Remote Assessment of Disease and Relapse in Major Depressive Disorder (RADAR – MDD)

Remote Digital Monitoring Workshop
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Overview

- Evidentiary Criteria Framework
- Statement of Need
- Context of Use
- Digital Study Design
- Benefit and Risk Assessments
- State of Evidence
- Technology Verification & Validation
- Translation of Evidence: Analytical & Clinical Validation
- Relationship to Existing Evidentiary Criteria Framework
- Panel and Audience Question and Answer
Evidentiary Criteria Framework – MDD case study

- Clinician assessments are based on intermittent, subjective patient self-reported symptoms affected by recall bias.
- Remote monitoring technologies (RMT) enable objective and continuous assessments in real-world settings, between clinic visits (more ecologically valid and less prone to placebo effects)
- Intensive data collection with low patient burden (reduced frequency of clinic visits)
- Potential for use in Phase 1/2/3 clinical trials: for stratification by digital phenotyping, for monitoring symptoms, as clinical endpoints.

Benefits of continuous monitoring using wearable devices
- **Stratification**: Enables drug development for under-served sub-population
- **Stratification**: Companion diagnostic approval concurrent with drug approval
- **Efficacy endpoint**: No efficacy measure qualified with FDA that reflects patient needs and deficits specific to the sub-population
- **Efficacy endpoint**: More robust to placebo effect, patient expectation
- **Efficacy endpoint**: Novel digital clinical efficacy endpoint for clinical trials in sub-population

- **Risks**
  - **Stratification**: Right patients not identified for therapy, limiting benefits
  - **Efficacy endpoint**: Failed clinical trials (false negative)

- **Risk mitigation**
  - Establishing analytical and clinical validity

**Need Statement**

**COU**

**Benefit**

**Risk**

**Evidentiary Criteria**

**Insomnia with Hyperarousal**
- Objective sleep assessment
  - Actigraphy + PPG HR
  - Actigraphy + HR/HRV
  - GSR, HR/HRV
- Fitbit Charge 2,3
- REST API
- Algorithm
- Stratifier

**Patient stratification** selection marker and monitoring in Phase 2/3 clinical trials
- **Efficacy endpoint** to demonstrate clinical benefit

**Underlying constructs can be measured and show promise**
- Typical depression (reduced sleep, appetite, weight loss) vs. atypical depression (increased sleep, appetite, weight loss)
- Depression + anxiety/agitation
- Depression + insomnia

- Device measurement characteristics, reportable range
- Reference range needs to be established
- Confirmation with independent datasets is needed
- Novel data analytics and statistical approaches are needed
Acknowledgement & Disclaimer

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Statement of need for MDD

MDD is a Heterogeneous Clinical Phenotype

DSM-5 Entry

A. Five or more of the following symptoms have been present during the same 2-week period (and at least 1 of the symptoms must be diminished interest/pleasure or depressed mood).
1. Depressed mood: For children and adolescents, this can also be an irritable mood
2. Diminished interest or loss of pleasure in almost all activities (anhedonia)
3. Significant weight change or appetite disturbance: For children, this can be failure to achieve expected weight gain
4. Sleep disturbance (insomnia or hypersomnia)
5. Psychomotor agitation or retardation
6. Fatigue or loss of energy
7. Feelings of worthlessness
8. Diminished ability to think or concentrate; indecisiveness
9. Recurrent thoughts of death, recurrent suicidal ideation without a specific plan, or a suicide attempt or specific plan for committing suicide

• Diagnosis is syndromal, with no valid diagnostic biomarker
• Includes increased sleep or decreased sleep; increased appetite or decreased appetite; agitation or retardation etc.
• Theoretically 10,377 different symptom combinations to give same diagnosis of MDD.
• Conventional antidepressant trials “lump” all types together.
• Symptoms measured by self report at infrequent intervals colored by recall bias

Two individuals could meet the DSM-5 criteria for MDD and have few, if any, symptoms in common
Statement of need for MDD

• Why are digital technologies needed for drug development in MDD?
  o Current outcome assessments are self-reported and therefore influenced by perception, symptom recall, and current symptom severity

• Technologies now able to measure symptoms of MDD
  o MDD symptoms include disrupted sleep, reduced sociability, reduced physical activity, changes in mood, prosody (speech pattern), and cognitive function
  o All of these domains of function/symptoms are amenable to quantitative measurement via remote measurement technology (RMTs)

• What is the added value of RMTs over current modalities?
  o RMT enables objective, passive and continuous assessments between clinic visits that are more ecologically valid and less prone to placebo effects
  o RMT allows more intensive data collection whilst lowering patient burden (e.g. reduced frequency of clinic visits)
Potential stratification by digital phenotyping

- **Pre-existing Candidate Stratifiers**
  - Promising measurements of MDD symptoms
    - Typical depression (reduced sleep, appetite, weight loss) versus atypical depression (increased appetite, weight and sleep)
    - Depression + anxiety/agitation
    - Depression + insomnia

- **Identification of New Stratifiers**
  - Data driven approaches to segment the population based on yet to be determined patterns e.g. of speech, activity, sociability, affective reactivity etc.

In absence of reliable biomarkers, a digital phenotype may help understand heterogeneity of depression by measuring underlying depression constructs.
Improving Endpoints for Clinical Trials

For Phase 2 and 3 studies, FDA recognizes two measures of depression in adults:
- Hamilton Rating Scale for Depression (1960)
- Montgomery-Åsberg Depression Rating Scale (1978)

“Gold standard” measures were developed with virtually no primary validation.

A clinician scores the severity of multiple symptoms based on an unstructured clinical interview (limited by brief observation of symptoms, i.e., temporal resolution).

Reporting of symptoms may be affected by current state (e.g., report of sleep over last week affected by how one slept last night).

Scoring of symptoms is affected by clinician’s own interpretations and biases (including guessing allocation group).

There is no “magic” to these measures – their regulatory acceptance reflects convention and does not represent a true gold standard.

Depression trials rely on developed clinician assessments based on intermittent, subjective, patient reported measurements.

No gold standard to measure depression.
Improving Endpoints for Clinical Trials

- Remote measurement technologies (RMT) provide more **objective, quantifiable, continuous measures** of clinical symptoms that are important to patients
  - **Active RMT (aRMT)** – provides patient reported outcomes with higher temporal resolution than current clinical trial design – allowing fluctuations between visits to be captured – e.g., self-reporting symptoms through apps
  - **Passive RMT (pRMT)** – sensor data from wearable and smartphones – could provide insights into untapped dimensions of depression – e.g. motor activity (retardation/agitation), sleep, sociability etc.

- These measures could be **aggregated to give an indicator of clinical outcomes in defined subgroups**

*Note that there are no reference ranges for continuous measures for either Context of Use (COU) - potential stratification by digital phenotyping or for improving endpoints*
Contexts of Use (COUs)

- **Use Statement:**
  - Patient stratification/selection marker for clinical trials (this COU is lower risk)
- **Conditions for qualified use:**
  - Diagnostic - to identify individuals with a subtype of disease
  - Monitoring - to detect change over time in the degree or extent of disease
- **What decision is going to be made for drug development?**
  - Patient selection in Phase 2 and 3 clinical trials
  - Monitoring over time – cross-sectional, longitudinal assessment

- **Use Statement:**
  - Efficacy endpoint to demonstrate clinical benefit (this COU is higher risk)
- **Conditions for qualified use:**
  - Prognostic - indicate likelihood of a clinical event, disease recurrence or progression, in the absence of a therapeutic intervention
- **What decision is going to be made for drug development?**
  - Endpoint for efficacy in registration trials (Phase 3)

- **What is the population involved?**
  - Distinct biological and phenotypic sub-type of MDD, inadequately treated by current medications.
- **What factors will define the limits of the decision?**
  - Ability to obtain an indication for use in the MDD sub-population
  - Limits of agreement with the standard conventional assessment
  - Acceptability to users
Digital Technologies Study Design - RADAR-MDD

- **Broad inclusion of digital technologies – RADAR is a discovery study:**
  - Wearable sensors – FitBit Charge 2 (accelerometry, heart rate, sleep)
  - Smartphone sensors
  - ESM assessment
  - Speech
  - Mood (PHQ8)
  - Self-esteem
  - Cognition (THINC-IT)

- **How were the digital technologies selected?**
  - Considered by FDA to be a “low-risk device”

- **How was the patient perspective taken into account?**
  - Understanding the end users’ requirements
RADAR-MDD is a comprehensive discovery effort that will identify a subset of the most meaningful measures.
Patient Involvement in RADAR Digital Studies

Preventing vulnerability & stigmatisation of individuals & groups

Focus Groups
- UK
  - Multiple sclerosis
  - Epilepsy
  - Depression
- Spain
  - Multiple sclerosis
  - Epilepsy
  - Depression
- Italy
  - Multiple sclerosis
  - Epilepsy
  - Depression

Systematic Review
- Facilitators & barriers to adoption of RMT
- Technical requirements
- Preferences for predictors
- Facilitators & barriers (e.g. privacy)
- Preferences affecting engagement & adherence

Surveys (across Europe)

Discrete Choice Experiments

Pilot Studies
- Consultation to WP4, 5 & 6: assessment of patient acceptability

Policy Document

UK

Surveys (across Europe)

Technical requirements

Preferences for predictors

Facilitators & barriers (e.g. privacy)

Preferences affecting engagement & adherence

Pilot Studies

Consultation to WP4, 5 & 6: assessment of patient acceptability
Engaging Patient Input Early in the Process

**RADAR-MDD Study Design - Data Collection**

### Clinical Assessments
- Depression Relapse (IDS-SF/CIDI-SF)
- Anxiety (GAD7)
- Quality of life (WSAS)
- Illness Perceptions (BIPO)
- Depression Remission (IDS-SF/CIDI-sf)

### Passive RMT (wearable and smartphone sensors)

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**Process Evaluation**
- Qualitative interview
- Technology Acceptance
- Perceived Usage Questionnaire

**PHQ8 mood monitoring** (every 2 weeks)
(assess in process evaluation)

**Active RMT**
- ESM Assessment (monthly)
- Cognition (monthly)
- Speech (monthly)

**Contextual Variables**
- 3-monthly
  - Service use (modified CSR)
  - Life events (LTE-SR)
  - Treatment use

**Endpoint Assessments**
- Device usability
- Technology appraisal
- Satisfaction, ease of use
- Qualitative interview
- All outcomes & contextual variables

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[Image showing the study design and data collection process with timelines and categorizations]
Flow of data from biology to decision

Each step needs evidence!

Data transfer can occur at any step

Data security

* Stakeholder input should be addressed as appropriate
From Wearables and Smartphones to Disease Insights

- Validated and qualified digital biomarkers for use in clinical trials
- Algorithms & Analytics on pre-processed data
- Technology platform for data collection and management. Low level data reduction and processing. (certified medical device) (RADAR BASE)
- Wearable devices and smartphones (‘bring your own’, ‘plug and play?’)

Disease Level Insight

Digital Sensor Biomarkers for MDD subtyping and efficacy monitoring

- Psychomotor Retardation
- Sleep Structure
- Fatigue
- Respiration
- Physiological Stress

- Actigraphy
- Speech Features
- Respiratory Acoustics
- HR/HRV
- Oxygen Saturation
- Skin Conductance
- ePRO

- Accelerometer
- Phone Microphone
- Photoplethysmography (PPG)
- Skin Electrode
- Pulse Oximetry
- Patient Diary App

Sensors (raw data)
Benefit Assessment

**Patient stratification**

- **What is the relative perceived benefit of the new measure vs. the current standard (if there is one)?**
  - Enables drug development for underserved sub-population

- **How will the measure impact drug development and regulatory review?**
  - Companion diagnostic approval concurrent with drug approval

**Efficacy Endpoint**

- **What is the relative perceived benefit of the new measure vs. the current standard (if there is one)?**
  - No efficacy measure qualified with the FDA that corresponds to patient needs and deficits specific to this MDD sub-population
  - More robust to placebo effect / patient expectation

- **How will the measure impact drug development and regulatory review?**
  - Qualification of a novel digital clinical efficacy endpoint prior to study start

**When in the drug development lifecycle is the measure intended to be used?**

- Exploratory POC (Phase I/II) and confirmatory Phase III trials

**Is the benefit of the measure to the individual or society?**

- Pathway for new drugs with novel mechanisms targeting patient unmet needs of this sub-populations
  - Efficacy measures that with more ‘ecological validity’ that better represent patient needs
  - More facile collection of real-world impact of medications in real world use, allowing better health economic decisions
  - Smaller faster trials with higher PTRS attract more drug development investment
## Risk Assessment

### Patient stratification

- **What is the potential consequence or harm if the measure’s performance is not aligned with expectations based on the COU?**
  - Right patients not identified for therapy, limiting benefits

### Efficacy Endpoint

- **What is the potential consequence or harm if the measure’s performance is not aligned with expectations based on the COU?**
  - Failed clinical studies (false negatives)

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- **What is the severity of the disease or condition? What are the unmet needs of the population defined in the COU?**
  - Currently no way to develop and test novel interventions for this subgroup of depression that is not well-served by current treatments

- **What is the relative overall perceived incremental risk vs. benefit of the new measure vs. the current standard?**
  - Little to no incremental risk vs. better identification of a subtype (benefit)

- **Is the risk of the measure to the individual or society?**
  - Companion diagnostic requiring bespoke medical device limits access to patients
  - Digital divide prevents selection of patients from an underprivileged socio-economic status (e.g., no access to digital tools that indicate inclusion)
  - Patient voice not adequately captured due to over-reliance on objective passive measures
Current Evidence Available

- Sufficient evidence available that sleep disturbance can be identified via actigraphy based digital measures
- Plausible evidence available that hyperarousal can be identified by combination of self-reports and physiological measures from wearable sensors
- Assessment of depression severity from physiological and behavioral phenotyping plagued by ‘lack of gold-standard’

<table>
<thead>
<tr>
<th>Subtype</th>
<th>Conventional Measures</th>
<th>Novel Digital Measures</th>
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<tbody>
<tr>
<td>Atypical/Typical Depression</td>
<td>Sleep (Insomnia Severity Index)</td>
<td>Objective Sleep Assessment (Wearable sensor [actigraphy + PPG heart rate], Phone interaction)</td>
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<tr>
<td>Atypical/Typical Depression</td>
<td>Sleep Quality/Staging/Architecture, Circadian Rhythm Imbalances (PSG)</td>
<td>Actigraphy + HR/HRV + Respiration</td>
</tr>
<tr>
<td>Atypical/Typical Depression</td>
<td>Hyperarousal, HPA axis overactivation (via interview?)</td>
<td>Wearable tech for GSR, HR/HRV-Clinical assessments of autonomic function phone interaction</td>
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State of Evidence

Additional evidence needed to meet the minimum evidentiary standards given the benefit/risk assessment:

- Additional analytical and clinical validation needed
- Gaps in the data that would need to be filled in order to make a confident decision for the stratification COU:
  - Correlation with existing gold-standards (?)
  - Sensors and algorithms: population norms, variability, cut-offs
  - Biological validity and clinical utility of digital sensor-identified subgroups within MDD
Technology Verification & Validation

Technology = sensor + platform + algorithm(s): Sensor → Platform → Algorithm

Passive Monitoring
- IoT sensor
- Third Party
- RESTful API connection

Active Monitoring
- RADAR-base pRMT App
- e.g. Third Party App Integration

RADAR-base IoT Connector

RADAR-base Questionnaire App

RADAR-BASE

Automated (real-time) Analyses & Aggregation

Visualizations

Data Extraction and Storage, Batch Analysis

<table>
<thead>
<tr>
<th>Sensor</th>
<th>Platform</th>
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<tbody>
<tr>
<td>Wearable</td>
<td>FitBit Charge 2,3</td>
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<tr>
<td>Smartphone</td>
<td>iPhone, Android</td>
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<td>Active Collection</td>
<td>Mobile App/Browser</td>
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Project Management
RADAR-MDD Participant Board

Fitbit HR

Fitbit Sleep

Fitbit Wear Time

Fitbit Steps
Clinical Validation

Characteristics of Types of Evidence

Causality
• is there a compelling case for it being causal so there is less of a need for evidence of universality

Plausibility
• is the biology of the measure so compelling that it adds to the weight of evidence for acceptance

Proportionality
• to what extent does the measure explain the disease or the change in disease

Specificity or potential off-target effects?

Universality
• to what extent is there evidence across drug mechanisms or across different populations
Evidentiary Criteria Framework – MDD case study

- Clinician assessments are based on intermittent, subjective patient self-reported symptoms affected by recall bias.
- Remote monitoring technologies (RMT) enable objective and continuous assessments in real-world settings, between clinic visits (more ecologically valid and less prone to placebo effects).
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Risks:
- **Stratification**: Right patients not identified for therapy, limiting benefits.
- **Efficacy endpoint**: Failed clinical trials (false negative).

Risk mitigation:
- Establishing analytical and clinical validity.

Need Statement

COU

Benefit

Risk

Evidentiary Criteria

Insomnia with Hyperarousal
- Objective sleep assessment
  - Actigraphy + PPG HR
  - Actigraphy + HR/HRV
  - GSR, HR/HRV
- Fitbit Charge 2,3
- REST API
- Algorithm
- Stratifier

Patient stratification selection marker and monitoring in Phase 2/3 clinical trials
- **Efficacy endpoint** to demonstrate clinical benefit

Underlying constructs can be measured and show promise:
- Typical depression (reduced sleep, appetite, weight loss) vs. atypical depression (increased sleep, appetite, weight loss).
- Depression + anxiety/agitation.
- Depression + insomnia.

Device measurement characteristics, reportable range.
- Reference range needs to be established.
- Confirmation with independent datasets is needed.
- Novel data analytics and statistical approaches are needed.
Alignment with biomarker evidentiary criteria framework

*Ability to identify MDD subtype – Insomnia with Hyperarousal*

**What fits?**
- **Pre-existing candidate stratifiers**
  - Underlying constructs which can be measured and already show promise
    - Typical depression (reduced sleep, appetite, weight loss) vs. atypical depression (increased appetite, weight and sleep)
    - Depression + anxiety/agitation
    - Depression + insomnia
- **Identification of new stratifiers**
  - Data driven approaches to segment the population based on yet to be determined patterns (e.g., speech, activity,
    - Sociability, affective reactivity, etc.)

**What doesn’t fit?**
- **Patient input**
  - Patient perspective is important for stratifying subgroups on clinically meaningful features
Panel Discussion

Moderator: Linda Brady
Panel – Follow up Questions

- Lack of reliable and valid ‘ground truth’
- Objective measures vs. patients’ subjective experience
- Explainability vs. performance: which should we pick?
- Change control: Iterative open source development of software vs regimented design control
- Separation of data collection hardware (on-body commercial grade devices, smartphones from algorithms and disease insight)
Analytical Validation

Technology = sensor + platform + algorithm(s)

- Interest in the concept of a market-place/ecosystem (open source tools) for building blocks to build digital pathways/tools?
- Regulatory process SOUP (software of unknown provenance) -- widely applicable to all digital biomarker/COAs
- Validation of platform in part separate component or all together as one use case?
  - Advantages/disadvantages. (e.g., reusability)

- Managing rate of software changes and third-party platforms e.g. Android dependency changes. What needs to be re-validated? How to manage risk?
- Requirements for verification & validation - acceptability of:
  - Black box algorithms (e.g., Neural Nets vs. interpretable models)
  - Black box processed data (e.g., Fitbit mapping accelerometer → steps/sleep etc.)
- Widening of the pre-cert type programs?
  - Might an organization set up to manage RADAR-Base qualify for such a program?
Panel - Questions and Answer Session

- If the device or algorithm changes, what is the process?
- How do you iterate on advances in technology without losing time?
- How does the industry and FDA keep up with the rapid iterative changes in technology?
Panel Questions and Answer Session

• Industry and FDA need to consider how the Technology interact:
  
  Sensor → Platform → Algorithm

• Sensors
  
  o Use of opaque / proprietary processed data (e.g. Fitbit sleep algo). This may also change depending on the whims of the vendor
  o Equivalency & standardization of data, active and passive
    ▪ e.g. active ICHOM for passive data, OneM2M, OMH
    ▪ e.g. can one accelerometer on a phone be compared with another, one questionnaire vs another (may depend on content and presentation)

• Platform
  
  o How the data is aggregated, transmitted, structured/organized/schematized. What controls need to be in place around what the "sensor" produces and what is presented to the algorithm?
  o Handling missing data, network issues, latency of synchronization (e.g. participant syncs Fitbit data days/wks after data collected)
    ▪ Rapid iteration of software dependencies (e.g. Android OS updates)
    ▪ Open source libraries (SOUP)
Panel Questions and Answer Session

• **Algorithm**
  - Realtime (handling missing data, late synchronized issues, out of order data etc.)
  - Validation of individualized models (n=1). Issues with defining correct baseline or understanding when a baseline has changed
  - Blackbox (e.g., deep learning type). How are we to treat these types of models that may demonstrate greater power than explainable models but may contain unknowns or unexpected behavior?

• **Regulatory pathway (commercial, FDA cleared, etc.)**
  - Current FDA considerations:
    - No existing evidence of Technology typically required in De Novo + Class I/II submissions.
    - FDA rationale likely based on benefit v. risk calculation
  - How to assess the validity of Technology with multiple components?
  - How to account for rapidly developing changes in Technology (e.g., Open source components)?
  - Pre cert type programme for core, community owned components?
Panel Questions and Answer Session

- Regulatory pathway (commercial, FDA cleared, etc.)
  - Current EMA considerations:
    - This case study presented valid arguments questioning the current “gold standards” for measuring depression. In order to overcome the limitations of the current measurements and establish new measures, the new measures should exhibit a very strong link to clinically relevant outcomes and provide evidence that a reversal in the scores improves patient outcomes.
    - The identification of “new” MDD subtypes may impact the generalizability and external validity, particularly if the diagnostic criteria for inclusion/patient eligibility for treatment aren’t entirely conclusive. This will also need to be considered as a factor in the Health Technology Assessment.
    - As presented, there is some question about the clarity of the final aim.
      - Would this:
        - Provide rationale for additional indication claims (e.g., improvement of sleep patterns in MDD patients with insomnia)?
        - Allow patients to self-monitor?
        - Provide feedback to a treating physician?
aRMT Firebase Event Generation

How it works...

Events

- qr_code_scanned
- screen_view
- questionnaire_started
- questionnaire_finished
- send_success
- notification_received
- notification_open
- notification_dismissed

...Lots of other events generated tracking other aspects of user interaction
Additional Information
Technology Verification & Validation

Technology = sensor + platform + algorithm(s): Sensor → Platform → Algorithm

Sensors: Sleep Architecture / Hyperarousal

- How does the "algorithm" produce the measurement?
  - Fitbit Charge HR2 & 3 (proprietary FitBit Algorithms in all cases, no raw data provided)
    - Fitbit Sleep report on device (based on PPG and Accelerometer)
    - Heart rate via PPG → processed on device (black-box). PPG particularly required to determining sedentary behavior from sleep
    - Steps, Calories, Activity (sedentary, active)
  - RADAR-base active app
    - We do not use a sleep diary as the study duration is long. But we do collect some questionnaire information on Sleep Quality via PHQ8
    - Speech data i) free speech ii) scripted speech tasks
  - RADAR-base passive app
    - Android Phone sensors: Light, Accelerometer, Phone Touch Interaction, GPS. Android API does not provide guarantees on fulfilling a request for data, and iOS is very constrained about allowing data collection in the background.
    - Periodic sampling of background audio features (30sec every 1hr) collected by the RADAR-base passive app (non-raw audio)

Platform for Data Collection:

- RADAR-base
  - REST-connector used to collect data from Fitbit REST-API (Server-to-Server data collection). Initial data is collected via the Fitbit App
  - RADAR-backend infrastructure based on Apache Kafka to stream data
  - RADAR-base data is organized in standardized schema, based on Open mHealth Guidelines but using AVRO format for serialization
Technology Verification & Validation

Technology = sensor + platform + algorithm(s)

Sensors: Sleep Architecture / Hyperarousal - How does the "algorithm" produce the measurement?
Algorithm Features Being Explored: Data still being gathered (Projected completion ~2021)

- **Fitbit Sleep** is reported by the device's proprietary algorithm and reports sleep quantity, quality and type, the preference was to have raw data from the device, but this was a sacrifice based on need for a device that would fit the device selection profile of the study
  - Sleep classic: asleep, restless, and awake and sleep stages: deep, light, rem, and wake
- **Hyperarousal**
  - Fitbit Heart Rate
  - GPS entropy measures
  - Phone interaction events
  - Speech features
  - Phone inertial sensors (Accelerometer)

- We are taking these types of features (along with others) and using them to stratify sub-groups of depression
  - Unsupervised (for group discovery) and supervised approaches using active and passive data features (cross sectional)
  - Few-shot and meta-learning approaches for generating individualized models