Submission of comments on Enroll-HD: Registry for Huntington's Disease

Comments from:

Name of organisation or individual
1. **Roche**
2. **Novartis**

Please note that these comments and the identity of the sender are public unless a specific justified objection is received.

.

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

1. General comments

Line number(s) of the relevant text (e.g., Lines 20-23)	**Stakeholder number** **(To be completed by the Agency)**	**General comment (if any)**	**Outcome (if applicable)** **(To be completed by the Agency)**
	ROCHE	Unclear whether Enroll-HD considers a data sharing mechanism providing files in SDTMs format (in case of a FDA post-marketing requirement).	Not subject to this qualification. No change required.
	ROCHE	About data collection of AEs and comorbidities: 1. Enroll-HD does not capture AEs while 4 reportable events are captured. It is unclear from the document how comorbidities and underlying conditions are captured in Enroll-HD. Clear classification of comorbidities, especially for background incidence rates of events which may become potential identified or suspected risks. (e.g. line 525 it is stated that one event "mental health event requiring hospitalization" is currently coded using MedDRA terms. If MedDRA coding is already available within Enroll-HD, could it be possible to use it to capture all comorbidities pre-authorization of therapies for HD?)	This information will be nested in the individual post authorisation study protocols. No change required.
	ROCHE	Clarification on the points below would be appreciated: 1. TMS and weight variables important to include 2. for Enroll-HD lite, in person assessments would be preferable	1. TMS and weight are captured by Enroll-HD, Tables 10 and 11 of Briefing Package 2 of 2 Supplement 2. Enroll-Lite will be introduced in the next Enroll-HD protocol amendment, projected for 2022 and is not subject to this Qualification opinion. Whether the

Line number(s) of the relevant text (e.g., Lines 20-23)	**Stakeholder number** **(To be completed by the Agency)**	**General comment (if any)**	**Outcome (if applicable)** **(To be completed by the Agency)**
			leaner assessment battery will be collected remotely or in-clinic is currently evaluated. A sentence is included in answer to Q1: "Whether remote assessments will be possible is subject to ongoing investigations." line 359
	ROCHE	Proposed change: changes to protocol from different sponsors to be captured to quantify additional burden.	"Changes to protocol from different sponsors need to be captured to quantify additional patient burden." is included in answer to Q2 ll 447-448.
	ROCHE	Proposed change: validation of HD specific endpoints to be added.	Not subject to this qualification. No change required.
	ROCHE	Proposed change: alignment between academic research and Enroll-HD database on HD index.	Not subject to this qualification. See https://doi.org/10.1002/mds.28944 published earlier this year. Being so, this does not impact QO, since modifications cannot arise from Enrol-HD. No change required.
	ROCHE	Comment: addition of an MRI scan for the purpose of the new staging framework may limit the eligibility of patients, study sites and re-categorisation as an interventional study.	Agreed. It is mentioned that the infrastructure of the registry is flexible and may also serve for specific PASS/PAES studies in which case the Enroll-HD data specified by the PASS/PAES protocol becomes **primary** data. No change required.
	ROCHE	Clarification requested on which patients are followed up until death. Proposed change: Use ICD 10 coding for cause of death to minimize investigator bias in the cause of death reporting which may have a big	In the event of participant death, date and cause of death will be recorded. Free text response is possible. For specific PASS/PAES protocols review of death certificates to verify the cause of death can be implemented.

Line number(s) of the relevant text (e.g., Lines 20-23)	**Stakeholder number** **(To be completed by the Agency)**	**General comment (if any)**	**Outcome (if applicable)** **(To be completed by the Agency)**
		impact on the outcomes (SAE) collected in a PASS study.	No change required.
	ROCHE	Proposed change: appropriate medical records are included at the point of data entry into the EDC to ensure capture of all medications is appropriate and correct. Clarification: how Enroll-HD could consider ensuring the quality of pharmacotherapies at the points of data entry at the annual site visit to limit the missingness anticipated between visits.	It is stated ll 419-423: Core data components - **which are mandatory and must be completed or reviewed and updated at each visit** - include participant demographic information, HD clinical characteristics, comorbid conditions, **disease-related treatments and other therapies**, and several assessments designed to assess motor, function, behavioural, and cognitive performance. Enroll-HD collects all treatments related to HD and any other diseases including pharmacotherapies, non-pharmacologic therapies and nutritional supplements. Treatment and onset dates are reviewed for completeness and accuracy by onsite monitors with reference to source documents (including medical records). It is acknowledged that because Enroll-HD visits are annual short-term treatments may be forgotten / not collected. Can be mitigated by connecting Enroll-HD data to EHRs. Specific PASS/PAES protocols that are nested in the Enroll-HD study could include more frequent data collection and evaluate missingness. Information is added in Q3 answer ll 580 ff.

Line number(s) of the relevant text (e.g., Lines 20-23)	**Stakeholder number** **(To be completed by the Agency)**	**General comment (if any)**	**Outcome (if applicable)** **(To be completed by the Agency)**
	ROCHE	Clarification: is it anticipated that data from the China network will be accessible as part of global post authorisation studies?	The following was stated: As a first step in expanding Eroll-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 centres in China. The staff at these Chinese sites have been trained in the Enroll-HD assessments, and all assessments have been translated into Mandarin. The answer is yes: Enrol-HD has established and supports a Chinese HD Network. Information is added Q1 line 322.
	ROCHE	Proposed change: linkage between HD specific scales such as UHDRS and medical records would be useful	It is stated in the Briefing Book Where data are entered directly into the EDC, the EDC is the source document; however, where possible, key variables are also checked against medical records for accuracy. In Europe, Latin America, and Australasia, Onsite Monitors have access to participants' medical records in addition to Enroll-HD specific paper source documents, to verify symptom onset data as well as reportable events, comorbid conditions, and therapies. Apart from that line 686: allow for SDV against medical records. No change required.

Line number(s) of the relevant text (e.g., Lines 20-23)	**Stakeholder number** **(To be completed by the Agency)**	**General comment (if any)**	**Outcome (if applicable)** **(To be completed by the Agency)**
	ROCHE	Comment: it is not clear how the retention will be encouraged in the case of a nested PA study.	This will be subject to the specific study protocol. No change required.
	ROCHE	Clarification requested on whether caregivers and general healthy volunteers are also recruited.	In the briefing book the following is stated: Individuals eligible to participate in Enroll-HD are classified into two major categories: • Carriers: This group is the primary registry population and consists of HDGECs. • Controls: This group is the comparator study population and consists of individuals who do not carry the HD gene expansion. The two major categories are further subdivided into six different subgroups of eligible participants: • Manifest/Motor-manifest HD: HDGECs with clinical features that are regarded, in the opinion of the investigator, as diagnostic of HD. • Pre-Manifest/Motor-manifest HD: HDGECs without clinical features regarded as diagnostic of HD but with a confirmed HD expansion genetic test. • Genotype Unknown[1]: A first or second degree relative (i.e., related by blood) of a known HDGEC, who has not undergone predictive testing for HD and therefore has an undetermined HDGEC status. • Genotype Negative: A first or second degree relative (i.e., related by blood) of a known HDGEC, who has undergone predictive testing for HD and is known *not* to carry the HD expansion. • Family Control: Family members or individuals not related by blood to HDGECs (e.g., spouses, partners, caregivers). • Community Controls: Individuals unrelated to HDGECs who did not grow up in a family affected by HD.[2]

Line number(s) of the relevant text (e.g., Lines 20-23)	**Stakeholder number** **(To be completed by the Agency)**	**General comment (if any)**	**Outcome (if applicable)** **(To be completed by the Agency)**
			[1] It is unusual to allow individuals without a confirmed diagnosis into a study; however, in the case of genetic diseases where many of the potential carriers are not willing to undergo predictive genetic testing it is an acceptable practice that allows for a larger recruitment base and a greater representativeness of the recruited population. After research genotyping, the gene negative group provides a valuable comparator group. The percentage of 'genotype unknown' participants varies by region: Europe 10.2%, North America 14.6%, Latin America 34.7%, and Australasia 7.2% of the total cohort (based on the participant's HD category at their last visit, as of April 24, 2020). [2] Community controls are not actively recruited unless needed for a specific platform study. There are currently only 16 community control participants in Enroll-HD. Information added line 163 ff under Target population of use.
	ROCHE	Line 252-271 – not clear how any of this section on linkages to EMRs is relevant to the current section on data-base representativeness and external benchmarking. Linkage would just achieve more data with the same patients.	Acknowledged. However, comparison to public databases could provide data **to compare** the distribution of categories of important variables such as age, gender or prevalence of disease-related drug exposure. However, Enroll-HD is not linked to national databases. ll 298 ff No change required.
	NOVARTIS	Comment:	The Enroll-HD study is funded by the CHDI Foundation, Inc. (https://chdifoundation.org/). CHDI Foundation is a

Line number(s) of the relevant text (e.g., Lines 20-23)	**Stakeholder number** **(To be completed by the Agency)**	**General comment (if any)**	**Outcome (if applicable)** **(To be completed by the Agency)**
		How is Enroll-HD funded? Information regarding funding sources would be useful.	privately-funded, not-for-profit biomedical research organization in the US devoted to Huntigton´s disease. Information added ll 41-43

2. Specific comments on text

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome *(To be completed by the Agency)*
Line 2	**ROCHE**	Comment: the statement that registries are important tools for the advancement of therapeutics is a limited view on their utility and impact, especially understanding disease cannot be dissociated from advancement of therapeutics. Proposed change (if any): high-quality disease-specific patient registries are important tools for **the improvement of disease epidemiology understanding and** the advancement of therapeutics.	Accepted. Wording added.
Line 3-4	**ROCHE**	Comment: clinical epidemiology research should be added, mentioning natural history studies is not sufficient. Proposed change (if any): they can be used for recruitment in clinical trials, natural history studies, **clinical epidemiology research**, health economic studies, and the collection of bio-samples.	Accepted. Wording added.
Line 39-45	**ROCHE**	Comment: text is very similar and redundant with text "observational cohort study" line 25-32. Proposed change (if any): Suggest to only have the section "observational cohort" adding not redundant text from line 39-45.	Only partly accepted. Since line 40 ff emphasized that the Enroll-HD study is central to the Enroll-HD-platform. Reworded with information on funding.

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome *(To be completed by the Agency)*
Line 55-56	**ROCHE**	Comment: text is "As of April 1, 2020, 14,428 participants have been recruited in Europe, of whom 11,335 are HDGECs." Proposed change (if any): as of April 1, 2020, 14,428 participants **from Europe are still active**, of whom 11,335 are HDGECs.	Not accepted. Reworded and inclusion of figure ll 56 ff. See also Novartis comment below
Line 57-58	**ROCHE**	Comment : "Benchmarking Enroll-HD against another large 58 cohort study showed strikingly similarity with respect to age, sex, and ethnic composition". Proposed change : include appropriate reference.	Accepted. Reference to REGISTRY and Q1 is included.
Line 150-151	**ROCHE**	Comment : clinical efficacy and safety evaluation of therapeutic interventions in HD, **supporting post-marketing.** Proposed change **:** pre-marketing (e.g. as source of natural history for external comparator data (e.g. see line 165 (paragraph Bii). and post-marketing.	Not accepted since the heading refers to stage of Drug Development. See also context of use. Pre-authorisation is not in the remit of this CoU
Line 663-664	**ROCHE**	Comment : as above. "post authorisation studies in HD". Proposed change : include pre-authorisation.	Not accepted since this is not subject of the qualification. See context of use.
Line 642	**ROCHE**	Comment : "it is agreed that the PDS may only provide information on aggregate data". Proposed change : clarification on whether the PDS includes patient level data.	Not accepted.

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome *(To be completed by the Agency)*
Lines 25 – 32 Lines 39 - 45	**NOVARTIS**	Comment: Lines 39-45 are repetitive with lines 25-32. It was difficult to determine if this referred to the same observational cohort or a different study.	See answer to same ROCHE comment above
Line 29	**NOVARTIS**	Comment: More clarification needed on 13 countries in Europe, which one participates in enrol-HD and which countries will it expand into and when?	Information is included in Q 1 line 253 ff No change required.
Line 52	**NOVARTIS**	Comment: More clarification is expected regarding the study start and the date of the most recent data. It is suggested to state why participants are no longer active (how many are lost to follow up, how many died, etc.)	Partly accepted. It is stated line 40 that the Enrol-HD study was established in July 2012 (ClincalTrials.gov identifier added) and in line 56 most recent data assessed in this qualification procedure as of April 1 2020. A Figure of the Briefing Book is included for clarification. See also Roche comment above
Line 54	**NOVARTIS**	Comment: More details on the registry sites would be welcomed. Are these primary care physicians or specialists? Affiliated with a hospital or private practice?	It is stated in the "Site Requirements for Participation in Enroll-HD" (Appendix 1 in the original documentation) the site requirements. The PI must be a trained professional, MD or in exceptional circumstances a PhD with MD support, and the staff must be trained in HD and perform annual certifications in UHDRS. Not primary care. Both public or private institutions.
Line 56 - 58	**NOVARTIS**	Comment: references should be provided	Reference to REGISTRY included. See comment above

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome *(To be completed by the Agency)*
Line 77 - 78	**NOVARTIS**	Comment: When will the targeted pregnancy data collection begin? More details about this would be helpful.	See line 718. Based on feed-back of EMA the proposed Pregnancy form has been revised. This is stated. No change required.
Line 117	**NOVARTIS**	Comment: Clarification around who assesses the risk for participant re-identification would be welcomed. How is this done? More details would be helpful.	Accepted: The following is added: To ensure the data are HIPAA (Health Insurance Portability and Accountability Act)-compliant and the risk for re-identification is low, the de-identification process makes use of two main methods: 1) the "Safe Harbor" method and 2) the "Expert Determination" Method. As part of the de-identification and quality control process in Enroll-HD, these methods are applied sequentially.
Line 171	**NOVARTIS**	Comment: Drug safety evaluation studies: what safety data would be collected? In lines 91-94 it states that only suicide attempts, completed suicide, mental health events and death are collected. In the context of drug safety studies, additional data need to be collected.	Reference is made to question 3. The following is added Line 580 ff: 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. All TEAEs should be coded using MedDRA.