Clinical Outcome Measures in HD: Beyond UHDRS

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HD-RSC
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- **Salary**: Rush University Medical Center

Unified Huntington's Disease Rating Scale

- Originally published 1996 – Revised 1999
- Assesses Motor, Cognitive, Behavioral and Functional capacity
- ClinRO administration
- Good internal consistency, inter-rater reliability for Motor
- Sensitivity to change Motor, TCF and Behavior

Unified Huntington's Disease Rating Scale

- Delphi panel – yes?
- Review of existing scales - yes
- Focus groups – no
- Cognitive pretesting patients – no
- Cognitive pretesting HCP – no
- Translations – yes, but not validated process

Goncalves JNNP 2014

Unified Huntington's Disease Rating Scale

- Motor assessment – good clinimetrics
- Behavior, Functional and Cognitive – not so good
  - Behavioral – ClinRO, no patient input, multiplicative scoring
  - Functional – ClinRO, no patient input, scoring issues
  - Cognitive – Limited domains, no patient input, raw score scoring

Cognitive Assessment– HD-CAB

- Topic worthy of separate conference!
- Excellent review chapter in Handbook of Clinical Neurology (vol 144 – Huntington Disease) by Dr. Stout
  - Basic framework for assessing cognition in clinical trials – focus on HD
  - HD-CAB development and validation
  - Pathway for continued development of cognitive outcome in HD

Expanding Behavioral and Functional Assessments – 2 Approaches

- Modify existing scales
  - Hospital Anxiety Depression Scale – Snaith Irritability Scale

- Develop new scales
  - Problem Behavior Assessment – Short

  - FuRST 1.0

Datasets

- Three datasets
  - Enroll-HD-Plus-Perodic-Dataset-2016-10-R1
    - 8,165 Registry data records (HDCAT & ID)
    - 17,187 Enroll data records (HDCAT & ID)
  - Enroll-SPS014-2016-R1
    - 2,098 Registry data records (HADS-SIS & ID)
    - 17,187 Enroll data records (HADS-SIS & ID)
  - Data-project-0844
    - 25,636 Data records
    - 7,451 Individual HADS-SIS item scores

- Combine and Clean
  - Match on ID
  - Merge with HDCAT, HADS-SIS, PBA-s, FuRST, demographics
  - Select only BASELINE visits (n = 8714) and BASELINE for HDCAT Manifest (n = 4752)

HADS-SIS

- Combine two scales with some overlap
  - Original structure – 2 factors for HADS (depression and anxiety) and 2 factors for SIS (inward and outward irritability)
  - Translated into 11 languages - ? Method
- Clinimetrics
  - Reliability acceptable
  - Construct validity
    - Factor structure different
      - two factor is a more parsimonious explanation (negative affect; agitated affect)
  - Translation process inadequate

Problem Behaviors Assessment

- 11 items shorted version of the PBA-HD
  - Developed by "expert panel"
  - ClinRO
  - Multiplicative scoring (severity * frequency)
- Clinimetrics
  - Reliability low but acceptable
  - Possible "floor effect" for 8 items
  - Poor factor structure results
  - Impossible score values due to multiplicative scoring
    - 5, 7, 9, 10, 11, 13, 14, 15 impossible values – changes distribution and adversely affects variance structure

Functional Rating Scale Taskforce FuRST 1.0

- 2010 – FuRST workgroups
  - Expert panels (Delphi group)
  - Focus groups (pre-manifest HD; early HD; caregivers) 101 in person: 16 telephone.
  - Item development
  - Field testing
  - Item refinement
- 2012 – 21 item FuRST 1.0 developed
  - distribution and adversely affects variance structure

Functional Rating Scale Taskforce FuRST 1.0

1. Irritability/Anger

	Frequency			
This item assesses both irritability (proneness to annoyance) as well as anger (strong displeasure with self or others, accompanied by signs of autonomic arousal).	**Never/ Absent**	**Rarely/ Sometimes**	**Frequently**	**Almost all of the time/Always**
Symptom Intensity				
Absent Not irritable	**0**			
Mild Somewhat irritable, but no overt expression of irritability.		**1**	**1**	**2**
Moderate Irritable, minor autonomic arousal (e.g. slight flushing or palpitations), no overt expression of irritability		**1**	**2**	**3**
Severe Irritable, definite autonomic arousal (e.g. tremulous voice, shaking, close to tears) easily irritated and feeling angry, with mild overt expression of irritability (example, short-tempered, snap at others, expression of frustration, passive aggressive).		**2**	**3**	**4**
Very Severe Extremely irritable, autonomic arousal with definite expression of irritability/anger (e.g. getting into arguments, shouting, cursing, loss of temper).		**3**	**4**	**4**

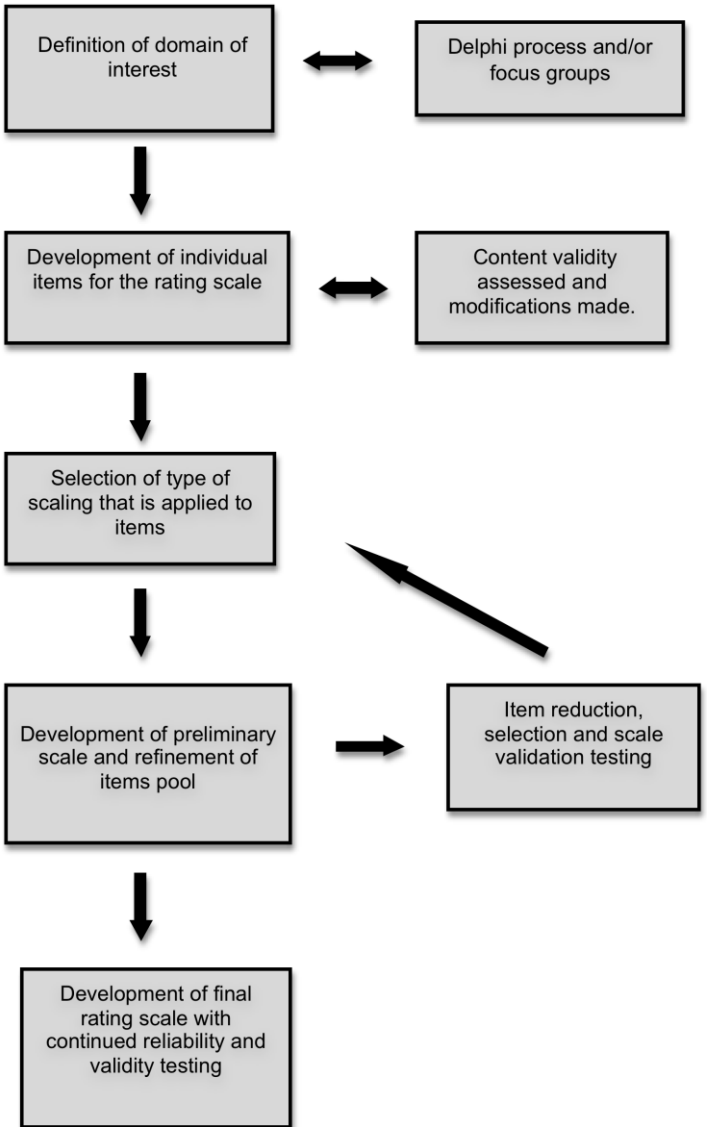
Limitations of FuRST 1.0

- Construction
  - Only telephone focus group (n = 16) data analyzed. Multilingual groups (English, Portuguese, French and Dutch) not used to identify domains.
  - Complicated GRID scoring depending on level of expertise of rater
    - No cognitive pre-testing and no follow-up Delphi review
  - No functional impact on some items

- Field Testing (n = 96: 63 Pre-HD; 33 HD)
  - All items $\geq$ 50% with scores 0 – 1
    - Floor effects?
  - Item-to-total correlations low on some items

- Review Team recommended modification of FuRST 1.0

Reasons for measurement failures? (avoiding mistakes of the past)



Reasons for measurement failures?

- Defining the domain of interest
  - Information on importance from the source (clinicians, patients, caregivers, other stakeholders)

- Defining assessment source (PRO, ClinRO, ObsRO, PerfO)
  - PRO (insight? FuRST 2.0 example)
  - ClinRO and ObsRO (knowledge of unknowable events)
  - PerfO (time consuming, difficult to quantify, ? relationship to disease markers)

- Defining scaling approach (summary, additive, multiplicative)

- Develop items (stem and anchor)

- Feedback from stakeholders – Cognitive Pretesting

- Modification and validation

The Future???

- Wearables?

Adams – Digit Biomark 2017;1:52-63