Qualification Advice List of Issues: Enroll-HD Response

Enroll-HD: Registry for Huntington's Disease

Introduction

On March 8, 2021 CHDI Foundation submitted an application to the EMA for a Qualification Opinion for Enroll-HD as a registry to be used as a data source and/or infrastructure support for post-authorisation studies of medicinal products. References to "Supplement" refer to that submission. On June 11, 2021, EMA responded with a list of 38 issues to be addressed in writing. This document responds to those 38 issues.

Enroll-HD is an integrated clinical research platform serving several different functions. The organising principle of Enroll-HD is to expedite Huntington's disease (HD) research and therapeutics development. This is achieved through leveraging clinical data and bio-samples from the Enroll-HD study cohort and through the clinical research infrastructure. To support Enroll-HD's broad functionality – including the core Enroll-HD study of 20,000 current participants – a comprehensive, robust, and centralised operational infrastructure was developed alongside a strong oversight infrastructure, well-positioning Enroll-HD to fulfill EMA's recommendations for registries. See Supplement Section 2. Enroll-HD's strengths include exhaustive capture of time elements and core data elements, use of common coding systems and terminologies, extensive data quality management, robust governance, and thorough processes for data sharing. In the Supplement, we presented evidence supporting the representativeness of the Enroll-HD study participant population with respect to that of the broader HD population, and emphasised the sizeable nature of the cohort for a rare genetic disorder, and the diverse nature of the cohort with respect to HD disease spectrum coverage. We also outlined planned improvements to standardise the collection of pregnancy data in Enroll-HD and to integrate compliance with country-level pharmacovigilance requirements (see Supplement Sections 7 and 9 and Question 11).

To fully evaluate the potential of Enroll-HD, it is important to recognize the following about Huntington's disease:

1) HD is a fully penetrant autosomal dominant genetic disease when the CAG expansion in the Htt gene is 40 repeats or larger. This means a positive genetic test has a positive predictive value of virtually 100%.

2) Before genetic tests became available in 1996, the disease could only be diagnosed by the presence of characteristic clinical symptomatology in the context of compatible family history. Today, the genetic test can be the basis for diagnosis, however a long-standing fear of social and economic stigmatization has kept the standard for diagnosis focused on clinical assessment rather than on genetic testing. This practice is slowly changing.

3) HD follows a very protracted pathogenic process. Clinical manifestations that are easily observable and detectable by medical examination become apparent usually in the 4th decade of life. However, subtle symptoms and/or signs tend to present much earlier, around the beginning of the 3rd decade, and biomarkers of disease progression, such as volumetric changes in deep brain structures (indicative of atrophy), may be detected even earlier. The disease is lifelong, spanning about six decades. The rate of progression of clinical features is slow, and disability milestones (e.g., first

detectable clinical symptoms, first functional deterioration, etc.) are separated by several years. The decades-long chronology of the disease process makes the annual visits in Enroll-HD sufficiently granular to capture the relevant events.

4) To reconcile the contradiction of diagnosing the disease based on clinical features that occur in the 4th decade, when the pathogenic process starts at birth, different nomenclatures have been used. Frequently the period before the clinical diagnosis is called "pre-manifest" or "prodromal" or both, contrasting with the period after clinical diagnosis, called "manifest." Furthermore, the reluctance of physicians to change their diagnostic practices has led to the creation of many alternative methods for describing "onset" of HD. Recently, there has been an effort to standardize the terminology of the disease life-course; a staging system has been developed that encompasses the entirety of the disease process from birth to death and defines the disease on the basis of the genetic test. This is the HD Integrated Staging System (HD-ISS).[1] In the future, we will map the Enroll-HD cohort to the HD-ISS and we will use HD-ISS to define the Enroll-HD population (via a future amendment to the Enroll-HD protocol).

5) The current pipeline of therapies for HD can be organized into two main categories, each with a few sub-classes. The main categories are: 1) disease-modifying therapies aiming at reducing the rate of progression, delaying disability, or rescuing functionality, and 2) symptomatic treatments aiming at ameliorating impairments. Among the disease-modifying therapies there are three important subtypes: a) gene therapies and nucleic acid therapeutics aimed at the Htt gene or genetic modifiers; b) cellular therapies through transplantation or gene therapy aimed at inducing the transformation of existing brain cells into neurons; and 3) therapies aimed at downstream targets. It is out of scope to discuss all these approaches in detail, but worth noting that HD pathogenesis is triggered by a gain of function mutation. In other genetic diseases where the mutation is a loss of function there is an expectation that when a functioning gene is successfully introduced in the system the quantitative changes in function are rapid and substantive (e.g., Spinal muscular atrophy, Leber hereditary optic retinopathy, Duchenne muscular dystrophy). In HD, because of the nature of the mutation, there is no expectation for rapid effects for any disease-modifying treatment; if such beneficial effects exist, they will be slowly accrued. Hence our conviction that the cadence of annual visits in Enroll-HD will remain appropriate.

The proposed context of use is **revised** as follows:

The Enroll-HD data collected per the Enroll-HD protocol can be a source of **secondary** data for drug utilization studies and post-authorisation safety and efficacy studies (PASS and PAES). Specific PASS/PAES studies can also be nested in Enroll-HD, in which case the Enroll-HD data specified by the PASS/PAES protocol becomes **primary** data for PASS/PAES studies.

To clarify, we propose that Enroll-HD can be used in two different ways: 1) as a data source for drug utilization studies or PASS/PAES; and 2) as a platform to support nested PASS/PAES. In option 1, Enroll-HD would be a source of secondary data. In option 2, nested PASS/PAES, Enroll-HD would be a source of primary data; each study will be treated as nested but have an independent protocol (an example of a nested protocol within Enroll-HD is provided in our response to Question 23, attached as Appendices A & B). Briefly, each of these nested studies will be conducted under its own protocol with specified inclusion and exclusion criteria, thus defining a sub-population within the Enroll-HD cohort. The data collected under the Enroll-HD protocol will be merged with the data collected under the PASS/PAES protocol; all such data would be

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[1] *The new Huntington's disease Integrated Staging System (HD-ISS)*, presentation by Tabrizi, S. & Long, J. at CHDI's 16th Annual HD Therapeutics Conference (April 27-29, 2021), *Available at* https://chdifoundation.org/2021-conference/#tabrizi.

considered primary data for the PASS/PAES. Data monitoring and analysis plans will be detailed in the protocol of each PASS/PAES. Plans for monitoring of Adverse Events would be specific to each PASS/PAES. The use of Enroll-HD data and infrastructure to support nested PASS/PAES eases the burden on the marketing authorisation holder (MAH) as well as on participants.

In the future and in conjunction with a MAH, we plan to seek scientific advice on Enroll-HD's use for *specific* nested PASS/PAES proposals. These post-marketing studies may require additional data or more frequent data points to appropriately evaluate drug effectiveness and drug safety. Exactly how this would be accomplished is dependent on the protocol of the PASS/PAES.

The answers to the 38 questions posed by the EMA follow. The answers appear in order, except the response to Question 23, which is attached as Appendices A & B.

Patient population and representativeness

1. It is unclear if readiness for genetic testing as one of the aims of Enrol HD creates a selection bias with respect to the general comparability to the broad HD population. Please comment.

Answer: Readiness for genetic testing is not one of the aims of Enroll-HD. Although an objective of Enroll-HD is to facilitate clinical research, unknown genetic status with respect to CAG length is not a hinderance to this objective. Allowing enrolment of people who don't want to know their genetic status is considered an advantage against selection bias. In Enroll-HD, participants can have "unknown" gene status, where they have not undergone local genetic testing and the participant's HD gene status is unknown to the participant himself, the site investigator, and the site team. Although all Enroll-HD participants undergo *research* genotyping, the results of this genotyping are not shared with the participants or investigators. Supplement Footnote * (p12) explains that it is acceptable to allow individuals without a confirmed diagnosis into a study in diseases like HD where some individuals may be unwilling to undergo predictive testing. In fact, "genotype unknown" participants make up 10% of the Enroll-HD cohort in Europe.

Despite the fact that Enroll-HD does not require genetic testing, the study sample has a higher rate of predictive testing than is observed in the general 'at risk' population.[2] This is likely reflective of the characteristics of the sample, which is more highly educated, and typically more likely to participate in research. Efforts to expand socioeconomic diversity in Enroll-HD are described in our response to Questions 24 and 25.

2. Retention in the study as a function of stage of manifest disease at baseline visit could also be of interest and should be examined.

Answer: Please see Question 32.

3. On the one hand, it is agreed that self-enrolment may enhance patient representativeness by potentially extending coverage to underrepresented patient groups and additional regions, but on

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[2] Baig SS, Strong M, Rosser E, et al. 22 Years of predictive testing for Huntington's disease: the experience of the UK Huntington's Prediction Consortium [published correction appears in Eur J Hum Genet. 2016 Oct;24(10):1515] [published correction appears in Eur J Hum Genet. 2017 Nov;25(11):1290]. *Eur J Hum Genet*. 2016;24(10):1396-1402. doi:10.1038/ejhg.2016.36.

the other hand, self-enrolment may also lead to a selection because self-enrolled patients are usually not representative (e.g., younger patients who are familiar with digital tools).

<ol type="a">
The Applicant is asked to explain the status of Self-Enrol as part of the Enrol HD Registry, and how the problem that self-enrolled patients may be a highly selected group could be reduced or addressed.

<u>Answer</u>: Enroll-HD and Self-Enroll are independent studies; Self-Enroll is not a part of the Enroll-HD registry. We are hopeful that Self-Enroll participants will subsequently engage in Enroll-HD, either due to their mobile experience or because with progression of symptoms they may feel the need/desire to attend clinic visits. We agree and acknowledge that the participant population in Self-Enroll may be impacted by (self) selection bias, in that it will likely be enriched for (typically younger) individuals who are more comfortable/familiar with digital technologies. Given the limited number of younger participants in Enroll-HD (<12% participants are <30 years old at study entry), this is an advantage – Self-Enroll will provide an avenue into a harder-to-reach HD population subgroup. Engaging younger individuals – far from disease onset – is of great interest, affording the opportunity to improve our understanding of the developmental pathology of HD. At this time, data from Self-Enroll will not be used for PASS/PAES studies.

<ol type="a" start="2">
Please explain how the self enrolled database will be linked to the clinician based database.

<u>Answer:</u> Self-Enroll will use the HDID system, the same system already used in Enroll-HD (and many other HD studies and trials). Each participant in Enroll-HD receives a unique ID which is generated using a secure system and is based on unchanging variables (e.g. date of birth). In this way, if an Enroll-HD participant joins another study, the data from both studies can be linked using the HDID. See Supplement 2.2.3.1.4 & 11.1.

<ol start="4">
Enroll-Lite will be introduced in the next Enroll-HD protocol amendment, projected for 2022. It is unclear which assessments are foreseen and how they will be validated in comparison with the on-site assessments.

<u>Answer:</u> Enroll-Lite will be included in the planned amendment to the Enroll-HD protocol to accommodate participants with advanced disease (approximately equivalent to Shoulson-Fahn stage 3 and higher). At this phase of the disease, attending Enroll-HD visits becomes burdensome and the completion of the entire set of Enroll-HD assessments becomes difficult due to fatigue. Therefore, Enroll-Lite will allow for remote visits and reduce the number of assessments.

As shown in the schedule of assessments for Enroll-Lite (LoI Table 1), participants will be able to choose between in-person and remote visits on an annual basis. Most measures included in the remote visits collect demographic or clinical history information about the participant. As such, we do not expect significant validity risk for remotely collected data using these measures but will monitor for systematic differences between data collected in-person and remotely. In addition, two measures, the Huntington's Disease Structured Interview of Function (HD-SIF) and Huntington's Disease Clinical Status Questionnaire (HDCSQ), are novel and therefore, require clinimetric/psychometric evaluation. The HD-SIF is a collection of structured interviews designed to standardize data collection, enabling assignment of ratings on the UHDRS© '99 functional scales (i.e., Total Functional Capacity, Functional Assessment, and Independence Scales). HDCSQ is a modified version of the Huntington's Disease Clinical Checklist (HDCC) that is more appropriate for people in the later stages of HD (e.g., it includes additional later stage milestones). These measures will undergo clinimetric analyses as part of CHDI's planned Later Stage Assessment (LSA) study. The LSA study will evaluate (a) the convergent validity of scores obtained from in-person and remotely delivered HD-SIF administrations with scores from in-person UHDRS '99 functional scale administrations and (b) for systematic differences in the data from later stage participants collected using the HDCC in Enroll-HD and the HDCSQ as part of LSA. The LSA study is expected to be complete by the end of 2022.

LoI Table 1: Assessments included in In-person and Remote Enroll-Lite Annual Visits

Assessments	Visit Type	
	In person	Remote contact
Socio-demographic information	X	X
Medical history	X	X
Comorbid conditions (updated)	X	X
Current therapies (pharmacotherapy, non-pharmacotherapies, and nutritional supplements; updated)	X	X
Weight	X	
HD Clinical Status Questionnaire	X	X
UHDRS-TMS	X	
Huntington's Disease SIF (UHDRS-TFC, FAS, and IS)	X	X
Mini-Mental State Examination	X	

5. It is currently not entirely clear what the Applicant means by 'targeted recruitment' to enrich the treatment population in case of approfocusved treatments. The Applicant is invited to elaborate further on how this should be done.

Answer: As needed, depending on the approved treatment, Enroll-HD can either create a nested study focused on the target population using a protocol developed by the MAH/pharmaceutical company in accordance with the PASS/PAES requirements or introduce a minor protocol amendment that does not alter Enroll-HD's overall eligibility criteria but does focus site recruitment on the targeted sub-population. The latter will be the best solution if a new therapy becomes widely available and access is not constrained, while the nested PASS/PAES is usually the appropriate approach when a therapy is newly introduced in the market.

6. Patients < 18 years of age are underrepresented in Enrol HD. While the restricted inclusion criteria for non-adults can be understood from an ethical point of view, these lead to even lower coverage of the estimated HDGEC population below 18 years of age in Enroll-HD and the absence of an age-appropriate control group. The Applicant is invited to discuss the appropriateness of the registry for younger patients.

Answer: The Enroll-HD study was designed for an adult, as opposed to a pediatric, HD population. Pediatric HD has a clinically distinct presentation relative to adult-onset HD, and there is no pediatric version of several Enroll-HD assessments. Symptomatic children were permitted to enter the study to gain insight into pediatric disease manifestations with the aim of keeping families together in research, not because of a specific focus on recruiting children. We acknowledge that pediatric HD – where the disease occurs before the age of 18 – is important and relevant, although extremely rare. U.S. claims data suggests that only 4.2% to 4.8% of HD patients are under 18. However, we recognize the need to serve this underrepresented population and intend to include a pediatric cohort as part of the forthcoming Enroll-HD protocol amendment.

Core data and time elements

7. **The Applicant should explain how the qualification of investigators (including training) regarding DCL assessment is ensured.**

Answer: To qualify as an Enroll-HD investigator, an individual must be a neurologist, psychiatrist, or have received a similar level of formal training. In addition, experience in management of Huntington's disease is a requirement for Enroll-HD site principal investigators. Each year all raters receive training in the use of UHDRS, with a focus on motor training. The training includes a collection of videos depicting real patients being rated by experienced neurologists. To get certification, the raters must evaluate a set of HD patients (via video) and their rating of each HD patient must be in accordance with the ratings provided by a team of experienced neurologists/HD specialists. New patient training videos are provided each year and each Enroll-HD PI must "pass" the course to receive their annual certification. The training is freely available on the Enroll-HD Clinical Training portal (https://hdtraining.enroll-hd.org/).

Scoring DCL cannot be certified because DCL is a clinical judgment based on experience with HD patients. The Diagnostic Confidence Level (DCL) is a single item that is part of the UHDRS Motor Assessment.[3] This item can be scored between 1 to 4 (1 is "non-specific motor abnormalities (less than 50% confidence)"; 2 is "motor abnormalities that may be signs of HD (50 – 89% confidence)"; 3 is "motor abnormalities that are likely signs of HD (90 – 98% confidence)" and 4 is "motor abnormalities that are unequivocal signs of HD (≥99% confidence)").

The anchors of the scores in the DCL are inherently subjective because they rely on the observer's confidence that the motor signs they are observing are attributable to HD. Like the diagnosis of many other neurodegenerative diseases (e.g., dementia, Parkinson's disease) there is a degree of variability in these judgments that are not just influenced by clinical experience and training but also by the observer's personality traits, the economic implications of making an explicit diagnosis, and the patient's implicit or explicit preference. When the DCL item was established, no explicit instructions were created, other than the heading of the item: "DIAGNOSIS CONFIDENCE LEVEL: To what degree are you confident that this participant meets the operational definition of the unequivocal presence of an otherwise unexplained extrapyramidal movement disorder (e.g., chorea, dystonia, bradykinesia, rigidity) in a participant at risk for HD?". This statement *refers* to an "operational definition," but no such definition is provided. The DCL item has obvious limitations due to its construct, and the interrater reliability has been reported to be only moderate (k=0.67).[4] Nevertheless, although interrater reliability has not been further formally evaluated, when used in large cohorts, the individual scoring variability is smoothed, and the reliability of DCL when compared to other measures of disease progression has been generally good. The progression of DCL from 1 to 4 correlates well with other markers of disease progression, including TMS – a more objective measure – for which the Enroll-HD investigators are annually certified. Analysis of the Enroll-HD dataset shows this relationship with TMS (LoI Figure 1) and with the CAP score (Age x CAG) which is the best-recognised measure of exposure to the toxic mutant protein (LoI Figure 2). Several independent studies showed similar findings.[5,6,7]

[3] Huntington Study Group (Kieburtz K, primary author). The Unified Huntington's Disease Rating Scale: Reliability and Consistency. Mov Dis 1996;11:136-142. *Available at https://huntingtonstudygroup.org/uhdrs/.*

[4] Hogarth, P., Kayson, E., Kieburtz, K., Marder, K., Oakes, D., … Rosas, D. (2005). *Interrater agreement in the assessment of motor manifestations of Huntington's disease.* Movement Disorders, 20(3), 293-297. doi:10.1002/mds.20332.

[5] Garcia, T. P., Wang, Y., Shoulson, I., Paulsen, J. S., & Marder, K. (2018). *Disease Progression in Huntington Disease: An Analysis of Multiple Longitudinal Outcome*s. Journal of Huntington's Disease, 1–8. doi:10.3233/jhd-180297.

[6] Long J.D., Langbehn D.R., Tabrizi S.J., et al. (2017). V*alidation of a prognostic index for Huntington's disease*. Movement disorders: official journal of the Movement Disorder Society. 2017;32:256–263.

[7] Liu, D., Long, J.D., Zhang, Y. *et al.* (2015). *Motor onset and diagnosis in Huntington disease using the diagnostic confidence level.* J Neurol 262, 2691–2698. https://doi.org/10.1007/s00415-015-7900-7.
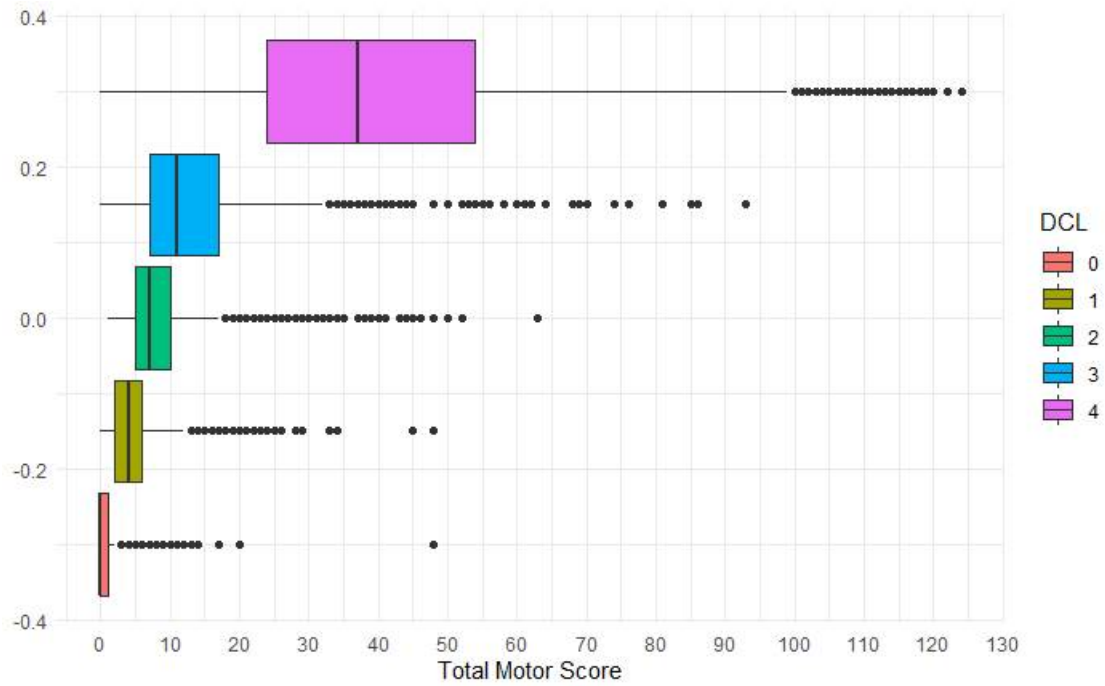
Lol Figure 1: Relationship between DCL and TMS.
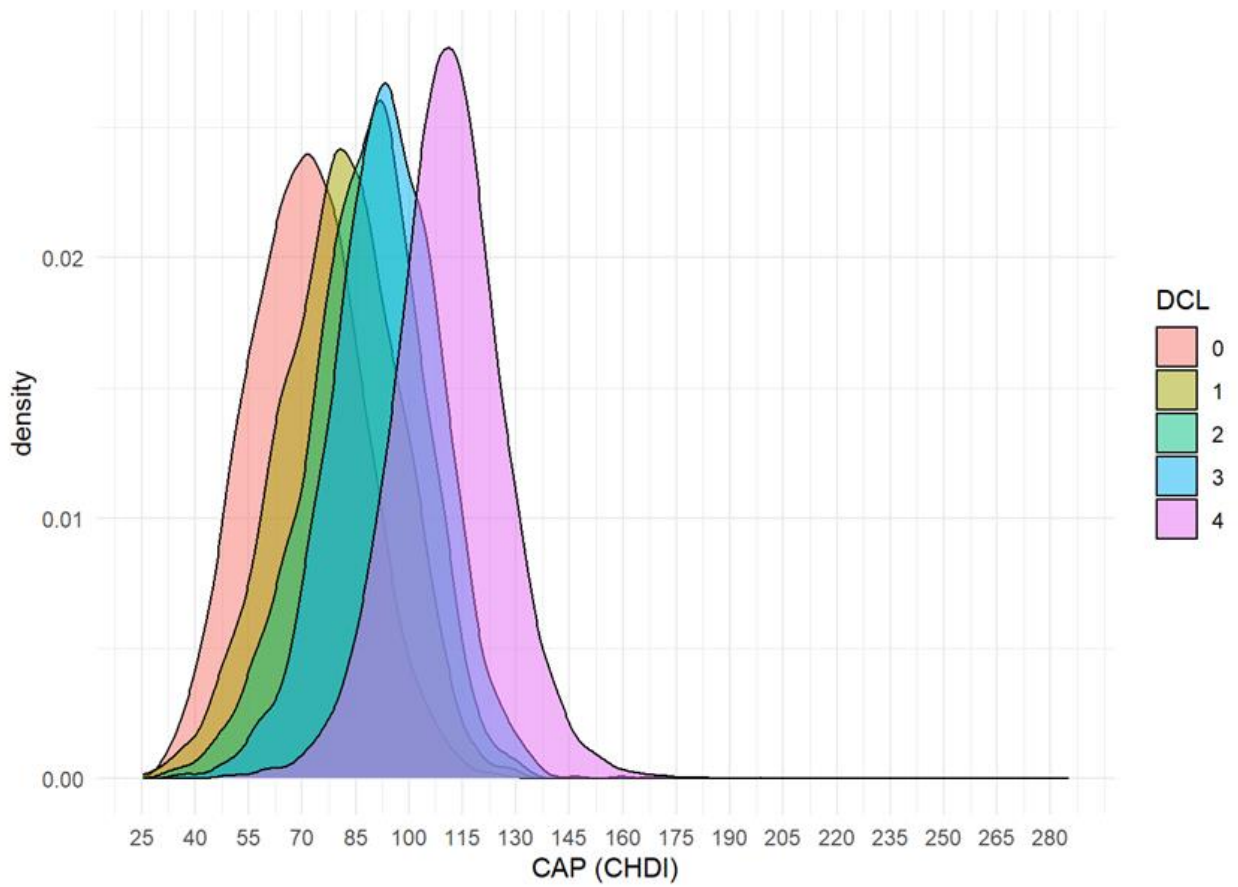
Lol Figure 2: Relationship between DCL and CAP.

8. The Applicant should explain and justify the chosen definition for "disease onset, any domain".

Answer: We believe that this question references an entry in Table 9 of the Supplement (a copy is provided below for reference). HD is a slow progressing autosomal dominantly inherited disease with subtle symptom onset in adulthood, so identifying the precise date of diagnosis has historically been challenging. For purposes of genetic linkage analysis, clinical definition of HD was based on the onset of *unequivocal* motor symptoms. This definition is imprecise as the first HD symptoms might be identified in other domains (e.g., behavioral, cognitive). Therefore, the variable of "disease onset in any domain" was important to capture in Enroll-HD. In Enroll-HD, several variables are recorded that may be considered as disease onset depending on the context. This allows researchers to decide which onset variable is most appropriate for their own studies. Below, Table 9 has been annotated with the justification for including each of the variables in the original protocol.

A new staging system (HD-ISS, see footnote 1) is being developed that better defines disease stages based on pre-determined cut-offs for specific assessments. We believe this landmark development will enable the HD community to better stage participants and enable researchers to have clear delineation points for analysis. It is expected that this new categorization scheme will be incorporated in the next amendment of the Enroll-HD protocol.

Currently, at each Enroll-HD visit, the rater reviews the assessments and determines if the participant is experiencing symptoms consistent with HD. If the rater feels that the symptoms are consistent with HD, the rater will change the HD categorization from "premanifest" to "manifest" and select the domain(s) that lead the rater to make this determination (e.g., cognition, motor, psychiatric, ocular motor, other, or mixed (meaning multiple domains)). The first time a rater categorizes a participant as manifest is a milestone captured in the dataset.

Excerpt from Table 1: Availability of core time element data (as defined by EMA 2018 discussion paper section 5.3) in Enroll-HD.

Date	EMA comments	Availability in Enroll-HD	Variable	Variable Label	eCRF	Reason for Inclusion in Protocol	DD page # (Append ix 2)
Date of diagn osis	Depending on the disease, for ex. date of definite diagnosis using a validated method such as MRI, histology, cyto-genetic method, etc.	Yes	*lbdtc*	Date of report (local CAG) NB: If the participant is pre-symptomatic at the time of local CAG test, and has a family history of HD, this indicates **date of genetic diagnosis**. If the participant is symptomatic at the time of local CAG test, *without* family history of HD, clinical diagnosis is confirmed by genetic testing; therefore, date of local genetic test may be used as **date of clinical diagnosis**.	CAG	Presence of CAG length >39 is required to establish genetic diagnosis of HD. Testing may occur before or after onset of symptoms.	16
			svstdtc & *diagconf*	Date of first visit at which diagnostic confidence level (DCL) is updated from '1', '2', or '3' to '4.' NB: Indicates **disease onset, motor**.	Variable items (Follow-up visit); Motor	DCL is an integral part of the HD assessment scale UHDRS. The rater assigns a DCL	49; 67

Date	EMA comments	Availability in Enroll-HD	Variable	Variable Label	eCRF	Reason for Inclusion in Protocol	DD page # (Append ix 2)
						of "4" when convinced that motor signs and symptoms are unequivocall y due to HD.	
			svstdtc & *hdcat*	Date of visit at which *hdcat* is updated from 'premanifest' to 'manifest.' NB: Indicates **disease onset, any domain**.	Variable items (Follow-up visit);	This allows the rater to establish the onset of symptoms due to HD in domains other than motor such as behavioral or cognitive.	49; 8
			hddiagn	Date of clinical HD diagnosis (based on symptoms in any domain) NB: Indicates **disease onset communicated to participant**.	HDCC	This records the event when the participant was informed by a physician that his symptoms are due to HD. This is relevant in participants who get presymptom atic testing or family screening.	13

9. Neuroimaging may play an important role regarding evaluation of disease progression of HD in the future. However, it is currently unclear, whether neuroimaging could be implemented in the registry, preferably with central reader evaluation, please elaborate.

<u>Answer:</u> We agree with the EMA evaluation that neuroimaging is increasingly recognized as an important progression biomarker for HD. The new HD categorization system (HD-ISS), recategorizes patients from Stage 0 to Stage 1 when a change in caudate or putamen volume is demonstrable.

To support the use of Enroll-HD as a data source for post marketing studies, the following efforts will help provide imaging data on Enroll-HD participants:

1. ImageClarity is a forthcoming platform study that involves multimodal state-of-the-art brain MRI imaging of HDClarity participants. The Enroll-HD platform initiated the HDClarity study in 2016. The HDClarity study includes CSF collection via an annual lumbar puncture in a subset of Enroll-HD

participants. The study is offered to all subjects at sites participating in HDClarity, provided that the participant meets the inclusion/exclusion criteria. Since the HDClarity study began in 2016, approximately 600 participants have enrolled at 25 Enroll-HD sites. The plan is to initiate up to 60 sites and up to 2500 participants. All HDClarity participants will be invited to participate in ImageClarity if they meet the inclusion/exclusion criteria. The ImageClarity protocol is under development, with first participant in estimated for Q1'22. The data will be read and analysed by a central reader.

2. Additionally, in the next planned amendment of the Enroll-HD study, volumetric MRI will be included as an optional assessment. The brain MRI sequence will be abbreviated (e.g. T1 weighted imaging) to obtain information on the brain volume as well as the volume of basal ganglia such as caudate and putamen, which are the primary and earliest affected brain structures in HD. This will help in staging the disease as well as following disease progression. A decision between central reading and local reading of this MRI has yet to be finalized.

Should an Enroll-HD nested post-marketing study require specific MRI sequences, these will be included in the protocol for the nested PASS/PAES study and data recorded accordingly. The MRI studies done in the context of the PASS/PAES study can be evaluated by a central reader if this is a protocol requirement.

10. From the annotated eCRF, form "pharmacotherapy", it is not fully clear whether only disease related or also relevant concomitant therapies should be entered by the investigator, however respective information should be captured mandatorily as recommended in section A.3.2 of the Draft Guideline on registry-based studies. Please amend as appropriate.

Answer: All pharmacotherapies are captured. Enroll-HD collects all treatments related to HD *and* any other disease, and the indication for the medication is also captured. (Note that while there are not many drugs labelled for HD, there are several therapies used for HD symptoms.) LoI Figure 3 shows how the data for both pharmaceutical and non-pharmaceutical therapies are entered into the EDC. As shown in the second screenshot, the nonPharmacoTx are coded based on a dropdown menu. Information on nutritional supplements (e.g., vitamins) is also collected on a separate but similar form.
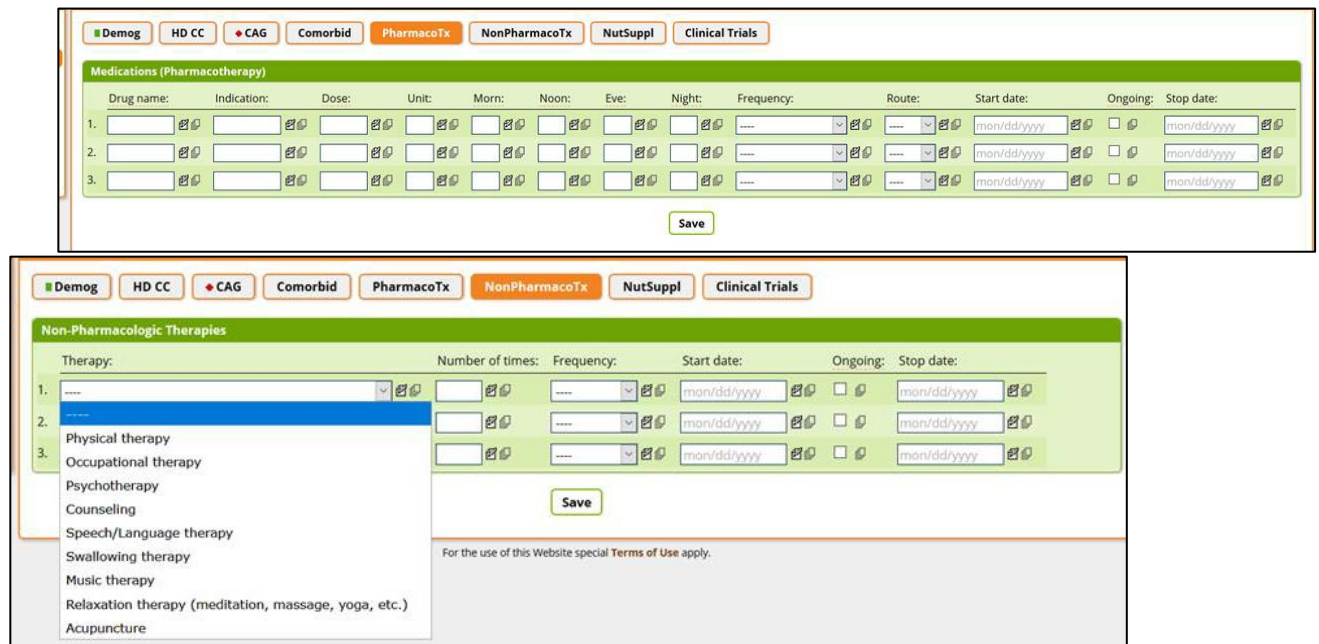
LoI Figure 3: Pharmaceutical and non-pharmaceutical therapies captured in the EDC.

Finally, LoI Tables 2-4 show each type of therapeutic data for sample participants from PDS5.

Lol Table 2: Pharmacotx example. *See Data Dictionary (Appendix 2), page 18-21.*

HDID (recoded) subjid	Drug name cmtrt__modify	Drug name - Code cmtrt__decod	Ingredient cmtrt__ing	Ingredient – Code (ATC) cmtrt__atc	Indication cmindc__modify	Indication - Coded cmindc__decod	Total Daily Dose cmdostot	Unit cmdose__cmdosu	Frequency cmdosfrq	Route cmroute	Start Day cmstdy	Ongoing cmenrf	End Day cmendy
1	Xenazine	RX000090013	Tetrabenazine	N07XX	Chorea	CX997675208	37.5	milligram	1	1	0	0	283
1	Aleve	RX000126663	Naproxen sodium	G02CC,M01AE,M02AA	Back pain	CX862962203	440	milligram	1	1	-400	0	1045
1	Xenazine	RX000090013	Tetrabenazine	N07XX	Chorea	CX997675208	100	milligram	1	1	283	0	1198
1	Celexa	RX000069660	Citalopram hydrobromide	N06AB	Anxiety	CX797206714	20	milligram	1	1	194	1	
1	Clonazepam	RX000134155	Clonazepam	N03AE,N05BA	Insomnia	CX959836908	0.25	milligram	1	1	-355	0	1061
1	Risperidone	RX000128945	Risperidone	N05AX	Chorea	CX997675208	2.5	milligram	1	1	1075	0	1098
1	Daypro	RX000072712	Oxaprozin	M01AE	Back pain	CX862962203	600	milligram	1	1	1045	1	
1	Risperidone	RX000128945	Risperidone	N05AX	Chorea	CX997675208	3	milligram	1	1	1098	0	1339
1	Austedo	RX000241387	Deutetrabenazine	N07XX	Chorea	CX997675208	48	milligram	1	1	1199	0	1641

Lol Table 3: Nonpharmacotx example. *See Data Dictionary (Appendix 2), page 24-25.*

HDID (recoded) subjid	Therapy cmtrt	Number of times cmfrq	Frequency cmdosfrq	Start day cmstdy	Ongoing cmenrf	End day cmendy
2	1	1	2	-164	0	201
2	1	3	2	201	1	
2	1	4	2	932	1	

Lol Table 4: Nut_supp example. *See Data Dictionary (Appendix 2), page 21-23.*

HDID (recoded) *subjid*	Type *cmcat*	NutSuppl Supplement – Modified Term *cmtrt__modify*	NutSuppl Supplement - Code *cmtrt__decod*	NutSuppl Supplement -ATC Code(s) *cmtrt__atc*	NutSuppl Supplement - ingredient(s) *cmtrt__ing*	Total daily dose *cmdostot*	Unit *cmdosunit*	Frequency *cmdosfrq*	Start day *cmstdy*	Ongoing *cmenrf*	End day *cmendy*
3	1	Vitamin e	RX000126883	A11HA,D02AX,D03AX	Tocopherol	1000	2	1	-1490	1	
3	1	Cod-liver oil	RX000152993	A11CB,D03AA	Cod-liver oil	415	2	1	-137	1	
3	1	Omega 3	RX000085060	C10AX	Fish oil	1000	2	1	-759	1	
3	1	Coq10	RX000071684	A16AX,C01EB	Ubidecarenone	300	2	1	1955	1	
3	1	Cannabis sativa	RX000143738	V90	Cannabis sativa	1	6	10	2063	1	

11. In the context of collecting pregnancy data, the Applicant is encouraged to collect data on Gravida (number of total previous pregnancies) and Para (number previous live births) in place of data points 2.1 and 2.2 currently outlined in table 13 under supplement section 7.

<u>Answer:</u> Based on the feedback provided by the EMA, the proposed Pregnancy form (Table 13) has been revised as shown here.

Label	Type	Parameter
1. Current pregnancy?	boolean	- Yes - No
If the answer is yes to question 1, the following questions (1.1-1.3) will appear in the EDC.		
1.1. Date of last menstruation	date	
1.2. Weeks of pregnancy	number	
1.3. Any medical complications during the pregnancy?	boolean	- Yes - No
1.3.1 If yes, please check as many as apply:	multiple choice	- Pregnancy-induced hypertension - Pregnancy-induced diabetes - Pre-eclampsia - Eclampsia - Intra uterine growth retardation (IUGR) - Polyhydramnios - Oligohydramnios - Multiple pregnancy (e.g. twins or triplets) - Other
1.3.1.1 If other, please describe:	text	
2. Have there been previous pregnancies?	boolean	- Yes - No - Unknown
If the answer is yes to question 2, the following questions (2.1-2.9.1) will appear in the EDC.		
2.1 Number of total previous pregnancies (excluding current pregnancy, if any)	number	
2.2 Number of previous live births	number	
2.3 Were any of the pregnancies twins or multiple pregnancies?	boolean	-Yes -No
If the answer is yes to question 2.3, the following question (2.3.1) will appear in the EDC.		
2.3.1 Per multiple pregnancy: year	date	
2.4 Per pregnancy: delivery date	date	
2.5 Per pregnancy: full-term or preterm birth	boolean	- Full-term - Preterm
2.6 Per pregnancy: natural delivery or c-section	boolean	- Natural - C-section
2.7 Per pregnancy: History of congenital malformation in the child?		- Yes - No
If the answer is yes to question 2.7, the following questions (2.7.1-2.7.1.1) will appear in the EDC.		
2.7.1 Specify:	boolean	- Cardiac - Kidney - Developmental delay

		- Dysmorphism - Other
2.7.1.1 If other, please describe:	Text	
2.8. Per pregnancy: Any medical complications during the pregnancy?	boolean	- Yes - No
If the answer is yes to question 2.8, the following questions (2.8.1-2.8.1.1) will appear in the EDC.		
2.8.1 Check as many as apply:	multiple choice	- Pregnancy-induced hypertension - Pregnancy-induced diabetes - Pre-eclampsia - Eclampsia - Intra uterine growth retardation (IUGR) - Polyhydramnios - Oligohydramnios - Multiple pregnancy (e.g. twins or triplets) - Other
2.8.1.1 If other, please describe:	text	
2.9 Any spontaneous terminations?		
If the answer is yes to question 2.9, the following question (2.9.1) will appear in the EDC.		
2.9.1 Per termination: What trimester did the termination occur?	boolean	- First - Second - Third
3. Post-menopausal?	boolean	- Yes - No

12. **The Applicant is highly encouraged to include "reason for discontinuation" of disease-related treatments, which is not yet implemented in the eCRF.**

<u>Answer:</u> It is agreed that the collection of a "reason for discontinuation" of a treatment is important and will be captured in the future update of the EDC. To capture this, a new field will be added to the PharmacoTx form that will be mandatory when a 'stop date' is entered.

13. **The capture of dates in form of YYYY is seen with concerns since it may result in misclassification of exposure leading to biased results. The Applicant is requested to discuss how this limitation may be addressed, e.g., by more frequent assessments (if yes, how often would be feasible?) and/or by linkage with medical record information from attending physicians.**

<u>Answer:</u> We believe that the reviewer is referencing Section 4 (p33) of the Supplement:

"The EDC permits entry of incomplete dates (i.e., MM/YYYY, YYYY) for specific variables - treatment and symptom onset dates - as participants are often unable to recall these to exact date (DD/MM/YYYY) resolution".

To clarify, exact dates of treatment and onset variables are collected wherever possible, and MM/YYYY resolution is used *only* where recollection of the exact date is not feasible. The YYYY format is used *only* when participants cannot be any more specific than the year. Treatment and onset dates are also reviewed for completeness and accuracy by onsite monitors with reference to source documents (including medical records) where possible and permissible.

Annual visits are appropriate for evaluation of HD natural history given the slow progression of the disease. However, as needed, specific PASS/PAES protocols that are nested in the Enroll-HD study could include more frequent data collection, either via in-person visits or by phone. For data collection in PASS/PAES protocols where the exact duration of exposure may be necessary for safety/ efficacy evaluation, data will

be recorded as such and data collection in "YYYY" format will not be permitted. Frequency of data collection will be determined by the protocol. See Appendices A & B.

14. Section 6 Harmonisation of Terminologies–Supplement 2 mentioned that medical treatment will be documented by ATC coding, but no data field is provided in the eCRF (PharmacoTx). The same applies for the comorbidities – only a body system code can be entered in the eCRF. The Applicant is requested to clarify this discrepancy.

Answer: To ensure consistency of the data, coding for PharmacoTx (and indication) and comorbidities is done by a central coding team. The site enters the data into the EDC including drug name (either brand name or generic is acceptable), indication (why the participant is taking the medication), dose, frequency, time of day the medication is taken, start date, and where appropriate, stop date. Once the visit is signed by the study PI, the coding team reviews the PharmacoTx and Comorbidity forms for additions/changes and codes each element (see LoI Figure 4). Since some coding schemes are licensed under specific terms, distribution of these codes may only be provided to researchers based on the coding license. Not all study sites have all coding licenses in place, so the codes are not visible to the study sites in the EDC; however, ATC (level 4) codes are always provided for medications in PDS releases.
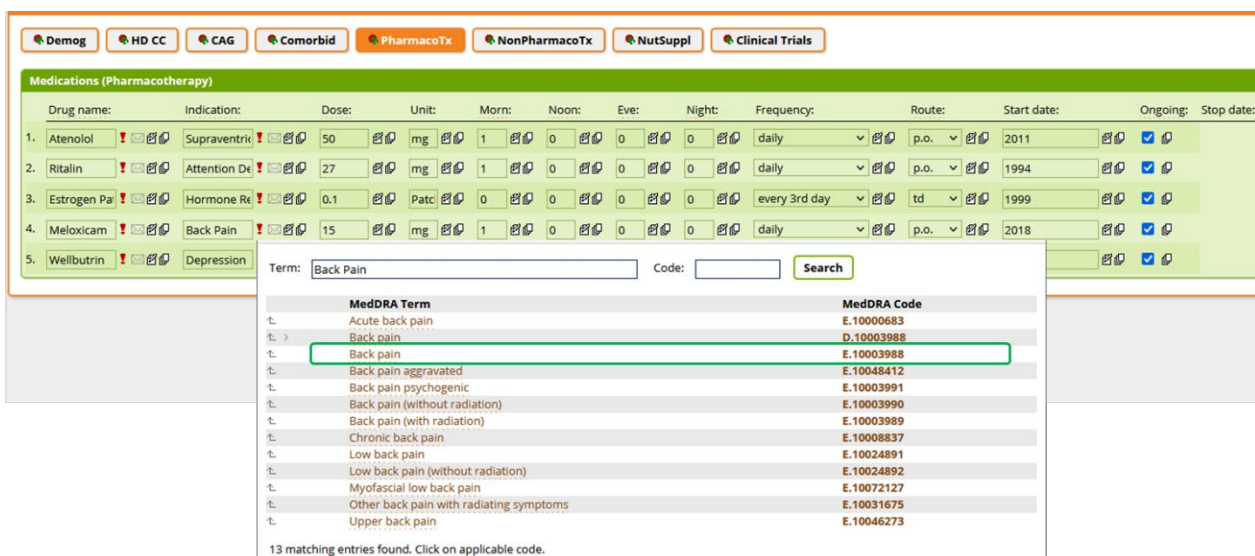
LoI Figure 4: Screenshot of MedDRA coding screen.

15. The Applicant is requested to provide further information how date and cause of death are determined, e.g., via contacting relatives, via the residents' registration office or death registers. A free-text field may be included to enable the possibility to note further common causes of death in HD patients, such as cardiovascular events, which have been reported in literature to constitute a major cause of early death in HD.

Answer: Mortality data are provided to Enroll-HD study sites typically via participants' families, although other sources are sometimes used; the source of data from which/whom mortality data were obtained is indicated by the variable *dsinfo*.

Cause of death (*dsend*) is also included on the Mortality form. This variable has categorical response options, including common causes of death in HD (e.g., pneumonia, suicide). A response of 'other' prompts completion of a free-text variable (*dsendoth*) enabling provision of additional information. Cardiovascular disease could be added as an additional response option to cause of death; this is a common cause of death

universally (in the general and HD population), although respiratory disease remains the leading cause of death in HD.[8,9]

The Data Safety Monitoring Committee (DSMC) reviews each reportable event, including participant death. During this review, the DSMC may request additional information from the site on such events. Further, onsite monitors perform source data verification of such events where possible, and discrepancies or missing data trigger queries for the site to act on and resolve.

For specific PASS/PAES protocols, review of death certificates to verify the cause of death can be implemented.

Variables captured on the Mortality form are included in the Data Dictionary (Appendix 2, pages 19-21) and provided in LoI Figure 5 for ease of reference.

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[8] Solberg O.K., Filkuková P., Frich J.C., Feragen K.J.B.. (2018). *Age at Death and Causes of Death in Patients with Huntington Disease in Norway in 1986-2015*. J Huntingtons Dis. 2018;7(1):77-86. doi:10.3233/JHD-170270.

[9] Heemskerk A., Roos R.A. (2012). *Aspiration pneumonia and death in Huntington's disease*. PLOS Currents Huntington Disease. 2012 Jan 30. Edition 1. doi: 10.1371/currents.RRN1293.

3.1.2 Form "Mortality"

This form is part of the General visit.

Section General

Label	Domain	Study	Cat	Variable	Type	Parameter	Coding	Unit	Transformation	Availability
Assessment date	DS	ENR	Mortality	dsdtc	date					Not available
Assessment day	DS	ENR	Mortality	dsdy	number			days	Transformed into days relative to baseline date of Enroll-HD.	Available upon SRC approval

Section Death Report Form

Label	Domain	Study	Cat	Variable	Type	Parameter	Coding	Unit	Transformation	Availability
Date of death	SUPPDS	ENR	Mortality	dssdtc	number					Not available
Year of death	SUPPMH	ENR	FHx	deathy	number			Year		Not available
Age of death	SUPPDS	ENR	Mortality	dssage	number			Years	Age at death, e.g. "75" Calculated from date of birth and date of death	PDS
Place of death	SUPPDS	ENR	Mortality	dsplace	single choice	- home - hospital - nursing home - hospice care	- 1 - 2 - 3 - 4			PDS
Cause of death	SUPPDS	ENR	Mortality	dsend	single choice	- pneumonia - other infection - cancer - stroke - trauma - suicide - other	- 1 - 2 - 3 - 4 - 5 - 6 - 7			PDS
Please specify	SUPPDS	ENR	Mortality	dsendoth	text					Not available
Was an autopsy performed?	SUPPDS	ENR	Mortality	dsautop	single choice	- no - yes	- 0 - 1			Available upon SRC approval
Result of autopsy	SUPPDS	ENR	Mortality	dsautopr	text					Not available
Information obtained primarily from	SUPPDS	ENR	Mortality	dsinfo	single choice	- spouse/family - friend - physician/nurse - patient's medical record - obituary in newspaper - death certificate - other	- 1 - 2 - 3 - 4 - 5 - 6 - 7			Available upon SRC approval
Please specify	SUPPDS	ENR	Mortality	infooth	text					Not available
Comments?	SUPPDS	ENR	Mortality	dscom	boolean	- yes - no	- 1 - 0			Available upon SRC approval
Comment	CO	ENR	Mortality	coval	text					Not available

Lol Figure 5: Mortality Form variables and availability. Source: Enroll-HD Data Dictionary (2020-10-R1).

16. The four reportable events currently systematically captured in the Enroll-HD protocol as events related with the disease itself could potentially also occur as TEAEs and should therefore all be coded using MedDRA terms.

Answer: Agreed. A specific PASS/PAES protocol that is nested in Enroll-HD will require monitoring of specific TEAEs. These will be captured and appropriately coded for participants enrolled in that study. Currently, a mental health event requiring hospitalization is coded using MedDRA. The other 3 events reported in Enroll-HD (death, suicide attempt, and completed suicide) are not coded using MedDRA.

17. The Applicant is asked to briefly explain how the information on drug exposure (including over the counter (OTC) medication) and adverse events is collected, e.g. (i) via personal interview at each examination, (ii) by scanning the individual medicinal products which are brought along by the study participant within the scope of the examination or (iii) by reviewing the medical records.

Answer: At each visit, all medications (captured on the PharmacoTx CRF), nutritional supplements, non-pharmacotherapies (e.g., acupuncture), and comorbidities are reviewed by site staff, discussed with the

participant, and updated in the EDC as appropriate. The PharmacoTx form includes the collection of both prescription drugs and over the counter medications. See Question 10 for additional information about this form. There is no specific direction provided to the PI for how these data should be obtained but based on discussions with several PIs all three of the techniques listed in Question 17 are employed. Additionally, in countries where monitoring of medical records is currently permitted, monitors verify the EDC inputs against available medical records to ensure completeness and correctness.

Adverse events are not currently collected in Enroll-HD, only reportable events. Reportable events are described in Sections 2.2.3.1.5 and 9 of the Supplement. For reporting of adverse events related to medications, the investigators are instructed to follow the pharmacovigilance processes of the country in which they practice.

When the data on medications is provided to researchers in either a PDS or SPS, the total daily dose is provided. Total daily dose is calculated by multiplying the standard dose by the daily frequency of intake. For example, 5 mg of prednisone taken twice a day results in a daily dose of 10 mg. See LoI Figure 6 for a screenshot of the PharmacoTx form in the Enroll-HD EDC.

LoI Figure 6: Screenshot of the PharmacoTx form in the Enroll-HD EDC.

18. When using existing data from the Enroll-HD Registry to supplement post-authorisation safety studies, it should be considered that missing information of concomitant medication applied for a short time period may bias the results. Provided that the conduct of a PASS with data from the Enroll-HD Registry is considered feasible, the extent of missing information should be discussed as a study limitation in the respective study protocol.

Answer: Enroll-HD visits are annual, and medication review is performed at each visit. It is therefore plausible that treatments that happened during the year for a short period of time (for example, a course of antibiotics or pain medication for an acute injury) are forgotten and not collected. If a PASS/PAES study plans to use the Enroll-HD data *alone*, then this limitation must be acknowledged. There are ways to mitigate this, however, including connecting the Enroll-HD data to Electronic Health Records (EHR). EHRs are available in most of the countries where Enroll-HD operates. However, there are still many challenges regarding the interoperability of formal registries like Enroll-HD and EHR-generated data.[10,11] Several initiatives under the aegis of the European Commission are addressing the issue of the interoperability. Among those initiatives, the European Institute for Innovation through Health Data (i~HD) has produced the groundwork to facilitate the linkage of many datasets.[12] We are confident that Enroll-HD data processes put Enroll-HD in a good position to become interoperable with EHR data. However, we recognize that for this

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[10] Nicholson N., Perego A. (2020). *Interoperability of population-based patient registries*. J Biomed Informatics X. 2020;6:100074.

[11] Pacurariu A., Plueschke K., McGettigan P., et al. (2018). *Electronic healthcare databases in Europe: descriptive analysis of characteristics and potential for use in medicines regulation*. BMJ Open 2018;8:e023090. doi:10.1136/ bmjopen-2018-023090.

[12] *Electronic Health Records for clinical research* (24th April 2020). Innovation News Network. *Available at https://www.innovationnewsnetwork.com/electronic-health-records-for-clinical-research/4930/.*

to happen we will have to collaborate with multiple entities external to Enroll-HD; the process described by Lovenstone[13] is an example of what must be achieved.

Finally, if a PASS/PAES requires more granular medication data, the PASS/PAES should be planned as a nested study, as explained in Appendices A & B, and could include more frequent data collection, either via in-person visits or by phone.

19. **It should be considered that different data quality and/or different formats and coding may limit the conduct of a pooled analysis; the Applicant should thus critically reflect whether the collected data are suitable for pooled analyses.**

<u>Answer:</u> All Enroll-HD data are formatted, coded, and made available using internationally recognised standards, namely ATC, MedDRA, and WHO-DD. Additionally, the Enroll-HD variables were created using CDISC as a reference. The use of these standards supports future pooled analysis with other datasets that use similar standards or can be converted to them. It is expected that all clinical trial data will use the same data standards as Enroll-HD, hence pooled analysis of such datasets are relatively easy to accomplish. Data retrieved from EHR (the challenges of linkage with EHR databases are discussed in Question 18) pose a greater challenge for pooled analysis because there is no widely-implemented or agreed standard for this data format and variable naming. There are, however, several initiatives like the standards and interoperability framework in the U.S. and the Fast Healthcare Interoperability Resources (FHIR) in Europe that are providing tools to facilitate pooling different data sources including EHR. Finally, Enroll-HD collects the "raw" data, which is then centrally coded, so as new standards are implemented or existing standards are changed, Enroll-HD can convert the data to the appropriate format. Given the data standards adopted in Enroll-HD, we are confident Enroll-HD data will not be the limiting factor in future pooled analysis.

20. **Please discuss if incentives are offered to patients and if so how this is expected to be dealt with, and how different the Applicant population is from the "regular" PAES / PASS population.**

<u>Answer:</u> There are no financial incentives provided for participation in Enroll-HD. Travel is reimbursed, but this is a right and an ethical requirement, not an incentive. Even though there are no economic incentives provided, there are many psychological incentives for participating in Enroll-HD, including being part of a community, the ability for the entire family to participate, and being informed about prospective clinical trials in a timely fashion.

<u>Data sharing</u>

21. **The data should be presented in the PDS in such a way that a Applicant can directly assess whether the Enroll-HD Registry is an appropriate data source or not – at best without requesting the SPS. Please comment.**

<u>Answer:</u> We provide a substantial volume of data documentation and cohort summary data via the Enroll-HD website to assist applicants in such an assessment (e.g., <u>data dictionary</u>, <u>cohort summary</u>, <u>coverage charts</u>). The data dictionary is especially helpful to identify the variables that are included in the PDS (highlighted in green), variables that are available via an SPS request (highlighted in yellow) and variables that are collected as part of Enroll-HD but never provided to requestors, such as visit dates (highlighted in red) (see LoI Figure 5, above). Further, we are also developing a data visualization application for research use ('Enroll-HD Data Explorer'); critically, this application includes a feasibility tool enabling researchers to filter the population by several factors to arrive at a sample size limited to their required parameters.

22. **The Applicant is requested to clarify whether a request for an SPS extraction is chargeable or free.**

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[13] Lovestone, S., and the EMIF Consortium. (2019). *The European medical information framework: A novel ecosystem for sharing healthcare data across Europe.* Learn Health Sys.2019;e10214. wileyonlinelibrary.com/journal/lrh2 1 of 13. https://doi.org/10.1002/lrh2.10214.

Answer: To encourage the use of Enroll-HD and research in HD, all data are provided free of charge (including SPS data extractions and associated data quality control review).

Issues to be addressed in writing <u>and</u> during the discussion meeting

<u>Context of use</u>

23. The Applicant is invited to provide an example (either concrete or hypothetical) of a PASS and/or PAES protocol and to evaluate whether the Enroll-HD registry can capture the data needed to address the PASS/PAES objectives.

See Appendices A & B for response to Question 23. Appendix A is a synopsis of a hypothetical PASS/PAES. Appendix B is an operational summary of how this hypothetical PASS/PAES could be nested within Enroll-HD.

<u>Patient population and representativeness</u>

24. The Applicant is invited to discuss potential implications of selection bias and lack of ethnic and socioeconomic diversity of the Enrol HD registry for globally nested studies.

Answers to Questions 24 and 25 are combined into a single response below.

25. The plan to identify new sites in new countries with higher ethnic and socioeconomic diversity is endorsed but the Applicant is invited to undertake or outline plans for a feasiblity assessment where potential impacts on future studies are evaluated.

Answer: Ethnic diversity within clinical trials and post-authorization studies is important in establishing, or demonstrating the generalizability of, safety and efficacy outcomes in minority populations. HD is principally a disease of Caucasian ancestry, and typically less prevalent in other ancestral groups in which prevalence may be driven by founder effect clusters or genetic admixture. There are, however, exceptions to these prevalence rules, particularly in African countries (discussed in response to Question 29b).

To address representation of diversity reflective of that observed in the HD population in Enroll-HD, existing sites have been encouraged to engage and recruit minority families with HD. Several mobile "outreach" sites have been established in Canada, Columbia, New Zealand, and Australia. Mobile outreach clinics are an extension of an active Enroll-HD site that periodically (e.g., once a quarter) sets up an HD clinic in remote areas that have severely affected populations. These populations greatly facilitate research efforts by providing large pedigree maps, but also enrich the Enroll-HD dataset with ethnic diversity. However, we recognize that these populations may not be reachable for all potential HD therapeutics immediately after market approval for these new therapeutics.

In the last year two additional sites started up in Latin America, and three more are in the process of being activated. We have an established track record in opening sites in lower income countries (e.g., Argentina, Chile, Columbia), and with this experience and local contacts in place, we are confident in our plans to further expand into new Latin American countries to enrich our population for individuals of non-Caucasian ancestry and varied socioeconomic status.

Furthermore, as a first step in expanding Enroll-HD into China, we have established and support a Chinese HD Network which allows us to have an open dialogue with HD clinicians in China to share research and best clinical practice. The network has about dozen HD specialists that have established HD centers in China. The staff at these Chinese sites have been trained in the Enroll-HD assessments, and all assessments have been translated into Mandarin.

26. The Applicant should discuss if the registry can implement using linked databases to individually map every HD patient to e.g., national hospital /pharmacy HD site/health insurance data.

Answer: It is theoretically possible in most of the countries where Enroll-HD is active and where national registries are available, to leverage national hospital, pharmacy data, or insurance data to map most of the HD participants in these regions. As already mentioned in Questions 18 and 19, the main limitation on this type of mapping is technical and related to the interoperability of the different sources. The issue of interoperability transcends Enroll-HD. It is very much dependent on national and regional efforts that have political, social, and economic components besides the technical ones. Given the efforts the European Commission is investing in solving these matters, we are confident the linkage of different types of registries will be possible. Enroll-HD has the adequate data infrastructure in place to participate when possible.

Note that public databases are unlikely to map every HD patient, particularly because the current practice of diagnosing HD is based not on the genetic test but on clinical symptomology which only occurs late in the course of the disease. For that reason, many HD patients might exist in public databases without being coded as HD.

27. Please discuss whether the patient and investigator commitment is similar in Enroll-HD to clinical trials and how clinical decisions (including pharmacology data – dose titrations and changes) have been registered, for use as data source as proposed.

Answer: As discussed in Question 20, participants in Enroll-HD are highly committed to the study for a variety of reasons, including potential access to clinical trials because Enroll-HD is often an entry point for such trials. Investigator commitment is high as well because Enroll-HD provides the site with a steady and reliable source of income. Moreover, data and research tools are readily accessible (many Enroll-HD PIs also conduct HD research), while data from clinical trials may be difficult for investigators to access. Finally, because of the nature of Enroll-HD, often the investigator is involved in treating entire families, which creates strong relationships and builds personal commitment.

Regarding pharmacotherapy, there are currently very few drugs labelled for HD, which is the main reason that Enroll-HD does not currently collect granular details of drug regimens. Nonetheless, Enroll-HD captures some clinical decisions, including why a participant is taking a given drug. Both medications and co-morbid conditions are coded. However, we acknowledge that because Enroll-HD has annual visits, there can be recall-related limitations in collecting pharmacology data. See Questions 17 & 18. This is therefore a limitation in using Enroll-HD as a data source. However, when a PASS/PAES is nested within Enroll-HD, the protocol for that PASS/PAES can include more frequent data collection for both HD and non-HD drugs with attention on clinical decision making, either via in-person visits or by phone. See Appendices A & B.

28. The exact purpose of the control groups not carrying the HD expansion within the framework of the intended registry based studies as well as their representativeness should be discussed and justified, respectively.

Answer: While controls are not intended to participate in either PASS or PAES, controls are an asset for HD research. For example, Mills, et al. evaluated the effects of natural aging on cognitive and motor assessments using data from healthy controls in Enroll-HD, enabling the development of normative curves for various assessments (e.g., UHDRS motor, SDMT, Stroop Word Reading).[14] These curves can be used as references for clinical characterization in HD.

The control population in Enroll-HD consists mostly of family members (spouses, care givers, close friends) of the HD gene expansion carrier and gene negative HD family members. As illustrated in LoI Figures 7 and 8, the family controls closely match the age distribution of the manifest participants. The gene negative controls more closely match the age distribution of premanifest participants.

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[14] Mills J.A., Long J.D., Mohan A., J Ware J.J., Sampaio C. (2020). *Cognitive and Motor Norms for Huntington's Disease*. Archives of Clinical Neuropsychology, Volume 35, Issue 6, Pages 671–682, https://doi.org/10.1093/arclin/acaa026.
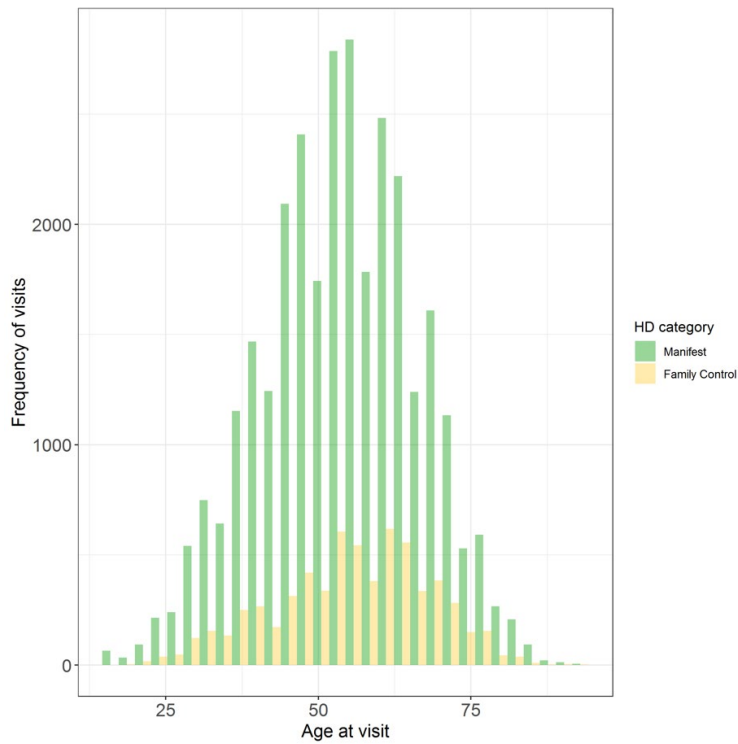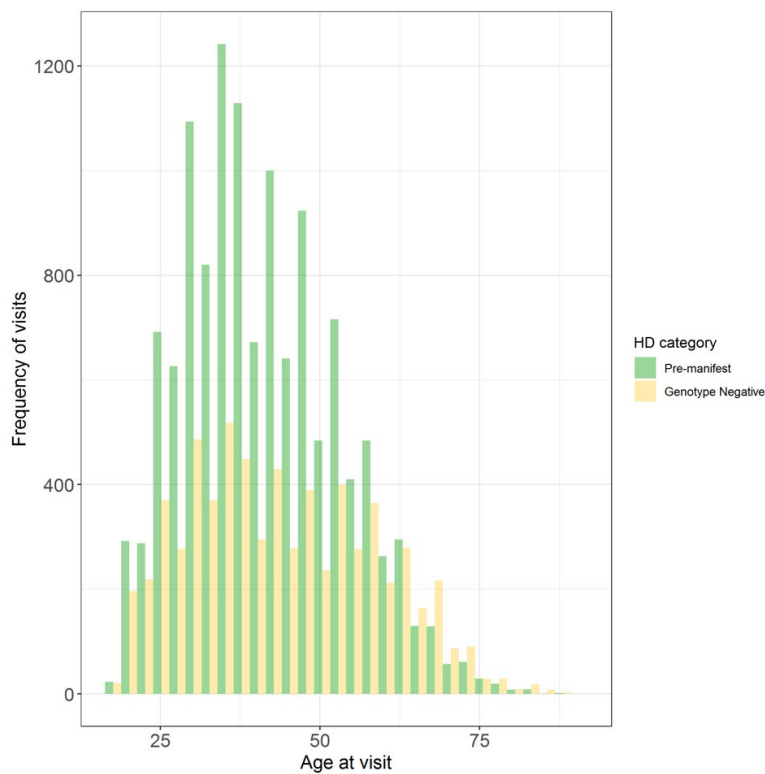
LoI Figure 7: Frequency diagram of manifest HDGECs in Enroll-PDS5 (green) compared to family controls (yellow).

LoI Figure 8: Frequency diagram of Pre-manifest HDGECs in Enroll-PDS5 (green) compared to genotype negative participants (yellow).

Core data and time elements

29. The Applicant is invited to discuss the impact of the lack of data on clinical decisions on the registry, and its use as source data. Although ethnicity as a variable impacting on disease or treatment response biomarkers seems to be covered for the EU population, how well does the Applicant consider it covered given the relevant prevalence of North African population in some EU countries?

<u>Answer:</u> This question has two parts: a) data on clinical decisions; b) differences between EU populations and Northern Africa populations.

a)   Enroll-HD captures data regarding some clinical decisions during the annual visits. The indications for any treatment are captured in the PharmacoTx form; similarly, the interruption of those medications or interventions is registered (see Questions 10 and 17). During a future EDC release, the reason for changes to medications can be captured to provide additional information about clinical decision making. For reportable events, Enroll-HD collects detailed information on the event (coded using MedDRA), event onset and end date, and related interventions (see Data Dictionary (Appendix 2) pages 59-62). A limitation of the current Enroll-HD protocol is that adverse events are not collected. However, reporting of adverse events follows the rules of each country's pharmacovigilance practice, which are generally aligned but may have distinct nuances. The tracking of any pharmacovigilance report could be added to the EDC as required by PASS/PAES.

b)   For the reasons explained below, we expect current Enroll-HD biomarkers to apply equally well to Northern African populations, although it is possible that different genetic markers may limit the availability of certain genetic therapies.

As described in Question 25, HD is much more frequent in populations of European ancestry. This high prevalence is associated with a specific haplotype (A). In countries of other ethnic backgrounds, namely in Africa and Asia, where haplotypes B and C are more frequent, the disease is much rarer. HD can also occur in clusters of high prevalence. The most well-known cluster is located in the region of Lake Maracaibo in Venezuela where the prevalence is estimated to be 700/100,000.[15] These clusters of very high prevalence usually have an identified European founder.

There are some exceptions to these prevalence rules, meaning that within continents with low prevalence, there are countries with reported high prevalence, most notably in Egypt and Tunisia.[16,17] The genetic background of HD in Egypt is not known, but it is possible that the mutation originated de novo. A recent publication traces the origin of HD in the Middle East to an individual of sub-Saharan African ancestry that is likely the founder (the descendants of this individual localized in Ethiopia before moving to the Middle East), and suggests that HD mutation might have appeared independently in this group, and possibly several more times across the globe.[18]

Following this logic, it is possible, although not proven, that North African immigrants living in European countries may have different genetic biomarkers than the populations of European ancestry. Nonetheless, the available evidence suggests that the HD mutation is *not* pleiotropic. The adult clinical phenotype is qualitatively similar across populations of different genetic backgrounds, and the main milestones in disease

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[15] Avila-Giron R., et al. (1973). *Medical and social aspects of Huntington's chorea in the state of Zulia, Venezuela.* Advances in Neurology 1973;1:261-266.

[16] Luxner, L. (2019). *Egypt Leads World in Huntington's Prevalence, But Lacks Clinical Trials on the Disease, Report Says.* Huntington's Disease News. July 16, 2019. *Available at* https://huntingtonsdiseasenews.com/2019/07/16/egypt-leads-world-in-huntingtons-prevalence-but-lacks-clinical-trials-on-the-disease-report-says/?cn-reloaded=1.

[17] Brahim D.H-B., Chourabi M., Amor S.B., et al. (2014). *Modulation at Age of Onset in Tunisian Huntington Disease Patients: Implication of New Modifier Genes.* Genetics Res Int. 2014;2014:1–5.

[18] Squitieri F., Mazza T., Maffi S., et al. (2020). *Tracing the mutated HTT and haplotype of the African ancestor who spread Huntington disease into the Middle East*. Genet Med. 2020;22:1903–1908.

progression – striatal atrophy, motor and cognitive impairments, functional disability – follow the same pattern independent of the ethnic background.[19,20,21,22,23,24] Therefore, biomarkers of disease progression should be relevant independently of the ethnic background[25] and potentially useful as biomarkers of treatment response. There is the possibility that different genetic backgrounds will cause differences in disease severity because they might be associated with longer CAGs, and as such the frequency of juvenile HD might be higher in certain populations as well. But independent of ethnic background, all Huntington's disease cases are connected by the production of mutant huntingtin protein, which is the product measured in the most common assay used to show target engagement. For these reasons we think the assessments included in Enroll-HD and the disease progression biomarkers in use in clinical studies (e.g., volumetric MRI, CSF mHTT, CSF NFL) are relevant for the follow-up of all adult cases of HD independent of the genetic or ethnic background.

However, we recognize the differences in genetic background will have an impact in the use of targeted gene therapies, where the target is a specific SNP or a particular haplotype, because populations that do not carry the targeted genetic marker will not be able to be treated. This is an important problem for the generalization of access, but goes beyond the remit of Enroll-HD.

30. **The number of tests is extensive and requires a quite considerable assessment time. Although assessment will be performed only once yearly, this may still demotivate some patients and it is unclear, if the order in which the assessments will be performed might have an impact on the results, i.e. due to fatigue. Please comment.**

Answer: It takes about 90 minutes for an Enroll-HD participant to complete the core assessments, and another 30-45 minutes to complete all the (discretionary) extended assessments. This represents an average. The actual time varies depending on the participant's ability, which extended assessments are completed, and if the participant elects to participate in the optional components (e.g., biobanking). Over the last eight years over 60,000 visits have been conducted in Enroll-HD. Figure 16 of the Supplement illustrates the completeness of core and extended assessments as a function of all visits. Each core assessment is completed at almost all visits (range: 92.2%-99.6%), indicating that the assessment battery is well tolerated. The cognitive extended assessments also have a notable completion rate (71.6%-85.7%).

Fatigue can be a factor for some participants, especially participants at later stages of the disease. One of the aims of Enroll-Lite is to reduce the burden for these participants by reducing the number of assessments conducted during a study visit. See Question 4. The issue of fatigue is left to the study site as they are instructed to provide for the welfare of the participant first, including offering breaks as needed, determining if it is appropriate to administer one or more assessments, deciding if it is appropriate to continue with the visit, or determining if the participant can continue in the study.

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[25] Apolinário T.A., Rodrigues D.C., Lemos M.B., Paiva C.L.A., Agostinho L.A. (2020). *Distribution of the HTT Gene A1 and A2 Haplotypes Worldwide: A Systematic Review.* Clin Medicine Res. 2020;18:145–152.

The order of the assessments is not prescribed in the study except for the cognitive assessments. The Cognitive Manual provides administration instructions for all the cognitive assessments (in both core and extended batteries) including the appropriate order of administration, which is especially important for cognitive testing. The four core assessments are completed first in a specified ordered, followed by the extended assessments, again in a specific order. If a site opts not to conduct one or more assessments, then that assessment is skipped but the order of assessments remains unchanged.

The amount of time it takes to participate in Enroll-HD does not appear to be a deterrent for participation.

31. In case of future approval of disease modulating medicinal products, time elements outlined in EMA´s discussion paper 2018 currently not being captured by Enroll-HD might become crucial for PASS/PAES, e.g. dates of cure or significant improvements, date of relapse and date of resolution of significant events associated with the disease. The Applicant is invited to explain whether plans are in place for collecting these data.

<u>Answer:</u> None of the treatments currently in clinical development, or even in early phases of discovery, aim to cure HD. There are approaches based on transplantation of cell therapies to the brain or inducing cell transformation within the brain that theoretically may provide significant improvement of existing symptoms. However, even if these treatments are successful there is a lag time of several months, if not a year, for changes to be noticeable. Given the slow progression of the disease, which spans more than four decades from the detection of the first signs of brain atrophy until death,[26,27,28,29,30] we think Enroll-HD annual visits will be able to capture changes in the rate of progression and delays in important milestones (i.e., assessments that cross established thresholds or the beginning of functional impairment). Nevertheless, if more granularity is deemed necessary, capturing additional data (including imaging and biomarkers) as part of a nested study can be done, as described in Appendices A & B.

32. The current PDS5 overview (Data lock point: October 31, 2020) shows that >50% of the study participants (baseline, n= 21,116) have been enrolled for no longer than two years (3rd examination, n= 9,498). The Applicant is requested to comment whether this is due to sharply increasing recruitment in recent years or whether there is an unusually high proportion of loss to follow-up beyond two years after enrollment.

Responses to Questions 2 and 32 are combined into a single response below. We speak first to the topic of retention, which applies to both questions, and second to the topics of recruitment and missed visits, which apply to Question 32.

A participant is considered as "retained" in the Enroll-HD study until the point at which a Premature End form or Mortality form is completed. A participant can decline in-person visit for several consecutive years without being considered discontinued. These visits are considered "missed visits." Therefore, the rate of retention cannot be directly inferred by the number of visits accrued per person, as discussed in more detail below. Given the continual and staggered recruitment of new participants into Enroll-HD, we performed

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[29] Tabrizi, S. J. *et al.* (2009). *Biological and clinical manifestations of Huntington's disease in the longitudinal TRACK-HD study: cross-sectional analysis of baseline data.* Lancet Neurol 8, 791-801, doi:10.1016/S1474-4422(09)70170-X.

[30] Paulsen, J. S. *et al.* (2008). *Detection of Huntington's disease decades before diagnosis: the Predict-HD study.* J Neurol Neurosurg Psychiatry 79, 874-880, doi:10.1136/jnnp.2007.128728.

survival analysis to assess study retention wherein all participants are aligned to a date-independent time 'zero' (i.e., timepoint of individual study entry). The results of such analyses were presented in the submitted Supplement, with participants stratified into premanifest and manifest groups (Section 3.6, p30-31). As reported in the Supplement, attrition of participants in Enroll-HD is relatively low, particularly among the premanifest cohort (~80% probability of continued participation at seven years post study entry). Expanding upon these analyses, we now present survival probabilities for all participants, *stratified by HD category* (LoI Figure 9), and, as requested, manifest individuals *stratified by Shoulson-Fahn TFC stages I-V* (LoI Figure 10). These results are presented in Kaplan Meier curves in which the 'event' is defined as follows:

1. Discontinuation due to study withdrawal (as indicated by Premature End form completion);

2. Discontinuation due to study withdrawal or loss to follow-up (i.e., failure to attend two consecutive visits and no phone contact completed during this period);

3. Discontinuation due to death;

4. Discontinuation due to study withdrawal, loss to follow-up, or death.

The survival probabilities reported here (and in the Supplement) should be interpreted with two caveats: 1) the number of participants on which survival curves are based decreases substantially as time (years) increases, thus the precision of these estimates decreases as a function of time; and 2) passive withdrawal from the study under the 'lost to follow up' category requires participant failure to attend two consecutive visits; thus there is an obligatory time delay before retention at any given date can be calculated, and as such the survival probabilities for event scenarios 2 and 4 may be overestimates.

Survival probabilities vary as a function of disease stage (LoI Figures 9,10), with the lowest survival probabilities observed in disease stage 5 (end-stage disease) ubiquitously; such effects becoming more pronounced as time (years) increases. We note however, that even in the most advanced disease stage, in the most extreme scenario (discontinuation due to study withdrawal, loss to follow-up, or death), survival probability at 3 years is ~80%, and at 5 years is ~50%.
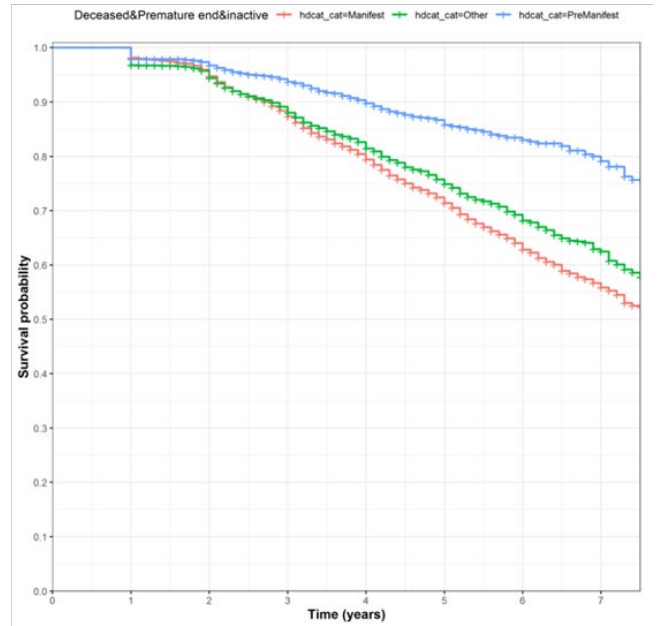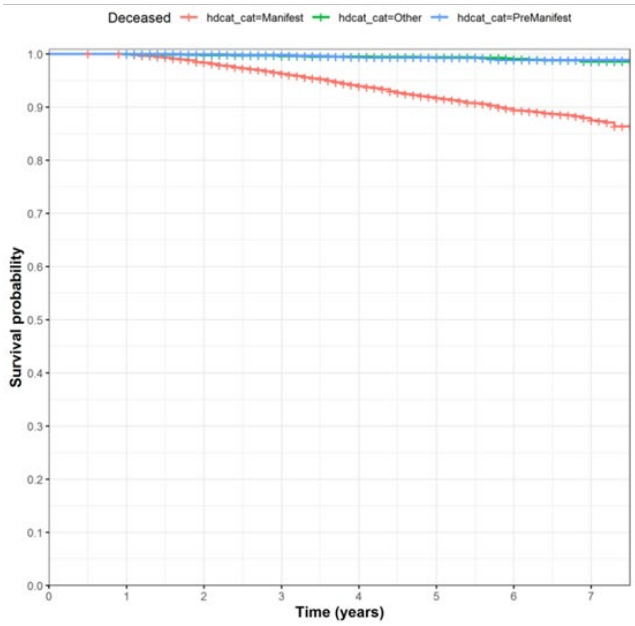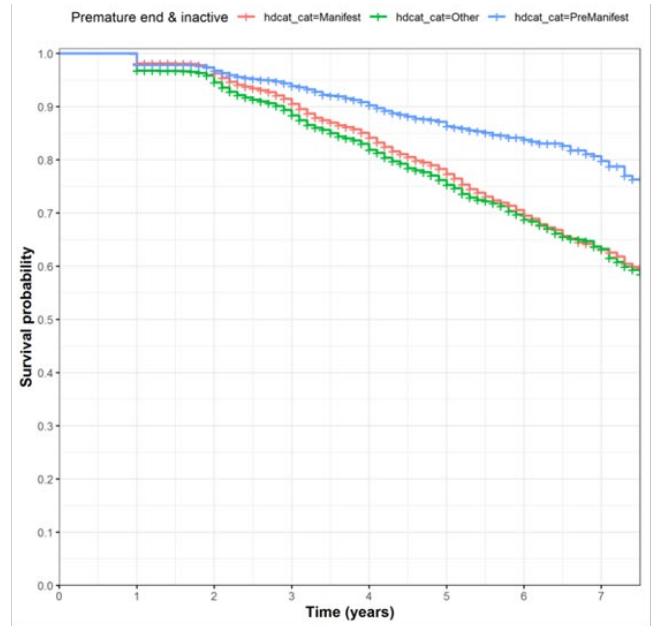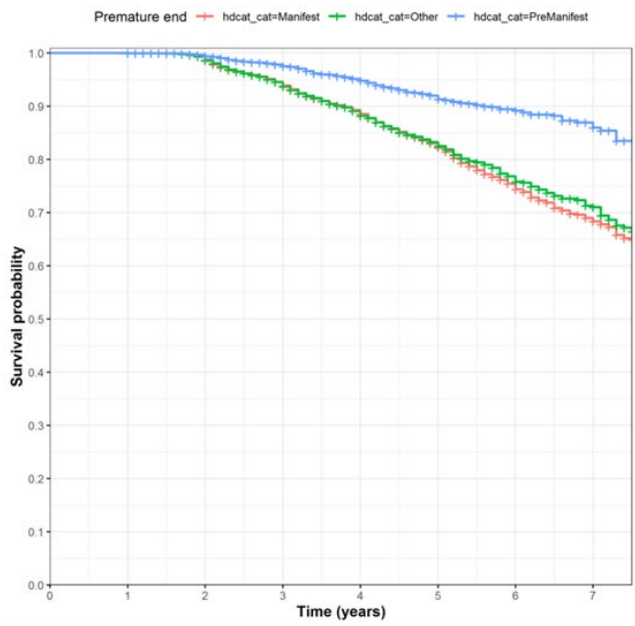
Lol Figure 9. Survival probabilities in Enroll-HD: all participants stratified by HD category (premanifest; manifest; other [genotype negative and family controls]). *Top left:* event = study withdrawal, as indicated by Premature End form completion. *Top right:* event = study withdrawal or loss to follow-up, i.e., failure to attend two consecutive visits and no phone contact completed during this period. *Bottom left:* event = death. *Bottom right*: event = study withdrawal, loss to follow-up, or death. Data cut April 1, 2020.
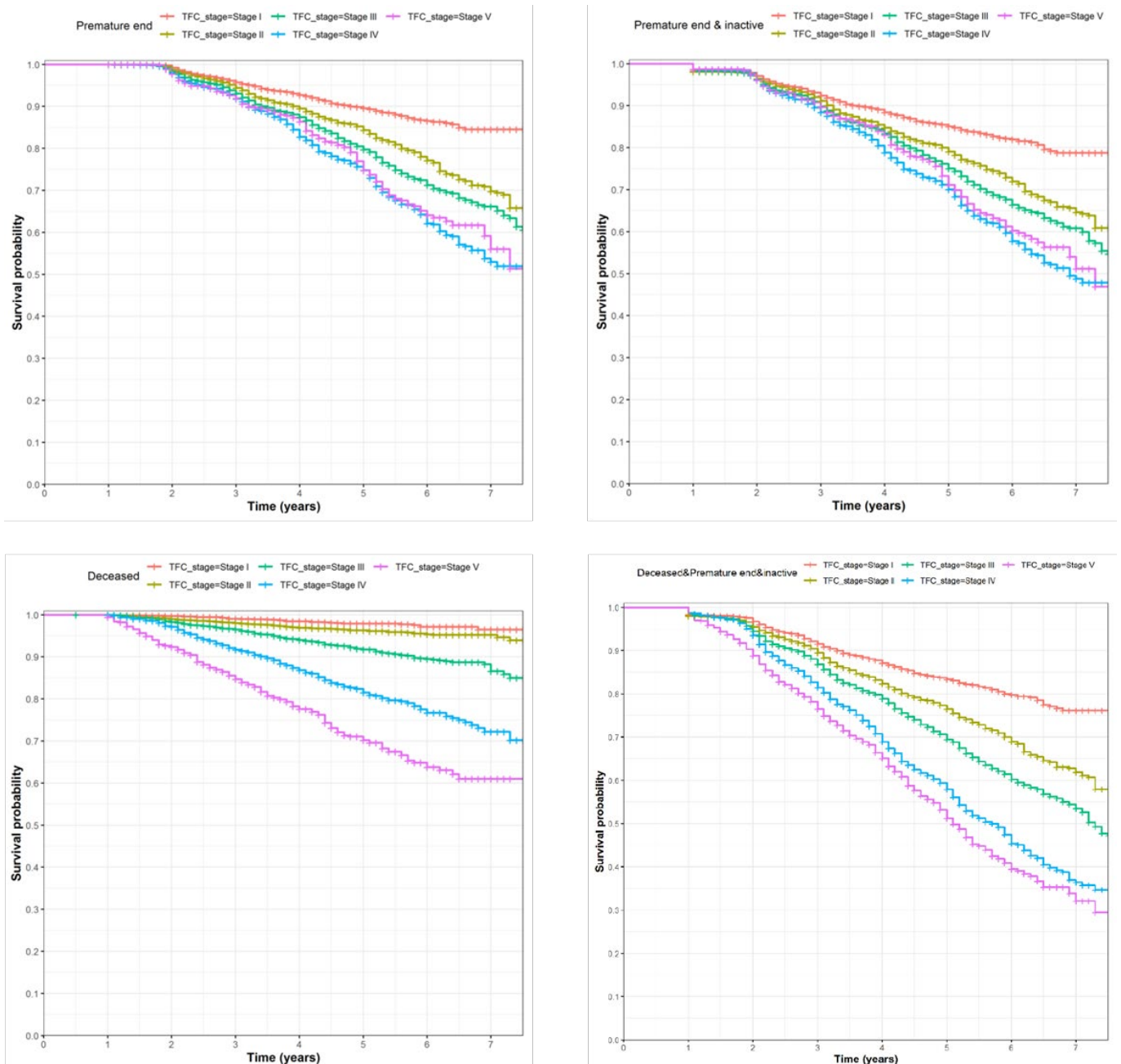
LoI Figure 10. Survival probabilities in Enroll-HD: manifest participants stratified by Shoulson-Fahn TFC disease stages I-V. Top left: event = study withdrawal, as indicated by Premature End form completion. *Top right:* event = study withdrawal or loss to follow-up, i.e., failure to attend two consecutive visits and no phone contact completed during this period. *Bottom left:* event = death. *Bottom right*: event = study withdrawal, loss to follow-up, or death. Data cut April 1, 2020.

The mean number of visits/participant in Enroll-HD PDS5 (which includes both current *and* discontinued participants; see definitions in Table 15 of the Supplement) is 2.65. While mean visits/participant is a useful metric, it can present a misleading picture with regards to participant retention, as it is influenced not only by participant drop-out, but also by recruitment rate (as the question highlights) and missed visits.

Enroll-HD is a 'living' study with continual recruitment and continual activation of new study sites. Not all participants, nor sites, were present from 'day zero', and as such few participants have had the opportunity to participate in the maximum observed number of visits, as indicated in the PDS Overview document referenced. To illustrate the growth (and recruitment rate) of Enroll-HD since the study launched in 2012, we include a plot of cumulative sample size (total recruitment) in Enroll-HD as a function of time (LoI Figure 11).
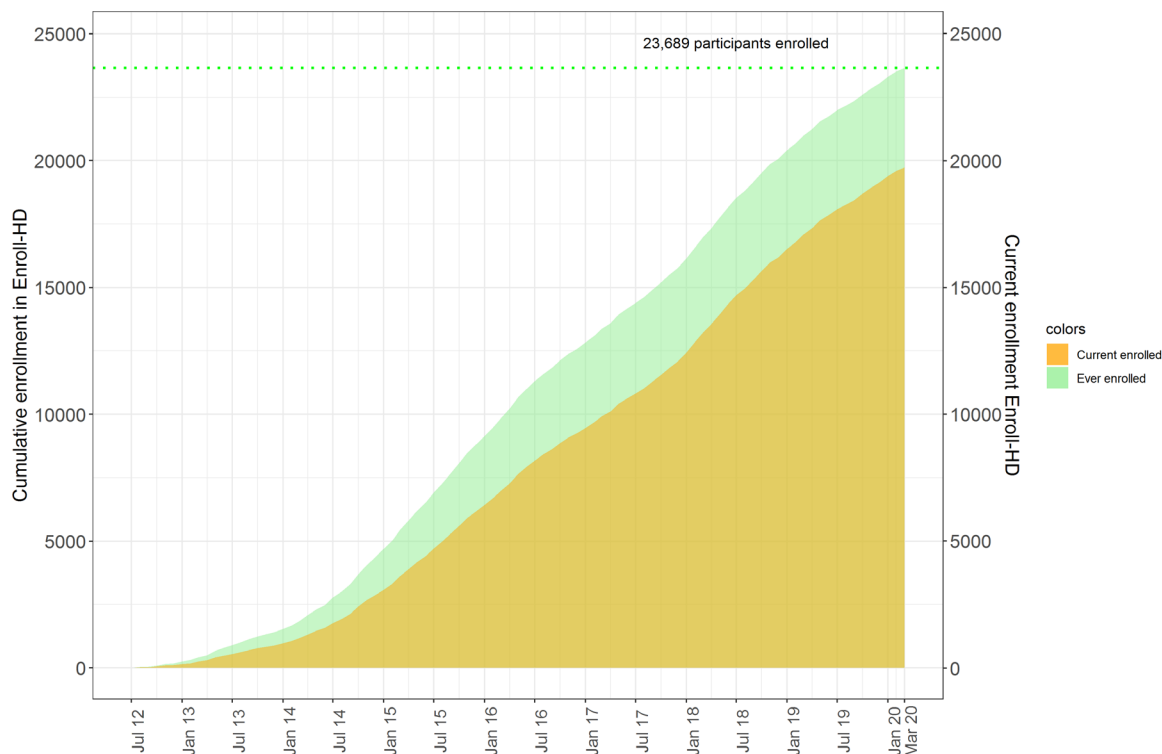
LoI Figure 11. Enrolment in Enroll-HD (study start-up to April 1, 2020). Green panel indicates cumulative total enrolment (i.e., ever enrolled), yellow panel indicates current enrolment (i.e., participants who do not have a Premature End or Mortality form completed).

We recognize, however, that the observed visit count per participant in Enroll-HD PDS5 (Oct 2020), falls short of the count expected given the rate of recruitment and above-reported retention rates. This disparity is driven by missed visits.

The Enroll-HD protocol requires yearly visits of participants within a time window spanning +/- 3 months of their due date (i.e., the anniversary date of their baseline visit). If a participant neither attends a visit within this six-month window and an "out of window" visit is not conducted in the subsequent six-month period, this constitutes a missed visit. Enroll-HD site staff will initiate phone contact(s) to determine if the absence is health related and to determine the health status of the participant (see Data Dictionary (Appendix 2), Form 'Missed Visit', page 184-186). Missed visits are observed in Enroll-HD. Participants voluntarily miss visits – sometimes several consecutive years – then return, while others are actively paused, for example while participating in clinical trials. The median period between *conducted* in-person visits is 374 days (i.e., 1.02 years) – in line with protocol – although these data are extremely positively skewed (skewness statistic = 3.77), with values as extreme 2488 days (i.e., 6.82 years) observed (see LoI Figure 12). A total of 3,310 outlying values were observed above the upper bound threshold of 532 days (i.e., 1.46 years). To provide a frame of reference for the volume of missed visits in Enroll-HD, the total number of participant-years represented in Enroll-HD from FPI to April 1, 2020, is 72,794 person-years. The total number of visits conducted in Enroll-HD in the same time frame for 23,689 participants is 64,350 equating to about 67% annual visit compliance.

Enroll-HD is a natural history study, and as such we are lenient in our retention requirements; participants are not automatically withdrawn or discontinued from the study for missing visits and may return at any time. A PASS/PAES protocol is expected to apply more rigid thresholds. For example, in the PACE-HD study (a randomized controlled trial of physical activity nested in Enroll-HD) the retention rates at one year were 86.4% and 84.9% for controls and treated participants, respectively.
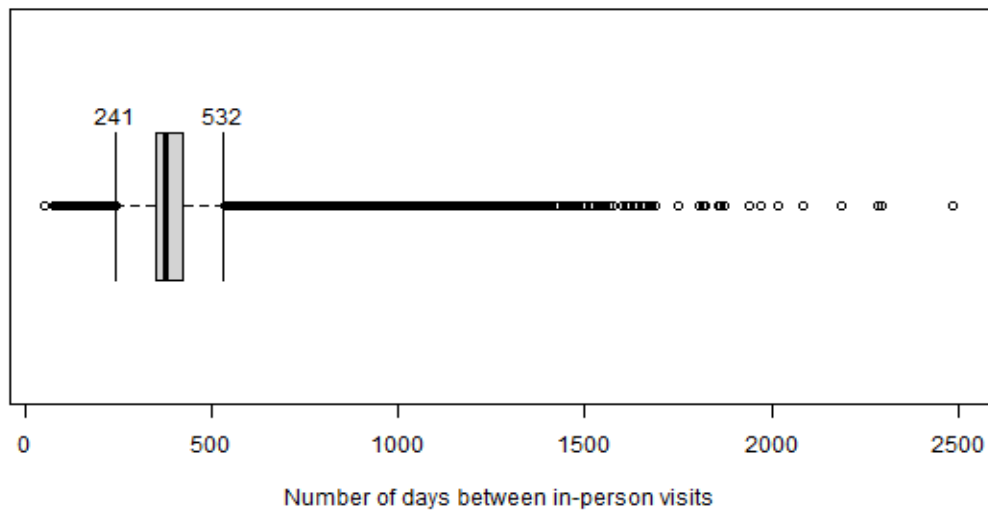
LoI Figure 12. Time (days) between conducted in-person visits in Enroll-HD. *Total observations plotted = 36,876. Participants represented = 14,392 (i.e., Current Enroll-HD participants as of April 1, 2020, with at least two visits). Median (Q2) = 374 days (i.e., 1.02 years). Q1 = 350 days (i.e., 0.96 years). Q3 = 423 days (i.e., 1.16 years). Lower whisker = Q1-[1.5*IQR]; 241 days (i.e., 0.66 years). Upper whisker = Q3+[1.5*IQR]; 532 days (i.e., 1.46 years).*

33. Additional data elements will likely be required for future PASS/PAES e.g. all causes of hospitalization, co-morbidities and observed events. The Applicant is requested to provide information on the process of how to implement additional data elements in the registry, such as systematic liver function tests, and whether this may be possible for individual studies.

<u>Answer:</u> The mechanism by which additional data elements can be added is through nesting a study in Enroll-HD, as described in Appendices A & B. Each PASS/PAES will have unique data collection requirements. These requirements will likely include collection of additional data (assessments, labs, PROs, adverse events, etc.) not currently captured in Enroll-HD. If the PASS/PAES is nested within Enroll-HD and uses the same EDC system, the PASS/PAES unique data would be captured in the EDC system but in a separate study, independent of the Enroll-HD study. The Enroll-HD EDC system automatically links the two studies at a participant/visit level using the HDID. While the data are maintained and stored as separate studies, linking the data is a built-in feature of the system. For example, if a PASS/PAES required routine labs (e.g., WBC, RBC, CRP, etc.) to be performed, a CRF within the EDC would be created (like the one below) and would be available for the PASS/PAES participants.

LoI Figure 13: EDC for routine labs collected in HDClarity, a nested study in Enroll-HD.

If both studies are maintained in the Enroll-HD EDC, then data extraction of a complete PASS/PAES dataset, which contains data from the Enroll-HD study as well as the PASS/PAES, is easier because all the data is designed to be extracted together, system checks between studies can be implemented, and variables can be unified.

If the PASS/PAES is nested in Enroll-HD but *does not use the Enroll-HD EDC* and instead uses a CRO-provided EDC, linkage of the data can still be achieved by using the HDID linking tool. Data is extracted from the Enroll-HD EDC and the CRO's EDC which can be concatenated to produce the analysis dataset(s). This may require additional work to reconcile inconsistencies, line up variables and visits, and perform data cleaning, but it is possible. Either way it is ideal if data collected in each study does not overlap extensively to reduce both participant burden and inconsistencies

34. Caution should be applied when implementing additional elements and time points for nested PASS, as this may turn a study with primary data collection into an interventional trial. The question on whether the study design is based on primary or secondary data collection is decisive if MAHs are obliged to submit reports of ADRs to EudraVigilance. In case of primary data collection it might be of advantage to consider ICSR exchange tools /reconciliation tools as well as to standardize ADR collection and capturing. Please comment.

<u>Answer:</u> The mechanics of a nested PASS/PAES are discussed in detail in Appendices A & B. Each nested PASS/PAES will have specific additional elements, but the hypothetical case discussed in Appendices A & B represents one extreme scenario because it deals with a gene therapy study that is administered surgically to the brain. For this situation, a large number of additional elements need to be captured. As explained in Appendix B, this PASS study will have its own protocol and IRB approval. There is no risk that Enroll-HD will be considered interventional because the additional elements only apply to the sub-population of Enroll-HD that participate in the PASS/PAES study. Moreover, the nested PASS is an independent study that leverages data and participants from the Enroll *registry*; it does not affect the Enroll-HD *study*, nor the data gathered therein.

As designed in Appendix B, nested PASS will always be primary data collection because this data will be collected prospectively under a specific protocol to address specific objectives (even if it is collected via the Enroll-HD framework.) In this situation the ICSR exchange/reconciliation tools can be used, and such use will be described in the protocol of the nested PASS/PAES. The mock-up in Appendix B clearly denotes the plan to standardize the ADR collection.

There are other situations where Enroll-HD may be used as a secondary data source, namely when the PASS will use data from Enroll-HD and EHR to acquire the needed information. This approach might be suitable when the treatment of interest is a small molecule, administered orally, and has the advantage of significantly enlarging the potential population of interest to several thousand individuals. In this situation, tying the cases to the ADRs reported to Eudravigilance is of critical relevance. We plan to facilitate this process in Enroll-HD by updating the EDC to incorporate a field that denotes that an ADR has been submitted to pharmacovigilance as appropriate for PASS/PAES.

<u>Data quality control mechanisms</u>

35. The Applicant is invited to discuss: a) how will external validity of data be anticipated when using the registry as source data (for example, will the sites be selected to fill a dataset as source data based on their specific performance in relevant quality items, or will they be randomly selected)? b) the quality control is frequently outsourced in clinical trials, with external companies evaluating data quality, ensuring an independent assessment; how independent will in-house quality control be?

<u>Answer:</u>

(a) There are multiple ways to select data from the Enroll-HD dataset that can be used for a PASS/PAES. For studies that use the core Enroll-HD assessments as outcome measures of interest, the extracted dataset can be the totality of the Enroll-HD dataset, or a subgroup selected on the basis of disease stage or other participant characteristics. This type of approach is driven by the participant characteristics and not by site. There are situations where the applicant might want to restrict the analysis to certain countries, and this is also possible. In this case the external validity in countries not included in the analysis will have to be assessed. It seems unlikely there will be a situation where the focus is on particular sites, as this would be a significant limitation on external validity.

In the Enroll-HD protocol there is a group of optional (extended) assessments that are collected at the discretion of the sites. If the PASS/PAES is focused on an outcome collected by an extended assessment, the sites and participants that can be the focus of the study are a sub-set of the total Enroll-HD population and its external validity will have to be evaluated.

Overall, a sufficiently large sub-population of Enroll-HD will have good external validity based on the representativeness of the Enroll-HD population, as explained in Supplement Section 3.

(b) A PASS/PAES nested within Enroll-HD would include two types of data: data from Enroll-HD collected in the Enroll-HD visits; and additional data collected according to the PASS/PAES protocol. For the first type of data, monitoring and QC will follow the Enroll-HD procedures detailed in the Supplement (Section 8). The Enroll-HD remote monitoring team and statistics team are independent of any site study staff. The second type of data (the data elements collected to support PASS/PAES) would technically be part of another study (which operates within the same EDC as Enroll-HD) and would have its own data quality and monitoring plan. The Enroll-HD team could handle the monitoring of the PASS/PAES data, if required. Alternatively, the data monitoring and QC of the PASS/PAES may be conducted by a CRO, in which case the Enroll-HD team can share the processes and SOPs to assure consistency between the Enroll-HD processes and the ones in the PASS/PAES. All data access within the EDC is granted by study, by role. Thus, specific access to the PASS/PAES data elements can be granted to allow a CRO to monitor only the appropriate data.

In this circumstance (the PASS/PAES data monitoring is conducted by a separate team), coordination between the monitoring teams (Enroll-HD monitors and PASS/PAES monitors) to ensure that all study data are monitored and ready for reporting is required. The monitoring schedule would be dictated by the needs of the PASS/PAES. The PASS/PAES monitoring plan would describe the data required from Enroll-HD, the frequency of the data extract from Enroll-HD, and the required status of each visit (e.g., the visit must be

closed and signed). The extracted data from Enroll-HD will be QC'd and monitored before release to the PASS/PAES. Monitoring priority is automatically assigned in the EDC based on the priority of the study, however, if specific visit data are critical to meet deadlines, these visits can be moved to the top of the priority list manually. See Appendix B for additional operational details.

36. **The Applicant describes a shortcoming with regard to monitoring and source data verification of data collected in North America. This should be more extensively justified.**

<u>Answer:</u> It is agreed that the inability to review medical records as part of the source data verification in the U.S. is a significant limitation. This decision dates from the original development of the U.S. ICF and has long been planned to be corrected as part of a protocol amendment. The first protocol amendment is now in the drafting stages and clarification of access to medical records will be addressed. In conjunction with the clarification in the protocol regarding access to medical records, the U.S. ICF will also be revised to inform participants that their medical records will be accessed during their participation in Enroll-HD.

37. **Please clarify if the Enroll-HD informed consent covers access to medical records and source data verification by representatives of the competent authorities (e.g., inspectors), in order to enable inspections of studies that access data from the Enroll-HD registry.**

<u>Answer:</u> Yes, the ICF allows for data audits. Section 5 of the ICF states that "the study site investigator may share a copy of this consent form and records that identify you with the following people/oversight entities," including both entities that "maintain, manage, and monitor the information collected in the study" and "Representatives of national and foreign governmental and regulatory agencies and health authorities, such as the … European Medicines Agency (EMA)." See Appendix 8.

<u>Data sharing</u>

38. **Patient representatives are not considered as stakeholders with potential access to datasharing via PDS, let alone SPS. Only researchers from "a recognised institution" will have access to data. Please clarify the term "recognised institution" as it may seem arbitrary and at the Applicants discretion.**

<u>Answer:</u> CHDI aims to lower the barriers to data access and to make Enroll-HD data widely available to all researchers for the pursuit of HD research. As a data controller governed by GDPR, however, CHDI is required to meet specific obligations for data sharing and data security. To ensure that CHDI meets these obligations, and that the data are used in accordance with the ICF, CHDI requires data recipients to sign a data use agreement on behalf of their institution, company, or organization and to provide a description of their research project (this description is made publicly available on the Enroll-HD website). CHDI verifies that the data recipient is associated with the disclosed research organization prior to providing access. Verification that the recipient belongs to a recognized institution includes determining that the institution, company, or organization exists (has a website, is a legal entity, etc.) and the researcher is affiliated with the organization (e.g., has a valid email address associated with the entity).

The term "researcher" is broad. It includes **anyone doing HD research**, including not only academic institutions and pharmaceutical companies **but also lay associations**. The data are not provided to individuals or even directly to students without a supervisor, because it is difficult to verify that they have the necessary data security provisions in place and, in the unlikely event of a security breach, that CHDI would be able to contact them to provide notification. Enroll-HD participants desiring access to the data to perform HD research could do so through any of these channels – for example if they worked for an academic institution (there are several examples of this) or through their patient-focused organization or association.