Real-World Digital Biomarkers from a Symptomatic Community Population with Cognitive Impairment

CAMD Digital Biomarker Conference: Use of Biosensors in Clinical Trials: Barriers & Solutions to the Current Landscape

31st March – 1st April 2016

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AGENDA

- Background to IXICO
- IXICO’s Cygnus Study - Symptomatic Community Population with Cognitive Impairment
  - Aims
  - The Cygnus Dataset
  - Feedback from focus group on wearable devices
  - Key Issues and Solutions
IXICO - Broadening Technology and Data Capability

Clinical Trial Imaging Biomarkers

Safety
- ARIA-E
- ARIA-H
- PML

Efficacy
- Structural MRI
- PET - FDG, Amyloid, Tau and other tracers
- Advanced MRI measures – ASL, DTI and fMRI

Enrichment / Stratification

HCV as an enrichment of clinical trial populations
- EMA qualification – complete
- FDA – in progress

Disease progression models
- Biomarkers in combination with other clinical and demographic data.
IXICO - Broadening Technology and Data Capability

Clinical Decision Support Tools

Assessa®
- Decision support for dementia diagnosis
- CE marked medical device (Class 2a)
- Focus on neurodegeneration

Patient Support Tools

mehealth®
- Integrated patient portals and smartphone applications
- Data collection for physician, patient, carers etc.
- Data analytics on data from > 12000 patients

Assessa®
- Decision support for dementia diagnosis
- CE marked medical device (Class 2a)
- Focus on neurodegeneration

MyBrainBook®
- Personalized support for people with cognitive impairment
- Web app providing care plans, personal profiles, daily tasks & reminders....
- Evaluated in 3 NHS Innovation TestBeds
- Co-developed with patient/carers

Confidential, IXICO plc 2016
Aims of the Cygnus Study

- **Collecting real world data at memory services and from patients and carers**
  - standardized longitudinal real world data including outcomes from a large sample of symptomatic patients presenting with memory concerns and their carers, post-diagnosis collection of longitudinal data over 1 year
  - Validate methods and technology for capturing, integration and analysing data and make it actionable for stakeholders (researchers, Pharma, providers and commissioners)
  - Enable prospective evaluation of cost of care in the NHS and evaluate the cost effectiveness of digital interventions

- We hope that the data collected in Cygnus can be used to support the qualification of digital biomarkers with regulators.
A validated, standardized dataset will be collected over a one year follow up period and includes:

- demographic
- health and clinical history
- clinical assessments (as performed by the MAS)
- the ICHOM dementia standard dataset
- post-diagnostic interventions
- medical events information

Two sub-studies to evaluate data collect from mobile and wearable devices

- **Sub-study A**: collection of patient and carer report outcomes from mhealth applications at home on a weekly basis.
- **Sub-study B**: collection of activity and sleep data using a wearable device over a 12 week period.
Sub study A: Patient & Carer Reported Outcomes

- For patients and study partners
- A reminder will be sent weekly (by SMS or email) to enter the following self-reported outcomes for the duration of the study.

Sub study B: Wearable Devices

- For patients and study partners
- Physical activity and sleep data will be collected continuously from the device for a 12 week period during the 12 month study.
- A tolerability and acceptability questionnaire will be carried out upon completion of the sub-study at week 12.

Wearables & PRO Sub-studies

- Physical Activity
- Sleep
- Frequency of Social Contact
- Depression and Anxiety
- Subjective Memory
- Subjective Sense of Burden

- Number of steps
- Distance
- Time spent awake
- Duration of light sleep cycle
- Duration of deep sleep cycle
- Raw accelerometer data
Cohort Population, Size and Recruiting Centres

People with cognitive impairment or possible dementia, referred to a MAS by their GP/PCP

GP → MAS → Study Participant

Partner, family member or close friend of the study participant

Study Partner

Sites:
4 NHS Mental Health Trusts across the North of England

- Manchester Mental Health and Social Care Trust
- Mersey Care NHS Trust
- Tees, Esk and Wear Valleys NHS Foundation Trust
- Northumberland, Tyne & Wear NHS Foundation Trust

500 participants ~50:50
Cygnus Study Data Sets & Timelines

- **Sub-study A – Patient and Career Reported Outcomes**
  - weekly data collection
- **Sub-study B – Wearables**
  - single 12 week period
- **Core Data Set**
  - 3 monthly data collection

- **Recruitment**: n ~50:50
  - Patient / Study Partner
- **Follow-up**: 3 monthly data collection
- **FPFV**

- **Data Collection Timelines**:
  - Baseline, 3 month, 6 month, 9 month, 12 month

- **Yearly Breakdown**:
  - 2016: Q1, Q2, Q3, Q4
  - 2017: Q1, Q2, Q3, Q4
# In-house Evaluation of Wearable Devices

<table>
<thead>
<tr>
<th></th>
<th>Price</th>
<th>Comfort</th>
<th>Step Count</th>
<th>Clock</th>
<th>Raw data</th>
<th>Ease of use</th>
<th>Data access</th>
<th>Battery life</th>
<th>Aesthetics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fitbit Charge</td>
<td>80</td>
<td>Good</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>OK</td>
<td>Web</td>
<td>5 days</td>
<td>OK</td>
</tr>
<tr>
<td>Garmin Vivofit</td>
<td>60</td>
<td>Good</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>OK</td>
<td>Web</td>
<td>1 year</td>
<td>OK</td>
</tr>
<tr>
<td>Axivity</td>
<td>150</td>
<td>Poor</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Good</td>
<td>Raw</td>
<td>30 days</td>
<td>Poor</td>
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<tr>
<td>wGT3X-BT Monitor</td>
<td>300+</td>
<td>?</td>
<td>with process</td>
<td>No</td>
<td>Yes</td>
<td>?</td>
<td>Raw</td>
<td>25 days</td>
<td>Poor</td>
</tr>
<tr>
<td>Withings Activite Pop</td>
<td>100</td>
<td>Good</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>OK</td>
<td>API</td>
<td>8 months</td>
<td>Good</td>
</tr>
</tbody>
</table>
Withings Activité Pop

- Withings is a France and Boston based consumer electronics company
- Manufacture a number of digital health devices including for tracking activity, weight, blood oxygen and pressure....
- Activité Pop is an activity track watch that automatically tracks steps, runs, swims and calories
- Water resistant
- Sleep analysis
- No charging - *8 month cell battery*

IXICO’s mehealth® Platform

- Secure, online, decision support software for clinicians.
- Integrated patient portals and configurable smartphone applications for patient engagement and data collection between visits.
- Used by over 12,000 patients
We organised a workshop with the West London Mental Health NHS Trust in order to introduce the sub-study to a panel of patient and carers.

- 4 male, 8 females of which 5 were carers (spouses, friends, and children).

**Aim**

- introduce the study to representatives of the target population (MCI and early dementia).
- obtain their feedback on the study design, study documentation (Patient Information Sheet), wearable devices in general and on the Withings Activité Pop).

**Format of the workshop**

- semi-structured and open discussion (2 x 45mins)
- presentation and discussion of device and purpose of study
- review and discussion of documentation
Wearables Focus Group – Key Findings

Participant were

- positive, keen to participate in a study with such devices, and found it interesting, innovative, and also something they hadn't seen before
- positive about the specific device as it looks like an ordinary watch, and would be happy to wear one in the frame of a clinical study or clinical care
- keen to see the data themselves (e.g.: about their exercise) and for supporting self-care,
- not concerned about data security or data privacy issues (even though they were specifically asked).
What is the acceptability and tolerability of these devices to patients

- privacy of home-based monitoring
- infrastructure availability
- transport of data (i.e. pc, phone, Bluetooth etc.)
- storage of data
Solution - Acceptability and Tolerability

- **Focus groups aimed at acceptability and tolerability**
  - involve patients, carers and patient advocacy groups
    - continue to use them in a consistent way (i.e. they don't stop wearing/using them, they are able to keep them charged and syncing with the infrastructure)
    - how to engage with subjects during a clinical study to address any issues of non-use or poor data, especially in populations that have cognitive impairment.
  - results provided as evidence to ethics committees of acceptability of protocol

- **Co-development with patients and carers to gain additional insights**

- **Cygnus focus group - few points**
  - Majority of participants had Wi-Fi at home
  - Liked the watch as a device, liked having choice of color
  - Data sharing description was well received
Solution - Acceptability and Tolerability

- Review of past studies
  - PLM, in conjunction with the Institute of Medicine, conducted a survey of 2,125 PLM members and found that 94% of responders are willing to share their health information on social media if it helps doctors improve care
    

- Obtaining this sort of tolerability and data quality information is one of our key objectives in our Cygnus study.
What is regulatory path for use as drug development tools: authentication, data quality assurance, outlier detection, validation; how does this depend on context of use?
Solution – Regulatory Path

There is existing regulatory framework for digital data collection in clinical trials
  • i.e. Computerized cognitive testing in a clinic, ePRO
  • GCP and FDA 21 CFR Part 11

Clinical / real-world use for Personal Health Data
  • Global demand for interoperability in eHealth, telemedicine, and telehealth solutions
  • ISO/IEEE 11703 – Personal Health Data (PHD) Standards
    - Group of standards addressing interoperability of PHDs
    - Simpler communication model
  • HIPAA, EU Data Protection Directive (GDPR), PIPEDA
Solution – Regulatory Path: Authentication

- **Authentication:** Work in progress!

- **Challenge:** wearable sensors don’t typically have a way to login!
  
  - Customized solution working with device
  - Work with device manufacturers
  - Co-develop with patient groups

- We are currently working on solutions to solve authentication challenges.
Solution – Regulatory Path: Data Quality

- Effective monitoring is critical for the protection of subjects and the integrity and quality of the data produced.

- **Start with quality:**
  - Develop a quality management plan focusing on highest risk for generating errors
  - Monitoring approach
  - Improved training and procedures

- Once these issues are better understood and solutions implemented to control for these issues, further data can be collected to discover and validate a digital biomarker.
Summary

- Pre-competitive model is appropriate - need to engage with regulators and readiness for use in clinical trials and clinical practice.

- Lessons learned from qualification of imaging biomarkers
  - Difficult to secure access to retrospective data
  - Issues with the data (not collected for the purpose)

- In the Cygnus study we are:
  - using a consumer grade wearable device in a prospective clinical study
  - collecting data to GCP standards
  - aiming to addressing issues of acceptability to subjects, compliance

- Strategically important and keen to collaborate
  - rights to use Cygnus dataset with regulators
  - Cygnus dataset could help inform how the data standards should be defined
Further information

Integrating the Healthcare Enterprise
IHE Web: [www.ihe.net](http://www.ihe.net)  PCD Web: [www.ihe.net/pcd](http://www.ihe.net/pcd) and [www.accenet.org/ihe](http://www.accenet.org/ihe)

Continua Health Alliance
Web: [http://www.continuaalliance.org](http://www.continuaalliance.org)

National Institute of Standards and Technology
Web: [http://www.nist.gov](http://www.nist.gov)
Medical Devices: [http://www.nist.gov/medicaldevices](http://www.nist.gov/medicaldevices)