A digital motor score for sensitive detection of disease progression in early manifest Huntington's disease

Louis-Solal Giboin,[1] Cedric Simillion,[1] Johannes Rennig,[1] Atieh Bamdadian,[1] Fiona Kinsella,[2] Peter McColgan,[3] Edward J Wild,[2] Michael Lindemann,[1] Florian Lipsmeier,[1] Jonas Dorn[1]

1. Roche Pharmaceutical Research and Early Development, pRED Informatics, F. Hoffmann-La Roche Ltd, Basel, Switzerland;
2. Huntington's Disease Centre, UCL Queen Square Institute of Neurology, University College London, London, UK;
3. Roche Products Ltd, Welwyn Garden City, UK.

What does this mean for the Huntington's disease (HD) community?

The number of participants required for a clinical trial is directly related to how sensitively disease progression can be tracked. Furthermore, the larger a clinical trial, the longer it takes to recruit participants. The HD digital motor score has better sensitivity to change compared with standard clinical assessments, and may thus enable smaller/faster early-stage trials (sample size reduction by >75% possible). This means that, within the same timeframe, more therapies can be evaluated in a rare disease with a limited pool of potential study participants.

Objective

To evaluate whether a combination of select features derived from motor assessments from the Roche Huntington's disease (HD) digital monitoring platform (DMP) into a single HD digital motor score (HDDMS) allows quantification of disease progression in people with Huntington's Disease Integrated Staging System (HD-ISS) Stage 2 and HD-ISS Stage 3 HD with higher sensitivity than standard clinical assessments.

Background

- The development of novel therapeutics for HD requires sensitive assessments of symptoms, especially for individuals with early-stage HD. The current standards, such as the composite Unified Huntington's Disease Rating Scale (cUHDRS) are valid, reliable and able to detect changes in large Phase III studies.[1]
- However, in-clinic assessments are influenced by the interaction between rater and study participant, by their ordinal scale intervals, as well as day-to-day fluctuations of symptoms.
- Here, we propose an HDDMS, constructed from active digital motor assessments performed frequently at home, to sensitively assess progression of HD in both early and late disease stages.

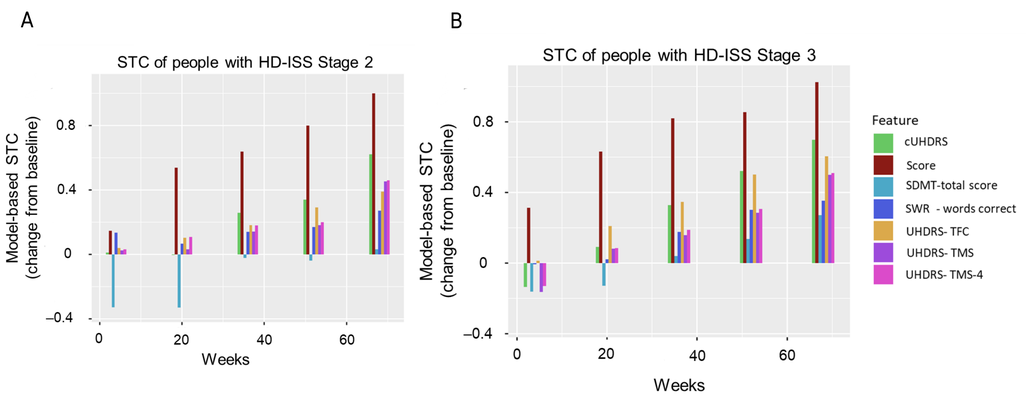
Methods

- We combined the digital features collected with the Roche HD DMP[2] in several studies (HD Natural History Study [NCT03664804], open-label extension of the tominersen Phase I/IIa study [NCT03342053], GENERATION HD1 [NCT03761849] and the Digital-HD study), into a dataset of over 1,000 individuals with HD.
- This dataset was divided into a development (N=141) and a validation dataset (N=319), which were used to build the HDDMS and to evaluate its generalisability and measurement properties.
- The top features were selected based on high sensitivity to change (STC), high intraclass correlation coefficient (ICC), and good cross-sectional correlation with cUHDRS. In addition, longitudinal feature progression had to be congruent with known-group differences from the Digital-HD study. STC was calculated from the estimates of change from baseline by a mixed model with repeated measures (MMRM) as: STC=estimate of change/standard deviation (SD).
- The top-ranked feature of each test was input to factor analyses, combining both exploratory and confirmatory factor analysis, to find the best measurement model and to test measurement invariance over time and between datasets. Individual scores were calculated using the regression method.

Results

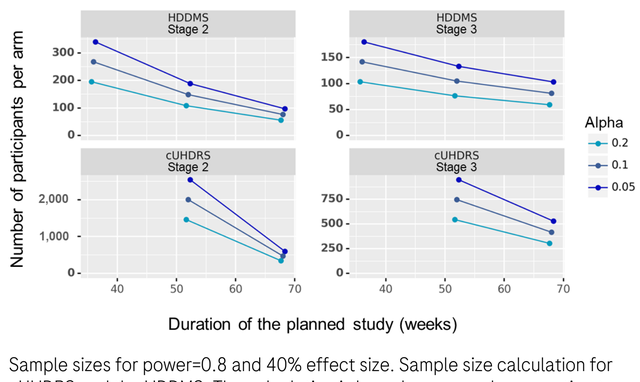
The HDDMS has a high sensitivity to change, resulting in lower sample sizes of people with HD-ISS Stage 2 or 3 in the GENERATION HD1 study.

Figure 1. STC of the HDDMS versus clinical assessments in people with HD-ISS Stage 2 or 3



HD-ISS Stage 2 (N=113) and Stage 3 (N=610). cUHDRS, SWR, SDMT and TFC were multiplied by −1 so all features have the same directionality of progression (higher scores indicate the worse outcomes).

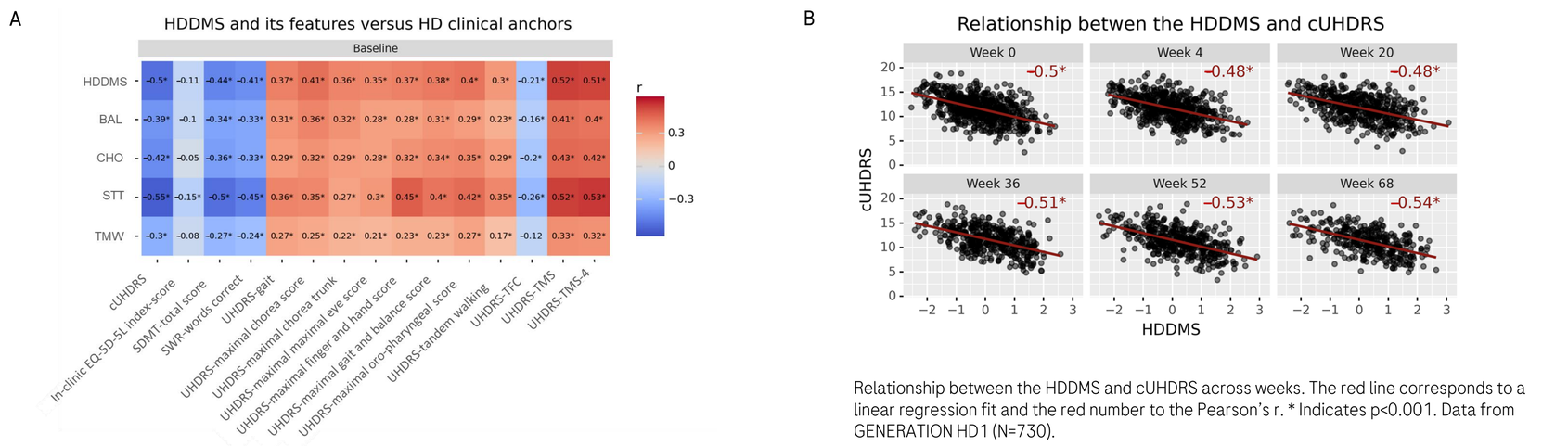
Figure 2. Sample size calculation for cUHDRS and the HDDMS



Sample sizes for power=0.8 and 40% effect size. Sample size calculation for cUHDRS and the HDDMS. The calculation is based on mean change estimate from the GENERATION HD1 PLB and the pooled SD from the Q16W and PLB. No data were shown for cUHDRS at Week 36 to improve readability.

The HDDMS and its features significantly and consistently correlate with clinical anchors.

Figure 3. (A) Correlation heatmap; (B) relationship between HDDMS and cUHDRS



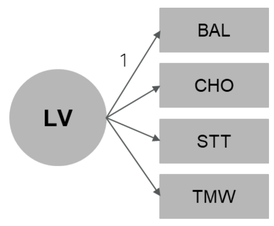
Label and colour = Pearson's r. * Indicates p <0.001.

Relationship between the HDDMS and cUHDRS across weeks. The red line corresponds to a linear regression fit and the red number to the Pearson's r. * Indicates p<0.001. Data from GENERATION HD1 (N=730).

The HDDMS shows strong measurement invariance on the validation dataset.

Figure 4. (A) Measurement model; (B) fit indices of measurement model; (C) loadings and individual score weights

A



Measurement model (with a loading of 1 for the BAL feature in order to identify the model). This model had the best fit on the development dataset compared with the other hypothesised measurement models and was strongly invariant in regard to time (tested up to Week 68).

B

	Development	Validation	Full dataset
P-value scaled	0.72	0	0
CFI scaled	1	0.961	0.982
RMSEA scaled	0	0.062	0.043
SRMR	0.063	0.060	0.031

Fit indices of the measurement model with strong invariance over time (fixed intercept and fixed loadings). For validation, the same intercepts and loadings were used. Then, on the full dataset (development and GENERATION HD1), the model was re-fit (with strong measurement invariance over time) in order to fine tune model parameters later used to calculate individual scores.

C

Feature	Loadings	Standardised loadings	Score weights
BAL	1	0.6993	0.5464
CHO	0.9159	0.7492	0.3840
STT	0.7830	0.6549	0.2260
TMW	0.7280	0.5580	0.2115

RMSEA better be <0.08; SRMR, better be <0.08; CFI, better be >0.9. We used scaled test statistics to account for possible non-normality in the features.

Conclusions

- A score built from four digital motor assessments showed a markedly increased sensitivity to change (STC) in people with Huntington's Disease Integrated Staging System (HD-ISS) Stage 3 and even HD-ISS Stage 2 (diagnostic confidence level 4); the STC at Week 20 was comparable to the STC of composite Unified Huntington's Disease Rating Scale at Week 69.
- Thanks to the large digital dataset collected across the Roche HD programme, development and validation of the HD digital motor score were performed on datasets from different clinical trials. Together with the good measurement properties observed, this increases confidence in the generalisability of the score.

Acknowledgements

We thank all study participants, the staff, and the study investigators. The open-label extension (OLE) study was initially sponsored by Ionis Pharmaceuticals, and transferred to F. Hoffmann-La Roche Ltd. The Digital-HD study is sponsored by the University College London (UCL), supported by a research grant to UCL from F. Hoffmann-La Roche Ltd. The authors thank Dylan Trundell for his contributions to this poster. Medical writing and editorial support were provided by Ayesha Babar, of Chrysalis Medical Communications, UK, in accordance with GPP2022 (https://www.ismpp.org/gpp-2022).

Abbreviations

BAL, balance; CFI, Comparative Fit Index; CHO, chorea; cUHDRS, composite Unified Huntington's Disease Rating Scale; DMP, digital monitoring platform; EQ-5D-5L, EuroQol 5-dimension 5-level; HD, Huntington's disease; HDDMS, HD digital motor score; HD-ISS, HD Integrated Staging System; ICC, Intraclass Correlation Coefficient; LV, latent variable; MMRM, mixed model for repeated measures; PLB, placebo; Q16W, every 16 weeks; RMSEA, root mean square error of approximation; SD, standard deviation; SDMT, Symbol Digit Modalities Test; SRMR, standardised root mean square residuals; STC, sensitivity to change; STT, Speeded Tapping Test; SWR, Stroop Word Reading; TFC, Total Functional Capacity; TMS, Total Motor Score; TMW, Two-minute Walking Test.

References

1. Schobel SA, et al. *Neurology*. 2017; 89:2495–2502;
2. Lipsmeier F, et al. *J Med Internet Res*. 2022; 24:e32997.

Please scan using your QR reader application to access this poster on your mobile device. NB: there may be associated costs for downloading data. These costs may be high if you are using your smartphone abroad. Please check your mobile data tariff or contact your service provider for more details. Alternatively, this can be accessed at: https://bit.ly/42IuDPd

Presented at CHDI 18th Annual Huntington's Disease Therapeutics Conference, Dubrovnik, Croatia; 24–27 April 2023