BMDs for Sleep

Sleep from actigraphy in normal elderly and neurodegenerative disease

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IXICO
Core Disease Symptoms
- Symptom severity
- Overall disease control
- Activities daily living
- Cognitive function
- Pain

Mood Disturbances
- Depression, anxiety, agitation

Circadian Rhythm Disturbances
- Day-time drowsiness, night-time activity

Sleep
- Total sleep time
- Sleep efficiency
- Wakes after sleep onset
- Sleep onset latency
- Sleep time during day

Activity
- Total activity
- Intensity of activity
- Timing of activity
- Steps
- Gait metrics
- Bradykinesia
Introduction to IXICO

Digital healthcare company focused on brain health, neurodegeneration and progressive diseases

- Founded in 2004, went public in October 2013 (AIM-listed)
- Around 60 employees in UK, US, France, Germany
- Acquisition of Optimal Medicine in 2015 provides new capabilities in mobile device technologies

Primary focus is on the needs of the pharmaceutical industry to support

- Development of drugs in clinical trials
- Use of drugs in the clinic to improve patient safety and outcomes

Capabilities include:

- 12 year track record in imaging-derived biomarkers for enrichment, safety and efficacy with 10 of the top 15 pharma companies, many other smaller pharma and biotechs.
- Digital health technologies and services as digital companions to drugs such as Assessa PML for MS with Biogen
- Wearable biosensors throughout clinical trials and alongside marketed drugs
IXICO’s imaging solution

**TrialTracker™ Platform**

**Quantitative analysis**

**Regulatory compliant data handling**

**Radiology reads**

**to Pharma / CRO**

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**Operational Delivery**

**Imaging Site**
- Set up scanner for study
- Upload data to IXICO
- Respond to queries

**IXICO: site management**
- Train, qualify and manage imaging sites
- Image data management
- Data transfers to sponsor

**IXICO - reads**
- Radiology reads
- Quantitative analysis
- Read results “real time” for eligibility and safety

**CRO**
- Support site qualification
- Escalation of non-responsive sites
- Receive study results
Biosensors – Builds on Existing Imaging Technology

TrialTracker™ Platform

IXICO actigraphy algorithms

Regulatory compliant data handling

Data Driven AI (continuous improvement)

to Pharma / CRO

3rd Party Device
Axivity AX3

Withings

Other 3rd party actigraphy devices
Biosensors – Builds on Existing Imaging Technology

TrialTracker™ Platform

IXICO actigraphy algorithms

Regulatory compliant data handling

Data Driven AI (continuous improvement)

to Pharma / CRO

Operational Delivery

Clinical Site
- Distribute devices to subjects
- Train subjects
- Support subjects

CRO (or IXICO)
- Train and monitor sites
- Upload data (or train site to upload data)
- Device distribution to sites

IXICO
- Train CRO
- Provide subject training material
- Process raw device data to generate endpoints

Sponsor
- Write protocol
- Receive study results
Extracting Clinical Value From Actigraphy Metrics

Activity
- day time activity
- evening activity
- nocturnal activity
- quantity and quality
- tremor
- bradykinesia
- PD on/off
- falls
- etc.

Sleep
- sleep latency
- sleep efficiency
- number of awake times
- awake time duration
- circadian rhythm
- sleep stages
- etc.

Individual signature

Evolution
Assessment 1
Assessment 2

Daily profile

Disease signature

Risk
Diagnosis
Prognosis
Treatment response

e.g. Alzheimer’s, Parkinson’s, ADHD, mood disorders, psychosis…
Collecting data for training algorithms to measure sleep – CONTEXT study

**CONTEXT**

Actigraphy vs Polysomnography (PSG) and Sleep Diaries

- **Clinical data**
  - Clinical and sleep assessments: e.g.
    - REM Behaviour Sleep Disorder Screen
    - Restless legs syndrome questionnaire
    - Pittsburgh Sleep Quality Index
    - Epworth Sleepiness Scale (daytime sleepiness)

- **Sleep Laboratory**
  - PSG & actigraphy
  - 1 night

- **Home**
  - Sleep diaries & actigraphy
  - 14 nights

- **30 subjects** (patients & controls)
- **Device data, PSG & sleep diary outcomes compared**
- **End points & algorithms defined for control & disease groups**
Multisite deployment of sleep BMDs – CYGNUS Study

Feasibility of collecting high quality and actionable wearable data in real world settings

Clinical assessment

0, 3, 6, 9, 12 m

Plus service utilisation

Home assessment

Weekly for 3m

Self-reported outcomes, quality of life, mood, finances, burden

2 weeks

2 weeks of raw data collection + weekly mood ratings (HAD scale)

or

3 months

or

3 months of “minute data”

Actigraphy

Axivity

or

Withings

35 subjects - (memory clinic patients & their study partners)

Target subject n=200

Define best methods of data collection, and correlations between different methods (subjective, objective, passive, remote, clinical)
**CONTEXT**

**Study Data**

- **Day 1 Overnight sleep lab**
  - Simultaneous PSG & actigraphy

- **Day 2-14 home recording**
  - Sleep diary & actigraphy

**Sleep diary**

**PSG**

**Actigraphy**
Actigraphy sleep algorithms

Cole-Kripke algorithm\(^1\), as used by Actigraph

- Measure “counts per minute (cpm)” by counting the times the signal crosses zero

- Label sleep / wake minute by weighted sum of cpm 4 minutes back and 3 minutes ahead:

\[ D = P \times (A_{-4}W_{-4} + A_{-3}W_{-3} + A_{-2}W_{-2} + \]
\[ A_{-1}W_{-1} + A_0W_0 + A_{+1}W_{+1} + A_{+2}W_{+2}) \]

- Minute-segments with \( D \) above a certain threshold are labelled awake, others asleep

ESS algorithm\(^2\), as used by Axivity

- Estimation of Stationary Sleep-segments

- Measure variability (standard-deviation) for each 1-sec interval

- Second-segments with variability above a threshold are labelled awake, others asleep

- In a further step, sleep segments <10min are labelled awake
Comparison of Sleep Efficiency Metrics

- 22 healthy elderly subjects and 4 elderly Parkinson’s patients (encircled)

**Cole-Kripke algorithm**, as used by Actigraph

**ESS algorithm**, as used by Axivity

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1 Cole et al, 1992, Sleep 2 Borazio et al 2014, IEEE Int Cnf on Health Inf
Deep learning to improve sleep measurement from actigraphy

Derived metrics:
- Sleep /awake status
- Sleep efficiency
- Total time asleep
- Total time awake
- Sleep onset latency
- Times awake

Binary (.cwa)

Download data → Extract raw data → Normalize data → Extract features → Derive metrics → Predict sleep
Sleep/Awake Status

- 84 year old female control
- 1 night in sleep lab
- PSG + actigraphy

CONTEXT

1 = Asleep
0 = Awake

1 Borazio et al 2014, IEEE Int Cnf on Health Inf
Sleep Efficiency

- 66% - PSG
- 90% - ESS algorithm
- 69% - IXICO’s DLS algorithm

Actigraphy

ESS interpretation of actigraphy

IXICO DLS interpretation of actigraphy

1 Borazio et al 2014, IEEE Int Conf on Health Inf
Measuring sleep: Benefits of deep learning method

Same data processed with competing algorithms and IXICO deep learning algorithm

Used by Actigraph

Used by Axivity

IXICO Deep Learning Sleep

Accepted for presentation at MDS 2017 (Vancouver) and invited to present at Alz Assoc Research Round Table, June 2017
Precision of sleep measures

- recall (sensitivity) and precision (positive predictive value) for classifying sleep/awake state and sleep efficiency with Cole-Kripke, ESS and DLS.

Cole-Kripke

ESS

Deep learning sleep
Subjects (n=17) wear 2 biosensors (on same wrist) while undergoing PSG
Apply algorithm trained with deep learning on other subjects to both sets of sensor data
Measure difference in sleep efficiency

<table>
<thead>
<tr>
<th>Algorithm</th>
<th>Sleep efficiency variability</th>
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<tbody>
<tr>
<td>Cole-Kripke</td>
<td>3.1%</td>
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<tr>
<td>ESS</td>
<td>6.6%</td>
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<tr>
<td>DLS</td>
<td>5.2%</td>
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</table>
Operational challenges

- **Device acceptability:** ensure the subjects use the devices
  - Wear any wearable
  - Sync with any data portal
  - Recharge if necessary

- **Data quality:** collect usable data for the study

- **Site training:** ensure subjects are provided with devices with any instructions/training

- **Distribution of devices:** get devices to the subject and link to the subject IDs

- **Information security:** address privacy and integrity of data

- **Data handling:** get data from devices into any clinical trial systems with no loss or risk of mis-labelling

- **Adverse event:** handling adverse events from devices (most commonly from straps)
Regulatory approach

- “being regulatory inspection ready”
- Validation of computer system as “fit for purpose”
- Analytical validity – depending on context of use
- Clinical validity – depending on context of use
Regulatory approach: learn from imaging

- One image analysis platform supports data from multiple scanners (Philips, Siemens, GE)
- One set of acquired images can generate multiple endpoints (e.g. hippo volume, whole brain volume)
- Acquisition device and analysis device can be separate medical devices
- Biomarker can be output of analysis device, using standardized data from acquisition devices
Regulatory approach: learn from imaging

- One BMD analysis platform supports data from multiple BMDs
- One set of acquired images can generate multiple endpoints (e.g., sleep efficiency, gait speed)
- Acquisition device and analysis device can be separate medical devices
- Biomarker can be output of analysis device, using standardized data from acquisition devices
Current solution: Keep simple

- Raw data device “wear for two weeks and post back”
- All analysis in closed computer system (no blue tooth, smart phones, clouds etc)

Future

- Continuous raw data for 3 months
- Auto synchronization where possible (but not mandatory) of summary data
- Additional sensors.....
Conclusions

- There are numerous applications of passive measurement of sleep on elderly patients and those with neurodegenerative diseases
- Operational and regulatory challenges can be significant in this population
- We have a solution that is in-use in multi-centre studies in these populations
- Performance “tuned” using deep learning methods to provide good correlation with PSG for sleep efficiency
- Test:re-test is ~5%
### TECHNOLOGY ATTRIBUTES AND GAPS

**Concept-of-Interest measured:**

<table>
<thead>
<tr>
<th>CONSIDERATION</th>
<th>ATTRIBUTE</th>
<th>GAP</th>
<th>COMMENTS</th>
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</thead>
<tbody>
<tr>
<td>510K compliant</td>
<td>no</td>
<td>CDRH pre-sub meeting + funding</td>
<td>We have capability to CE mark (expected 2018). Question about predicate device for CDRH</td>
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<tr>
<td>FDA cleared for specific use case</td>
<td>no</td>
<td>As above</td>
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<tr>
<td>Time stamp of data acquisition</td>
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<tr>
<td>Biometric validation of user</td>
<td>no</td>
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<td>Currently device attached to subject by investigator and we have QA to detect removal</td>
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<tr>
<td>Analytical validation</td>
<td>Yes</td>
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<td>Test: re-test</td>
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<td>Clinical validation</td>
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<td>Against PSG</td>
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<td>Secure data transfer</td>
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<td>GCP compliant for audit trail</td>
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