How to define what is meaningful in digital measures of Physical Activity: a CNS case study

ADDS Presentation

February 27th , 2024

Session objectives

1. Understand why it is important to select meaningful measures for patients
2. Discuss required steps to identify meaningful measures and build the evidence to support content validity
3. Apply learnings in the context of a CNS case study

It is important to select meaningful measures to patients when developing digital endpoints to avoid regulatory set-backs

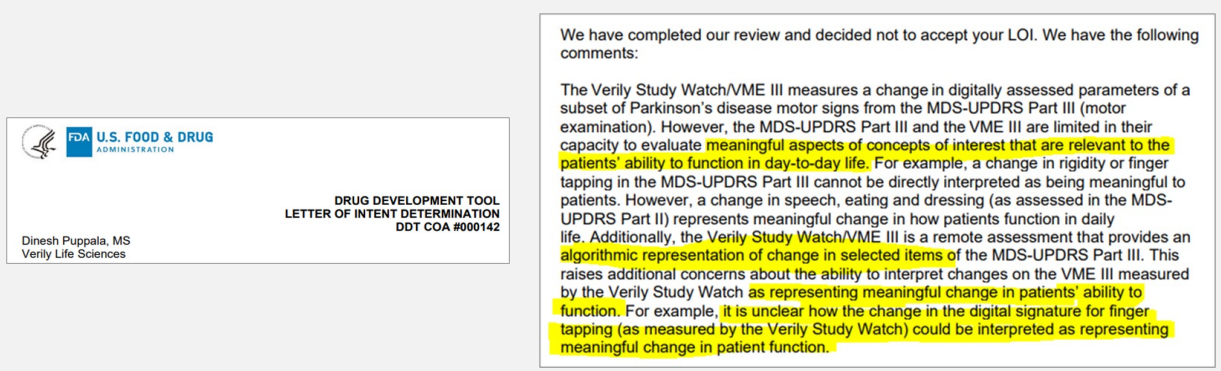
Common Pitfall: Lack of understanding of the patient-relevant concepts

Example: “I saw a cool device at a conference, can we fit that in the trial somehow?”

Experimenting with **new technology based solely digital feasibility** without linking it to a meaningful aspect of health to the patient

FDA

- FDA has rejected Verily's request to use a **wrist-worn wearable device to track changes in the motor symptoms** of clinical trial subjects with Parkinson's disease
- FDA questioned whether the wearable device can show if an intervention has a **meaningful effect on patients**, leading it to reject Verily's Letter of Intent



U.S. FOOD & DRUG ADMINISTRATION

DRUG DEVELOPMENT TOOL
LETTER OF INTENT DETERMINATION
DDT COA #000142

Dinesh Puppala, MS
Verily Life Sciences

We have completed our review and decided not to accept your LOI. We have the following comments:

The Verily Study Watch/VME III measures a change in digitally assessed parameters of a subset of Parkinson's disease motor signs from the MDS-UPDRS Part III (motor examination). However, the MDS-UPDRS Part III and the VME III are limited in their capacity to evaluate meaningful aspects of concepts of interest that are relevant to the patients' ability to function in day-to-day life. For example, a change in rigidity or finger tapping in the MDS-UPDRS Part III cannot be directly interpreted as being meaningful to patients. However, a change in speech, eating and dressing (as assessed in the MDS-UPDRS Part II) represents meaningful change in how patients function in daily life. Additionally, the Verily Study Watch/VME III is a remote assessment that provides an algorithmic representation of change in selected items of the MDS-UPDRS Part III. This raises additional concerns about the ability to interpret changes on the VME III measured by the Verily Study Watch as representing meaningful change in patients' ability to function. For example, it is unclear how the change in the digital signature for finger tapping (as measured by the Verily Study Watch) could be interpreted as representing meaningful change in patient function.

Not sure if your endpoint is a digital COA or digital biomarker? Consider feasibility to demonstrate content validity

Digital COA

- "A measure that directly describes or reflects how a patient feels, functions, or survives"

- **Measured digitally**
- **Needs to demonstrate content validity**

Digital Biomarker

- "Characteristic that is measured as an indicator of normal biological processes, pathogenic processes, or responses to an exposure or intervention, including therapeutic interventions"

- **Measured digitally**
- **Needs to demonstrate a link to pathophysiology or biological process**

The same digital measure can be a digital COA or a digital biomarker

- Coughing rates can be used as a direct measure of how patient functions in their day to day.
- ***Example**: Coughing rates when collected using a smartphone were found to have a relationship with health related QOL in patients with COPD [1]*

- Coughing rates can be reflective of a pathogenic progress.
- ***Example**: Higher early coughing rates were associated with more favorable clinical outcomes in COVID-19 patients [2].*

- Examples of objectives:
  - Support efficacy (e.g., evaluate change in a physical activity measure)
  - Support safety (e.g., evaluate adverse effects)
  - To better understand a disease (e.g., symptomatology)

- Examples of objectives:
  - Predict clinical events (e.g., probability of hospitalization)
  - Predict adverse events (e.g., fever in CAR-T)
  - Support efficacy as a surrogate endpoint
  - To better understand a disease (e.g., explore risk factors)

1] Cook, N., el at., (2019). Impact of cough and mucus on COPD patients. International Journal of Chronic Obstructive Pulmonary Disease, 1365-1376.
2] Altshuler, E., et al. (2023). Digital cough monitoring–A potential predictive acoustic biomarker of clinical outcomes in hospitalized COVID-19 patients. Journal of Biomedical Informatics, 138, 104283.

A key requirement of FDA regulatory guidance is to generate content validity evidence for the digital endpoint

Fit-for-purpose DHT

Validation — *Confirmation that the DHT meets its expected performance specifications*

Verification — *Confirmation that the parameter that the DHT measures is measured accurately and precisely.*

Interoperability — *Demonstrate that the resulting DHT measurements are interpreted appropriately*

Usability and acceptability — *Assess the ability for participants to efficiently use the DHT in a relevant setting and ensure compliance*

Digital measure validation

Content validity — ***Evidence that the DE measures a Health Concept that is important/meaningful to patients and clinician***

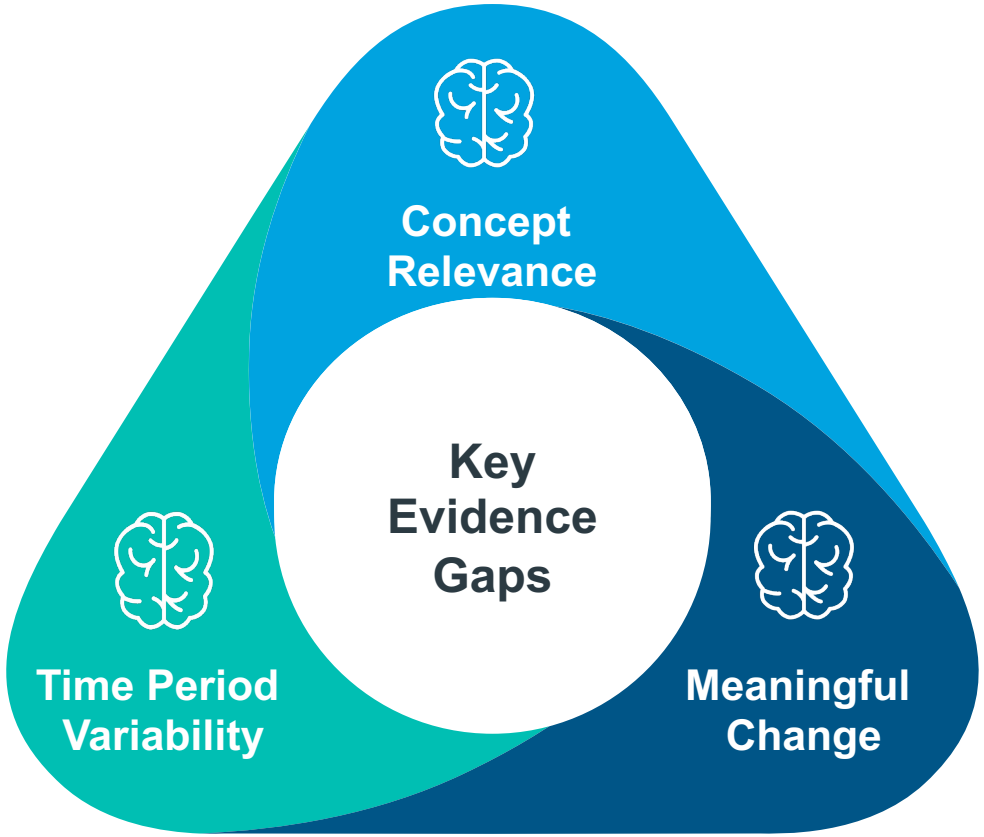
Analytical Validity — *Assess whether an algorithm meets performance specification (including accuracy and reliability)*

Clinical Validity — ***Construct:*** *statistical and predictive properties of endpoints (accuracy, reliability and specificity)*

Reliability*: statistical and predictive properties of endpoints in terms of test-retest reliability*

Ability to detect change*: Evidence that the measure can identify differences over time*

The FDA has identified three key evidence gaps in the content validity required to support digital endpoints



Concept relevance

- Identify the concepts **relevant** to patients and what benefits a patient can distinguish (what they want to improve or not worsen)

Meaningful change

- Identify how patients would perceive **meaningful change** to enable identification of anchors

Time period variability

- Understand the **variability** of physical activity to justify appropriate implementation of a time period

There are strategic approaches to address challenges related to potential evidence gaps

Confounding factors

Linking digital variables to meaningful aspects of health can be challenging and should consider patient behavior. E.g., physical activity provides an objective understanding of a patient's medical condition and treatment impact but is also influenced by patient behavior[1].

Patient description of experience

Variables collected from digital sensors are not necessarily measures that are readily meaningful to patients, or align with how patients describe their condition, function or feelings. Hence, it is important to use relevant language when speaking with patients.

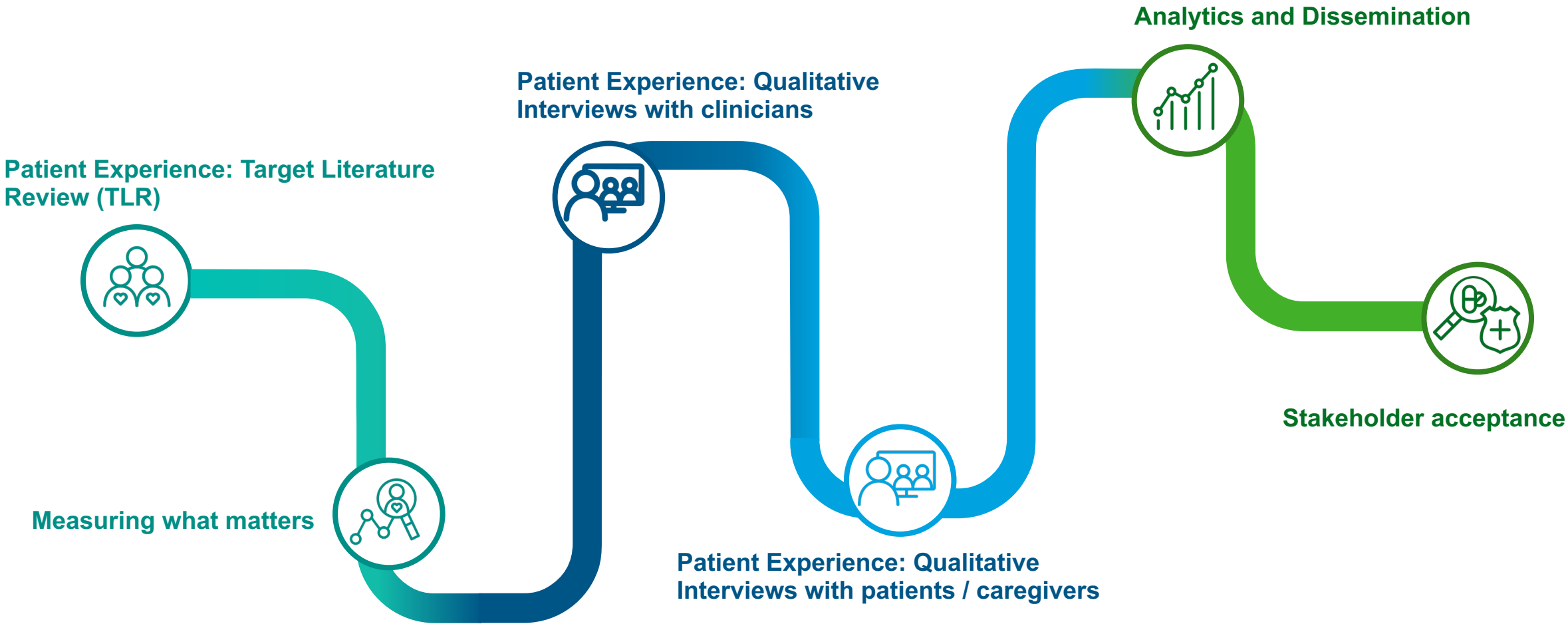
For example, actigraphy may measure steps and duration however misses intensity of physical activity

Time period collection

It is important to define and justify the collection time period, for the data capture window. Elements such as variability in days, device battery life, patients' disease journey will be important considerations to take into account for trial design and implementation.

Source: 1. Cascino, T. M., et al. (2019). Barriers to physical activity in patients with pulmonary hypertension. Pulmonary circulation, 9(2), 2045894019847895.

So, how do we generate evidence for content validity in alignment with FDA requirements



HTA: Health Technology Assessment; HCP: Healthcare Professional

Using established frameworks can guide exploration of concepts and measures of interest in the context of physical activity

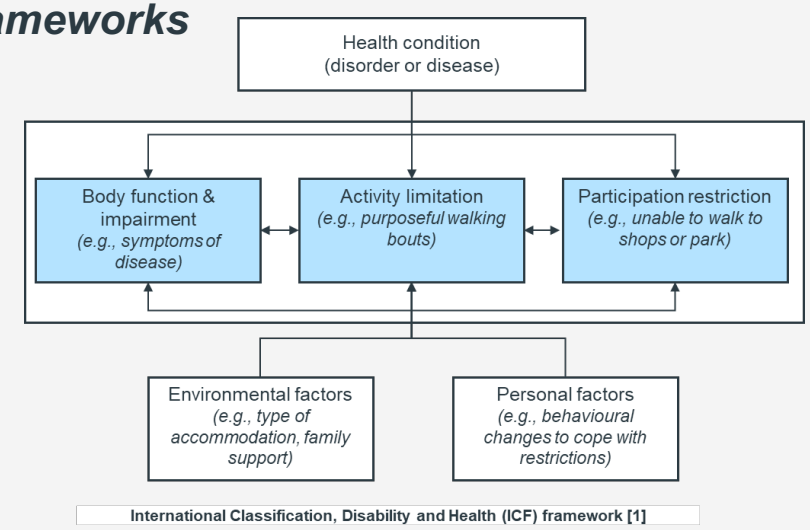
Concept Elicitation

- Start with knowing what you want to measure and why. Link it to a meaningful aspect of health (MAH)
- Identify aspects of health affected by the disease that are meaningful to patients and clinically relevant and elicit the important concepts to patients

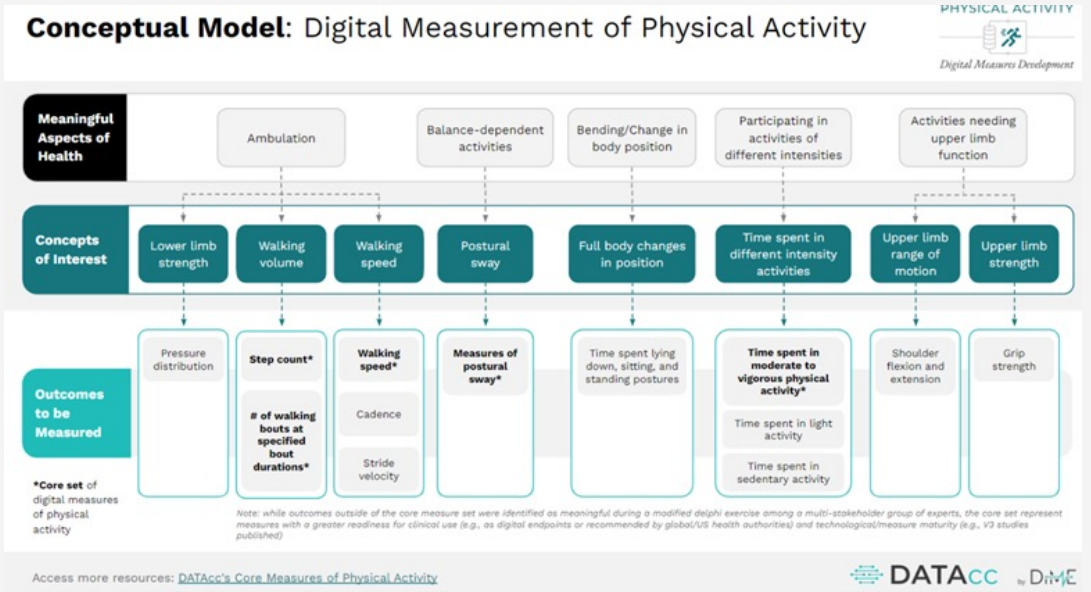
Cognitive Debriefing

- Define measure relevance
- Establish meaningful change by having patient define "bothersome" categories for the measure of interest and ask them about the level of change required for a meaningful change to be observed

Frameworks



International Classification, Disability and Health (ICF) framework [1]



ICF: International Classification of Functioning, Disability and Health
DiMe Conceptual Model https://datacc.dimesociety.org/resources/the-conceptual-model-a-core-set-of-digital-measures-for-physical-activity/

Example of digital measures that have some level of relevance across TAs and need to be debriefed in the context of each indication

Number of walking bouts at specified bout durations

Step count

Walking speed

Time spent in MVPA

Measures of postural sway

Core set of digital measures in Physical Activity

https://datacc.dimesociety.org/digital-measures-physical-activity/all-core-measures/

Why CNS?

Unmet Need

- Strong unmet needs and expanding disease burden (15% increase in DALYs 2010-2019)[1]
- **1 in every 8 people in the world live with a mental disorder**
- CNS disorders account for 27% of the global economic impact of disease burden

Rapid Growth

- Neuroscience is a rapidly growing market CAGR +8% 2022-2028[2]
- Estimated total market size of disorders involving **motor complications** by 2030 is ~4.5B USD
- Investments in neuroscience biotech increased last decade 15% CAGR in range of deals 2011-20213

Digital Feasibility

- Technological advances create new, potentially more meaningful and continuous opportunities for measurement

Limited Scales

Legacy CNS scales are limited due to:

- No patient or caregiver input; most developed with clinician input only (not in line with PFDD)
- Developed primarily for diagnosis / differential diagnosis and not to detect treatment benefit
- Psychometric properties are not adequate

1Global Health Data, DALY: Disability-adjusted life years, 2Evaluate Pharma, CAGR forecast 2022-2028 (only captures CNS), 3Global neuroscience market size and growth, Deloitte Insights (only captures CNS

Generating content validity evidence for a new digital tool in a patient population with motor complications: A case study

About Multiple System Atrophy (MSA)

- Rare, neurodegenerative disease that typically leads to death in 6-10 years after symptom onset
- Onset usually age 50-60
- Characterized by **autonomic failure** (orthostatic hypotension, genitourinary dysfunction with sexual dysfunction and urinary incontinence, anhidrosis and constipation) AND **motor symptoms**
- Two motor subtypes:
    - **MSA-Parkinsonism**: Stiff muscles, slow movement, tremors, soft voice, problems with posture and balance
    - **MSA-Cerebellar:** Problems with muscle coordination (ataxia), unsteady gait, loss of balance, slurred speech, blurred or double vision, dysphagia

Treatment Focus

- Remains an incurable disease
- Available symptomatic treatments only have a modest and transient effect
- No treatments significantly slow the aggressive course of MSA
- Currently, there is a robust pipeline of potentially disease-modifying agents
- Sponsor X has come to IQVIA PCS to generate the content validity evidence for a de novo digital COA – **wearable sensor that measures activity**
- Sponsor X believes that activity measures are meaningful to patients and measures disease progression

These are the steps that need to be performed to generate evidence for content validity of digital measures of physical activity in MSA

Patient Experience: Target Literature Review (TLR)

First, conduct a TLR to identify key concepts of MSA relevant to patients and use this data to create a preliminary conceptual model of the patient experience in MSA

Measuring what matters

Next, we will identify digital devices to measure the patient experience

Patient Experience: Qualitative Interviews with clinicians

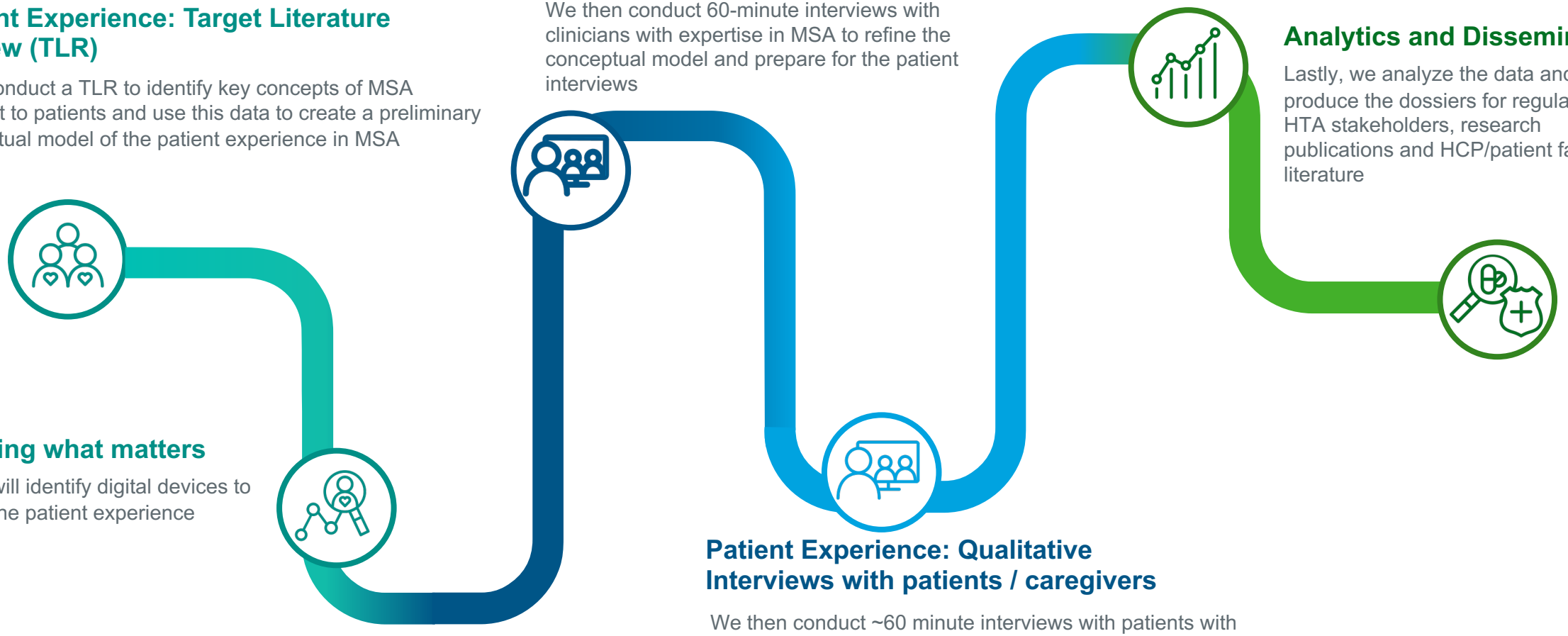
We then conduct 60-minute interviews with clinicians with expertise in MSA to refine the conceptual model and prepare for the patient interviews

Patient Experience: Qualitative Interviews with patients / caregivers

We then conduct ~60 minute interviews with patients with MSA and their caregivers to refine the conceptual model and define concepts of interest

Analytics and Dissemination

Lastly, we analyze the data and produce the dossiers for regulatory and HTA stakeholders, research publications and HCP/patient facing literature



HTA: Health Technology Assessment; HCP: Healthcare Professional

A TLR can be used to identify key concepts and derive relevant measures of physical activity in MSA that need to be debriefed

Illustrative

Illustrative Conceptual Model for physical activity in MSA

Signs and symptoms

Motor symptoms
- Leg motor restlessness
- Restless leg syndrome

Autonomic dysfunction
- Urinary symptoms
  - Problem with bladder control
- Orthostatic hypotension
- Unstable blood pressure

Sexual dysfunction
- Gynecological disorders
- Genital hyposensitivity

Other symptoms
- Restlessness without urge to move

Physical functioning limitations

Limitations with mobility
- **Problems with mobility**
- Slow movements
- **Falling**
- **Balance problems**
- Problems with manual dexterity
- Problems with fine motor skills

Limitations in sexual activity
- Sexual inactivity
- Erectile dysfunction
- Anorgasmia

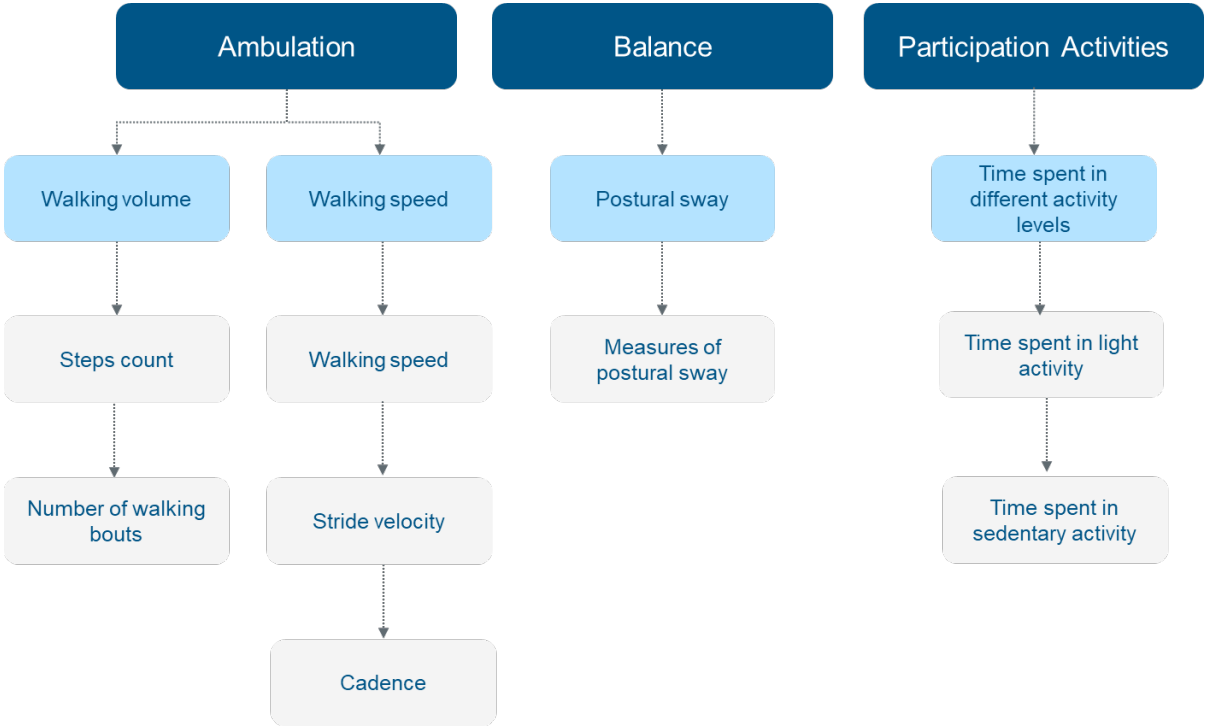
Activity participation restrictions

Dependence on others
- Unable to stay at home alone

Reduced daily activities
- **Preventing activities of daily living (eating, dressing, going to the washroom)**

Reduced communication
- Having to repeat self
- Required use of communication device
- Less talkative
- Difficulty being understood

Reduced social activities
- Social withdrawal
- Difficulty maintaining social life



Patient interviews will help to validate and refine identified concepts and measures and determine meaningfulness

Population with complex needs

- **Experienced moderators working with complex patient populations** should be used

Tailored approach

- **Tailor the interview approach** to meet the needs of the individual patients – can a patient with MSA be expected to remain engaged and focused for a 90-minute interview?
- **Prepare in advance**

Specific Training

- Moderators should complete **project-specific training** with subject-matter experts to ensure they are prepared to conduct interviews with patients with MSA

Factors that may impact a patient with MSA ability to participate in an interview

- Cognitive impairment
- Slurred speech / slowed speech
- Inappropriate laughing
- Fatigue, discomfort
- Apathy

Key takeaways

1. It is important to demonstrate that the digital measure selected and used in the clinical trial is meaningful to patients and to generate the right evidence for content validity (meaningfulness and relevance)
2. Leveraging existing approaches and frameworks will help teams be more successful in generating the right evidence
3. CNS disorders are complicated as they most often involve heterogeneous clinical presentations – cognitive, motor, behavioral, psychiatric, physical symptoms – making measurement difficult
4. Generating content validity evidence in CNS disorders requires careful thought, planning, and expertise - knowledge of the target population is optimal

Questions?

Thank You for Your Time

Salma.Ajraoui@iqvia.com

Stella.Karantzoulis@iqvia.com

@Stella Karantzoulis, PhD Abpp-Cn

@Salma Ajraoui, PhD