



## Scientific Opinion Request

Application for Qualification Opinion for 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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Project Code	Enroll-HD Registry (RPI: PRD/0000022975)
Intended indication(s)	Huntington's Disease (HD)
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## Executive Summary

High-quality disease-specific patient registries are important tools for the advancement of therapeutics. They can be used for recruitment in clinical trials, natural history studies, 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 draft guideline on registry-based studies (the “EMA 2020 guideline”), 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.”) This submission explains how Enroll-HD serves as a high-quality registry for Huntington’s disease, in line with the EMA 2020 guideline and 2018 discussion paper. This document provides a brief overview, a context of use outline, and questions and answers. More detail can be found in the Supplement and accompanying Appendices, cross-referenced here.

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. See Supplement Section 1.

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 symptomology - alongside HD family members and non-HDGECs. Approximately 19,000 participants remain actively engaged, and the study continues to recruit and operate from 157 clinical sites in 20 countries (including 13 European countries). 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.

Central to the Enroll-HD platform is the global Enroll-HD study, established in July 2012. Approximately 25,000 participants have been recruited to date, of whom 19,000 are still actively engaged. Participants attend annual study visits during which they complete a series of standardised assessments. “Core” assessments are administered routinely at each visit, and additional “extended” and/or “optional” assessments are performed at the discretion of the investigator or the participant, respectively. All data are collected by trained site personnel and entered into a centralised Electronic Data Capture (EDC) system, common to every study site. A comprehensive overview of data and bio-samples collected in the study, alongside a description of the current cohort, is contained in the Supplement.

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. 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 present evidence supporting the representativeness of the Enroll-HD study participant population with respect to that of the broader HD population, and emphasise 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 outline 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). Plans for monitoring of Adverse Events would be specific to each future Post-Authorisation Safety Study (PASS).

The Supplement addresses each of the following areas in detail; here, we provide a brief summary.

**Patient Population:** Since the study began, 23,689 participants have been recruited, 18,758 are still active, and the study continues to recruit new participants. 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. We estimate that Enroll-HD currently provides 18% coverage of the European manifest HD population. Benchmarking Enroll-HD against another large cohort study 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. See Supplement Section 3.

**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 2020 guideline A.3. See Supplement Section 4.

**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 2020 guideline A.3.2 and EMA 2018 discussion paper section 5.4. See Supplement Section 5.

**Common Terminologies:** As an integrated platform, Enroll-HD uses common terminologies for diseases, symptoms, medicinal products, reportable events, and all other data. See Supplement Section 6.

**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. See Supplement Section 7.

**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 2020 guideline A.4.3-A.4.4 and section 5.6.4 of the EMA 2018 discussion paper. See Supplement Section 8.

**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 (see Supplement Section 10). Enroll-HD is well-suited for nesting PASS because Enroll-HD has experience working with academics and pharmaceutical companies to create other nested studies, and because Enroll-HD already has the key infrastructure, including patient population and site expertise. See Supplement Section 9 and Question 3, below.

**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. See Supplement Section 10.

**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 participants in Enroll-HD and steps are taken to reduce the risk of re-identification below a predetermined threshold before data release. See Supplement Section 11.

## 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](http://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*) totaling 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.

### 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:

- 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.

In the future and in conjunction with a marketing authorisation holder, we plan to seek advice/qualification on Enroll-HD's use for specific post-authorisation efficacy studies (PAES) and PASS proposals. These post-marketing studies may require additional data or more frequent data points to appropriately evaluate drug efficacy/effectiveness and drug safety. Exactly how this would be accomplished is dependent on the protocol of the PASS/PAES, but we believe that Enroll-HD has the potential for nesting such studies because of its strong centralised infrastructure and because Enroll-HD has experience working with external partners and with nesting other platform studies.

## Questions & Answers

1. **Question:** 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?

**Answer:** 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. In Europe, Enroll-HD currently operates in 13 countries and plans to expand to 4 additional EU countries. There are 90 actively recruiting registry sites and 18 more 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 Huntington Disease Gene Expanded Carriers (HDGECs). Of these, 7,712 were manifest (i.e. at or beyond the point of clinical onset) at study entry. 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. See Supplement Sections 3.4-3.5.

The Enroll-HD European HDGEC sample is both extremely large and extremely diverse with respect to HD disease spectrum coverage. See EMA 2020 guideline 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.

2. **Question:** 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?

**Answer:** 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.

3. **Question:** 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?

**Answer:** 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.<sup>1</sup>

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

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<sup>1</sup> See, e.g., Griffin B, Suttrop 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.

2020 guideline. One way is for the sponsor 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 sponsor the Enroll-HD data, which the sponsor will need to combine with the data the sponsor 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 sponsor 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 sponsors, 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 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](http://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 company 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.

4. **Question:** 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?

**Answer:** 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.

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

**Answer:** 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 minimise the risk of participant identification. Access to the PDS is easy and fast via the Enroll-HD webpage ([www.enroll-hd.org](http://www.enroll-hd.org)) and only requires the requester to be a researcher at a recognised 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 ([www.enroll-hd.org](http://www.enroll-hd.org)). 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 sponsors as needed.