Quality of Life in Huntington's Disease: Critique and Recommendations for Measures Assessing Patient Health-Related Quality of Life and Caregiver Quality of Life

Tiago A. Mestre, MD, MSc,[1]* Noelle E. Carlozzi, PhD,[2] Aileen K. Ho, PhD,[3] Jean-Marc Burgunder, MD,[4] Francis Walker, MD,[5] Aileen M. Davis, PhD,[6] Monica Busse, BSc, BSc (Med), Hons. MSc (Med), PhD,[7] Lori Quinn, EdD, PT,[8] Filipe B. Rodrigues, MD,[9,10,11] Cristina Sampaio, MD, PhD,[12] Christopher G. Goetz, MD,[13] Esther Cubo, MD,[14] Pablo Martinez-Martin, PhD,[15] Glenn T. Stebbins, PhD,[11] and Members of the MDS Committee on Rating Scales Development

[1]*Parkinson's Disease and Movement Disorders Center, Division of Neurology, Department of Medicine, The Ottawa Hospital Research Institute, University of Ottawa Brain and Mind Institute, Ottawa, Canada*
[2]*Department of Physical Medicine and Rehabilitation, University of Michigan, Ann Arbor, Michigan, USA*
[3]*School of Psychology and Clinical Language Sciences, University of Reading, Reading, UK*
[4]*Swiss HD Center, NeuroZentrumSiloah and Department of Neurology, University of Bern, Bern, Switzerland*
[5]*Department of Neurology, Wake Forest School of Medicine, Winston Salem, North Carolina, USA*
[6]*Krembil Research Institute, University Health Network and Institute of Health Policy, Management and Evaluation and Rehabilitation Institute, University of Toronto, Toronto, Canada*
[7]*Centre for Trials Research, Cardiff University, Wales, UK*
[8]*Department of Biobehavioral Sciences, Teachers College, Columbia University, New York, NY, USA*
[9]*Huntington's Disease Centre, Institute of Neurology, University College London, London, UK*
[10]*Clinical Pharmacology Unit, Instituto de Medicina Molecular, Lisbon, Portugal*
[11]*Laboratory of Clinical Pharmacology and Therapeutics, Faculty of Medicine, University of Lisbon, Lisbon, Portugal*
[12]*CHDI Foundation/CHDI Management, Princeton, New Jersey, USA*
[13]*Department of Neurological Sciences, Rush University Medical Center, Chicago, Illinois, USA*
[14]*Department of Neurology, Hospital Universitário Hermanos Yagüe, Burgos, Spain*
[15]*National Center of Epidemiology and Centro de Investigación Biomédica en Red sobre Enfermedades Neurodegenerativas (CIBERNED) Carlos III Institute of Health, Madrid, Spain*

ABSTRACT: The compromise of quality of life in Huntington's disease is a major issue, both for individuals with the disease as well as for their caregivers. The International Parkinson and Movement Disorder Society commissioned a review of the use and clinimetric validation status of measures used in Huntington's disease to assess aspects related with quality of life and to make recommendations on their use following standardized criteria. We included both patient-centered measures (patient health-related quality-of-life measures) and caregiver-centered measures (caregiver quality-of-life measures). After conducting a systematic literature search, we included 12 measures of patient health-related quality of life and 2 measures of caregiver quality of life. Regarding patient-centered measures, the Medical Outcomes Study 36-Item Short-Form Health Survey is "recommended" as a generic assessment of health-related quality of life in patients with Huntington's disease. The 12-Item Short Form Health Survey, the Sickness Impact Profile, the 12-item World Health Organization Disability Assessment Schedule, and the Huntington's Disease Health-Related Quality of Life questionnaire are "suggested." No caregiver-centered quality-of-life measure obtained a "recommended" status. The Alzheimer's Carer's Quality of Life Inventory and the Huntington's Disease Quality of Life Battery for Carers are "suggested." Recognizing that the assessment of patient health-related quality of life can be challenging in Huntington's disease, as patients may lack insight and there is insufficient clinimetric testing of these scales, the committee concluded that further validation of currently available health-related quality-of-life measures should be undertaken, namely, those Huntington's disease–specific health-related quality-of-life

*__Corresponding author__: Dr. Tiago A. Mestre, Parkinson's disease and Movement Disorders Center, Division of Neurology, Department of Medicine, University of Ottawa, 1053 Carling Avenue, Ottawa ON K1Y 4E9, Canada; tmestre@toh.on.ca

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measures that have recently been reported and used.
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Huntington's disease (HD) is a complex neurodegenerative disorder in which motor, cognitive, and behavioral manifestations have a significant impact on the health-related quality of life (HRQoL) of patients. The concept of HRQoL has been developed to express the aspects of overall quality of life (QoL) that can be clearly shown to be related to health, physical or mental.[1] The World Health Organization (WHO) defines health as "a state of complete physical, mental, and social well-being not merely the absence of disease."[2] The WHO lists the following functioning domains as being part of HRQoL: physical, social, relational, and emotional well-being.[1] Although the term "QoL" is often used interchangeably with the term "HRQoL," QoL is a much broader multidimensional concept. The WHO defines QoL as "the individuals' perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns."[1] Another important concept that is often used in QoL literature is health status (HS). HS is defined as the perceived health in descriptive terms of physical and mental symptoms, disability, and social dysfunction related to the health condition.[3] It is different from HRQoL in that it lacks judgments and reactions.[3] As stated in a similar review for HRQoL measures used in Parkinson's disease, it is reasonable to consider HS as a relevant factor for HRQoL, which is a component of QoL in general.[4]

HRQoL is an important patient-reported outcome that constitutes a core assessment of the efficacy of clinical interventions in HD, as these interventions ideally seek to not only improve patients' symptoms but also ultimately to improve patient QoL. It is therefore important that valid and reliable measures are available that can be used in HD. In addition to measures centered on patients (patient-centered HRQoL measures), we also included measures centered on caregivers and their own QoL (caregiver-centered QoL measures), recognizing that HD impacts the "global" QoL of caregivers and a potential change in QoL is not necessarily related to health and may include other aspects of life.[5,6]

Methods

Organization and Critique Process

The Committee on Rating Scales Development of the MDS appointed a team of 10 members (subcommittee) to review clinical measures used in HD to assess HRQoL measures; these members included specialists in HD and an expert in scale development and clinimetrics (A.M.D.). Two subcommittee members evaluated each measure. If a subcommittee member was involved in the development of a measure, he/she was not involved in its review. Data were extracted into a pro-forma form provided by the MDS and adapted for the purpose of the current review. The assessment of the measure included the description of the measure, its availability, context of use, and reported clinimetric properties in patients with HD. All subcommittee members jointly assessed the completed reviews of the measures. Any unresolved issues and limitations of the critiqued measures were identified for discussion and reporting. The final recommendations were based on consensus among the subcommittee members and the liaison member of the Committee on Rating Scales Development of the MDS (E.C.).

Selection of Measures

The methodology for this review was modeled on a previously used methodology.[7] A literature search was performed using Medline on PubMed, Web of Science, EMBASE, and Psychinfo. The keywords used in the search included the following: "Huntington*" OR "Westphal variant" OR "juvenile Huntington,*" and the terms "scale" OR "questionnaire" OR "index" OR "measure" as well as the keywords "Quality of life," "QoL," "health-related quality of life," "HRQoL," and "health status." For each identified clinical measure, a search was conducted for the terms "Huntington's disease" or "Huntington disease" or "Huntington*" and the name of the measure. Manuscripts published before October 17, 2016, were retrieved using the above search strategy and thoroughly screened by the chair of the subcommittee (T.A.M.) to ascertain which measure had been used in each study.

Inclusion/Exclusion for Review

Measures used at least once in HD populations (patients at risk, presymptomatic gene carriers, and symptomatic HD patients) were included. Measures were excluded from review if they were not available in English, were only mentioned in reviews but not used in an original study, were created for a specific study without any information about their structure or use, or if the full paper was not available (eg, abstract

TABLE 1. Classification system for scale recommendation

Category	Criteria
"Recommended"	(1) Scale has been used in HD populations. (2) Use in HD by groups other than the original developers and data on its use were available.[a] (3) The available clinimetric/psychometric data in HD support the goals of screening (eg, evaluation of sensitivity/specificity, score cut-off points, and reliability) or measurement of severity (eg, evaluation of reliability, construct validity, and score discrimination across levels of symptom severity).
"Suggested"	(1) Scale has been used in HD populations. (2) Only 1 other criteria (2) or (3) from the above recommended category applies.
"Listed"	(1) Scale has been applied to HD populations, but no further criterion met.

HD, Huntington's Disease.
[a]For rating scales not originally developed for use in HD, criterion 2 was fulfilled if used in at least 1 group in HD that reported any kind of clinimetric/psychometric data in HD.

format only). In terms of construct of measures, the subcommittee decided to include all measures proposed by developers to capture HRQoL, QoL, or HS that have been used in HD studies.

Criteria for Rating

We followed the Classification System for Scale Recommendation used by the MDS that uses the following 3 criteria: (1) use in HD populations, (2) use in HD by groups other than the original developers and data on its use are available, (3) the available clinimetric/psychometric data in HD support the goals of measurement of severity (eg, evaluation of reliability, construct validity, and score discrimination across levels of symptom severity). Specific to this review, although HRQoL is not a symptom per se, it reflects the multidimensional construct of the impact of a disease/condition on QoL. The ability to differentiate across different levels of severity still stands as fundamental for a valid assessment of HRQoL (or caregiver QoL) in observational studies or clinical trials (for further details, see Table 1.)

Results

Identified Measures and Their Use in Clinical Research

A total of 21 clinical measures that have been used in HD research studies were identified. Two of these measures were excluded after abstract review because of inadequacy of the measure construct (see Supplementary Material). The remaining 19 clinical measures were included for an in-depth review. Three measures were excluded because (1) their sole use in HD was in case series without any clinimetric data available (the Manchester Assessment of Quality of Life, the Fatigue Impact scale), (2) it was created solely for a single study (a nonstandardized QoL question). We grouped the 16 remaining measures into patient-centered HRQoL measures (n = 14) and caregiver-centered QoL measures (n = 2) (see Table 2).

For patient-centered HRQoL measures, only The Medical Outcomes Study 36-Item Short-Form Health Survey was (SF-36) received a classification of "recommended" as a generic assessment of health status in manifest HD (severity). The 12-Item Short Form Health Survey (SF-12), the Sickness Impact Profile (SIP), the Huntington's Disease Health-Related Quality of Life Questionnaire (HDQoL), and the 12-item World Health Organization Disability Assessment Schedule (WHODAS 2.0) were classified as "suggested" (see table 3 for clinimetric details of recommended and suggested measures, and the Supplementary Material for reviews of all assessments classified as "suggested with caveats" or "listed").

For caregiver-centered QoL measures, no measure was "recommended" for any of the purposes considered in this review. The Alzheimer's Carer's Quality of Life Inventory (ACQLI) and the Huntington's Disease Quality of Life Battery for Carers (HD-QoL-C) were classified as "suggested" (see the Supplementary Material for overviews of all assessments classified as "suggested with caveats" or "listed").

Patient-Centered HRQoL Rating Scales

Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36). The SF-36 is an easy-to-administer self-reported set of generic measures of patient health status developed by the RAND Corporation as part of the Medical Outcomes Study. The SF-36 assesses 8 functional dimensions–physical functioning, physical role limitations, mental health, emotional role limitations, social functioning, energy/vitality, pain, and general health perceptions—that can be summarized into 2 scores (physical and mental) and a global utility index.[8] The SF-36 has been widely used in HD,[9-12] and the vast majority of the data were collected using version 1 of the SF-36. The most current SF-36 version 2 has less ambiguous wording, improved layout, enhanced response choices for some items, and increased cross-cultural validity.

Internal consistency has been shown for the SF-36 subscales and domain and component scores (Cronbach's $\alpha \geq 0.80$).[9-12] The test-retest reliability coefficients, as measured by intraclass coefficient (ICC), have been reported to be >0.70 for all domains, apart from the "emotional role" domain (ICC = 0.63). The mental health summary score has been shown to correlate only with the Beck Depression Inventory (BDI),

TABLE 2. Summary of all included scales in HD

Scale/Questionnaire	Developed for use in HD	Scale has been applied to HD populations	Used by other groups beyond the original developing group	Appropriate clinimetric testing in HD	Recommendation level	Comments
Patient-Centered Assessments						
Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36)	No	Yes	Yes	Yes	Recommended as a generic assessment of health status in manifest HD (severity)	Most of the clinimetric data in HD were generated using older version 1
Medical Outcomes Study 12-Item Short-Form Health Survey (SF-12)	No	Yes	Yes	No	Suggested as a generic assessment of health status in manifest HD (severity)	
Sickness Impact Profile (SIP)	No	Yes	Yes	No	Suggested for assessing perceived health status in manifest HD (severity)	
12-item World Health Organization Disability Assessment Schedule (WHODAS) 2.0	No	Yes	Yes	No	Suggested for assessing health status in HD (severity)	
The Huntington's Disease health-related Quality of Life questionnaire (HDQoL)	Yes	Yes	Yes	No	Suggested for assessment of health-related QoL in HD (severity)	
EQ-5D	No	Yes	Yes	No	Suggested with caveats	Minimal clinimetric data available
RAND-12 Health Status Inventory (HIS)	No	Yes	Yes	No	Suggested with caveats	Used in a single study
Neuro-Quality of Life (Neuro-QoL)	No	Yes	Yes	No	Suggested with caveats	Used in a single study
PROMIS Global Health (PROMIS)	No	Yes	Yes	No	Suggested with caveats	Used in a single study
Huntington Disease Health-Related Quality of Life (HDQLIFE)	Yes	Yes	No	No	Listed	
WHO-Quality of Life-BREF (WHOQOL-BREF)	No	Yes	No	No	Listed	
Quality of Life Index (QoL Index)	No	Yes	No	No	Listed	
Huntington Quality of Life Instrument (H-QoL-I)	Yes	Yes	No	No	Listed	
HD-PRO-TRIAD	Yes	Yes	No	No	Listed	
Caregiver-Centered Assessments						
The Alzheimer's Carer's Quality of Life Inventory (AQLI)	No	Yes	Yes	No	Suggested for assessing quality of life for HD caregivers (severity)	
Huntington's Disease Quality of Life Battery for Carers (HD-QoL-C)	Yes	Yes	Yes	No	Suggested for assessing quality of life for HD caregivers (severity)	

EQ-5D, EuroQol Five-Dimension Questionnaire; HD, Huntington's Disease.

TABLE 3. Summary of clinimetric data of all instruments used in HD with a recommendation level of "recommended" or "suggested"

Scale	Internal consistency	Test-retest reliability	Construct validity	Group known validity	Responsiveness	Ceiling/floor effect	Sensitivity/ specificity	Translation status[a]
Patient-Centered Assessments								
Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36)[b]	+	+	+	+	+/−	NR	NR	Widespread
Medical Outcomes Study 12-Item Short-Form Health Survey (SF-12)	−	−	+	+	+/−	NR	NR	Widespread
Sickness Impact Profile	+	+/−	+/−	−	NR	NR	NR	English
12-item World Health Organization Disability Assessment Schedule	+	NR	+/−	+	NR	Ceiling effect	NR	Widespread
The Huntington's Disease health-related Quality of Life questionnaire	+	+	+/−	−	−	Ceiling effect	NR	English
Caregiver-Centered Assessments								
The Alzheimer's Carer's Quality of Life Inventory	+	NR	NR	NR	NR	Acceptable floor and ceiling effect	NR	English, French, German, Italian, Spanish
Huntington's Disease Quality of Life Battery for Carers	+	+/−	+/− (sparse)	NR	NR	Acceptable floor and ceiling effect	NR	English, French Italian

Data regarding Minimally Clinically Important Difference was not assessed in any of the scales. (+) - good performance, (+/−) contradictory data or very limited data, (−) poor performance. HD, Huntington's disease; NR, not reported
[a]We list the languages officially recognized as being used for scale translation, widespread = scale translation has been recognized in more than 5 languages
[b]The SF-36 was the only rating scale "recommended." Remaining scales were "suggested."

whereas the physical health summary score of the SF-36 correlates with the BDI and a patient's self-rated and clinician's rating of patients' level of functioning/ independence level, but no factor analysis has been conducted for the SF-36 in this population. The SF-36 (total score, vitality score, and mental component score) have been shown to be sensitive to change in manifest HD clinical trials.[9,11,13]

Recommendation. The SF-36 is "recommended" as a generic assessment of health status in manifest HD (severity). The physical summary score seems to have better construct validity in HD. It is not known if the more recent SF-36 version 2 performs equally well in HD as the SF-36 version 1.

Medical Outcomes Study 12-Item Short-Form Health Survey (SF-12). The SF-12 is a 12-item shorter version of the SF-36. It covers the same functional dimensions as the SF-36 but includes fewer items and thus is quicker to administer (2 minutes vs 8-12 minutes for the SF-36).[14] It has been used less extensively in HD than the SF-36.[8] It is currently being used in Enroll-HD, but no data have been reported.[15] Various degrees of convergent validity have been reported between the SF-12 physical and mental health components, and the components of the HD-PRO-Triad (SF-12 physical component, Pearson correlations: motor, −0.79; cognition, −0.77; emotion/ behavioral dyscontrol, −0.47; total score, −0.76; SF-12 mental component, cognition, −0.61; motor, −0.51; total score, −0.61), and emotion/behavioral dyscontrol; Pearson correlation: −0.53, all $P < .05$).[16] The SF-12 physical component, but not the mental health component, has been shown to be sensitive to change following multidisciplinary rehabilitation.[17]

Recommendation. The SF-12 is "suggested" as a generic assessment of health status in manifest HD (severity), as it lacks test-retest reliability data and internal consistency data.

Sickness Impact Profile (136 Items). The SIP is a generic measure of self-reported health status,[18] consisting of 136 items covering 12 categories grouped into 2 subscales (physical and psychosocial). Scores are presented as a percentage of maximal dysfunction ranging from 0 to 100; a higher score indicates a higher level of dysfunction. The SIP can take up to 30 minutes to complete. The SIP has been used in 2 studies in manifest HD,[19,20] and a modified version using only 3 of the 12 categories was used in trial for

cognition in HD.[21] Internal consistency has been reported to be high (Cronbach's $\alpha > 0.80$),[19] as has test-retest reliability (ICC > 0.70) for scores of subscales and all categories, aside from the "emotional behavior" (ICC = 0.49) and "work" (ICC = 0.68) categories.[19] The SIP total score has been shown to correlate with both the patient's self-rated (Spearman correlation, −0.69) and clinician's rating (Spearman correlation, −0.64) of patients' level of functioning/independence (all $P < .01$), with the BDI (Spearman correlation, 0.47; $P < .01$), and with the Unified Huntington's Disease Rating Scale–Total Motor score (UHDRS-TMS; Spearman correlation, 0.32; $P < .05$). The Psychosocial subscale has been shown to correlate with both the patient's self-rated and the clinician's rating of patients' level of functioning/independence, whereas the Physical subscale has been shown to correlate with both the BDI and the UHDRS-TMS in addition to both the patient's self-rated and the clinician's rating of patients' level of functioning/independence.[19] In a head-to-head comparison with the SF-36, the SIP was shown to have a worse clinimetric performance with less robust construct validity and test–retest reliability. In addition, motor symptoms appeared to influence some strictly nonmotor dimensions of the SIP.[19]

Recommendation. The SIP is "suggested" for assessing health status in manifest HD (severity). There are limited clinimetric data on its use in HD, and it performs worse than the SF-36 in a head-to-head comparison.

12-item World Health Organization Disability Assessment Schedule (WHODAS) 2.0 . The WHODAS 2.0 was developed by the WHO and is often considered a generic function-related measure of health status, and consequently it was decided by consensus to include it in this review and not in the review of measures for assessment of functional ability in HD. The WHODAS 2.0 can be administered as interviewer-, self-, and proxy-administered forms. The WHODAS 2.0 12-item version, which is reviewed here, takes 5 minutes to complete and covers the following 6 domains: cognition, mobility, self-care, getting along, life activities, and participation. The WHODAS 2.0 12-item has been used in three studies including both premanifest and manifest HD.[22-24] Internal consistency has been shown with a Cronbach's α of 0.94 (95% CI, 0.93-0.94).[22] Moderate convergent validity has been reported between the WHODAS 2.0 and other HRQoL assessments such as the RAND-12 (Pearson correlations ranging from −0.76 to −0.41), and the EuroQol Five-Dimension Questionnaire (Pearson correlations ranging from = −0.65 and −0.49).[22] The scores in the WHODAS 2.0 differ significantly across the disease spectrum from the premanifest stage to late HD.[22] In premanifest HD, cross-sectional differences between low-, mid- and high-disease burden groups have been reported.[23] In premanifest HD, only the companion-rated (proxy) version of the WHODAS 2.0 has been shown to be sensitive to change over a period of 3 years.[23]

Recommendation. The WHODAS 2.0 12-item is "suggested" for assessing health status in HD (severity), as it lacks important clinimetric development in HD, namely, for test-retest reliability testing and requires more robust construct validity.

HDQoL. The HDQoL is a patient-reported questionnaire that was specifically developed for use in HD to assess HRQoL.[25] The HDQoL covers the following 3 main domains: "primary physical and cognitive," "primary emotions and self," and "primary services."[25] It takes about 22 minutes to complete. The HDQoL has been used in 1 study by authors[26] other than the group[25,27] who originally developed it. The internal consistency of each of the domains has been shown to vary: "primary services" (Cronbach's $\alpha = 0.76$), "primary emotions and self" (Cronbach's $\alpha = 0.89$), and "primary physical and cognitive" (Cronbach's $\alpha = 0.96$). Test-retest reliability has been reported, but as this was evaluated with Cronbach's α it does not provide a true adequate measure of concordance.[25] Item ceiling effects range from 12.5% to 50%.[25]

Recommendation. The HDQoL is "suggested" for assessment of HRQoL in HD (severity), as there are limited clinimetric data, namely related with construct validity and test-retest reliability.

Caregiver-Centered QoL Measures

The Alzheimer's Carer's Quality of Life Inventory (ACQLI). The ACQLI was developed to assess caregiver QoL in Alzheimer's disease.[28] It is a quick (<5 minutes) questionnaire that consists of 30 items to which the caregiver answers true or not true; 1 point is given for each true answer, giving a possible total score of 30. The ACQLI has been used in a single HD study, in a head-to-head comparison with the HD-QoL-C. The ACQLI [29] showed excellent internal consistency (Cronbach's $\alpha = 0.95$).[29]

Recommendation. The ACQLI is "suggested" for assessing QoL for HD caregivers (severity), as its use in HD is limited to a single study in HD and clinimetric data in HD are limited to internal consistency.

Huntington's disease quality of life battery for carers (HD-QoL C). The HD-QoL-C is a HD-specific, multidimensional measure for family or caregivers of patients with HD. It is based on the domains and facets of the Comprehensive Quality of Life Scale for Adults.[30] Two versions are available: a long form that consists of 34 items that incorporate measures on "practical aspects of caregiving" (n = 9), "satisfaction with life" (n = 8), and "feelings about living with HD" (n = 17), and a short form that consists of 20 items (3 items on "satisfaction of life," and 17 items on "feelings about living with HD").[29] The HD-QoL-C has been used in 4 studies in HD.[9,29,31,32] Internal consistency of the long form has been shown for the domains "satisfaction with life" (Cronbach's $\alpha = 0.91$) and "feelings about living with HD" (Cronbach's $\alpha = 0.84$), but not for the domain "practical aspects of caregiving" (Cronbach's $\alpha = 0.62$).[29] For the short form, internal consistency has been shown ("satisfaction with life," 0.92; total score, 0.88).[29] A low correlation has been reported between the HD-QoL-C and the WHO Quality of Life Short Form,[32] and the Huntington Quality of Life Instrument (correlations 0.22 to 0.28; all $P < .01$).[31]

Recommendation. The HD-QoL-C is "suggested" for assessing QoL for HD caregivers (severity). It warrants additional clinimetric development, namely in terms of validity, reliability, and data reproducibility by other groups.

Discussion

We report here the results of an in-depth review of 14 measures used in HD studies to evaluate patient-centered HRQoL. The SF-36 is the only measure that can be classified as "recommended" to measure patient's HRQoL in terms of severity. None of the HRQoL measures developed specifically for HD have undergone sufficient clinimetric development to warrant a similar classification level. There were no HRQoL measures recommended to measure change of severity over time. Regarding patient-centered HRQoL measures, the subcommittee identified the following topics that warrant consideration when developing these types of measures:

1. The inherent subjective nature of self-reporting HRQoL warrants a special comment as HD patients often lack insight regarding the presence or severity of their symptoms. Along the same lines, the progressive cognitive impairment experienced by HD patients is likely to introduce additional difficulties in ensuring the reliability of patient-reported HRQoL in HD, namely, at later stages. Proxy reporting was rarely included in the measures reviewed here and could be further assessed and considered as a strategy to mitigate the previously mentioned limitations of patient-reported outcomes in HD.
2. As HD is a rare disease, studies often require a multicenter, multinational design that raises the need for validation of HRQoL and QoL measures across different cultures. In this review, there were no data available on a formal cross-cultural validation for any of the included measures when applied to HD populations. Consequently, cross-cultural validation should be implemented in future development programs of HRQoL measures in HD.
3. We discussed the need for a generic measure versus a disease-specific measure. Given the complexity of the clinical presentation of HD, it is likely that a generic scale will not capture all the disease features that significantly impact on the HRQoL of these patients, and thus a disease-specific measure may be better positioned to capture HRQoL in HD in a valid manner. On the other hand, although disease-specific measures are usually more sensitive, generic measures are able to capture global aspects of health that may be overlooked by the specific scales. A disease-specific measure that incorporates items likely found in generic measures is possibly the best approach.

The committee also looked at caregiver-centered QoL measures. We recognize that these measures have their own issues. In this review, we included 2 caregiver-centered QoL measures, 1 developed in Alzheimer's disease and another specifically developed for HD. Although caregivers play a role in caring for patients with a wide range of neurodegenerative disorders, and there are many features in common between caring for such patients and caring for a progressively dependent patient, there are limited data available to determine if similarities across neurodegenerative disorders are sufficient to warrant a general QoL scale or whether caregiver QoL needs to be disease specific. A caregiver-centered measure that considers both disease-specific items and more generic items would likely be the best approach.

In the current review we identified several measures that were "listed." In many cases, these measures have had limited evaluation of their measurement properties in HD. Still, other recently developed HD-specific measures are in the initial stages of comprehensive measurement property testing, these include the Huntington Disease Health-Related Quality of Life, the HDQoL, or HD-PRO-TRIAD. Importantly, some of these newer measures incorporate patient stakeholders in their development, a contribution deemed essential by regulatory agencies such as the US Food and Drug Administration for patient-reported outcomes supporting labeling claims.[33] Further testing of the measurement properties and uptake of these measures by groups other than the developers is required to

determine their real value in evaluating HRQoL in HD patients. The committee concluded that the evaluation of the measurement properties of the currently available measures that are included in this review, namely those developed specifically for HD, is warranted. This should be a priority for HD researchers, considering for example the increasing importance of patient-reported outcomes in the development of novel therapies and their subsequent approval by regulatory authorities.

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Supporting Data

Additional Supporting Information may be found in the online version of this article at the publisher's website.