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

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Abstract

The compromise of quality of life (QoL) in Huntington's disease (HD) is a major issue, both for individuals with the disease as well as for their caregivers. The International Parkinson and Movement Disorder Society (MDS) commissioned a review of the use and clinimetric validation status of measures used in HD to assess aspects related with QoL, and to make recommendations on their use following standardized criteria. We included both patient-centered measures (patient Health-related (HR) QoL measures) and caregiver-centered measures (caregiver QoL measures). After conducting a systematic literature search, we included 12 measures of patient HRQoL and 2 measures of caregiver QoL. Regarding patient-centered measures, the Medical Outcomes Study 36-Item Short-Form Health Survey is "recommended" as a generic assessment of HRQoL in patients with HD. 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 QoL 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 HRQoL can be challenging in HD, as patients may lack insight and there is insufficient clinimetric testing of these scales, the committee concluded that further validation of currently available HRQoL measures should be undertaken, namely, those HD-specific HRQoL measures that have recently been reported and used.

INTRODUCTION

Huntington's disease (HD) is a complex neurodegenerative disorder in which motor, cognitive and behavioral manifestations have a significant impact on 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, be that 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 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), ~~the sub-committee the authors decided~~ we also ~~to~~ include**d** 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 (sub-committee) 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 sub-committee members evaluated each measure. If a sub-committee member was involved in the development of a measure, he/she was not involved in its review. Data were extracted into a *proforma* 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 sub-committee 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 sub-committee 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: "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", "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 sub-committee (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 (e.g., abstract format only). In terms of construct of measures, the sub-committee 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 three 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 (e.g., evaluation of reliability, construct validity, and score discrimination across levels of symptom severity). Specific to this review, while 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 19 clinical measures that have been used in HD research studies were identified. One of these measures was excluded after abstract review due to inadequacy of measure construct (see supplementary material). The remaining 18 clinical measures were included for an in-depth review. Four 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 Non-Standardized QoL question), and 3) the proposed construct was inadequate for the current review (the Caregiver Burden Inventory). We grouped the 14 remaining measures into patient-centered HRQoL measures (n=12) and caregiver-centered QoL measures (n=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 supplementary material for overview 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 (AQLI), and the Huntington's Disease Quality of Life Battery for Carers (HD-QoL-C) were

classified as "suggested" (see supplementary material for overview 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 (MOS). The SF-36 assesses eight functional dimensions: physical functioning, physical role limitations, mental health, emotional role limitations, social functioning, energy/vitality, pain, and general health perceptions, which can be summarized into two 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 was collected using version 1 of 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 Intra-Class 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), while 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's 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's correlation: -0.53, all $p<0.05$).[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 (SIP) 136 items

The SIP is a generic measure of self-reported health status,[18] consisting of 136 items covering 12 categories grouped into two 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 two 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's correlation: -0.69) and clinician's rating (Spearman's correlation: -0.64) of patients' level of functioning/independence (all $p< 0.01$), with the BDI (Spearman's correlation: 0.47, $p<0.01$), and with the Unified Huntington's Disease Rating Scale – Total Motor Score (UHDRS-TMS) (Spearman's correlation: 0.32, $p<0.05$). 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, while 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 non-motor 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.

World Health Organization Disability Assessment Schedule (WHODAS) 2.0 (12-item)

The WHODAS 2.0 was developed by the World Health Organization (WHO) 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 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 pre-manifest and manifest HD.[22-24] Internal consistency has been shown with a Cronbach's alpha of 0.94 (95% CI: 0.93 - 0.94).[22] Moderate convergent validity has been reported between the WHODAS 2.0 and other health-related quality of life assessments such as the RAND-12 (Pearson correlations ranging from - 0.76 to -0.41), and the EuroQol Five-dimension questionnaire (EQ-5D; 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 pre-manifest stage to late HD.[22] In pre-manifest HD, cross-sectional differences between low-, mid- and high- disease burden groups have been reported.[23] In pre-manifest HD, only the companion-rated (*proxy*) version of the WHODAS 2.0 has been shown to be sensitive to change over a period of three 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.

The Huntington's Disease Health-Related Quality of Life Questionnaire (HDQoL)

The HDQoL is a patient-reported questionnaire that was specifically developed for use in HD to assess HRQoL.[25] The HDQoL covers three 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 one 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 alpha 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 (AD).[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 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, multi-dimensional measure for family or caregivers of patients with HD. It is based upon the domains and facets of the Comprehensive Quality of Life Scale for Adults (ComQol-A5).[30] Two versions are available: a long-form that consists of 34 items which 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 four 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 (WHO-QoL

BREF),[32] and the Huntington Quality of Life Instrument (H-QoL-I; correlations 0.22 to 0.28, all $p<0.01$). [31]

Recommendation: The HD-QoL-C is "suggested" for assessing QoL for HD caregivers (severity). It warrants ~~further~~ **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 12 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 ~~intensity~~ **severity** over time. Regarding patient-centered HRQoL measures, the sub-committee 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 above-mentioned limitations of patient-reported outcomes in HD.
2) As HD is a rare disease, studies often require a multi-center multi-national 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 *vs.* 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 two caregiver-centered QoL measures, one 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 HDQLIFE, 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 (FDA) 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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References

1. The World Health Organization Quality of Life assessment (WHOQOL): position paper from the World Health Organization. Soc Sci Med 1995;41:1403-1409.
2. World Health Organization. Constitution of WHO: Principles. http://www.who.int/about/mission/en/
3. Sampaio CMD, Goetz CG, Schrag A. Rating scales in Parkinson's disease : clinical practice and research. New York ; Oxford: Oxford University Press, 2012.
4. Martinez-Martin P, Kurtis MM. Health-related quality of life as an outcome variable in Parkinson's disease. Ther Adv Neurol Disord 2012;5:105-117.
5. Aubeeluck AV, Buchanan H, Stupple EJ. 'All the burden on all the carers': exploring quality of life with family caregivers of Huntington's disease patients. Qual Life Res 2012;21:1425-1435.
6. Helder DI, Kaptein AA, Van Kempen GM, Weinman J, Van Houwelingen JC, Roos RA. Living with Huntington's disease: illness perceptions, coping mechanisms, and spouses' quality of life. Int J Behav Med 2002;9:37-52.
7. Schrag A, Barone P, Brown RG, et al. Depression rating scales in Parkinson's disease: critique and recommendations. Mov Disord 2007;22:1077-1092.
8. Ware JE, Jr., Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. Med Care 1992;30:473-483.
9. Thompson JA, Cruickshank TM, Penailillo LE, et al. The effects of multidisciplinary rehabilitation in patients with early-to-middle-stage Huntington's disease: a pilot study. Eur J Neurol 2013;20:1325-1329.
10. Khalil H, Quinn L, van Deursen R, et al. What effect does a structured home-based exercise programme have on people with Huntington's disease? A randomized, controlled pilot study. Clinical rehabilitation 2013;27:646-658.
11. Busse M, Quinn L, Debono K, et al. A randomized feasibility study of a 12-week community-based exercise program for people with Huntington's disease. J Neurol Phys Ther 2013;37:149-158.
12. Tabrizi SJ, Langbehn DR, Leavitt BR, et al. Biological and clinical manifestations of Huntington's disease in the longitudinal TRACK-HD study: cross-sectional analysis of baseline data. Lancet Neurol 2009;8:791-801.
13. Kloberg A, Constantinescu R, Nilsson MK, et al. Tolerability and efficacy of the monoaminergic stabilizer (-)-OSU6162 (PNU-96391A) in Huntington's disease: a double-blind cross-over study. Acta neuropsychiatrica 2014;26:298-306.
14. Pickard AS, Johnson JA, Penn A, Lau F, Noseworthy T. Replicability of SF-36 summary scores by the SF-12 in stroke patients. Stroke 1999;30:1213-1217.
15. Enroll-HD. A prospective registry study in a global Huntington's disease cohort: Clinical study protocol. 2011; https://www.enroll-hd.org/enrollhd_documents/Enroll-HD-Protocol-1.0.pdf
16. Carlozzi NE, Victorson D, Sung V, et al. HD-PRO-TRIAD Validation: A Patient-reported Instrument for the Symptom Triad of Huntington's Disease. Tremor Other Hyperkinet Mov (N Y) 2014;4:223.
17. Piira A, van Walsem MR, Mikalsen G, Nilsen KH, Knutsen S, Frich JC. Effects of a One Year Intensive Multidisciplinary Rehabilitation Program for Patients with Huntington's Disease: a Prospective Intervention Study. PLoS Curr 2013;5.
18. Bergner M, Bobbitt RA, Carter WB, Gilson BS. The Sickness Impact Profile: development and final revision of a health status measure. Med Care 1981;19:787-805.

19. Ho AK, Robbins AO, Walters SJ, Kaptoge S, Sahakian BJ, Barker RA. Health-related quality of life in Huntington's disease: a comparison of two generic instruments, SF-36 and SIP. Mov Disord 2004;19:1341-1348.
20. Helder DI, Kaptein AA, van Kempen GM, van Houwelingen JC, Roos RA. Impact of Huntington's disease on quality of life. Mov Disord 2001;16:325-330.
21. Cubo E, Shannon KM, Tracy D, et al. Effect of donepezil on motor and cognitive function in Huntington disease. Neurology 2006;67:1268-1271.
22. Carlozzi NE, Kratz AL, Downing NR, et al. Validity of the 12-item World Health Organization Disability Assessment Schedule 2.0 (WHODAS 2.0) in individuals with Huntington disease (HD). Qual Life Res 2015;24:1963-1971.
23. Kim JI, Long JD, Mills JA, Downing N, Williams JK, Paulsen JS. Performance of the 12-item WHODAS 2.0 in prodromal Huntington disease. Eur J Hum Genet 2015;23:1584-1587.
24. Paulsen JS, Long JD, Ross CA, et al. Prediction of manifest Huntington's disease with clinical and imaging measures: a prospective observational study. The Lancet Neurology 2014;13:1193-1201.
25. Hocaoglu MB, Gaffan EA, Ho AK. The Huntington's Disease health-related Quality of Life questionnaire (HDQoL): a disease-specific measure of health-related quality of life. Clin Genet 2012;81:117-122.
26. Quinn L, Debono K, Dawes H, et al. Task-specific training in Huntington disease: a randomized controlled feasibility trial. Phys Ther 2014;94:1555-1568.
27. Hocaoglu MB, Gaffan EA, Ho AK. Health-related quality of life in Huntington's disease patients: a comparison of proxy assessment and patient self-rating using the disease-specific Huntington's disease health-related quality of life questionnaire (HDQoL). J Neurol 2012;259:1793-1800.
28. Doward LC. The Development of the Alzheimer's Carers' Quality of Life Instrument Quality of Life Research 1997;6:639.
29. Hagell P, Smith S. A psychometric comparison of two carer quality of life questionnaires in Huntington's disease: implications for neurodegenerative disorders. J Huntingtons Dis 2013;2:315-322.
30. Cummins RA. The Comprehensive Quality of Life Scale (CoMQol-A5) Manual. . Toorak, Australia.: Deakin University, 1997.
31. Clay E, De Nicola A, Dorey J, et al. Validation of the first quality-of-life measurement for patients with Huntington's disease: the Huntington Quality of Life Instrument. Int Clin Psychopharmacol 2012;27:208-214.
32. Aubeeluck A, Buchanan H. The Huntington's Disease Quality of Life Battery for Carers (HDQoL-C). 2007; http://www.nottingham.ac.uk/nmpresearch/hdqol-c/documents.aspx
33. Guidance for industry: patient-reported outcome measures: use in medical product development to support labeling claims: draft guidance. Health Qual Life Outcomes 2006;4:79.