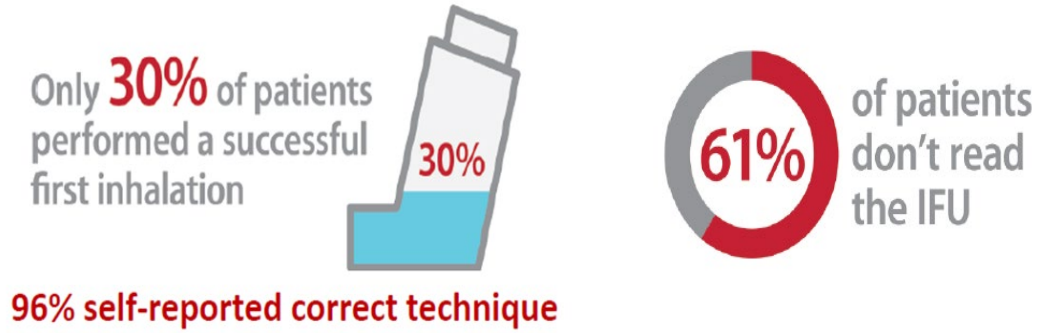


Bias in time of drug taken[3]



Adherence to inhaled therapies

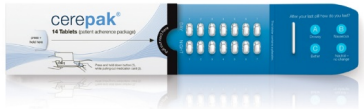
- Adherence to inhaled therapies in the COPD population is low (≤50%) and rates of incorrect inhalation technique can range from 35 to 85%[4-6], impacting clinical outcomes
- Inhaler technique as measured in one COPD study[7] :



[1]McCann, D.J., et. al., J. Clin. Psychopharmacol. 35, 566-573 (2015)., [2]Vrijens et. al. 2002, ECTS; [3]Tousset. et. al. 2005, PAGE,
[4]COPD Research and Practice 2015; 1:9; [5]CHEST 2018; 154(4):984-985; [6]CHEST 2016; 150 (2); 394-406; [7]oN drug Delivery, April 2018, 85:28

“Smart” Adherence Technology Options

Smart Packaging



AARDEX GROUP

AdhereTech

cmt

Ingestible Sensor

proteus DIGITAL HEALTH

etectRx

Smart Delivery Devices

adherium

teva

Propeller

Photographic Documentation

AiCure

- Technology options to provide **more accurate adherence data**
- Potential to **improve adherence** through dosing reminders and real-time transmission of data to HCP or clinical site
- Potential to **improve dosing technique** for non-standard routes of administration, (e.g. inhalers)

We are using smart dosing approaches in select late stage trials
Suite of smart dosing technology options to fit program/trial needs

Disclaimer: These are just a few examples of the technologies and not an endorsement of any product.

Patient-Centric Sample Collection Devices

Dried blood collection with electronic diary

- Fingerstick, spots on DBS card
- Time and date recorded by patient

Neoteryx Mitra VAMS

- Fingerstick with accurate volume collection
- Date and time automatically collected

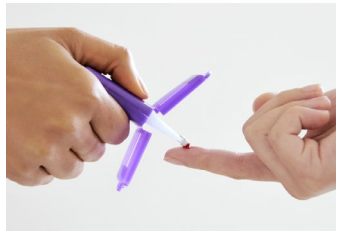
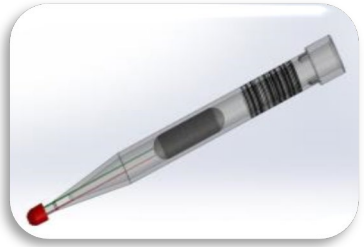
Seventh Sense TAP™ device

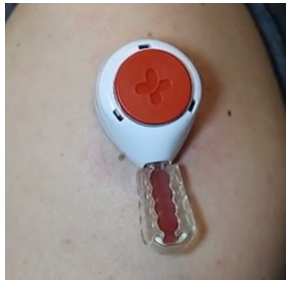
- Minimally invasive, micro-needle based
- Painless, no sharp exposure

Tasso

- External collection
- Painless, no sharp exposure



We have used patient-centric sampling approaches in several clinical trials to date.
Shift toward less painful, more automated sample collection with automated date/time stamps

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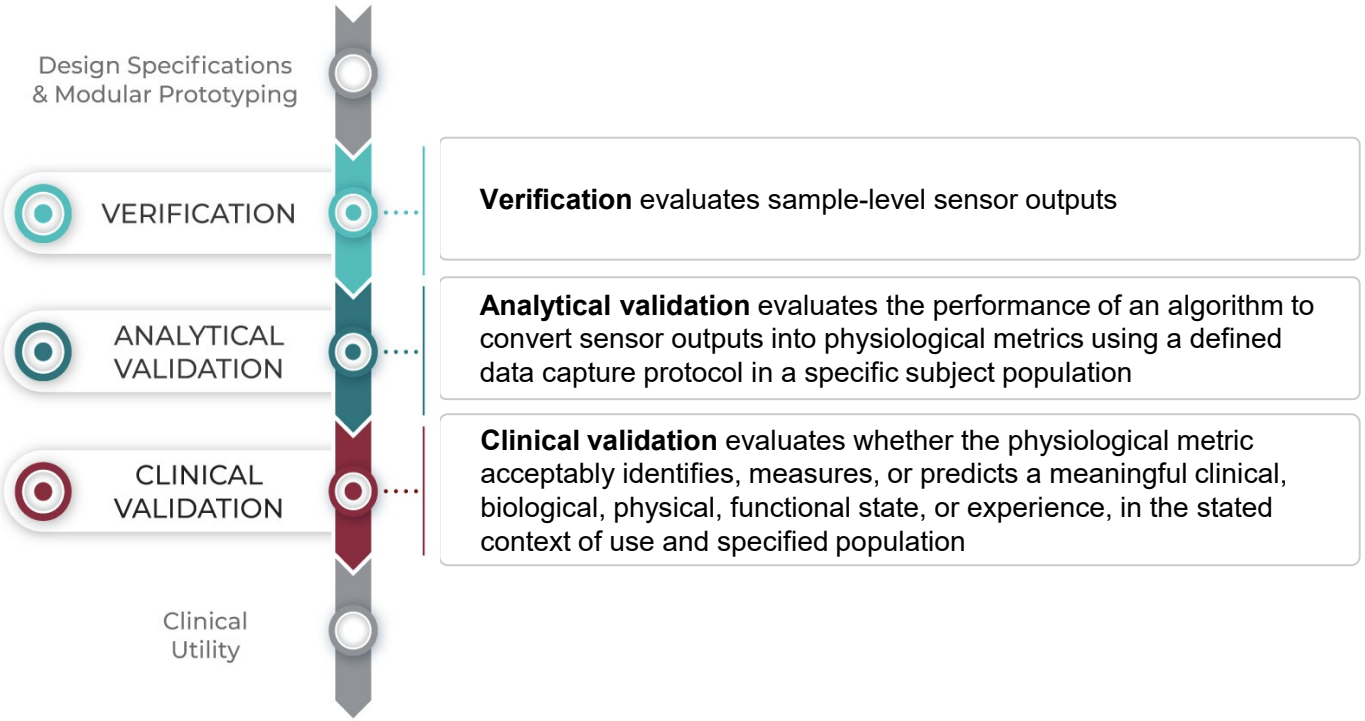
Resources for Use of Digital Clinical Measures

TOUR OF DUTY: Driving adoption

The Playbook: Digital Clinical Measures

Introducing the essential guide for successful remote monitoring across *clinical research*, *clinical care*, and *public health*.

V3 Framework:



Source: playbook.dimesociety.org and https://www.nature.com/articles/s41746-020-0260-4

Precompetitive Collaboration is Critical

Areas of potential pre-competitive collaboration:

- Technology and platform development
- Studies to enable technology maturation
- Development of digital biomarkers for specific disease states
- Development of data standards
- Sharing experience (successes and failures)
- Shaping policy

TransCelerate BIOPHARMA INC.
ACCELERATING THE DEVELOPMENT OF NEW MEDICINES

DiME
Digital Medicine Society

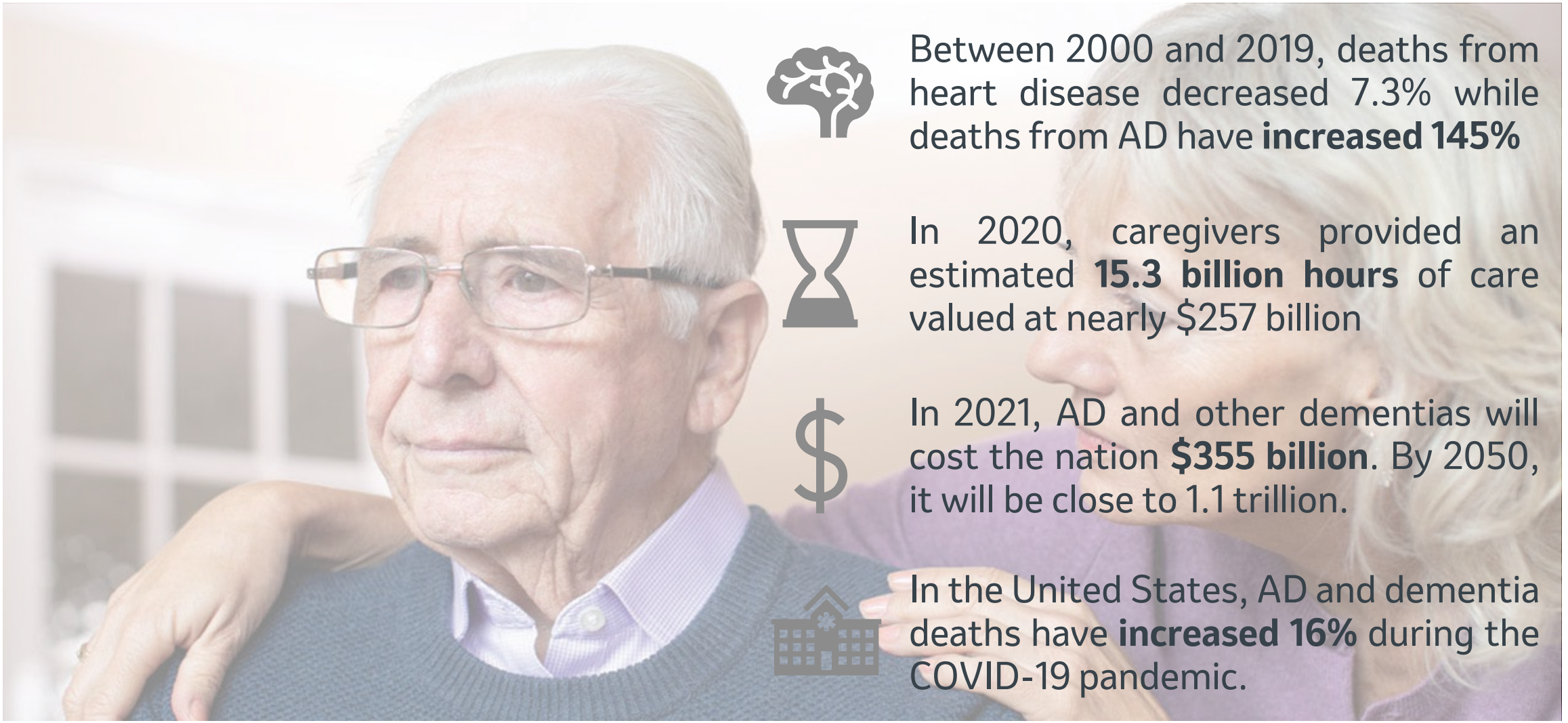
CPP PARKINSON'S CONSORTIUM
Critical Path for Parkinson's 3DT

imi innovative medicines initiative

IQ INTERNATIONAL CONSORTIUM for INNOVATION & QUALITY in PHARMACEUTICAL DEVELOPMENT
Patient-centric sampling IQ group

CLINICAL TRIALS TRANSFORMATION INITIATIVE

Alzheimer's Diseases: Unmet Medical Need and Societal Burden



Between 2000 and 2019, deaths from heart disease decreased 7.3% while deaths from AD have **increased 145%**

In 2020, caregivers provided an estimated **15.3 billion hours** of care valued at nearly $257 billion

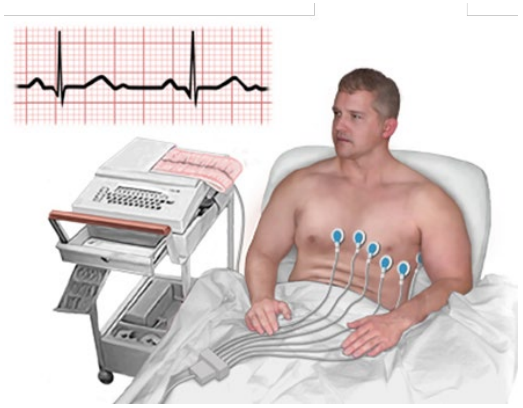
In 2021, AD and other dementias will cost the nation **$355 billion**. By 2050, it will be close to 1.1 trillion.

In the United States, AD and dementia deaths have **increased 16%** during the COVID-19 pandemic.

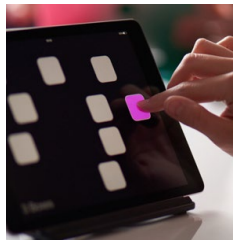
Source: https://www.alz.org/alzheimers-dementia/facts-figures

Digital Biomarkers: A new frontier for Alzheimer's Disease

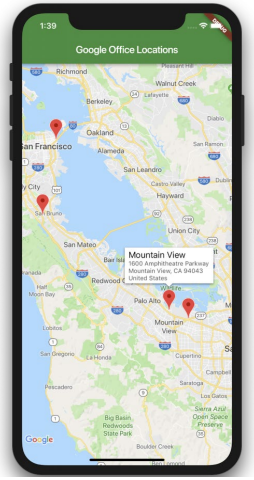
Clinical Endpoint



Active



Passive



Public

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Novel Data to Differentiate Healthy Control & Cognitive Impairment

MedCity News — Leading source for innovation in healthcare

MEDICAL DEVICES, HEALTH TECH

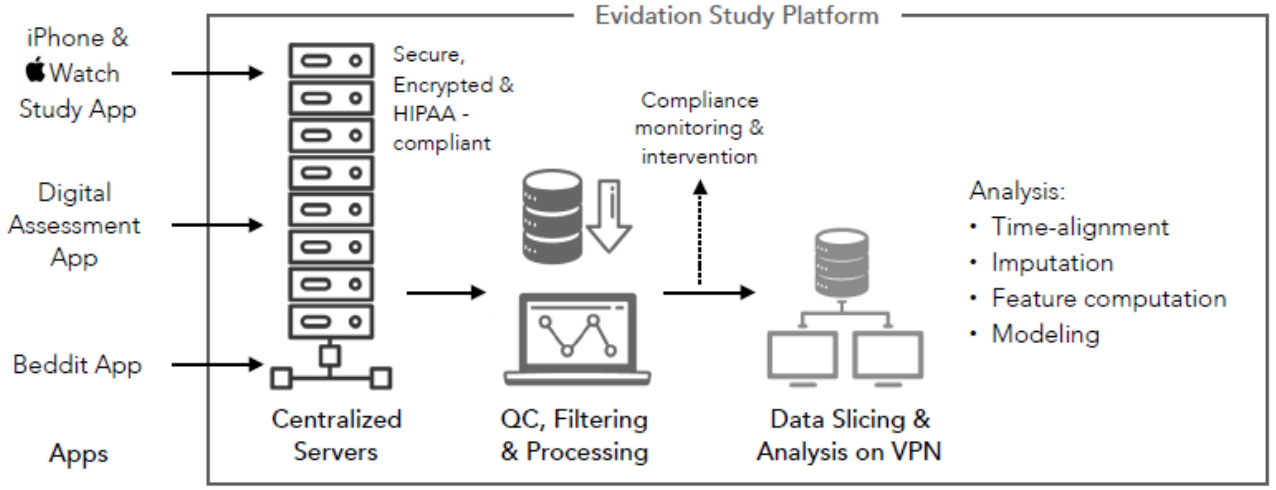
Evidation Health and Eli Lilly study uses Apple devices and apps to predict cognitive impairment

Study Details:

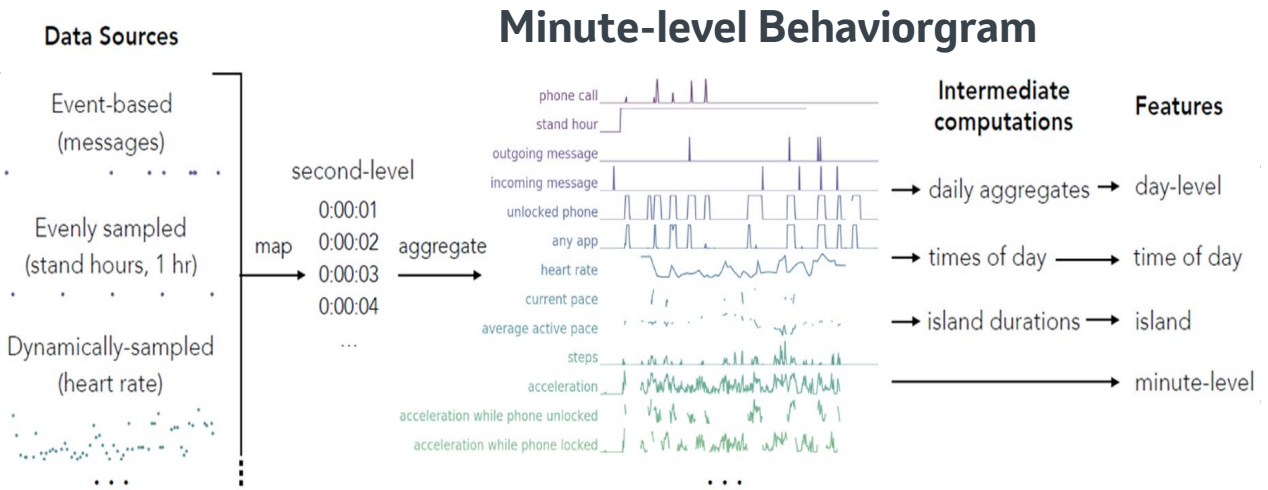
- 28 patients with MCI and 7 mild AD
- 82 healthy age-matched controls
- 12-week exploratory study

Features identifying cognitively impaired participants vs. healthy controls:

- Slower typing speeds
- Fewer text messages
- Later first steps
- Reliance on helper apps
- Poor survey compliance



Jankovic et al., *KDD '19* (2019)



Source: Jankovic et al., KDD '19 (2019)

Measuring Impairment with Novel Digital Signals (MINDS) Study

Study Details:

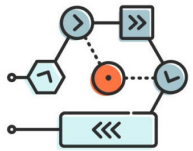
- 150 patients with MCI or early AD
- 150 healthy age-matched controls
- Duration: 6 months
- Population: US-only and remote

Primary Objectives:

- Differentiate MCI, early AD, and controls

- Classification Models

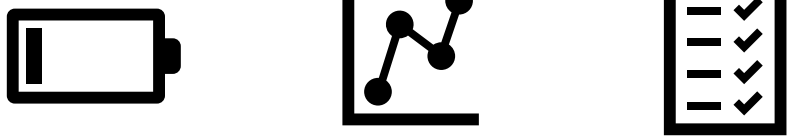
DEEP LEARNING



ALGORITHM

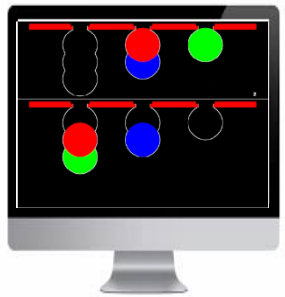
Secondary Objectives:

- Feasibility, variability and adherence

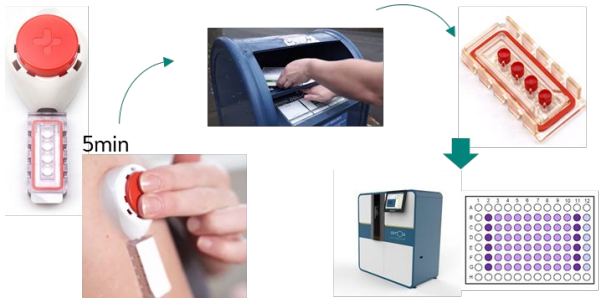


Wearables and Phones:

Cognition:



Blood-based Biomarkers:



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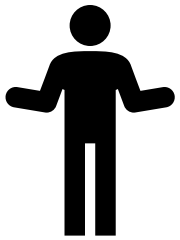
From Biology to Decisions

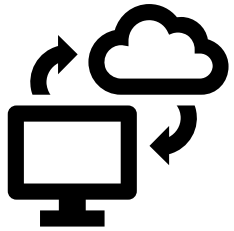
Biology	Device and data acquisition	Data storage	Data analysis

Clinical outcome assessments

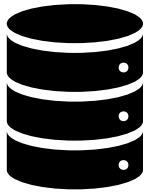


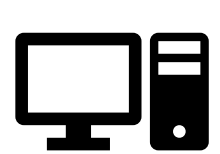
Raw sensor data

Transmit data



Centralized servers





AI/ML

Quality control

Visualization

Public

Source: Izmailova et al., Clinical and Translational Science (2020)

Summary and Future Directions

Digitally-Enabled Clinical Trials

MINDS Study

Synergistic Benefit

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Thank you!