Qualification opinion of the use of Enroll-HD (a Huntington's disease patient registry) as a data source and infrastructure support for post-authorisation monitoring of medical products

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[1] Last day of relevant Committee meeting.
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Executive Summary

High-quality disease-specific patient registries are important tools for the improvement of disease epidemiology understanding and the advancement of therapeutics. They can be used for recruitment in clinical trials, natural history studies, clinical epidemiology research, health economic studies, and the collection of bio-samples. These patient registries are foundational to drug discovery and development as well as the advancement of clinical care. They are especially critical for the rare diseases that have, in addition to limited patient cohorts spread over large geographic territories, diverse phenotypic presentation. Recognising the need for well-developed and comprehensive registries, EMA recently published a guideline on registry-based studies (EMA/426390/2021), the annex of which contains focused recommendations on quality data collection, standardisation of data elements, governance, and other guidelines for patient registries. (Other recommendations for good registry practice appear in the 2018 discussion paper "Use of patient disease registries for regulatory purposes – methodological and operational considerations." This is referred to herein as the "EMA 2018 discussion paper.")

Huntington's disease (HD) is an inherited autosomal dominant degenerative neurologic disease caused by an abnormal expansion of cytosine-adenine-guanine (CAG) repeats in exon 1 of the *huntingtin* gene *(HTT)*. Clinically, HD is typically an adult-onset degenerative disease with a protracted but relentlessly progressive course. The clinical disease course is characterised by early behavioural and psychological manifestations followed by the onset of involuntary movements, with simultaneous decline in cognitive function, ultimately leading to severe morbidity and disability and lastly a bed-bound state and death. Currently, treatment is limited to symptom management and optimisation of quality of life. There is no definitive treatment for HD, although several therapeutic interventions are currently in clinical trials.

Enroll-HD is an integrated clinical research platform serving several different functions:

1. **Patient registry**. A registry of HD patients, the data for which are collected via the Enroll-HD study.

2. **Observational cohort study**. The global Enroll-HD study collects natural history data in HD gene expanded carriers (HDGECs) - regardless of clinical symptomatology - alongside HD family members and non-HDGECs.   Participants attend an annual study visit during which they complete a series of "core" assessments and additional "extended" and/ or "optional" assessments at the discretion of the investigator or the participant, respectively. All the data is collected in a uniform manner by trained site personnel in a single Electronic Data Capture (EDC) system.

3. **Clinical research platform**. The platform is available to researchers, clinicians, and biotech/pharmaceutical companies, providing expert guidance, resources, training, frameworks, documents, infrastructure, data, and bio-samples.

The organising principle of Enroll-HD is to expedite 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.

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Central to the Enroll-HD platform is the global Enroll-HD study, established in July 2012 (NCT01574053; ENCEPP/DSPP/28517). The Enroll-HD study is funded by the CHDI Foundation, Inc. (https://chdifoundation.org/). CHDI Foundation is a privately-funded, not-for-profit biomedical research organization in the US devoted to Huntigton´s disease.

To support Enroll-HD's broad functionality - including the core Enroll-HD study - 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.

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.

Patient Population: As of April 1, 2020, 23,689 participants had enrolled in Enroll-HD (all participant categories considered, including controls). Of these, 19,737 (83.3%) are still currently enrolled (i.e., no Mortality form or Premature End form completed).

Figure: Enroll-HD participant flow diagram. Derived from data cut April 1, 2020.

In Europe, Enroll-HD operates in 13 countries and plans to expand to 4 additional EU countries, with 90 actively recruiting registry sites and 18 more sites in start-up in the EU alone. As of April 1, 2020, 14,428 participants have been recruited in Europe, of whom 11,335 are HDGECs. Of the 14,428 ever recruited as of April 1, 2020, 12,332 are still currently enrolled and 11,623 are still active.

It is estimated that Enroll-HD currently provides 18% coverage of the European manifest HD population. Benchmarking Enroll-HD against another large cohort study (REGISTRY, see Q1) showed strikingly similarity with respect to age, sex, and ethnic composition. Finally, the Enroll-HD HDGEC cohort is extremely diverse with respect to coverage across the entire HD disease spectrum.

Time Elements: Enroll-HD captures all relevant dates for HD progression, including most core time elements outlined in Table 2 of section 5.3 of the EMA 2018 discussion paper, and captures exact dates for important events and outcomes, as per EMA/426390/2021.

Core Data: The Enroll-HD protocol, including the assessment battery, was designed by HD clinicians and other HD specialists. It features both 'core' and 'extended' components. Core data components - which 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. Genetic information (CAG repeat length, as determined at a central laboratory) is assessed at the baseline visit for every participant, and genome-wide association study data are available for a subset of participants. Except for pregnancy and adverse events (discussed in more depth below), Enroll-HD captures all the data elements defined by EMA/426390/2021.

Qualification opinion of the use of Enroll-HD (a Huntington's disease patient registry) as a data source and infrastructure support for post-authorisation monitoring of medical products

Page 3/19

Common Terminologies: As an integrated platform, Enroll-HD uses common terminologies for diseases, symptoms, medicinal products, reportable events, and all other data.

Pregnancy: Pregnancy data, if reported by the participant or if complications occurred, are currently captured as part of medical history. However, to ensure complete and systematic capture of pregnancy data in Enroll-HD, the implementation of a targeted Pregnancy data collection form is planned. This form will capture, prospectively, data on pregnancy start date (and number of weeks of pregnancy, if pregnancy is ongoing) and pregnancy outcome. It will also capture retrospective collection of pregnancy and outcome data.

Data Quality Management: Ensuring data quality and integrity is fundamental to the Enroll-HD study. Quality control and assurance measures, designed to maximise data consistency, completeness, accuracy, and timeliness, are implemented and monitored at a participant, site, and global study level. These extensive measures include remote centralised statistical monitoring (CSM) (at both the participant level and the site level) and onsite data monitoring including source data verification. Regional Managers and Site Managers oversee site performance and study compliance using several data quality measurement tools: regular review of metrics generated in the EDC-based Data Quality Management dashboard and tracker, Site Metrics Cards, and Site CSM reports. Enroll-HD complies with all the data quality suggestions outlined in EMA/426390/2021 sections A.4.3-A.4.4 and section 5.6.4 of the EMA 2018 discussion paper.

Adverse Events and Safety: Because there are currently no treatments for HD, the only reportable events systematically captured in Enroll-HD are suicide attempts, completed suicide, mental health events requiring hospitalization, and death. Reportable events are reviewed by the data safety monitoring committee.

Governance: The governance structure is comprised of four independent committees, coordinated and managed by the Enroll-HD Clinical Platform Managers. The Scientific Oversight Committee is the major governing committee for the study and guides the overall scientific strategy, provides oversight of study conduct and progress, advises on centralised data analysis, and ensures adherence to study and platform goals. The Clinical Trial Committee interfaces between the Enroll-HD platform and academic/industrial collaborators conducting interventional HD clinical trials. The Scientific Review Committee ensures an ethically sound, fair, and a scientifically rigorous review of requests to access data and samples, reviewing requests for non-renewable samples and specified data sets from Enroll-HD and other platform studies. The Data Safety Monitoring Committee monitors participant safety and data quality.

Data Sharing and Participant Identification Risk: Enroll-HD takes great care to protect participant data and privacy. Enroll-HD site staff generate an "HDID" for each participant based on personal information using a secure one-way algorithm that does not store any of the entered information. All clinical data captured in Enroll-HD is coded using the HDID so that the participant's name, address, phone number, and any other personally identifying information is *not* contained in the EDC or in any Enroll-HD database. Because data and bio-sample sharing is essential to support HD research and the development of therapeutics for HD, the longitudinal, coded Enroll-HD clinical data and bio-samples are made available to any interested researcher working at a recognized research institution through a straightforward verification process. However, recoded participant level data and samples are provided to the research community only in accordance with three overarching principles: data and samples are only shared in accordance with EU GDPR rules, US HIPAA rules, and the participant's informed consent; an Enroll-HD Data Use Agreement and/or Material Transfer Agreement must be signed and the terms honoured by any requester; and the risk for participant re-identification is assessed for all

Qualification opinion of the use of Enroll-HD (a Huntington's disease patient registry)
as a data source and infrastructure support for post-authorisation monitoring of
medical products

Page 4/19

participants in Enroll-HD and steps are taken to reduce the risk of re-identification below a predetermined threshold before data release. 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.

Context of Use

General Area

Patient Disease Registries

General Description

The Enroll-HD study is a Huntington's disease (HD) registry and observational cohort study, and a central component of the Enroll-HD clinical research platform. The Enroll-HD study is approximately 8 years old and has 18,758 active participants (as of April 1, 2020). Data are acquired in accordance with a standard protocol, and include participant socio-demographics, clinical assessments, co-morbidities, and pharmacotherapies. CAG genotyping is performed at a central laboratory for every participant based on blood collected at baseline visit, and genome-wide data are available for many. Data on reportable events and mortality are also captured. If the participant consents, family history (pedigrees) may also be recorded. Follow-up visits take place annually, providing rich longitudinal data. The platform contains a fully integrated operational infrastructure to support the registry and study. This operational infrastructure includes a flexible Electronic Data Capture (EDC) system capable of multi-study integration, a training platform that provides certification for various HD-specific and general clinical practice courses, standardised informed consent forms (ICFs) and data use agreements that can serve as templates for other HD studies, an integrated governance framework that oversees different aspects of the Enroll-HD Platform, and a HD-community facing website (www.Enroll-HD.org) that provides information about the Enroll-HD study, research outcomes from the study, and other resources for HD families, clinicians, and researchers. In addition, the platform is also supported by various global processes and procedural SOPs and guidelines that ensure high quality and consistency in the data collected (including common coding methods) and by a monitoring infrastructure that supports the Enroll-HD study as well as other platform studies. This infrastructure includes common participant ID and data dictionary variables that allow HD study data from various studies to be linked, leveraging all HD research efforts.

Target Population for Use

Individuals with a gene-expansion mutation of the *huntingtin* gene (*HTT)* totalling 36 or more CAG repeats - regardless of clinical symptomology; non-gene-expanded individuals are available alongside the target cohort for use as a comparator group.

The Enroll-HD study is designed to collect data from a unique cohort which consists of two major participant categories and is further subdivided into six subgroups.

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.

Qualification opinion of the use of Enroll-HD (a Huntington's disease patient registry)
as a data source and infrastructure support for post-authorisation monitoring of
medical products

Page 5/19

Criteria for study exclusion are limited, encompassing only individuals that do not have an expansion of the HTT gene with choreic movement disorders or major nervous system disorders (e.g., stroke, Parkinson's disease).

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[4]: 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.[5]

Stage of Drug Development for Use

Clinical efficacy and safety evaluation of therapeutic interventions in HD, supporting post-marketing trials.

Intended Application

To use Enroll-HD as a data source and infrastructure support for registry-based studies (drug utilisation studies, drug efficacy/effectiveness studies, or drug safety evaluation studies).

A. **Drug utilisation studies**. Enroll-HD may be used to support drug utilisation studies both for total recorded population and by subgroups such as disease stage, age, gender, CAG length, phenotype, etc. Enroll-HD collects detailed longitudinal pharmacotherapy use, including start/stop dates, doses, and frequency, and centrally codes all data.

B. **Drug efficacy studies.** In addition to use of its infrastructure to support drug efficacy studies, data from Enroll-HD may be used:

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[4] 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).

[5] Community controls are not actively recruited unless needed for a specific platform study. There are currently only 16 community control participants in Enroll-HD.

Qualification opinion of the use of Enroll-HD (a Huntington's disease patient registry)
as a data source and infrastructure support for post-authorisation monitoring of
medical products

Page 6/19

      i.   To support assessment of post-authorisation efficacy using annual HD clinical assessment endpoints like Total Functional Capacity, Total Motor Score, the Symbol Digit Modalities Test, composite Unified Huntington's Disease Rating Scale; or

      ii.   As a source of historical control data that may be used for contextualisation, such as for comparative purposes in the context of non-randomised clinical trials (e.g., when this would be the only reasonable option) or to supplement control groups in randomised clinical trials (e.g., when the nature of the sham intervention precludes/limits randomisation).

    C. Drug safety evaluation studies. Enroll-HD may be used to collect safety data, with a particular focus on important identified and potential risks (adverse events). In this context, it is not only possible to assess cumulative annual incidence of these potential or identified risks (currently recorded as co-morbidities, reportable events, or deterioration in the clinical assessments), but it is also possible to perform comparative assessments of newly solicited safety data (adverse events of special interest) provided an appropriate control cohort can be constructed.

Summary context of use

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.

In the future and in conjunction with a MAH, scientific advice on Enroll-HD's use for *specific* nested PASS/PAES proposals will be sought. 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.

Qualification opinion of the use of Enroll-HD (a Huntington's disease patient registry)
as a data source and infrastructure support for post-authorisation monitoring of
medical products

Page 7/19

Question 1

CHDI considers that Enroll-HD's participant population renders it well-suited for use as a data source and supportive infrastructure for future post-authorisation safety studies (PASS) and post-authorisation efficacy studies (PAES) in HD. Does EMA agree?

Applicant's position: PASS and PAES require the evaluation and follow-up of relatively large cohorts of participants exposed to the treatments under study, and whenever possible control cohorts of participants treated with standard care or alternative comparators. CHDI considers Enroll-HD to be well-suited for use as a data source for future HD PASS/PAES. See Supplement Sections 3.1, 3.4.

Utilising estimates of HD prevalence in predominantly Caucasian populations, we estimate that 18% of the European manifest HD population is currently participating in Enroll-HD. Coverage of the European premanifest population in Enroll-HD is estimated to be between 3% and 4%. Benchmarking of the European Enroll-HD HDGEC sample to that of REGISTRY - a European cohort study conducted across >100 sites - revealed notable similarities with respect to age, sex, ethnic composition, and CAG length, underscoring the representativeness of the European Enroll-HD sample with respect to the broader European HD population.

The Enroll-HD European HDGEC sample is both extremely large and extremely diverse with respect to HD disease spectrum coverage. See EMA/426390/2021 section A.2. Given this, we expect that once treatments for HD are approved, Enroll-HD will naturally encompass people exposed to the target treatments. To the extent that there is inadequate natural enrollment of people using the target treatment, Enroll-HD can enrich the treatment population through targeted recruitment. Further, given the disease stage diversity within Enroll-HD, it can be used as a data source for studies of all different types of HD populations, including studies targeted at premanifest, early, and late stages of the disease.

CHMP answer

Enroll-HD is a global study operating in Europe, North America, Latin America, and Australasia. As of April 1, 2020, Enroll-HD encompasses 157 actively recruiting sites with 25 more in start-up. Since the study began in July 2012, 23,689 participants have been recruited, 19,737 are still currently enrolled and 18,758 are still active. Most of the participants, i.e., 62% are from Europe.

According to the Applicant Enroll-HD operates in 13 European countries including Norway, Switzerland, - and the UK, and plans to expand to 4 additional European countries, with 90 actively recruiting registry sites and 18 more sites in start-up in Europe alone. As of April 1, 2020, 14,428 participants have been recruited, of whom 11,335 are HDGECs with 7,712 manifest and 3,593 premanifest patients (at study entry). This builds up to approximately 18% of the European manifest HD population and between 3% and 4% of the European premanifest population which is covered in Enroll-HD.

Representativeness of the Registry population in comparison to the broad HD population covering all disease aspects and patient characteristics is of key importance. In order to justify the representativeness, the Applicant undertook three approaches:

1. Benchmarking against the REGISTRY data source.

REGISTRY was an observational cohort study of the European Huntington-Disease Network (EHDN) conducted across >100 sites between 2004 and 2017. The objectives and the target population of REGISTRY overlap with Enroll-HD in comparison to other available data sources which either concern only premanifest HD (Predict-HD, PHAROS) or are restricted to other regions of the world such as NA and Australia (COHORT) or are extremely small (TRACK+TRACK-On). Both populations of Enroll-HD

Qualification opinion of the use of Enroll-HD (a Huntington's disease patient registry)
as a data source and infrastructure support for post-authorisation monitoring of
medical products

Page 8/19

and REGISTRY were compared with respect to clinical and sociodemographic characteristics, the latter being quite similar between the sources with respect to age, sex and ethnicity. There is however a difference in educational level with a larger proportion of European Enroll-HD participants having a university level qualification (i.e., higher education) relative to the REGISTRY sample. In addition, the REGISTRY sample appears to be more advanced in disease stage at study entry relative to Enroll-HD, as reflected by CAP score, TFC score, and manifest status (i.e., DCL score), and Shoulson-Fahn disease stage.

Since many REGISTRY sites and personnel transitioned to Enroll-HD - roll-over patients constitute approximately 1/3 of the European Enroll-HD database- there is a certain flaw in this comparison. The Applicant already acknowledges that both samples suffer from overlapping selection biases. For the comparative exercise Enroll-HD participants who had previously participated in REGISTRY (n=4,414) were randomly assigned to either the Enroll-HD or REGISTRY samples to ensure independence of samples. However, this does not appear to be meaningful: No independent samples are required for benchmarking and including only 50% of the overlapping patients in each of the respective samples implies that these patients, which could have different characteristics than non-overlapping patients, may be underrepresented. Although the aim of this approach is understood a real benchmarking cannot be guaranteed. Of note, benchmarking was not undertaken with respect to the North American population which represents 32% of the registry participants and a comparison to COHORT for this population could have been provided since Enroll-HD also incorporates COHORT sites. During the discussion meeting it was clarified that the first protocol amendment is now in the drafting stages and clarification of access to medical records in the US 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.

Registry data can be benchmarked to external data source such as national electronic health records 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.

It is stated that individual medical records are accessible as source documents for Enroll-HD data in Europe, Australasia, and Latin America for purposes of SDV but not in North America.

The Applicant should explore 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. This might be easily possible e.g., in Scandinavian countries. During the discussion meeting it was highlighted that 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. Also, the linkage of different types of registries will be possible. Enroll-HD has the adequate data infrastructure in place to participate when possible. It has however to be noted 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 symptomatology 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. This is acknowledged.

1. *Assess Enroll-HD´s coverage relative to the global HD population*

It is recognised that there are underrepresented groups in Enroll-HD respective to the global HD population; i.e., patients of non-white ethnicity, patients < 18 years of age.

The Applicant is of the opinion that for purposes of supporting post-marketing surveillance in Europe, the under-representation of non-Caucasian ethnicities is a lesser problem because the prevalence of

Qualification opinion of the use of Enroll-HD (a Huntington's disease patient registry)
as a data source and infrastructure support for post-authorisation monitoring of
medical products
Page 9/19

HD in these groups is very low, and represent a small fraction of the European population. This is agreed. The plan to identify new sites in new countries with higher ethnic and socioeconomic diversity is endorsed. 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. Enroll-HD also has established and supports a Chinese HD network.

The biggest difference is however the genetic testing which is low in the general at-risk population (17%) in comparison to Enroll-HD (74%) probably most likely due to the fact that no curative treatment is currently available. During the discussion meeting it was explained that 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.

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. 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 underway as explained above.

2. *Representativeness across the Disease Spectrum*

Within the full Enroll-HD sample CAP scores range from 19 to 286, and TFC scores range from 0 to 13. This represents a broad spectrum and the full spectrum of possible scores on the TFC.

3. *Loss of follow up*

Retention of HDGECs who are premanifest at study entry is high, with 80% probability of continued participation at 7 years post study entry. For HDGECs who are manifest on study entry, a ~65% probability of continued participation is observed at 7 years. Overall, it is acknowledged that attrition is low in Enroll-HD but higher in the manifest HD participant group.

Retention in the study as a function of stage of manifest disease at baseline visit could also be of interest and should be examined. The Applicant provided an additional survival analysis to assess Enroll-HD study retention wherein all participants are aligned to a date-independent time 'zero' (i.e., timepoint of individual study entry). 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. It is however noted, 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%. Enroll-HD is a natural history study, and as such retention requirements are lenient; 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.

The Applicant outlines plans for a leaner assessment battery for participants with more advanced disease. For this a new platform named Enroll-Lite is being created and currently a pilot study is being conducted to assess and validate two new assessments designed for remote administration with the HD caregiver. Whether remote assessments will be possible is subject to ongoing investigations. Enroll-Lite will be introduced in the next Enroll-HD protocol amendment, projected for 2022.

Qualification opinion of the use of Enroll-HD (a Huntington's disease patient registry) as a data source and infrastructure support for post-authorisation monitoring of medical products

Page 10/19

Furthermore, it is stated that the introduction of "Self-Enroll" may overcome some barriers to recruitment and factors associated with drop-out. Self-Enroll is a digital registry and research platform for Huntington's disease that aims to remove barriers to enrolment and retainment, and to open geographical coverage to regions outside of the current Enroll-HD remit. 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 the other hand, self-enrolment may also lead to a selection because self-enrolled patients are usually not representative of the average HD patient (e.g., younger patients who are familiar with digital tools). During the Discussion meeting it was explained that Self-Enroll is not a part of the Enroll-HD registry and will not be used for PASS/PAES studies. It is more targeted to younger patients. Engaging younger individuals – far from disease onset – is of great interest, affording the opportunity to improve our understanding of the developmental pathology of HD. It is hoped that Self-Enroll participants will subsequently engage in Enroll-HD with progression of their symptoms. Generation of these data is endorsed.

Additional remarks

The purpose of the control groups not carrying the HD expansion within the framework of the intended registry based studies is currently not fully clear and should be explained (i.e., for what comparisons are the control groups intended to be used). During the discussion meeting it was explained that controls are not intended to participate in either PASS or PAES, controls are an asset for HD research. 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.

According to the Briefing Documents individuals under the age of 18 years may take part in the study only if they have a clinical diagnosis of HD in the setting of a positive genetic test. 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. During the discussion meeting it was explained that the Enroll-HD study was designed for an adult, as opposed to a paediatric, HD population. Paediatric HD has a clinically distinct presentation relative to adult-onset HD, and there is no paediatric version of several Enroll-HD assessments. Symptomatic children were permitted to enter the study to gain insight into paediatric disease manifestations with the aim of keeping families together in research, not because of a specific focus on recruiting children. However, it is intended to include a paediatric cohort as part of the forthcoming Enroll-HD protocol amendment which is appreciated.

In conclusion, the registry data generated via the Enroll-HD study protocol and the inclusion criteria specified in the protocol are generally considered reasonable for inclusion of a broad HD population.

The population enrolled so far covers most patient demographic variables, such as age, CAG repeats, symptom (soft and hard) start, date of diagnosis, ethnicity, etc. It is also understood that disease progression is followed with up-to-date clinical assessment tools. It is further accepted that the registry includes all types of HD populations, including pre-manifest, early and late-stage patients. Overall, Enroll-HD is well-suited for use as a data source and supportive infrastructure for future post-authorisation safety studies (PASS) and post-authorisation efficacy studies (PAES) in HD.

Question 2

Does Enroll-HD capture sufficient time elements and core data elements to allow Enroll-HD to be used as a data source and supportive infrastructure for post-authorisation registry-based studies?

Qualification opinion of the use of Enroll-HD (a Huntington's disease patient registry)
as a data source and infrastructure support for post-authorisation monitoring of
medical products

Page 11/19

Applicant's position: CHDI considers the time and core data elements captured in Enroll-HD to be essential for any future PASS/PAES. Although these elements may need to be supplemented with either more frequent assessments or the collection of additional data elements (determined by the type of medicinal product under evaluation), such adaptations will be straightforward to implement given the infrastructure and organisation of Enroll-HD.

Enroll-HD captures a vast amount of information, including the core and data time elements outlined in EMA 2020 guideline A.3.2 and in section 5.4 and Table 2 of section 5.3 of the EMA 2018 discussion paper. Enroll-HD operates under a single study protocol on a centrally managed electronic data capture (EDC) platform. The EDC provides a common data collection and reporting platform for every Enroll-HD site, ensuring that the data elements captured, as well as the format and definitions of data entered, are consistent, both within and across sites. See EMA 2020 guideline A.3.3. The EDC also features automated completion of certain time element fields (e.g., visit date), thereby maximising data accuracy, and mandatory fields, thereby maximising data completeness. Patient dates, disease dates, treatment dates, and observation dates are captured in full. Enroll-HD also captures important data elements. The Enroll-HD protocol, including the assessment battery, was designed by clinicians and other HD specialists. It features both 'core' and 'extended' components. 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. CAG repeat length testing is performed at the baseline visit for every participant. Data on reportable events and mortality are also captured. Extended assessments - which are optional for completion at each visit - comprise additional tests of motor, behavioural, and cognitive function, along with quality of life assessments and health and economic impact measures. See Supplement Sections 4 and 5.

In terms of understanding the effectiveness of future HD treatments, Enroll-HD is in a strong position because the data elements collected are considered standard for the evaluation of efficacy. Although visits are annual, Enroll-HD has mechanisms to collect data at extra time points (and potentially additional variables) as needed (see Question 3), which will augment the ability to conduct registry-based post-authorisation studies with tailored datasets. Additionally, as discussed below (see Question 3), the data captured in Enroll-HD contribute to information about safety, but may need study-specific complements because Enroll-HD does not currently collect specific adverse events. See Supplement Section 9.

CHMP answer

Enroll-HD operates under a single study protocol on a centrally managed electronic data capture (EDC) platform. The EDC provides a common data collection and reporting platform for every Enroll-HD site, ensuring that the data elements captured, as well as the format and definitions of data entered, are consistent, both within and across sites. The Applicant provided adequate information on so far implemented core and extended data elements. The core data elements – including information on administrative information, patient data, disease characteristics, relevant co-morbidities, disease-related treatments and concomitant therapies are generally in line with the Guideline on registry-based studies. The present core and data time elements, together with the extended element collection comprises a comprehensive set of information in all types of HD. The Applicant provided data supporting that the core assessment battery is well tolerated with an acceptable completion rate (range 92.2%-100%). Changes to protocol from different sponsors need to be captured to quantify additional patient burden.

Qualification opinion of the use of Enroll-HD (a Huntington's disease patient registry)
as a data source and infrastructure support for post-authorisation monitoring of
medical products

Page 12/19

Specific comments are made below:

Disease assessments:

There is currently no validated surrogate biomarker in HD. However, neuroimaging may play an important role with regard to evaluation of disease progression in the future, as e.g., brain atrophy has been described in literature to be detectable even in pre-symptomatic patients. Neuroimaging is not among the current data elements of Enroll-HD and it is unclear, whether neuro-imaging could be implemented in the Registry, preferably with central reader evaluation. During the discussion meeting it was explained that 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 the first participant expected in 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.

The Applicant further confirmed that concomitant therapies (pharmacotherapies as well as non-pharmaceutical therapies) are collected in the Registry as well as comorbidities. Recommendations concerning collection of pregnancy data, compliance with country-level pharmacovigilance requirements and reasons for discontinuation were immediately taken on board reflecting the operability of the registry.

Adverse Events and SSARs,

It is stated that Enroll-HD does not currently capture AEs and SSARs. Only four reportable events (suicide attempts, completed suicide, mental health events requiring hospitalisation, and death) are captured.

For the conduct of future PASS/PEAS, it is recommended to document all causes of hospitalization, co-morbidities and observed events. The possibility of collecting additional data elements (depending on the type of medicinal product being assessed) is welcomed and required for the conduct of future PASS/PAES, such as systematic collection of adverse events or additional laboratory values. The Applicant confirmed during the discussion meeting that more granular data elements will be included in

Qualification opinion of the use of Enroll-HD (a Huntington's disease patient registry)
as a data source and infrastructure support for post-authorisation monitoring of
medical products

Page 13/19

a specific PASS/PAES protocol that is nested in Enroll-HD which will require monitoring of specific TEAEs.

In conclusion, the present core and data time elements, together with the extended element collection comprises a comprehensive set of information in all types of HD. The registry platform is flexible enough to adapt to regulatory requirements and improvements were already undertaken.

Question 3

While Enroll-HD collects data annually, it has the capacity to easily nest protocols for PASS/PAES that require more frequent data collection. Does EMA believe this is sufficient for Enroll-HD to serve as a data source and supportive infrastructure for registry-based PASS/PAES?

Applicant's position: Enroll-HD data are collected annually. This poses a challenge in addressing hypotheses which relate to a shorter time window (e.g., the effects of an exposure/treatment over days, weeks, or months). However, Enroll-HD does capture chronic conditions and affords the opportunity to identify long-term drug reactions, which can contribute to the safety profile of a drug. In addition, Enroll-HD currently collects data on four reportable events (suicide attempts, completed suicide, mental health events requiring hospitalisation, and death), thus providing data on mortality and suicidality, important dimensions of safety. In terms of efficacy, Enroll-HD enables analysis and evaluation of long-term trends, with the expansive sample size and richness of longitudinal data affording substantial statistical power. For example, even though Enroll-HD data collection is annual, it has been used to inform questions about medications.[6]

In addition to the opportunities offered by annual data collection, Enroll-HD has existing infrastructure to support "nesting" PASS/PAES within the registry and, depending on the protocols of the nested studies, may be able to capture the safety or other information associated with specific treatments, including additional time points. Nesting could work in two possible ways, both of which we think compliant with the model of registry-based studies described in the EMA 2020 guideline. One way is for the Applicant to select study participants in Enroll-HD and recruit them for the additional protocol. (This is possible because the Enroll-HD informed consent allows participants to be contacted for further research.) Enroll-HD would then give the Applicant the Enroll-HD data, which the Applicant will need to combine with the data the Applicant acquires from their own protocol. The second way that nesting could work is to use Enroll-HD infrastructure to deploy the nested study, using the same EDC, sites, and investigators, even if the nested study contains additional data collection. Under this option, Enroll-HD would deliver to the Applicant a single dataset that integrates the Enroll-HD data and the data gathered under the nested protocol.

CHDI believes Enroll-HD is well suited for both aforementioned nesting approaches for several reasons. First, Enroll-HD has an established process to interface with Applicants, understands their requirements, and provides HD expertise and advice. See EMA 2020 guideline A.5. One of Enroll-HD's governance committees, the Clinical Trial Committee (CTC) is comprised of medical and Enroll-HD staff, as well as independent HD expert advisors who have deep knowledge of clinical trial design and methodology. Second, and as explained in more detail in the answers to Questions 4 and 5, Enroll-HD has well-established and standardised processes for data acquisition and data sharing. See EMA 2020 guideline A.6. Third, Enroll-HD has a training portal that allows for standardised training. Additional

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[6] S*ee, e.g.*, Griffin B, Suttorp Booth M, Busse M, Wild E, Setodji C, Warner J, Sampaio C, Mohan A. Estimating the causal effects of modifiable, non-genetic factors on Huntington Disease progression using propensity score weighting. *Parkinsonism and Related Disorders* 2021 (forthcoming); Shahn Z, Li Y, Sun Z, Mohan A, Sampaio C, Hu J. G-Computation and Hierarchical Models for Estimating Multiple Causal Effects from Observational Disease Registries with Irregular Visits. *AMIA Jt Summits Transl Sci Proc.* 2019 May 6;2019:789-798. PMID: 31259036; PMCID: PMC6568089.

Qualification opinion of the use of Enroll-HD (a Huntington's disease patient registry)
as a data source and infrastructure support for post-authorisation monitoring of
medical products

Page 14/19

rater training on specific assessments can be carried out in a variety of ways, such as online certification utilising Training Portal and interactive webinar training. Moreover, the Enroll-HD study protocol, electronic case report forms, and data dictionary are accessible on the Enroll-HD website (www.Enroll-HD.org). Enroll-HD also has a published policy for data sharing and other study data documentation in the format of standard international terminologies to support the use of the data and samples in research. These features make data standardisation and integration possible. Similarly, all of the assessments that Enroll-HD uses have a well-identified version and source, and Enroll-HD is in the position to give precise directions as to how and where to obtain licenses for any assessments not in the public domain. This way, nested studies can use exactly the same assessments as Enroll-HD if needed. Finally, Enroll-HD is able to assess study feasibility in-silico and help pre-select participants (or sites) for studies. For instance, Enroll-HD supported a biotech Applicant in an epidemiological survey to impute the frequency of specific single-nucleotide polymorphism (SNP) targets. Using this analysis, Enroll-HD helped guide the recruitment strategy by estimating the target SNP frequency among the subpopulations of European ethnicity. Integrating the genotypes of Enroll-HD participants with Enroll-HD clinical sites, Enroll-HD was able to suggest sites with a high number of target SNP-carriers to improve efficiency of enrolling the desired number of trial participants. Furthermore, to help promote the recruitment of participants throughout this trial, listings of potentially eligible participants were prepared by filtering the Enroll-HD database of each site participating in the clinical trial according to the corresponding entry criteria of the trial. Such listings are provided to the study sites at intervals throughout the trial to help the sites identify and recruit eligible participants.

Moreover, Enroll-HD has additional features useful for nesting studies that use Enroll-HD's infrastructure (in addition to its data). The modular EDC system can be adapted to add new electronic case report forms (eCRF) and easily capture additional data. For instance, HDClarity (NCT02855476, collection of cerebral spinal fluid) leverages medication data already entered in Enroll-HD, eliminating the need to replicate this data collection in HDClarity. Enroll-HD also has the ability to expand its extensive data monitoring (see Question 4) to include any additional data acquired under the nested protocol.

CHMP answer

The Enroll-HD study collects all important efficacy endpoints with respect to motor, function, cognition, behaviour/psychiatric and allows for collection of biomarkers in HD (see Q2).

With respect to safety only four reportable events (suicide attempts, completed suicide, mental health events requiring hospitalisation, and death) are currently routinely collected. Of note, while the four reportable events currently systematically captured in the protocol are evaluated as events related with the disease itself but not as adverse effects of (disease-related) treatments, only the "mental health event requiring hospitalization" of these events is currently coded using MedDRA terms. However, all these events could potentially also occur as TEAEs and should therefore be coded with MedDRA.

The annual data collection represents a limitation because it reduces the number of research questions that could be adequately addressed with the registry. It is agreed that this limitation may be acceptable for individual studies focusing on (i) medicinal products intended for long-term treatment and (ii) adverse events with late onset. During the discussion meeting the Applicant explained that annual visits are appropriate for evaluation of HD natural history given the slow progression of the disease. With regard to efficacy parameters, annual efficacy assessments may be generally appropriate. However, progression rates differ dependent on the evaluated subpopulation (e.g., with faster progression in non-adult HD or in subjects with high CAP scores, respectively). In addition,

Qualification opinion of the use of Enroll-HD (a Huntington's disease patient registry)
as a data source and infrastructure support for post-authorisation monitoring of
medical products

Page 15/19

considering that progression is not defined by appearance of a self-reported event but rather by active diagnosis, results may be influenced by visit frequency. Depending on the question of interest, more frequent evaluation time points might thus also be required from an efficacy point of view in the context of PAESs. 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.

The Applicant confirmed that, 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. 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. This can be mitigated by connecting Enroll-HD data to EHRs (electronic health records). 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. This is acknowledged and considered adequate.

The Applicant describes two nesting approaches. One way is for the Applicant to select study participants in Enroll-HD and recruit them for the additional protocol. In that case Enroll-HD would give the Applicant the Enroll-HD data, which the Applicant will need to combine with the data the Applicant acquires from their own protocol. The second way that nesting could work is to use Enroll-HD infrastructure even if the nested study contains additional data collection. Under this option, Enroll-HD would deliver to the Applicant a single dataset that integrates the Enroll-HD data and the data gathered under the nested protocol.

Since many PASS suffer from low recruitment, the possibility to improve study enrolment using participants from the Enroll-HD is supported – either to collect their own primary data or to use existing data from the Enroll-HD to supplement their own data.

A demonstrator project using Enroll-HD to support a hypothetical PASS/PAES

"Enroll-HYPO1:Prospective, Multi-Center, Multinational, Observational Study Nested in Enroll-HD Comparing Safety and Effectiveness of GTHYPO in treated and untreated Huntington's Disease Patients"

and an operational summary of how this hypothetical PASS/PAES could be nested within Enroll-HD was provided. The medicinal product of this hypothetical study was assumed to be a HTT lowering adeno-associated virus vector gene therapy administered by stereotactic surgery to deep structures of the brain. The submitted simulation provided reassurance that it is possible to seamlessly integrate Enroll-HYPO1 in Enroll-HD and develop an integrated dataset that can be easily analyzed as primary data.

In conclusion, Enroll-HD is fit to provide data for a specific HD PASS/PAES in the future.

A simulated demonstrator study was used to support that the infrastructure is flexible and can accommodate PASS/PAES specific requirements, including novel data elements and additional time points. Nevertheless, it should be noted that the adequacy of a future protocol will depend on the specific research question(s) of a future PASS/PAES.

Qualification opinion of the use of Enroll-HD (a Huntington's disease patient registry)
as a data source and infrastructure support for post-authorisation monitoring of
medical products

Page 16/19

Question 4

CHDI considers that the existing data quality control mechanisms established and implemented by Enroll-HD are sufficient to guarantee the integrity and reliability of the data. Does EMA agree?

Applicant's position: Ensuring data quality and integrity is fundamental to Enroll-HD. See EMA 2020 guideline A.4. Quality control and assurance measures, designed to maximise data consistency, completeness, accuracy, and timeliness, are implemented and monitored at a participant, site, and global study level. See Supplement Section 8. These extensive measures include automated data validity checks at point of data entry (implemented in the electronic data capture system), remote centralised statistical monitoring (CSM) (at both a participant and site level) and onsite data monitoring including source data verification. Regional Managers and Site Managers oversee site performance and study compliance using several data quality measurement tools and resources: regular review of metrics generated in the Data Quality Management dashboard and tracker, Site Metrics Cards, and Site CSM reports. Enroll-HD complies with all the data quality suggestions outlined in section 5.6.4 of the EMA 2018 discussion paper and section A.4 of the EMA 2020 guideline. Once there is a PASS/PAES protocol nested within Enroll-HD, the existing Quality Control processes can be applied to those nested studies.

CHMP answer

The data quality control mechanisms described include automated data validity checks at point of data entry (implemented in the electronic data capture system), remote centralised statistical monitoring (CSM) (at both a participant and site level in line with ICH E6(R2) guidance) and onsite data monitoring including source data verification. Regional Managers and Site Managers oversee site performance and study compliance using several data quality measurement tools and resources: regular review of metrics generated in the Data Quality Management dashboard and tracker, Site Metrics Cards, and Site CSM reports.

The quality control and assurances measures described in section 8 of the supplement are considered sufficient to ensure the integrity and reliability of the data in the Enroll-HD registry, assuming that they are implemented as outlined.

The Applicant describes a shortcoming with regard to monitoring and source data verification of data collected in North America, as the Enroll-HD informed consent does not cover monitors´ access to medical records.

However, with regard to data collected in the future the Enroll-HD informed consent should be updated in order to cover and enable monitors to access medical records.

During the discussion meeting it was confirmed that 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.

During the discussion meeting it was explained that 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.

Qualification opinion of the use of Enroll-HD (a Huntington's disease patient registry)
as a data source and infrastructure support for post-authorisation monitoring of
medical products

Page 17/19

In conclusion, the proposed systematic data quality control is apparently sufficient to ensure integrity and reliability of the data stored. 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.

Question 5

Does EMA consider that the release of periodic datasets (plus specified datasets as needed) a sufficiently broad data-sharing mechanism?

Applicant's position: Enroll-HD data are shared with the research community through two processes: Periodic Datasets (PDS) and Specified Datasets (SPS). PDS releases include the majority of the variables collected in Enroll-HD and are prepared every 1-2 years via a rigorous Quality Control procedure that ensures the data are accurate and complete, with a low risk of participant identification. During this process certain variables are transformed, aggregated, or suppressed (excluded) from the dataset to minimize the risk of participant identification. Access to the PDS is easy and fast via the Enroll-HD webpage (www.enroll-hd.org) and only requires the requester to be a researcher at a recognized institution willing to accept and sign the electronic click-through Data Use Agreement. Requester identity and affiliation are verified before access to the PDS is granted. There is no fee associated with clinical data access. Enroll-HD requires that data users follow principles of scientific independence and transparency similar to those found in the ENCePP Code of Conduct on scientific independence and transparency. Detailed information on Enroll-HD data access procedures is available on the Enroll-HD website (https://enroll-hd.org/for-researchers/access-data/). See Supplement Section 11.

Access to variables not included in the PDS, and/or non-transformed or non-aggregated data, may be obtained via SPS request, requiring application submission. (The Data Dictionary denotes which variables are available in the PDS and which are available via SPS request.) The Enroll-HD Scientific Review Committee (SRC) reviews the request and weighs the scientific potential of the proposed project against the increased risk for participant identification and recommends whether the requested dataset should be prepared and released. Through this process, Enroll-HD would also be able to share specific datasets with Applicants as needed.

CHMP answer

The Applicant's confirmation to share the Enroll-HD data with the research community through via Periodic Datasets (PDS) and Specified Datasets (SPS) is supported and accepted. The Data Dictionary provides an overview of which variables are available in the PDS and which are available via SPS request.

It is agreed that the PDS may only provide information on aggregate data of the most important variables and that additional data information (beyond that provided in the PDS) requires an application submission. The annual overviews of the status of data collection via the registry website are sufficient to ensure an up-to-date presentation of registry data. Provided information on data completeness in the PDS is welcomed.

The data should be presented in the PDS in such a way that a Applicant can directly assess whether the Enroll-HD is an appropriate data source or not – at best without requesting the SPS. In this context, it was explained that all data are provided free of charge including SPS data extractions and associated data quality control review. Similarly, no financial incentives are provided for participation in Enroll-HD. In this context it was also explained that it needs to be ensured that all data recipients belong to a recognized institution, i.e., anyone doing HD research, including not only academic institutions and pharmaceutical companies but also lay associations. The data however, are not

Qualification opinion of the use of Enroll-HD (a Huntington's disease patient registry)
as a data source and infrastructure support for post-authorisation monitoring of
medical products

Page 18/19

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.

Overall, it is agreed that the periodic and the upon-request specified datasets can be considered a sufficiently broad mechanism for datasharing.

CHMP overall conclusion

Enroll-HD is well-suited for use as a data source and supportive infrastructure for future post-authorisation studies in HD. The core and data time elements in the registry, together with the extended element collection comprises a comprehensive set of information in all types of HD. The registry platform is flexible enough to adapt to regulatory requirements and during the qualification improvements were already undertaken or are foreseen in the next future.

These comprise:

EDC CHANGES

- Pregnancy form including Gravida and Para

- Addition of "reason for change/discontinuation of medications"

- Integrate pharmacovigilance reporting

- Routes of administration/units mapped to EDQM

PROTOCOL AMENDMENT CHANGES

- Addition of structural MRI

- Implement new ISS categorization

- Paediatric sub-study

- Late-stage assessments (Enroll-Lite)

- Allow for SDV against medical records

A simulated demonstrator study was used to support that the infrastructure is flexible and can accommodate PASS/PAES specific requirements, including novel data elements and additional time points. The proposed systematic data quality control is apparently sufficient to ensure integrity and reliability of the data stored. Any future 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.

It is accepted that 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. Nevertheless, it should be noted that the adequacy of a future protocol will depend on the specific research question(s) of a future PASS/PAES.

Qualification opinion of the use of Enroll-HD (a Huntington's disease patient registry) as a data source and infrastructure support for post-authorisation monitoring of medical products

Page 19/19