The timing and impact of psychiatric, cognitive and motor manifestations of Huntington’s disease

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Abstract

Objective

To assess the prevalence, timing and functional impact of psychiatric, cognitive and motor manifestations of Huntington's disease (HD), we analysed retrospective clinical data from individuals with manifest HD.

Methods

The clinical manifestations of HD were analysed for 6316 individuals in the European REGISTRY study from 161 sites across 17 countries. Data came from clinical history and the Clinical Characteristics Questionnaire that assessed eight symptoms: motor, cognitive, apathy, depression, perseverative/obsessive behavior, irritability, violent/aggressive behavior, and psychosis. Multiple logistic regression was used to analyse relationships between symptoms and functional outcomes.

Results

The initial manifestation of HD is increasingly likely to be motor, and less likely to be psychiatric, as age at presentation increases. The nature of the first manifestation is not associated with pathogenic CAG repeat length. Symptom prevalence data from the patient-completed Clinical Characteristics Questionnaire correlate specifically with validated clinical measures. Using these data, we show that psychiatric and cognitive symptoms are common in HD, with earlier onsets associated with longer CAG repeats. 42.4% of HD patients reported at least one psychiatric or cognitive symptom before motor onset, with depression most common. Apathy and cognitive impairment tend to come later in the disease course. Each psychiatric or cognitive
manifestation of HD was associated with significantly reduced total functional capacity scores.

Conclusions
Psychiatric and cognitive symptoms occur before motor onset in many more HD patients than previously reported. They have a greater negative impact on daily life than involuntary movements and should be specifically targeted with clinical outcome measures and treatments.
Introduction

Huntington’s disease (HD) is a central neurodegenerative disorder caused by an expanded CAG repeat (>35 CAGs) in exon 1 of the Huntingtin gene (HTT)\(^1\). The length of the expanded CAG tract is inversely correlated with the age at first clinical manifestation of HD\(^2\,3\). Degeneration is most prominent in the medium spiny neurons of the striatum but occurs widely in the brain, leading to a progressive movement disorder, cognitive decline and ultimately death. The motor disorder usually includes chorea, and may also involve dystonia, coordination problems, oculomotor abnormalities and parkinsonism. In addition, individuals with HD develop a variable constellation of debilitating behavioural and psychiatric symptoms alongside their motor problems\(^4\,5\): these ‘non-motor’ symptoms remain under-recognised and under-treated. Prospective studies of individuals carrying a pathogenic HTT CAG repeat but many years from predicted clinical onset have shown they have few significant motor, cognitive or psychiatric deficits when compared with age and sex-matched controls\(^6\,8\). This implies there is a window for therapeutic intervention to preserve normal brain functions. It is therefore crucial to understand in detail the timing and impact of different manifestations of HD in order to target and assess potential disease-modifying therapies. Here we analyse in a large population the prevalence and timing of psychiatric, cognitive and motor manifestations of HD, their relationships with CAG repeat length, and their impact on day-to-day life.

The age at onset of the first clinical manifestation of HD, often difficult for patients, care partners and clinicians to define precisely, has been used as a specific milestone in the natural history of HD in individuals. The age at onset of chorea and/or other motor features (‘motor onset’) has proven particularly useful in genetic modifier studies of HD\(^9\,10\), although it is only a crude measure of a progressive
neuropathological process. The timing of HD clinical onset is typically recorded by a rating physician in observational studies such as the European REGISTRY, based on clinical information and symptom history from patients and care partners\textsuperscript{11–13}. This retrospective assessment cannot pick up the subtle earliest motor and non-motor signs, which are unnoticed by patients but detectable by HD specialists in prospective studies\textsuperscript{7}. The rater also records the initial major presenting symptom out of a choice of six: motor, cognitive, psychiatric, oculomotor, other or mixed. Given the complexity of the HD phenotype across multiple domains, later versions of REGISTRY incorporated the HD Clinical Characteristics Questionnaire (HD-CCQ)\textsuperscript{11}, asking individuals whether they had ever experienced a range of motor and psychiatric symptoms, and at what age those symptoms started\textsuperscript{14}. The eight symptom groups recorded were motor (any type), depression, irritability, violent or aggressive behaviour, apathy, perseverative/obsessive behaviour, psychosis and cognitive impairment sufficient to impact on work or daily living. Importantly, individuals with HD and their care partners, present in clinic for over 93%, reported the presence or absence of these symptoms independent of whether they considered them directly related to HD or not. These data on symptom onsets were collected alongside multiple quantitative assessments of HD phenotype, including the Unified Huntington’s Disease Rating Scale (UHDRS)\textsuperscript{15}, Hospital Anxiety/Depression Rating Scale (HADS) and the Snaith Irritability Scale (SIS). The UHDRS consists of a series of validated questionnaires, tools and examinations related to motor, cognitive, behavioural and functional impairments seen in HD.

Here we find that motor presentation of HD is increasingly common with later clinical onset but there is no relationship between CAG length and type of presentation. We validate the use of HD-CCQ data in a large HD population of over 6000 participants.
by showing strong and specific associations with validated scores of depression, irritability and cognition. We then use HD-CCQ data to show the high prevalence of psychiatric and cognitive symptoms in HD, often in advance of motor onset, and how they impact negatively on the daily lives of patients.

**Methods**

**Standard protocol approvals, registrations and patient consents**

Participants were in the multicentre, multinational, observational REGISTRY study of European HD ([http://www.ehdn.org/wp-content/uploads/2018/06/registry-protocol-3.0.pdf; NCT01590589](http://www.ehdn.org/wp-content/uploads/2018/06/registry-protocol-3.0.pdf; NCT01590589)). Data were accessed as part of European Huntington’s Disease Network (EHDN) data mining project 0791. Ethical approval for REGISTRY was obtained in each participating country, and all participants gave written informed consent.

**Participant data**

HD participant data, collected June 2004 - February 2016 across 161 sites in 17 European countries, was obtained for 6316 individuals (accessed October 2016) who had clinical HD onset, determined by the rating clinician in REGISTRY, and a confirmed pathogenic CAG length of 36-93 CAGs. Of these CAG sizes, 5027 were centrally determined by BioRep Inc. (Milan, Italy) in line with REGISTRY protocols and 1289 were derived by local diagnostic laboratories. Two estimates of the age at clinical onset of HD were used in this study. First, the clinician-estimated age at first HD manifestation based upon all available clinical evidence at the first REGISTRY visit (coded as ‘sxrater’). Having a ‘sxrater’ age at onset was required for inclusion in this study. Onset type was classified as motor, cognitive, psychiatric, oculomotor, other or mixed. As the clinician’s estimate was given as a date, age estimates were
calculated using the participant’s anonymised birthday; where only a year was given, July 15th was used for estimation (15/07/xxxx). Second, the ages at onset of different symptoms were determined from the HD Clinical Characteristics Questionnaire (HD-CCQ) which was completed by a healthcare professional, usually a HD-specialist nurse or similarly-qualified person, using responses from the individual with HD and their care partners (present in clinic in 93.1% of cases). The HD-CCQ comprises questions about eight symptoms commonly observed in HD, asking whether the participant has ever had the symptom (yes or no), and, if yes, the age at which the symptom was first experienced (Appendix 3). Information was available, at least in part, for 5609 individuals. The symptoms recorded (number of individuals with data) were: motor (5603), cognitive impairment sufficient to impact on work or daily living (5591), apathy (5584), depression (5595), perseverative/obsessive behaviour (5588), irritability (5586), violent or aggressive behaviour (5586) and psychosis (5589). For subsequent analyses, missing data were handled using pairwise deletion to maximise the number of individuals. Typically, the rater estimate of onset and initial HD-CCQ would be recorded at the first REGISTRY visit, sometimes by one clinician, and sometimes by a clinician and another qualified staff member such as HD-specialist nurse, depending on local clinic set-up. Subsequent visits updated the HD-CCQ: we used data from the most recent clinic visit.

The Hospital Anxiety/Depression Scale (HADS) and Snaith Irritability Scale (SIS) were completed by the participant at each clinic visit and provide measures of anxiety, depression and irritability at that specific time. We used lifetime highest total depression and total irritability scores from both the HADS and the SIS in analyses. Similarly, the symbol-digit modalities test (SDMT) and Stroop tests of cognitive ability
were administered as part of the UHDRS at each clinic visit. For the SDMT and Stroop, we used the total correct scores from the most recent clinic visit. Disease duration was estimated by taking the most recent visit and subtracting the clinician’s estimate of disease onset. The product of Problem Behaviours Assessment (PBA-s) severity and frequency scores from the most recent clinic was used for modelling purposes.

**Statistical analyses of clinical data**

Total depression scores from HADS, total irritability scores from SIS, the number of correct answers in the SDMT, the number of correct answers in Stroop tests or composite PBA-s scores were regressed on HD clinical characteristics data, age, CAG length, sex and disease duration (table 1). To calculate coefficients of determination ($R^2$ values, table 2), HD-CCQ age at onset data were natural log transformed. Only individuals with a known sex and a symptom onset ≥3 years were considered, and a residual vs leverage plot identified one influential data point passing Cook’s distance that was removed from all $R^2$ calculations. $P$ values were calculated comparing male and female $R^2$ values using Fisher’s transformation$^{16}$. A chi-square test was used to test for differences in symptom frequency, derived from the yes/no component of the HD-CCQ, between males and females.

Associations between binary responses in the HD-CCQ (1; experienced the symptom and 0; symptom not experienced) and clinical covariates were tested using logistic regression. The covariates used were sex, CAG length, alcohol consumption (units per week), tobacco use (cigarettes per day), education (years of education), total functional capacity (TFC) score and total motor score (TMS). An additional
analysis regressed the type of HD onset defined by the clinician, coded as a binary variable, on the clinician’s onset or CAG length (table e-2, doi:10.5061/dryad.pk0p2ngkz). This analysis was restricted to HD participants with CAGs 36-59, to be consistent with figure 1 subgroups, and also to adult-onset HD individuals (≥20 years). We also tested whether symptom presence was associated with the length of the wild-type (6-35 CAGs) and expanded CAGs (36-93 CAGs) alleles in individuals of known sex, and for whom both CAG lengths were known (table e-3, doi:10.5061/dryad.pk0p2ngkz). 19 individuals with a coincident formal diagnosis of schizophrenia, schizotypal disorder or schizoaffective disorder (ICD-10 F20, F21 or F25) were excluded from all models. It was not possible to formally exclude these symptoms being part of the HD phenotype in these few individuals.

Statistical analysis used R (version 3.6.0; R core team, 2019, https://www.r-project.org/).

**Data availability**

Further information and requests for data should be directed to Thomas H. Massey MA, BM BCh, DPhil (MasseyT1@cardiff.ac.uk). Anonymised summary data is available on request by qualified investigators. Furthermore, anonymised patient data is available from the European Huntington’s Disease Network (EHDN) upon request given their institutional assurance patient confidentiality will be upheld, and no attempt will be made to discover the identity of patients.

**Results**

The initial manifestation of HD varies with age and CAG length
We analysed the initial manifestation of HD for 6316 participants in REGISTRY\textsuperscript{11}, including 3083 males (48.8\%) and 3233 females (51.2\%). All participants had a confirmed genetic diagnosis of HD with a pathogenic CAG repeat length of 36-93 (figure e-1, doi:10.5061/dryad.pk0p2ngkz). The first symptom or sign of HD, determined by the rating physician, varied with the age at which HD became clinically manifest (figure 1A and table e-1, doi:10.5061/dryad.pk0p2ngkz). Individuals with onset before the age of 20, defined as juvenile HD, were equally likely to present with motor (24.5\%), cognitive (21.8\%) or psychiatric features (28.2\%). In contrast, the initial HD-related symptom or sign was more likely to be motor than psychiatric in adult-onset HD. As age at first manifestation increased (figure 1A and table e-2A, doi:10.5061/dryad.pk0p2ngkz) motor presentations became more likely (odds ratio (OR) = 1.06 per ten year increase in onset age, 95\% confidence interval (CI) 1.04-1.07; \( P = 7.4 \times 10^{-22} \)) but psychiatric presentations became less likely (OR = 0.96 per ten year increase in onset age, 95\% CI 0.95-0.97; \( P = 9.4 \times 10^{-16} \)). For people presenting over the age of 60, over two-thirds (68.6\%) had motor manifestations at clinical onset with far fewer having psychiatric (11.5\%) or cognitive (6.7\%) presentations. Next, we tested whether there was any relationship between pathogenic CAG repeat length, known to be inversely correlated with age at clinical onset, and the presenting phenotype. Interestingly, there was no significant relationship between CAG length (36-59 inclusive) and the relative proportions of motor, cognitive and psychiatric onset cases (figure 1B and table e-2B, doi:10.5061/dryad.pk0p2ngkz). For the few cases with data and repeat lengths of more than 59 CAG we observed a more balanced distribution of motor, cognitive and psychiatric onsets, mirroring the trends seen for the juvenile HD cases.
Psychiatric and cognitive symptoms captured by the Clinical Characteristics Questionnaire correlate with scores from validated clinical tools

The HD Clinical Characteristics Questionnaire (HD-CCQ) is completed directly by individuals with HD and their care partners about lifetime history and age at onset of eight motor, psychiatric and cognitive symptoms. In REGISTRY, this information was updated at each annual clinic visit. Since prevalence data from HD-CCQ have not been used in large analyses before we first tested how well they correlated with data from validated measures of depression (HADS), irritability (SIS) and cognition (SDMT and Stroop). To mitigate against potential effects of medication at certain times, we used the lifetime highest total depression and total irritability scores for each individual. For cognitive tests we used scores at the last recorded clinic visit as these would be expected to worsen progressively and be little affected by medication. Total depression score from HADS was significantly increased in individuals with depression recorded in HD-CCQ (table 1; increase of 1.49 units, 95% CI 1.09-1.89; \( P = 5.7 \times 10^{-13} \)). An increase in HADS score was also observed in individuals with HD-CCQ apathy, probably because apathy, common in HD, may be mistaken for depression by individuals and their care partners when completing the HD-CCQ. Total irritability score from SIS was significantly increased in individuals with HD-CCQ irritability (increase of 1.82 units, 95% CI 1.37-2.27; \( P = 2.0 \times 10^{-15} \)), and also with violent/aggressive behaviour (increase of 1.57 units, 95% CI 1.08-2.06; \( P = 3.3 \times 10^{-10} \)), as expected. Both SDMT and Stroop scores of cognitive ability were significantly decreased in individuals with cognitive impairment as recorded in HD-CCQ (reductions of 3.52 units, 95% CI 2.71-4.33; \( P = 2.3 \times 10^{-17} \) and 3.41 units, 95% CI 2.65-4.17; \( P = 1.4 \times 10^{-22} \), respectively). Significant associations between cognitive scores and motor and apathy symptoms were also observed. In addition,
we found robust and specific associations between neuropsychiatric symptoms recorded in HD-CCQ and their related symptoms scored using the validated short-form Problem Behaviors Assessment (PBA-s; supplemental table e-4, doi:10.5061/dryad.pk0p2ngkz). The specificity of the associations between HD-CCQ data and recognised clinical scales validated the use of HD-CCQ data in subsequent analyses.

Psychiatric symptoms are common in HD and are associated with CAG repeat length

We next analysed the lifetime prevalence of the eight symptoms recorded in HD-CCQ in 5609 individuals with HD at their most recent clinic visit (table 2). The mean age at last recorded clinic visit was 53.3 years; 53.5 years for males with data (range 10.4 – 92.6 years; N = 2569) and 53.2 years for females (range 7.9 – 90.2 years; N = 2698). Almost all (>99%) individuals with HD had experienced motor symptoms. Although these symptoms are not recorded explicitly in HD-CCQ, contemporaneous data from UHDRS showed that 96.8% of our study population had chorea, alongside variable amounts of incoordination, dystonia and rigidity. The next most prevalent symptom was depression, occurring in 64.5% of HD individuals with significantly more females affected than males (70.4% vs 58.2%; OR 1.70, 95% CI 1.52-1.90; \( P = 2.6 \times 10^{-21} \)). Cognitive impairment sufficient to impact upon work or activities of daily living, apathy and irritability were also each observed in over half of our HD population. Cognitive impairment and apathy were equally likely in males and females, but there was significantly more irritability observed in males (62.9% vs 56.9%; OR 0.78, 95% CI 0.70-0.87; \( P = 4.0 \times 10^{-6} \)). An excess of violent or aggressive behaviour was also observed in the male group (34.9% vs 27.0%; OR
0.69, 95% CI 0.62-0.77; \( P = 2.0 \times 10^{-10} \)). Psychosis was the least prevalent of the eight recorded symptoms, although this was still observed in over 11% of individuals with HD with no significant difference in prevalence between males and females.

There was a strong inverse correlation between pathogenic CAG repeat length (40-55 CAG inclusive) and mean age at symptom onset for all symptoms analysed (figure 2). We found no effect of wild-type CAG allele length on any symptom onset, nor any significant statistical interaction between expanded and wild-type repeat lengths (table e-3, doi:10.5061/dryad.pk0p2ngkz). Pathogenic CAG length explained 66.3% of the variance in age at onset of motor symptoms, in line with previous estimates\(^2,^3,^{17-23}\), but also between 37.5% and 61.9% of the variance in onset of each of the psychiatric symptoms analysed (table 2). Depression had the weakest association with CAG repeat length (\( R^2 = 37.5\% \)), likely reflecting the high prevalence of the symptom in the general population independent of HD and the lack of use of universal diagnostic criteria. CAG length accounted for significantly more of the variance in age at onset of perseverative/obsessive behaviour in males (table 2; \( P = 3.7 \times 10^{-3} \)) and irritability in females (\( P = 1.3 \times 10^{-3} \)).

The timing of motor and psychiatric symptoms in HD varies with symptom type and CAG length

Given that motor onset is often used as a specific milestone in the natural history of HD, we investigated the timing of each of the seven psychiatric/cognitive symptoms relative to the age at which motor symptoms first occurred (figure 2). The difference in age between motor onset and each of the psychiatric symptom onsets was approximately normally distributed, with a wide range of at least +/- 20 years in each case (figures 2 and e-2, doi:10.5061/dryad.pk0p2ngkz). In those patients reporting
depression, onset occurred before motor symptoms in 39.2% (N= 1369/3495). For patients with irritability, onset occurred before motor symptoms in 30.8% (N= 996/3235). Perseverative/obsessive behaviour tended to occur later in the disease course, after motor onset, as did psychosis although numbers were smaller. Cognitive impairment and apathy had the most positively skewed distributions with onset occurring after motor onset in 2179/3225 (67.6%) and 1981/2852 (69.5%) of individuals, respectively. Overall, 42.4% of HD patients (N= 2140/5042) reported at least one psychiatric or cognitive symptom in advance of motor onset, with a further 22.3% (N= 1126/5042) reporting at least one of these symptoms at the same time as motor onset.

We next assessed whether there were any patterns in the mean ages of onset of the different symptoms when plotted by CAG repeat length (figure 3). Some consistent relationships between symptoms were observed. Depression usually had the youngest mean age at onset, followed by motor impairment and then apathy and cognitive impairment as the latest symptoms. Mean age at onset of irritability preceded that of motor onset at shorter repeat lengths (40-43 CAGs, inclusive) but tended to follow it at longer repeat lengths (44-53 CAGs, inclusive). The mean difference in years from onset of first symptom to last decreased with CAG repeat length from approximately 8 years for 40 repeats to 4 years for 55 repeats (figure 3).

**Cognitive and psychiatric symptoms are significantly associated with reduced functional capacity**

To assess whether psychiatric, cognitive or motor symptoms were associated with altered functional abilities we used multiple logistic regression (table 4). This analysis
incorporated sex, pathogenic CAG length, duration of disease from clinical onset to last clinic visit, alcohol consumption, tobacco use, educational attainment, total functional capacity score and total motor score as predictors of the presence/absence of each HD-CCQ symptom. The presence of any of the psychiatric or cognitive symptoms was significantly associated with lower total functional capacity (TFC), an indication of impaired ability to work, manage personal finances and function independently. Cognitive impairment was most significantly associated with reduced TFC (OR per unit decrease in TFC = 1.28, 95% CI 1.23-1.35; \( P = 1.6 \times 10^{-25} \)). Depression was significantly associated with lower total motor scores (indicating fewer motor symptoms or signs), fitting with its prevalence early in the disease course. Finally, significant associations were observed between depression and female sex (OR = 1.77, 95% CI 1.44-2.17; \( P = 7.0 \times 10^{-8} \)) and tobacco use and irritability (OR per extra cigarette per day = 1.02, 95% CI 1.01-1.03; \( P = 1.0 \times 10^{-4} \)). Although not reaching strict criteria for significance after correcting for multiple tests, associations were also found between male sex and irritability (OR = 0.75, 95% CI 0.61-0.92; \( P = 5.4 \times 10^{-3} \)) and lower educational attainment and psychosis (OR per extra year of education = 0.92, 95% CI 0.88-0.97; \( P = 2.2 \times 10^{-3} \)).
Discussion

In this large study of over 6000 patients we have shown that the initial clinical presentation of HD varies significantly with age: late onset (>60 years) is usually associated with motor manifestations, whereas early onset (<20 years; juvenile HD) is associated with a wider range of motor, cognitive and psychiatric presentations (figure 1A). These results extend prior studies which have shown that motor presentation of HD is common in late-onset disease (65.5% of an earlier REGISTRY cohort\textsuperscript{24}), with more variable presentations in juvenile HD\textsuperscript{25,26}. Approximately 20% of HD patients present with rater-determined psychiatric features, in line with previous findings (table e-1, doi:10.5061/dryad.pk0p2ngkz\textsuperscript{11}). Cognitive onset of HD might be under-reported in older age-groups due to it being regarded as coincident ‘age-related’ change. Importantly, our results show there is little relationship between pathogenic CAG repeat length and onset type in adult-onset HD (figure 1B), despite both being associated with age at clinical onset. These data fit a model in which age at clinical onset is driven primarily by CAG repeat length, but modified by environmental factors and variants at other genomic loci\textsuperscript{10,23,27,28}. The age and physiology of the brain at clinical onset subsequently determines the types of symptoms that become manifest.

Previous analysis of a smaller cohort showed that the expanded CAG repeat is fully dominant for motor onset of HD, with no effect of the normal HTT CAG allele\textsuperscript{17}. We confirmed this result and showed that the same is true for all psychiatric and cognitive onsets (table e-3, doi:10.5061/dryad.pk0p2ngkz). The age at onset of each symptom recorded by HD-CCQ was inversely correlated with CAG length (figure 3), with motor symptoms best correlated and depression least correlated (table 3). These data are consistent with previous reports showing that CAG length accounts
for 47-72% of the variance in age at motor onset of HD\textsuperscript{29}, but do not fit with previous studies that reported no correlation between CAG repeat length and psychiatric symptoms\textsuperscript{30–33}. However, these studies were small and often examined incident psychiatric symptoms, which can fluctuate over time, rather than lifetime history as here. In addition, psychiatric manifestations might have been less easily defined as HD-related than motor features. Increasingly accurate CAG tract sizing will improve the accuracy of correlations between repeat length and symptoms\textsuperscript{10,34,35}.

Most modifier studies of HD have used age at motor onset as a quantitative trait. Motor signs (usually chorea) in the context of an expanded CAG repeat in $HTT$ have high specificity for HD and most individuals with manifest HD report motor symptoms. However, psychiatric and cognitive symptoms are often more debilitating for patients and can occur early in the disease course\textsuperscript{36}. These symptoms are common in HD (table 2), and much more prevalent than in the non-HD population\textsuperscript{5,14,37}. Neuropsychiatric symptoms are also likely underestimated in HD due to pathological unawareness of these traits by patients\textsuperscript{38}. Recent genetic evidence has shown that polygenic risk scores for psychiatric disorders, particularly depression and schizophrenia, are associated with increased risk of corresponding psychiatric symptoms in HD\textsuperscript{39}. This suggests that the expanded $HTT$ CAG repeat might lower the genetic threshold for manifestation of typical psychiatric symptoms\textsuperscript{39}.

In agreement, we found the expected relationships between female sex and depression and male sex and irritability in our cohort (table 4). Our finding that psychosis in HD had a nominally significant negative association with educational level (table 4) also corroborates work showing that higher levels of education are associated with decreased schizophrenia risk\textsuperscript{40}. 
The HD-CCQ captures quantitative information not available elsewhere on symptom prevalence and timing in the HD population. It provides particular insight into neuropsychiatric symptoms but is not designed to capture subtle early motor signs. The specificity of recorded HD-CCQ scores is shown by their correlation with validated scores of depression, irritability and cognition (table 1). Cognitive impairment measured by SDMT or Stroop correlated most strongly with lifetime history of cognitive impairment in HD-CCQ, as expected, but also showed significant correlations with motor symptoms and apathy. These results fit with other studies showing that these symptoms track together in the disease trajectory. There was also a significant association between cognitive impairment and psychosis, which fits the cognitive deficits observed in schizophrenia. Conversely, validated depression and irritability scores correlated well with their respective prevalence data from HD-CCQ but were not associated with motor or cognitive impairment (table 1).

Despite considerable variation in the timing of psychiatric symptoms relative to motor onset, there are some conserved patterns (figures 2 & 3). Depression, and less often irritability, can precede motor onset by many years. Conversely, apathy and cognitive impairment tend to occur after motor onset. Overall, the HD-CCQ data show that 64.8% of our HD population (N = 3266/5042) reported at least one psychiatric or cognitive symptom by the time of motor onset. This is a much higher figure than previously reported based on clinician estimates of first HD symptom (figure 1). The discrepancy probably arises because psychiatric symptoms in ‘pre-manifest’ individuals carrying the HD mutation are often attributed by clinicians to co-incident diagnoses rather than to HD itself. This is particularly true of depression which is common in young adults with or without HD. Clinically, it is impossible to distinguish between symptoms arising as a result of the HD mutation and those from
primary psychiatric disorders, particularly in younger pre-manifest patients who are potentially years from motor onset. Furthermore, environmental effects on mental health, such as living in a family with HD, should not be overlooked.

We acknowledge several potential biases in these data: they are retrospective, subject to recall bias, and cross-sectional. HD-CCQ data depend on patient and care partner interpretation of questions. The analyses are based on data from the most recent clinic visit which is at different points of the disease course in different individuals. We controlled for this by using disease duration, the time between first onset and last clinic visit, as a covariate in analyses. The use of psychoactive medications is found in up to 60% of HD patients and might confound motor and neuropsychiatric phenotypes\textsuperscript{11,44}. Of drugs prescribed for chorea, tetrabenazine can induce depression and antipsychotics can reduce irritability. They also suppress motor manifestations which might affect the total motor scores used here as a covariate (table 4). It is hard to control for these effects. Drugs prescribed to treat symptoms once they are present will not influence symptom onset data. We used worst-ever depression and irritability scores when validating the use of HD-CCQ to mitigate against the effects of medication prescribed at certain times.

It is not feasible to conduct detailed prospective studies of symptom onsets over many years in large HD populations and so data from HD-CCQ are invaluable. Since the HD-CCQ is part of ongoing longitudinal observational studies such as a ENROLL-HD, future analyses of larger populations will be possible and of benefit. The presence of psychiatric and cognitive symptoms in HD patients is associated with significantly reduced functional capacity, emphasising the importance of managing these symptoms that have deleterious effects on quality of life\textsuperscript{45,46}. It is notable that recent models of HD staging and progression do not directly include
these psychiatric and cognitive symptoms\textsuperscript{47–49}. Work is underway to include detailed psychiatric and cognitive ratings in ongoing observational studies and clinical trials to improve the accuracy of clinical outcome measures. Given the prevalence, timing and impact of psychiatric and cognitive manifestations of HD demonstrated here, their treatment must form a central part of assessing the efficacy of novel treatments that are potentially disease-modifying, such as Huntingtin lowering\textsuperscript{50}.

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J.F.G.: Scientific Advisory Board member and has a financial interest in Triplet Therapeutics, Inc. His NIH-funded project is using genetic and genomic approaches
to uncover other genes that significantly influence when diagnosable symptoms emerge and how rapidly they worsen in Huntington Disease. The company is developing new therapeutic approaches to address triplet repeat disorders such as Huntington’s Disease, Myotonic Dystrophy and spinocerebellar ataxias. His interests were reviewed and are managed by Massachusetts General Hospital and Partners HealthCare in accordance with their conflict of interest policies.

G.B.L.: Consulting services, advisory board functions, clinical trial services and/or lectures for Allergan, Alnylam, Amarin, AOP Orphan Pharmaceuticals AG, Bayer Pharma AG, CHDI Foundation, GlaxoSmithKline, Hoffmann-LaRoche, Ipsen, ISIS Pharma, Lundbeck, Neurosearch Inc, Medesis, Medivation, Medtronic, NeuraMetrix, Novartis, Pfizer, Prana Biotechnology, Sangamo/Shire, Siena Biotech, Temmler Pharma GmbH and Teva Pharmaceuticals. He has received research grant support from the CHDI Foundation, the Bundesministerium für Bildung und Forschung (BMBF), the Deutsche Forschungsgemeinschaft (DFG), the European Commission (EU-FP7, JPND). His study site Ulm has received compensation in the context of the observational Enroll-HD Study, TEVA, ISIS and Hoffmann-Roche and the Gossweiler Foundation. He receives royalties from the Oxford University Press and is employed by the State of Baden-Württemberg at the University of Ulm.

A.E.R.: Chair of European Huntington’s Disease Network (EHDN) executive committee, Global PI for Triplet Therapeutics

L.J. is a member of the scientific advisory boards of LoQus23 Therapeutics and Triplet Therapeutics.

T.H.M. is an associate member of the scientific advisory board of LoQus23 Therapeutics.
B.Mc., J-M.L., M.E.M., M.O., N.M.W., P.H.: nothing to disclose
### Appendix 1 – Authors

| Name                      | Location                                           | Contribution/Role                                                                 |
|---------------------------|----------------------------------------------------|-----------------------------------------------------------------------------------|
| Branduff McAllister, BSc, PhD | Cardiff University, Cardiff, UK                    | Organized data; Designed and executed statistical analyses; Wrote first paper draft; Reviewed and critiqued paper manuscript |
| James F. Gusella, PhD     | Massachusetts General Hospital, Boston, USA         | Reviewed and critiqued paper manuscript                                             |
| Bernhard Landwehrmeyer, MD, PhD | University of Ulm, Ulm, Germany                | Reviewed and critiqued paper manuscript                                             |
| Jong-Min Lee, PhD         | Massachusetts General Hospital, Boston, USA         | Reviewed and critiqued paper manuscript                                             |
| Marcy E. MacDonald, PhD   | Massachusetts General Hospital, Boston, USA         | Reviewed and critiqued paper manuscript                                             |
| Michael Orth, MD, PhD     | Swiss Huntington’s disease Centre, Bern, Switzerland | Reviewed and critiqued paper manuscript                                             |
| Anne E. Rosser, MB BChir, FRCP, PhD | Cardiff University, Cardiff, UK                  | Reviewed and critiqued paper manuscript                                             |
| Nigel M. Williams, BSc, PhD | Cardiff University, Cardiff, UK                    | Reviewed and critiqued paper manuscript                                             |
| Peter Holmans, BA, PhD    | Cardiff University, Cardiff, UK                    | Designed and conceptualized study; Designed and critiqued statistical analyses; Reviewed and critiqued paper manuscript |
| Lesley Jones, BSc, PhD (*) | Cardiff University, Cardiff, UK                    | Designed and conceptualized study; Wrote first paper draft; Reviewed and critiqued paper manuscript |
| Thomas H. Massey, MA, BM Bch, DPhil (*) (†) | Cardiff University, Cardiff, UK                  | Designed and conceptualized study; Wrote first paper draft; Reviewed and critiqued paper manuscript |

(*) indicates corresponding authors  
(†) indicates the principal investigator
# Appendix 2 – Co-investigators of the European Huntington’s Disease Network REGISTRY Study

| Name                     | Location | Contribution/Role                          | Name                     | Location | Contribution/Role                          |
|--------------------------|----------|--------------------------------------------|--------------------------|----------|--------------------------------------------|
| Raphael M. Bonelli       | 1,3      | Site Investigator, REGISTRY Steering Committee | Christoph Linder         | 4        | Site Investigator                          |
| Karen Hecht              | 1        | Site Investigator                          | Walter Pirker            | 4        | Site Investigator                          |
| Brigitte Herranhof       | 1        | Site Investigator                          | Dirk Liessens            | 5        | Site Investigator                          |
| Anna Holl (formerly Hödl)| 1        | Site Investigator                          | Godelinde Calmeyn        | 5        | Site Investigator                          |
| Hans-Peter Kapffhammer   | 1        | Site Investigator                          | Nele Somers              | 5        | Site Investigator                          |
| Michael Koppitz          | 1        | Site Investigator                          | Isabelle Delvaux         | 5        | Site Investigator                          |
| Sabine Liliek            | 1        | Site Investigator                          | Andrea Boogaerts         | 5,10     | Site Investigator                          |
| Markus Magnet            | 1        | Site Investigator                          | Anja Flamez              | 6        | Site Investigator                          |
| Nicole Müller            | 1        | Site Investigator                          | Sylvie de Raedt          | 6        | Site Investigator                          |
| Daniela Otti             | 1        | Site Investigator                          | Nick Alaerts             | 7        | Site Investigator                          |
| Annamaria Painold        | 1        | Site Investigator                          | Hichem Slama             | 7        | Site Investigator                          |
| Karin Reisinger          | 1        | Site Investigator                          | Frédéric Supiot          | 7        | Site Investigator                          |
| Monika Scheibl           | 1        | Site Investigator                          | Eric Constant            | 8        | Site Investigator                          |
| Helmut Schöggf           | 1        | Site Investigator                          | Anne-Françoise Gillardin| 8        | Site Investigator                          |
| Jasmin Ullah             | 1,40     | Site Investigator                          | Marie-Claude Léonard     | 8        | Site Investigator                          |
| Eva-Maria Braunwarth     | 2        | Site Investigator                          | Christine Verellen-Dumoulin| 8,9     | Site Investigator, REGISTRY Steering Committee |
| Florian Brugger          | 2        | Site Investigator                          | Françoise van de Wyngaerde| 8        | Site Investigator                          |
| Lisa Buratti             | 2        | Site Investigator                          | Michel Dupuis            | 9        | Site Investigator                          |
| Eva-Maria Hametner       | 2        | Site Investigator                          | Cécile Minet             | 9        | Site Investigator                          |
| Caroline Hepperger       | 2        | Site Investigator                          | Pascale Ribaï            | 9        | Site Investigator                          |
| Christiane Holas         | 2        | Site Investigator                          | Dominique Van Paemel     | 9        | Site Investigator                          |
| Anna Hotter              | 2        | Site Investigator                          | Wim Vandenbergh          | 10       | Site Investigator, REGISTRY Steering Committee |
| Anna Hussl               | 2        | Site Investigator                          | Dimphna van Reijen       | 10       | Site Investigator                          |
| Barbara Larcher          | 2        | Site Investigator                          | Petra Weckx              | 10       | Site Investigator                          |
| Philipp Mahiknecht       | 2        | Site Investigator                          | Michaela Kaiserova       | 11       | Site Investigator                          |
| Christoph Müller         | 2        | Site Investigator                          | Zuzana Šenkárová         | 11       | Site Investigator                          |
| Bernadette Pinter        | 2        | Site Investigator                          | Ondřej Bezdiček         | 12       | Site Investigator                          |
| Werner Poewe             | 2        | Site Investigator                          | Jiří Klemplí            | 12,166   | Site Investigator, REGISTRY Steering Committee |
| Eva-Magdalena Reiter     | 2        | Site Investigator                          | Olga Klemplíová         | 12       | Site Investigator                          |
| Klaus Seppi              | 2        | Site Investigator                          | Veronika Majerová-Labarburu| 12     | Site Investigator                          |
| Fabienne Sprenger        | 2        | Site Investigator                          | Tomáš Nikolai           | 12       | Site Investigator                          |
| Gregor Wenning           | 2        | Site Investigator                          | Jan Roth                | 12       | Site Investigator                          |
| Gunther Ladurner         | 3        | Site Investigator                          | Irena Stárková          | 12       | Site Investigator                          |
| Stefan Lilek             | 3        | Site Investigator                          | Louise Hasselstrom Madsen| 13       | Site Investigator                          |
| Daniela Sinadrosa        | 3        | Site Investigator                          | Anette Torvin Møller    | 13       | Site Investigator                          |
| Wolfgang Staffen         | 3        | Site Investigator                          | Lena Hjermind           | 14       | Site Investigator                          |
| Anna Maria Walleczek     | 3        | Site Investigator                          | Oda Jacobsen            | 14       | Site Investigator                          |
| Name                        | Location | Contribution/Role                      | Name                        | Location | Contribution/Role                      |
|-----------------------------|----------|----------------------------------------|-----------------------------|----------|----------------------------------------|
| Ida Unmack Larsen           | 14       | Site Investigator                       | Marie Bost                  | 23       | Site Investigator                       |
| Suzanne Lindquist          | 14       | Site Investigator                       | Bénédicte Gohier            | 23       | Site Investigator                       |
| Jørgen E. Nielsen          | 14       | Site Investigator, REGISTRY Steering Committee | Marie-Anne Guérid          | 23       | Site Investigator                       |
| Lisbeth Reuge             | 14       | Site Investigator                       | Audrey Olivier              | 23       | Site Investigator                       |
| Peter Roos               | 14       | Site Investigator                       | Julie Prouzet               | 23       | Site Investigator                       |
| Jette Stockholm           | 14       | Site Investigator                       | Adriana Prundean            | 23       | Site Investigator                       |
| Christina Vangsted-Hansen | 14       | Site Investigator                       | Clarisse Scherer-Gagou      | 23       | Site Investigator                       |
| Tua Vinther-Jensen        | 14       | Site Investigator                       | Christophe Verny            | 23       | Site Investigator                       |
| Annette Lok               | 15       | Site Investigator                       | Blandine Babiloni           | 24       | Site Investigator                       |
| Marianne Lundsgaard       | 15       | Site Investigator                       | Déborah Bled                | 24       | Site Investigator                       |
| Lene Wermuth              | 15       | Site Investigator                       | Sabrina Debruxelles         | 24       | Site Investigator                       |
| Christian Andersson       | 16       | Site Investigator                       | Charlotte Duché             | 24       | Site Investigator                       |
| Clara Nyberg              | 16       | Site Investigator                       | Sonia Fraisse               | 24       | Site Investigator                       |
| Jimmy Sundblom            | 16,121   | Site Investigator                       | Cyril Goizet                | 24       | Site Investigator                       |
| Maarit Peippo             | 17       | Site Investigator                       | Laetitia Jameau             | 24       | Site Investigator                       |
| Marijatta Sipponen        | 17       | Site Investigator                       | Danielle Lafoucrière        | 24       | Site Investigator                       |
| Anu Bruun                 | 18       | Site Investigator                       | Umberto Spampinato          | 24       | Site Investigator                       |
| Paivi Hartikainen         | 18       | Site Investigator                       | Julien Couttier             | 25       | Site Investigator                       |
| Seija Mäkipää             | 18       | Site Investigator                       | Bérengère Debilly           | 25       | Site Investigator                       |
| Mari Ollokainen           | 18       | Site Investigator                       | Christine Delaigue          | 25       | Site Investigator                       |
| Jaana Åman                | 19       | Site Investigator                       | Philippe Derost             | 25       | Site Investigator                       |
| Mikko Kärppä              | 19       | Site Investigator                       | Franck Durif                | 25       | Site Investigator                       |
| Jaakko Ignatius           | 20       | Site Investigator                       | Véronique Germain           | 25       | Site Investigator                       |
| Outi Jääskeläinen         | 20       | Site Investigator                       | Perrine Legendre            | 25       | Site Investigator                       |
| Outi Kajula               | 20       | Site Investigator                       | Sylvie Loiseau              | 25       | Site Investigator                       |
| Jukka Molanen             | 20       | Site Investigator                       | Ana Marques                 | 25       | Site Investigator                       |
| Aki Mustonen              | 20       | Site Investigator                       | Miguel Ulla                 | 25       | Site Investigator                       |
| Maire Santala             | 21       | Site Investigator                       | Tiphaine Vidal              | 25       | Site Investigator                       |
| Pia Eklund                | 22       | Site Investigator                       | Anne-Catherine Bachoud-Lévi| 26       | Site Investigator, REGISTRY Steering Committee |
| Heli Hiivola              | 22       | Site Investigator                       | Farideh Badei               | 26       | Site Investigator                       |
| Hannele Hyppönen          | 22       | Site Investigator                       | Marie-Françoise Boissé      | 26       | Site Investigator                       |
| Kirsti Martikainen        | 22       | Site Investigator                       | Lotfi Boudali               | 26       | Site Investigator                       |
| Marjut Ojala              | 22       | Site Investigator                       | Laurent Cleret de Langavant | 26       | Site Investigator                       |
| Sirkku Tätkäpää           | 22       | Site Investigator                       | Laurie Lemoine              | 26       | Site Investigator                       |
| Katri Tuuha               | 22       | Site Investigator                       | Graca Morgado               | 26       | Site Investigator                       |
| Philippe Allain           | 23       | Site Investigator                       | Katia Youssov               | 26       | Site Investigator                       |
| Dominique Bonneau         | 23       | Site Investigator                       | Agnès Annic                 | 27       | Site Investigator                       |
| Name                        | Location | Contribution/Role | Name                        | Location | Contribution/Role |
|-----------------------------|----------|-------------------|-----------------------------|----------|-------------------|
| Recka Barthélémy            | 27       | Site Investigator  | Jean-Philippe Azulay        | 29       | Site Investigator  |
| Christelle De Bruycker      | 27       | Site Investigator  | Marie Delfini               | 29       | Site Investigator  |
| Maryline Cabaret            | 27       | Site Investigator  | Alexandre Eusebio           | 29       | Site Investigator  |
| Anne-Sophie Carette         | 27       | Site Investigator  | Frédérique Fluchere         | 29       | Site Investigator  |
| Nicolas Carrière            | 27       | Site Investigator  | Aicha Guenam                | 29       | Site Investigator  |
| Eric Decorte                | 27       | Site Investigator  | Laura Mundler               | 29       | Site Investigator  |
| Luc Defebvre                | 27       | Site Investigator  | Karine Nguyen               | 29       | Site Investigator  |
| Marie Delliaux               | 27       | Site Investigator  | Sandra Benach               | 30       | Site Investigator  |
| Arnaud Delval               | 27       | Site Investigator  | Alexis Brice                | 30       | Site Investigator  |
| Alizé Depelchin             | 27       | Site Investigator  | Sarah Boster                | 30       | Site Investigator  |
| Alain Destee                | 27       | Site Investigator  | Perrine Charles             | 30       | Site Investigator  |
| Nelly Dewulf-Pasz           | 27       | Site Investigator  | Alexandra Durr              | 30       | Site Investigator  |
| Thibaut Dondaine            | 27       | Site Investigator  | Claire Ewenczyk             | 30       | Site Investigator  |
| Florence Dugauquier         | 27       | Site Investigator  | Hélène Francisque           | 30       | Site Investigator  |
| Kathy Dujardin              | 27       | Site Investigator  | Céline Jauffret             | 30       | Site Investigator  |
| Lucie Hopes                 | 27       | Site Investigator  | Damian Justo                | 30       | Site Investigator  |
| Pierre Krystkowiak          | 27,28    | Site Investigator  | Abdulrahman Kassar          | 30       | Site Investigator  |
| Marie-Hélène Lemaire        | 27       | Site Investigator  | Stephan Klebe               | 30,51    | Site Investigator  |
| Sylvie Manouvrier           | 27       | Site Investigator  | Fabien Lesne                | 30       | Site Investigator  |
| Eugénie Mutez               | 27       | Site Investigator  | Paolo Milani                | 30       | Site Investigator  |
| Mireille Peter              | 27       | Site Investigator  | Marie-Lorraine Monin        | 30       | Site Investigator  |
| Lucie Plomhause             | 27       | Site Investigator  | Tiffany Monnier             | 30       | Site Investigator  |
| Bernard Sablonnière         | 27       | Site Investigator  | Emmanuel Roze               | 30       | Site Investigator  |
| Clémence Simonin            | 27       | Site Investigator  | Alina Tataru                | 30       | Site Investigator  |
| Céline Tard                 | 27       | Site Investigator  | Maya Tchikviladzé           | 30       | Site Investigator  |
| Stéphanie Thibault-Tanchou  | 27       | Site Investigator  | Sandrine Bioux              | 31       | Site Investigator  |
| Isabelle Vuillaume          | 27       | Site Investigator  | Evangeline Bliaux           | 31       | Site Investigator  |
| Marcellin Bellonet          | 28       | Site Investigator  | Carole Girard               | 31       | Site Investigator  |
| Stéphanie Blin              | 28       | Site Investigator  | Lucie Guyant-Maréchal       | 31       | Site Investigator  |
| Simone Chen                 | 28       | Site Investigator  | Didier Hannequin            | 31       | Site Investigator  |
| Kamel Masmoudi              | 28       | Site Investigator  | Véronique Hannier           | 31       | Site Investigator  |
| Gilles Morin                | 28       | Site Investigator  | Séverine Jourdain           | 31       | Site Investigator  |
| Martine Roussel             | 28       | Site Investigator  | David Maltête               | 31       | Site Investigator  |
| Mélissa Tir                 | 28       | Site Investigator  | Dorothee Pouliquen          | 31       | Site Investigator  |
| Béatrice Schüler            | 28       | Site Investigator  | Mathieu Anheim              | 32       | Site Investigator  |
| Sandrine Wannepain          | 28       | Site Investigator  | Nadia Barun                 | 32       | Site Investigator  |
| Yassine Zouitina            | 28       | Site Investigator  | Ouhaid Laghag-Boukbiza      | 32       | Site Investigator  |
| Name                     | Location | Contribution/Role                  | Name                     | Location | Contribution/Role                  |
|--------------------------|----------|------------------------------------|--------------------------|----------|------------------------------------|
| Nadine Longato           | 32       | Site Investigator                  | Barbara Kaminski         | 36       | Site Investigator                  |
| Christophe Marcel        | 32       | Site Investigator                  | Peter Kraus              | 36       | Site Investigator                  |
| Clélie Philippps         | 32       | Site Investigator                  | Carsten Saft             | 36       | Site Investigator, REGISTRY Steering Committee |
| Gabrielle Rudolf         | 32       | Site Investigator                  | Christine Stamm          | 36       | Site Investigator                  |
| Gisèle Steinmetz         | 32       | Site Investigator                  | Christos Ganos           | 37,42    | Site Investigator                  |
| Christine Tranchant      | 32       | Site Investigator                  | Lars Stubbe              | 37,42    | Site Investigator                  |
| Caroline Wagner          | 32       | Site Investigator                  | Vera Tadic               | 37       | Site Investigator                  |
| Marie-Agathe Zimmermann  | 32       | Site Investigator                  | Jennifer Tübing          | 37       | Site Investigator                  |
| Leily Blondeau           | 33       | Site Investigator                  | Herwig Lange             | 38,48    | Site Investigator                  |
| Fabienne Calvas         | 33       | Site Investigator                  | Cecile Bosredon          | 39       | Site Investigator                  |
| Samia Cheriet            | 33       | Site Investigator                  | Ulrike Hunger             | 39       | Site Investigator                  |
| Helène Delabaere         | 33       | Site Investigator                  | Matthias Löhle           | 39       | Site Investigator                  |
| Jean-François Demonet    | 33       | Site Investigator                  | Antonia Maass            | 39       | Site Investigator                  |
| Laurent Marquine         | 33       | Site Investigator                  | Christiana Ossig         | 39       | Site Investigator                  |
| Jérémie Pariante         | 33       | Site Investigator                  | Simone Schmidt           | 39       | Site Investigator                  |
| Michèle Pierre           | 33       | Site Investigator                  | Alexander Storch         | 39       | Site Investigator                  |
| Elsa POMIES              | 33       | Site Investigator                  | Annett Wolz              | 39       | Site Investigator                  |
| Sandrine Rolland         | 33       | Site Investigator                  | Martin Wolz              | 39       | Site Investigator                  |
| Corinne Souyris          | 33       | Site Investigator                  | Zacharias Kohl           | 40       | Site Investigator                  |
| Christoph Michael Kosinski | 34      | Site Investigator                  | Christina Kozay          | 40       | Site Investigator                  |
| Eva Milkerelit           | 34       | Site Investigator                  | Jürgen Winkler           | 40       | Site Investigator                  |
| Daniela Probst           | 34       | Site Investigator                  | Ulrike Bergmann          | 41       | Site Investigator                  |
| Kathrin Reetz            | 34       | Site Investigator                  | Regina Böringer          | 41       | Site Investigator                  |
| Christian Sass           | 34,48    | Site Investigator                  | Philipp Capetian         | 41       | Site Investigator                  |
| Johannes Schiefer        | 34       | Site Investigator                  | Gerit Kammel             | 41       | Site Investigator                  |
| Christiane Schiangen     | 34       | Site Investigator                  | Johann Lambeck           | 41       | Site Investigator                  |
| Cornelius J. Werner      | 34       | Site Investigator                  | Miriam Mächtel           | 41       | Site Investigator                  |
| Markus Beuth             | 35       | Site Investigator                  | Simone Meier             | 41       | Site Investigator                  |
| Harald Gelderblom        | 35       | Site Investigator                  | Michel Rijntjes          | 41       | Site Investigator                  |
| Josef Priller            | 35       | Site Investigator                  | Birgit Zucker            | 41       | Site Investigator                  |
| Harald Prüß              | 35       | Site Investigator                  | Kai Boelmans             | 42       | Site Investigator                  |
| Eike Spruth              | 35       | Site Investigator                  | Ines Goerendt            | 42       | Site Investigator                  |
| Silvia Thiel             | 35       | Site Investigator                  | Walburgis Heinicke       | 42       | Site Investigator                  |
| Jürgen Andrich           | 36       | Site Investigator                  | Ute Hidding              | 42       | Site Investigator                  |
| Gisa Ellrichmann         | 36       | Site Investigator                  | Jan Lewerenz             | 42,50    | Site Investigator                  |
| Lennard Herrmann         | 36       | Site Investigator                  | Alexander Münchau        | 42       | Site Investigator                  |
| Rainer Hoffmann          | 36       | Site Investigator                  | Michael Orth             | 42,50    | Site Investigator                  |
| Name              | Location | Contribution/Role                      | Name              | Location | Contribution/Role                      |
|-------------------|----------|----------------------------------------|-------------------|----------|----------------------------------------|
| Jenny Schmalfeld  | 42       | Site Investigator                      | Katrin Barth      | 50       | Site Investigator                      |
| Simone Zittel     | 42       | Site Investigator                      | Andrea Buck       | 50       | Site Investigator                      |
| Gabriele Diercks  | 43       | Site Investigator                      | Julia Connemann   | 50       | Site Investigator, Site Investigator, Language Coordinator |
| Dirk Dressler     | 43       | Site Investigator                      | Daniel Ecker      | 50,163   | Site Investigator, Site Investigator, Language Coordinator |
| Flveryl Francis   | 43       | Site Investigator                      | Carolin Geitner   | 50       | Site Investigator                      |
| Sabine Gayde-Stephan | 43       | Site Investigator                      | Christine Held    | 50,163   | Site Investigator, Site Investigator, Language Coordinator |
| Heike Gorzolla    | 43       | Site Investigator                      | Andrea Kesse      | 50       | Site Investigator                      |
| Bianca Kramer     | 43       | Site Investigator                      | G. Bernhard Landwehrmeyer | 50 | Site Investigator, Site Investigator, REGISTRY Steering Committee |
| Rebecca Minschke  | 43       | Site Investigator                      | Franziska Lezius  | 50       | Site Investigator                      |
| Christoph Schrader| 43       | Site Investigator                      | Solveig Nepper    | 50       | Site Investigator                      |
| Pawel Tacik       | 43       | Site Investigator                      | Anke Niess        | 50       | Site Investigator                      |
| Michael Ribbat+   | 44       | Site Investigator                      | Ariane Schneider  | 50       | Site Investigator                      |
| Bernhard Longinus | 45       | Site Investigator                      | Daniela Schwenk   | 50       | Site Investigator                      |
| Carsten Möller    | 46       | Site Investigator                      | Sigurd Süssmuth   | 50       | Site Investigator                      |
| Katrin Bürk       | 46       | Site Investigator                      | Sonja Trautmann   | 50       | Site Investigator                      |
| Antje Lüsebrink   | 47       | Site Investigator                      | Melanie Vogel     | 50       | Site Investigator                      |
| Mark Mühlau       | 47       | Site Investigator                      | Patrick Weydt     | 50       | Site Investigator                      |
| Alexander Peinemann | 47      | Site Investigator                      | Thomas Musacchio  | 51       | Site Investigator                      |
| Michael Städtler  | 47       | Site Investigator                      | Christine Leybold | 51      | Site Investigator                      |
| Adolf Weindl      | 47       | Site Investigator                      | Kerstin Nöth      | 51       | Site Investigator                      |
| Juliane Winkelmann| 47       | Site Investigator                      | Claudia Cormio    | 52       | Site Investigator                      |
| Cornelia Ziegler  | 47       | Site Investigator                      | Olimpia Difruscolo | 52     | Site Investigator                      |
| Natalie Bechtel   | 48       | Site Investigator                      | Giovanni Franco   | 52       | Site Investigator                      |
| Heike Beckmann    | 48       | Site Investigator                      | Angela Nuzzi      | 52       | Site Investigator                      |
| Stefan Bohlen     | 48       | Site Investigator                      | Vittorio Scirucchio | 52    | Site Investigator                      |
| Nicole Göpfert    | 48       | Site Investigator                      | Claudia Serpino   | 52       | Site Investigator                      |
| Eva Hötzner       | 48       | Site Investigator                      | Marina de Tommaso | 52      | Site Investigator                      |
| Ralf Reilman      | 48       | Site Investigator                      | Giovanna Calandra-Buonaura | 53 | Site Investigator                      |
| Stefanie Rohm     | 48       | Site Investigator                      | Sabina Capellari  | 53       | Site Investigator                      |
| Silke Rumpf       | 48       | Site Investigator                      | Pietro Cortelli   | 53       | Site Investigator                      |
| Sigrun Schepers   | 48       | Site Investigator                      | Roberto Gallassi  | 53       | Site Investigator                      |
| Nathalia Weber    | 48       | Site Investigator                      | Roberto Poda      | 53       | Site Investigator                      |
| Michael Bachmeier | 49       | Site Investigator                      | Cesa Scaglione    | 53       | Site Investigator                      |
| Matthias Dose     | 49       | Site Investigator                      | Chiara Agosti     | 54       | Site Investigator                      |
| Nina Hofstetter   | 49       | Site Investigator                      | Sergio Barlati     | 54      | Site Investigator                      |
| Ralf Marquard     | 49       | Site Investigator                      | Silvia Compostella | 54  | Site Investigator                      |
| Alzbeta Mühlbäck  | 49       | Site Investigator                      | Eleonora Marchina | 54     | Site Investigator                      |
| Name                        | Location | Contribution/Role                  |
|-----------------------------|----------|------------------------------------|
| Alessandro Padovani         | 54       | Site Investigator                  |
| Michela Figorilli           | 55       | Site Investigator                  |
| Francesco Marrosu           | 55       | Site Investigator                  |
| Antonella Muroni            | 55       | Site Investigator                  |
| Valeria Piras               | 55       | Site Investigator                  |
| Melisa Vacca                | 55       | Site Investigator                  |
| Elisabetta Bertini          | 56       | Site Investigator                  |
| Caterina Bartoli            | 56       | Site Investigator                  |
| Fernanda Fortunato          | 56       | Site Investigator                  |
| Elena Ghelli                | 56       | Site Investigator                  |
| Andrea Ginestroni           | 56       | Site Investigator                  |
| Claudia Mechi               | 56       | Site Investigator                  |
| Marco Paganini              | 56       | Site Investigator                  |
| Silvia Piacentini           | 56       | Site Investigator                  |
| Silvia Pradella             | 56       | Site Investigator                  |
| Anna Maria Romoli           | 56       | Site Investigator                  |
| Sandro Sorbi                | 56       | Site Investigator                  |
| Giovanni Abbruzzese         | 56       | Site Investigator                  |
| Monica Bandettini di Poggio | 57       | Site Investigator                  |
| Giovanna Ferrandes          | 57       | Site Investigator                  |
| Paola Mandich               | 57       | Site Investigator                  |
| Roberta Marchese            | 57       | Site Investigator                  |
| Emilio Di Maria             | 57       | Site Investigator                  |
| Tiziano Tamburini           | 57       | Site Investigator                  |
| Alberto Albanese            | 58       | Site Investigator                  |
| Simona Castagliuolo         | 58       | Site Investigator                  |
| Anna Castaldo               | 58       | Site Investigator                  |
| Stefano Di Donato           | 58       | Site Investigator                  |
| Daniela Di Bella            | 58       | Site Investigator                  |
| Cinzia Gellera              | 58       | Site Investigator                  |
| Silvia Genitrini            | 58       | Site Investigator                  |
| Caterina Mariotti           | 58       | Site Investigator                  |
| Daniela Monza               | 58, 163  | Site Investigator                  |
| Lorenzo Nanetti             | 58       | Site Investigator                  |
| Marta Panzeri               | 58       | Site Investigator                  |
| Dominga Paridi              | 58       | Site Investigator                  |
| Paola Soliveri              | 58       | Site Investigator                  |
| Francesca Spagnolo          | 58       | Site Investigator                  |
| Franco Taroni               | 58       | Site Investigator                  |
| Chiara Tomasello            | 58       | Site Investigator                  |
| Giuseppe De Michele         | 59       | Site Investigator                  |
| Luigi Di Maio               | 59       | Site Investigator                  |
| Carlo Rinaldi               | 59       | Site Investigator                  |
| Marco Massarelli            | 59       | Site Investigator                  |
| Silvio Peluso               | 59       | Site Investigator                  |
| Alessandro Roca             | 59       | Site Investigator                  |
| Cinzia Valeria Russo        | 59       | Site Investigator                  |
| Elena Salvatore             | 59       | Site Investigator                  |
| Pierpaolo Sorrentino        | 59       | Site Investigator                  |
| Tecla Tucci                 | 59       | Site Investigator                  |
| Milena Cannelia             | 60       | Site Investigator                  |
| Valentina Codella           | 60       | Site Investigator                  |
| Francesca De Gregorio       | 60       | Site Investigator                  |
| Annuziata De Nicola         | 60       | Site Investigator                  |
| Francesca Elfani            | 60       | Site Investigator                  |
| Chiara Esposito             | 60       | Site Investigator                  |
| Tiziana Martino             | 60       | Site Investigator                  |
| Irene Mazzante              | 60       | Site Investigator                  |
| Martina Petrollini          | 60       | Site Investigator                  |
| Maria Simonelli             | 60       | Site Investigator                  |
| Maurizio Vezza              | 60       | Site Investigator                  |
| Ferdinando Squitieri        | 61       | Site Investigator                  |
| Barbara D’Alessio           | 62       | Site Investigator                  |
| Francesca Lovo              | 62       | Site Investigator                  |
| Anna Rita Bentivoglio       | 63       | Site Investigator                  |
| Anna Rita Bentivoglio       | 63       | Site Investigator, REGISTRY Steering Committee |
| Francesco Bove              | 63       | Site Investigator                  |
| Claudio Catalli             | 63       | Site Investigator                  |
| Raffaella Di Giacopo        | 63       | Site Investigator                  |
| Alfonso Fasano              | 63       | Site Investigator                  |
| Marina Frontali             | 63, 64   | Site Investigator                  |
| Arianna Guidubaldi          | 63       | Site Investigator                  |
| Tamara Ialongo              | 63       | Site Investigator                  |
| Gioia Jacopini              | 63, 64   | Site Investigator                  |
| Giovanna Loria              | 63       | Site Investigator                  |
| Name               | Location | Contribution/Role                        | Name               | Location | Contribution/Role                        |
|--------------------|----------|------------------------------------------|--------------------|----------|------------------------------------------|
| Anna Modoni        | 63       | Site Investigator                         | Mirella Waber      | 68       | Site Investigator                         |
| Martina Petracca   | 63       | Site Investigator                         | Carla Verstappen   | 69       | Site Investigator                         |
| Carla Piano        | 63       | Site Investigator                         | Ellen Økland       | 70       | Site Investigator                         |
| Piccininni Chiara  | 63       | Site Investigator                         | Blinkenberg        |          |                                          |
| Davide Quaranta    | 63       | Site Investigator                         | Erik Hauge         | 71       | Site Investigator                         |
| Silvia Romano      | 63,64    | Site Investigator                         | Hilde Tyvoll       | 71       | Site Investigator                         |
| Francesco Soleti   | 63       | Site Investigator                         | Olaf Aaserud       | 72       | Site Investigator                         |
| Marcella Solito    | 63       | Site Investigator                         | Nils Olaf Aanonsen | 72       | Site Investigator                         |
| Maria Spadaro      | 63       | Site Investigator                         | Kathrine Bjørgo    | 72       | Site Investigator                         |
| Flavia Torlizzi    | 63       | Site Investigator                         | Nancy Borgerod     | 72       | Site Investigator                         |
| Paola Zinzi        | 63,64,163| Site Investigator, Language Coordinator   | Elisabeth Dramstad | 72       | Site Investigator                         |
| Anna Modoni        | 63       | Site Investigator                         | Mirella Waber      | 68       | Site Investigator                         |
| Martina Petracca   | 63       | Site Investigator                         | Carla Verstappen   | 69       | Site Investigator                         |
| Carla Piano        | 63       | Site Investigator                         | Ellen Økland       | 70       | Site Investigator                         |
| Piccininni Chiara  | 63       | Site Investigator                         | Blinkenberg        |          |                                          |
| Davide Quaranta    | 63       | Site Investigator                         | Erik Hauge         | 71       | Site Investigator                         |
| Silvia Romano      | 63,64    | Site Investigator                         | Hilde Tyvoll       | 71       | Site Investigator                         |
| Francesco Soleti   | 63       | Site Investigator                         | Olaf Aaserud       | 72       | Site Investigator                         |
| Marcella Solito    | 63       | Site Investigator                         | Nils Olaf Aanonsen | 72       | Site Investigator                         |
| Maria Spadaro      | 63       | Site Investigator                         | Kathrine Bjørgo    | 72       | Site Investigator                         |
| Flavia Torlizzi    | 63       | Site Investigator                         | Nancy Borgerod     | 72       | Site Investigator                         |
| Paola Zinzi        | 63,64,163| Site Investigator, Language Coordinator   | Elisabeth Dramstad | 72       | Site Investigator                         |
| Anna Modoni        | 63       | Site Investigator                         | Mirella Waber      | 68       | Site Investigator                         |
| Martina Petracca   | 63       | Site Investigator                         | Carla Verstappen   | 69       | Site Investigator                         |
| Carla Piano        | 63       | Site Investigator                         | Ellen Økland       | 70       | Site Investigator                         |
| Piccininni Chiara  | 63       | Site Investigator                         | Blinkenberg        |          |                                          |
| Davide Quaranta    | 63       | Site Investigator                         | Erik Hauge         | 71       | Site Investigator                         |
| Silvia Romano      | 63,64    | Site Investigator                         | Hilde Tyvoll       | 71       | Site Investigator                         |
| Francesco Soleti   | 63       | Site Investigator                         | Olaf Aaserud       | 72       | Site Investigator                         |
| Marcella Solito    | 63       | Site Investigator                         | Nils Olaf Aanonsen | 72       | Site Investigator                         |
| Maria Spadaro      | 63       | Site Investigator                         | Kathrine Bjørgo    | 72       | Site Investigator                         |
| Flavia Torlizzi    | 63       | Site Investigator                         | Nancy Borgerod     | 72       | Site Investigator                         |
| Paola Zinzi        | 63,64,163| Site Investigator, Language Coordinator   | Elisabeth Dramstad | 72       | Site Investigator                         |
| Anna Modoni        | 63       | Site Investigator                         | Mirella Waber      | 68       | Site Investigator                         |
| Martina Petracca   | 63       | Site Investigator                         | Carla Verstappen   | 69       | Site Investigator                         |
| Carla Piano        | 63       | Site Investigator                         | Ellen Økland       | 70       | Site Investigator                         |
| Piccininni Chiara  | 63       | Site Investigator                         | Blinkenberg        |          |                                          |
| Davide Quaranta    | 63       | Site Investigator                         | Erik Hauge         | 71       | Site Investigator                         |
| Silvia Romano      | 63,64    | Site Investigator                         | Hilde Tyvoll       | 71       | Site Investigator                         |
| Francesco Soleti   | 63       | Site Investigator                         | Olaf Aaserud       | 72       | Site Investigator                         |
| Marcella Solito    | 63       | Site Investigator                         | Nils Olaf Aanonsen | 72       | Site Investigator                         |
| Maria Spadaro      | 63       | Site Investigator                         | Kathrine Bjørgo    | 72       | Site Investigator                         |
| Flavia Torlizzi    | 63       | Site Investigator                         | Nancy Borgerod     | 72       | Site Investigator                         |
| Paola Zinzi        | 63,64,163| Site Investigator, Language Coordinator   | Elisabeth Dramstad | 72       | Site Investigator                         |
| Anna Modoni        | 63       | Site Investigator                         | Mirella Waber      | 68       | Site Investigator                         |
| Martina Petracca   | 63       | Site Investigator                         | Carla Verstappen   | 69       | Site Investigator                         |
| Carla Piano        | 63       | Site Investigator                         | Ellen Økland       | 70       | Site Investigator                         |
| Piccininni Chiara  | 63       | Site Investigator                         | Blinkenberg        |          |                                          |
| Davide Quaranta    | 63       | Site Investigator                         | Erik Hauge         | 71       | Site Investigator                         |
| Silvia Romano      | 63,64    | Site Investigator                         | Hilde Tyvoll       | 71       | Site Investigator                         |
| Francesco Soleti   | 63       | Site Investigator                         | Olaf Aaserud       | 72       | Site Investigator                         |
| Marcella Solito    | 63       | Site Investigator                         | Nils Olaf Aanonsen | 72       | Site Investigator                         |
| Maria Spadaro      | 63       | Site Investigator                         | Kathrine Bjørgo    | 72       | Site Investigator                         |
| Flavia Torlizzi    | 63       | Site Investigator                         | Nancy Borgerod     | 72       | Site Investigator                         |
| Paola Zinzi        | 63,64,163| Site Investigator, Language Coordinator   | Elisabeth Dramstad | 72       | Site Investigator                         |
| Anna Modoni        | 63       | Site Investigator                         | Mirella Waber      | 68       | Site Investigator                         |
| Martina Petracca   | 63       | Site Investigator                         | Carla Verstappen   | 69       | Site Investigator                         |
| Carla Piano        | 63       | Site Investigator                         | Ellen Økland       | 70       | Site Investigator                         |
| Piccininni Chiara  | 63       | Site Investigator                         | Blinkenberg        |          |                                          |
| Davide Quaranta    | 63       | Site Investigator                         | Erik Hauge         | 71       | Site Investigator                         |
| Silvia Romano      | 63,64    | Site Investigator                         | Hilde Tyvoll       | 71       | Site Investigator                         |
| Francesco Soleti   | 63       | Site Investigator                         | Olaf Aaserud       | 72       | Site Investigator                         |
| Marcella Solito    | 63       | Site Investigator                         | Nils Olaf Aanonsen | 72       | Site Investigator                         |
| Maria Spadaro      | 63       | Site Investigator                         | Kathrine Bjørgo    | 72       | Site Investigator                         |
| Flavia Torlizzi    | 63       | Site Investigator                         | Nancy Borgerod     | 72       | Site Investigator                         |
| Paola Zinzi        | 63,64,163| Site Investigator, Language Coordinator   | Elisabeth Dramstad | 72       | Site Investigator                         |

**Additional Roles:**
- Registry Steering Committee
- Language Coordinator
| Name                               | Location | Contribution/Role       | Name                        | Location | Contribution/Role                                      |
|------------------------------------|----------|-------------------------|-----------------------------|----------|-------------------------------------------------------|
| Witold Soltan                      | 74       | Site Investigator       | Anna Kaminska               | 78       | Site Investigator                                      |
| Michal Szinwelski                  | 74       | Site Investigator       | Hubert Kwiecinski           | 78       | Site Investigator                                      |
| Michal Arkuszewski                 | 75       | Site Investigator       | Jakub Antczak               | 79       | Site Investigator                                      |
| Magdalena Błaszczyk               | 75       | Site Investigator       | Katarzyna Jachinska         | 79       | Site Investigator                                      |
| Magdalena Bocarska-Jedynak         | 75       | Site Investigator       | Wioletta Krysa              | 79       | Site Investigator                                      |
| Ewelina Ciach-Wysocka-Agnieszka Gorzkowska | 75     | Site Investigator       | Maryla Rakowicz             | 79       | Site Investigator                                      |
| Barbara Jasińska-Myga              | 75       | Site Investigator       | Rafał Rola                  | 79       | Site Investigator                                      |
| Aleksandra Kaczmarczyk             | 75       | Site Investigator       | Danuta Ryglewicz           | 79       | Site Investigator                                      |
| Gabriela Kłodowska – Duda          | 75       | Site Investigator       | Halina Sienkiewicz-Jarosz   | 79       | Site Investigator                                      |
| Grzegorz Opala                    | 75,76    | Site Investigator       | Iwona Stępnial              | 79       | Site Investigator                                      |
| Monika Rudzińska                   | 75,76    | Site Investigator       | Anna Sulek                  | 79       | Site Investigator                                      |
|                                    |          |                         |                             |          | Site Investigator                                      |
|                                    |          |                         | Grzegorz Witkowski          | 79,163   | Site Investigator, Language Coordinator               |
|                                    |          |                         | TTREGISTRY Steering        |          | Committee                                             |
| Daniel Stompel                     | 75       | Site Investigator       | Jacek Zaremba               | 79       | Site Investigator                                      |
| Krzysztof Banaszkiewicz           | 76       | Site Investigator       | Elżbieta Zdziennicka        | 79       | Site Investigator                                      |
| Dorota Boćwińska                   | 76       | Site Investigator       | Karolina Ziora-Jakutowicz   | 79       | Site Investigator                                      |
| Kamila Bojakowska-Jaremek          | 76       | Site Investigator       | Cristina Januário           | 80       | Site Investigator                                      |
| Małgorzata Dec                    | 76,76    | Site Investigator       | Filipa Júlio                | 80       | Site Investigator                                      |
| Natalia Grabinska                  | 76       | Site Investigator       | Manuel Almeida              | 81       | Site Investigator                                      |
| Małgorzata Krawczyk               | 76       | Site Investigator       | Ana Calado                  | 81       | Site Investigator                                      |
| Ewelina Kubowicz                   | 76       | Site Investigator       | Margarida Dias              | 81       | Site Investigator                                      |
| Michalina Małec-Litwinowicz        | 76       | Site Investigator       | Joana Morgado               | 81       | Site Investigator                                      |
| Agata Stenwak                     | 76       | Site Investigator       | Cristina Semedo             | 81       | Site Investigator                                      |
| Andrzej Szczudił                  | 76,76    | Site Investigator       | Leonor Correia Guedes       | 82,163   | Site Investigator                                      |
| Elżbieta Szczygiel                 | 76       | Site Investigator       | Miguel Coelho               | 82       | Site Investigator                                      |
| Magdalena Wójcik                   | 76,76    | Site Investigator       | Joaquim J Ferreira          | 82       | Site Investigator                                      |
| Anna Wasielewska                   | 76       | Site Investigator       | Andreia Magalhães           | 82       | Site Investigator                                      |
| Jacek Aniola Anna Bryl             | 77       | Site Investigator       | Tiago Mestre                | 82,163   | Site Investigator                                      |
| Anna Ciesielska                    | 77       | Site Investigator       | Tiago Mendes                | 82,83    | Site Investigator                                      |
| Aneta Klimberg                    | 77       | Site Investigator       | Dulce Neutel                | 82       | Site Investigator                                      |
| Jerzy Marcinkowski                 | 77       | Site Investigator       | Filipe Rodrigues            | 82       | Site Investigator                                      |
| Husam Samara                       | 77       | Site Investigator       | Anabela Valadas             | 82       | Site Investigator                                      |
| Justyna Sempłowicz                 | 77       | Site Investigator       | Cristina Costa              | 83       | Site Investigator                                      |
| Bartłomiej Wiśniewski              | 77       | Site Investigator       | Helena Cardoso              | 83       | Site Investigator                                      |
| Daniel Zielonka                    | 77       | Site Investigator       | Mariana Santos              | 83       | Site Investigator                                      |
| Anna Gogol (formerly Kalbarczyk)   | 78       | Site Investigator       | Gonçalo Caçao               | 84       | Site Investigator                                      |
| Piotr Janik                        | 78       | Site Investigator       | Sara Cavaco                 | 84       | Site Investigator                                      |
| Zygmunt Jamrozik                   | 78       | Site Investigator       | Joana Damásio               | 84       | Site Investigator                                      |
| Name                     | Location | Contribution/Role                                | Name                     | Location | Contribution/Role                                      |
|--------------------------|----------|--------------------------------------------------|--------------------------|----------|-------------------------------------------------------|
| Joana Fernandes          | 84       | Site Investigator                                 | Andrés de la Cerda       | 94       | Site Investigator                                      |
| Alexandra Gonçalves      | 84       | Site Investigator                                 | Esteban Muñoz            | 94       | Site Investigator                                      |
| Rui Loureiro             | 84       | Site Investigator                                 | Pilar Santacruz          | 94       | Site Investigator                                      |
| Inês Moreira             | 84       | Site Investigator                                 | Miguel Aguilar Barbera   | 95       | Site Investigator                                      |
| Marina Magalhães         | 84       | Site Investigator                                 | Ana Rojo Sebastián       | 95       | Site Investigator, REGISTRY Steering Committee        |
| Paula Salgado            | 84       | Site Investigator                                 | Sonia Arribas Pardo      | 95       | Site Investigator                                      |
| Carlos Andrade           | 85       | Site Investigator                                 | Dolores Badenes Guia     | 95       | Site Investigator                                      |
| Andreia Costia           | 85       | Site Investigator                                 | Noemí Calzado            | 95       | Site Investigator                                      |
| Carolina Garrett         | 85       | Site Investigator                                 | Laura Casas Hernanz      | 95       | Site Investigator                                      |
| Miguel Gago              | 85       | Site Investigator                                 | Juan Pablo Tartari       | 95       | Site Investigator                                      |
| Joana Guimarães          | 85       | Site Investigator                                 | Judith López Catena      | 95       | Site Investigator                                      |
| João Massano             | 85       | Site Investigator                                 | Pilar Quiléz Ferrer      | 95       | Site Investigator                                      |
| Joana Meireles           | 85       | Site Investigator                                 | Gemma Torre Carruesco    | 95       | Site Investigator                                      |
| Ana Monteiro             | 85       | Site Investigator                                 | Misericordia Floriach    | 96       | Site Investigator                                      |
| Diana Khasanova          | 86       | Site Investigator                                 | Robert Célia Mareca      | 96       | Site Investigator                                      |
| Zuleyka Zayalova         | 86       | Site Investigator                                 | Viladrich                | 96       | Site Investigator                                      |
| Sergey Illaroshkin       | 87       | Site Investigator, REGISTRY Steering Committee   | Jesús Miguel Ruiz Idiago | 96       | Site Investigator                                      |
| Sergey Klyushnikov       | 87       | Site Investigator                                 | Antonio Villa Riballo    | 96       | Site Investigator                                      |
| Olga Sidorova            | 87       | Site Investigator                                 | Antonia Campolongo       | 97       | Site Investigator                                      |
| Oleg Smirnov             | 87       | Site Investigator                                 | Ramon Fernandez de Bobadilla | 97    | Site Investigator                                      |
| Elizaveta Yudina         | 87,163   | Site Investigator, Language Coordinator          | Andrea Horta             | 97,163   | Site Investigator, Language Coordinator               |
| Yury Seliverstov         | 87,163   | Site Investigator, Language Coordinator          | Jaime Kulisevsky Bojarsky | 97       | Site Investigator                                      |
| Victoria Antonova        | 88       | Site Investigator                                 | Saul Martinez-Horta      | 97,163   | Site Investigator, Language Coordinator               |
| Svetlana Kopishinskaya   | 88       | Site Investigator                                 | Javier Pagonabarraga     | 97       | Site Investigator                                      |
| Maria Korotysh           | 88       | Site Investigator                                 | Jesus Perez Perez        | 97       | Site Investigator                                      |
| Rim Magzhanov            | 89       | Site Investigator                                 | Roser Ribosa             | 97       | Site Investigator                                      |
| Elena Safullina          | 89       | Site Investigator                                 | Carolina Villa           | 97       | Site Investigator                                      |
| Sergey Kurbatov          | 90       | Site Investigator                                 | Maria Angeles Acera      | 98       | Site Investigator                                      |
| Pilar Solis              | 91       | Site Investigator                                 | Koldo Berganzo Corrales  | 98       | Site Investigator                                      |
| Carmen Durán Herrera     | 92       | Site Investigator                                 | Juan Carlos Gomez Esteban | 98      | Site Investigator                                      |
| Patrocinio García Moreno | 92       | Site Investigator                                 | Amaia González           | 98       | Site Investigator                                      |
| Jordi Bas                | 93       | Site Investigator                                 | Beatriz Tijero Merino    | 98       | Site Investigator                                      |
| Núria Busquets           | 93       | Site Investigator                                 | Esther Cubo              | 99       | Site Investigator                                      |
| Matilde Calopa           | 93       | Site Investigator                                 | Cecilia Gil Polo         | 99       | Site Investigator                                      |
| Serge Jaumà Classen      | 93       | Site Investigator                                 | Natividad Mariscal       | 99       | Site Investigator                                      |
| Nadia Rodríguez Dedichá  | 93       | Site Investigator                                 | Jesús Sánchez            | 99       | Site Investigator                                      |
| Maria Teresa Buongiorno  | 94       | Site Investigator                                 | Sandra Gutierrez Romero  | 100      | Site Investigator                                      |
| Name                          | Location | Contribution/Role   |
|-------------------------------|----------|--------------------|
| José Matías Arbelo           | 100      | Site Investigator  |
| Rocío Malo de Molina         | 100      | Site Investigator  |
| Idaira Martin                 | 100      | Site Investigator  |
| Juan Manuel Periñez           | 100      | Site Investigator  |
| Beatriz Udaeta                | 100      | Site Investigator  |
| Fernando Alonso-Frech         | 101      | Site Investigator  |
| María del Valle Loarte        | 101      | Site Investigator  |
| Francisco Barrero             | 102      | Site Investigator  |
| Blas Morales                  | 102      | Site Investigator  |
| Belén Frades                  | 103      | Site Investigator  |
| Marina Ávila Villanueva       | 103      | Site Investigator  |
| Maria Ascension Zea Sevilla   | 103      | Site Investigator  |
| María del Mar Fenollar        | 104      | Site Investigator  |
| Rocío García-Ramos García    | 104      | Site Investigator  |
| Clara Villanueva              | 104      | Site Investigator  |
| Mónica Bascuñiana             | 105      | Site Investigator  |
| Marta Fatás Ventura          | 105      | Site Investigator  |
| Juan García Caldentey         | 105,106,109 | Site Investigator |
| Guillermo García Ribas        | 105      | Site Investigator  |
| Justo García de Yébenes       | 105      | Site Investigator  |
| José Luis López-Sendón Moreno| 105      | Site Investigator  |
| Verónica Mañanes Barral       | 105      | Site Investigator  |
| Patricia Trigo Cubillo        | 105,163  | Site Investigator, Language Coordinator |
| Cici Feliz                    | 106      | Site Investigator  |
| Pedro José García Ruiz        | 106      | Site Investigator  |
| Ana García                    | 106      | Site Investigator  |
| Rosa Guerrero López           | 106      | Site Investigator  |
| Antonio Herranz Bárcenas      | 106      | Site Investigator  |
| Asunción Martínez-Descals     | 106,163  | Site Investigator, Language Coordinator |
| Angel Martinez Pueyo          | 106      | Site Investigator  |
| Veronica Puertas Martin       | 106      | Site Investigator  |
| Noelia Rodríguez Martínez     | 106      | Site Investigator  |
| Teresa Montojo                | 106      | Site Investigator  |
| María José Sainz Artiga       | 106      | Site Investigator  |
| Vicenta Sánchez               | 106      | Site Investigator  |
| María Dolores Alarcón         | 107      | Site Investigator  |
| Carmen Antúnez Almagro        | 107      | Site Investigator  |

| Name                          | Location | Contribution/Role   |
|-------------------------------|----------|--------------------|
| Esther Diéguez                | 107      | Site Investigator  |
| Lorenza Fortuna               | 107      | Site Investigator  |
| Agustina Legaz                | 107      | Site Investigator  |
| Salvador Manzanares           | 107      | Site Investigator  |
| Juan Marín Muñoz             | 107      | Site Investigator  |
| María Martírio Antequera Torres Fuentesa Noguera Perea | 107 | Site Investigator |
| Laura Vivancos                | 107      | Site Investigator  |
| Sonia González                | 108      | Site Investigator  |
| Luis Menéndez Guisasola       | 108      | Site Investigator  |
| Marta Para Prieto             | 108      | Site Investigator  |
| René Ribacoba                 | 108      | Site Investigator  |
| Carlos Salvador               | 108      | Site Investigator  |
| Pablo Sánchez Lozano          | 108      | Site Investigator  |
| Inés Legarda Ramírez          | 109      | Site Investigator  |
| Dolores Moragues Benito       | 109      | Site Investigator  |
| Penelope Navas Arques         | 109      | Site Investigator  |
| Monica Rodríguez Lopera       | 109      | Site Investigator  |
| Barbara Vives Pastor          | 109      | Site Investigator  |
| Iltziar Gaston                | 110      | Site Investigator  |
| Fermin Garcia-Amigot          | 110      | Site Investigator  |
| María Dolores Martínez-Jaurrieta | 110  | Site Investigator  |
| Maria Antonia Ramos-Arroyo    | 110      | Site Investigator, REGISTRY Steering Committee |
| Astrid Adarmes                | 111      | Site Investigator  |
| Maravilla Bernal-Escudero     | 111      | Site Investigator  |
| Fátima Carrillo               | 111      | Site Investigator  |
| Silvia Jesús                  | 111      | Site Investigator  |
| Pablo Mir                     | 111      | Site Investigator  |
| Laura Vargas-González         | 111      | Site Investigator  |
| Fátima Damas Hermoso          | 112      | Site Investigator  |
| José Manuel García Moreno     | 112      | Site Investigator  |
| Javier Abril Jaramillo        | 112      | Site Investigator  |
| Carolina Mendez Lucena        | 112      | Site Investigator  |
| Eva María Pacheco Cortegana   | 112      | Site Investigator  |
| José Chacón Peña              | 112      | Site Investigator  |
| Luis Redondo                  | 112      | Site Investigator  |
| Violeta Redondo               | 112      | Site Investigator  |
| José Chacón Peña              | 112      | Site Investigator  |
| Luis Redondo                  | 112      | Site Investigator  |
| Violeta Sánchez Sánchez       | 112      | Site Investigator  |
| Name                        | Location | Contribution/Role                           | Name                        | Location | Contribution/Role                           |
|-----------------------------|----------|---------------------------------------------|-----------------------------|----------|---------------------------------------------|
| Cristina Melgar Fernandez  | 113      | Site Investigator                           | Tina Waliden                | 119      | Site Investigator                           |
| Maria Dolores Romero Lemos | 113      | Site Investigator                           | Måns Berglund               | 120      | Site Investigator                           |
| Maite Paredes Mata          | 113      | Site Investigator                           | Ghada Loutfi                | 120      | Site Investigator                           |
| Rocío Villagrán Casado     | 113      | Site Investigator                           | Carina Olofsson             | 120      | Site Investigator                           |
| María Bosca                 | 114      | Site Investigator                           | Eva-Lena Statin             | 120      | Site Investigator                           |
| Juan Andres Burguera        | 114      | Site Investigator                           | Laila Westman               | 120      | Site Investigator                           |
| Francisco Castera Brugada   | 114      | Site Investigator                           | Birgitta Wikström           | 120      | Site Investigator                           |
| José María Millán Salvador  | 114      | Site Investigator                           | Camilla Ekwall              | 121      | Site Investigator                           |
| Carmen Peiró Vilaplana      | 114      | Site Investigator                           | Marie-Lousie Göller        | 121      | Site Investigator                           |
| Pilar Solís                 | 114      | Site Investigator                           | Anders Johansson            | 121      | Site Investigator                           |
| Begonia Jeweinat Figuerola  | 114      | Site Investigator                           | Valter Niemelä              | 121      | Site Investigator                           |
| Paloma Millan Palanca      | 115      | Site Investigator                           | Dag Nyholm                  | 121      | Site Investigator                           |
| Elena Bellosta Diago       | 115      | Site Investigator                           | Leif Wiklund                | 121      | Site Investigator, REGISTRY Steering Committee |
| Javier López del Val        | 115      | Site Investigator                           | Jean-Marc Burgunder         | 122,161  | Site Investigator, REGISTRY Steering Committee |
| Laura Martinez Martinez     | 115      | Site Investigator                           | Jessica Koehli              | 122      | Site Investigator                           |
| Elena López                 | 115      | Site Investigator                           | Yanik Stebler               | 122      | Site Investigator                           |
| Jan Wahlström+              | 116      | Site Investigator, REGISTRY Steering Committee | Alain Kaelin              | 123      | Site Investigator                           |
| Ulrika Hasterery-Ugander    | 116      | Site Investigator                           | Irene Romero                | 123      | Site Investigator                           |
| Gunnel Fredlund             | 116      | Site Investigator                           | Michael Schüpbach           | 123      | Site Investigator                           |
| Radu Constantinescu        | 116      | Site Investigator                           | Sabine Weber Zaugg          | 123      | Site Investigator                           |
| Kajsa Lewin                 | 116      | Site Investigator                           | Federica Esposito           | 124      | Site Investigator                           |
| Liselotte Neleborn-Lingejär | 116      | Site Investigator                           | Jean-Marc Good              | 124      | Site Investigator                           |
| Maria Berglund              | 116      | Site Investigator                           | Karin Paus                  | 124      | Site Investigator                           |
| Peter Berglund              | 116      | Site Investigator                           | Francois Vingerhoets        | 124      | Site Investigator                           |
| Petra Linnsand             | 116      | Site Investigator                           | Christian Wider+            | 124      | Site Investigator                           |
| Åsa Petersén                | 117      | Site Investigator                           | Hans H. Jung                | 125      | Site Investigator                           |
| Jan Reimer                  | 117      | Site Investigator                           | Jens A. Petersen            | 125      | Site Investigator                           |
| Håkan Widner                | 117      | Site Investigator                           | Maria Ligon-Auer            | 125      | Site Investigator                           |
| Mouna Esmaeilzadeh          | 118      | Site Investigator                           | Violeta Mihaylova           | 125      | Site Investigator                           |
| Joakim Tedroff              | 118      | Site Investigator                           | Lorna Downie                | 126      | Site Investigator                           |
| Elisabeth Winnberg          | 118      | Site Investigator                           | Roisin Jack                 | 126      | Site Investigator                           |
| Stanislav Benaminov        | 119      | Site Investigator                           | Kirsty Matheson             | 126      | Site Investigator                           |
| Elisabeth Björnsson         | 119      | Site Investigator                           | Zosia Miedzybrodzka         | 126      | Site Investigator                           |
| Daniel Merrick              | 119      | Site Investigator                           | Daniela Rae                 | 126      | Site Investigator                           |
| Martin Paucar               | 119      | Site Investigator                           | Sheila A Simpson            | 126      | Site Investigator                           |
| Sven Pålhagen               | 119      | Site Investigator, REGISTRY Steering Committee | Fiona Summers             | 126      | Site Investigator                           |
| Per Svenningsson            | 119      | Site Investigator                           | Alexandra Ure               | 126      | Site Investigator                           |
| Name                     | Location | Contribution/Role                          | Name                     | Location | Contribution/Role                          |
|--------------------------|----------|--------------------------------------------|--------------------------|----------|--------------------------------------------|
| Vivien Vaughan           | 126      | Site Investigator                          | Sarah Hunt               | 132      | Site Investigator                          |
| Timothy Harrower         | 127,135  | Site Investigator                          | Lesley Jones             | 132      | Site Investigator                          |
| Nathan Vernon            | 127      | Site Investigator                          | Una Jones                | 132      | Site Investigator                          |
| Shahbana Akhtar          | 128      | Site Investigator                          | Hanan Khalil             | 132      | Site Investigator                          |
| Jenny Crooks             | 128      | Site Investigator                          | Sara Minster             | 132,163  | Site Investigator, Language Coordinator    |
| Adrienne Curtis          | 128      | Site Investigator                          | Michael Owen             | 132      | Site Investigator                          |
| Jenny de Souza (Keylock) | 128      | Site Investigator                          | Kathleen Price           | 132      | Site Investigator                          |
| John Piedad              | 128      | Site Investigator                          | Jenny Townhill           | 132,163  | Site Investigator, Language Coordinator    |
| Hugh Rickards            | 128      | Site Investigator                          | Anne Rosser              | 132      | Site Investigator                          |
| Jan Wright               | 128      | Site Investigator                          | David Goudie             | 133      | Site Investigator                          |
| Diane Haig-Brown         | 129,154  | Site Investigator                          | Lindsay Buchanan         | 133      | Site Investigator                          |
| Janet Craven             | 129,154  | Site Investigator                          | Paula McFadyen           | 133      | Site Investigator                          |
| Andrew Pallett           | 129      | Site Investigator                          | Alison Tonner            | 133      | Site Investigator                          |
| Steve Simpson            | 129,154  | Site Investigator                          | Anne-Marie Taylor        | 133      | Site Investigator                          |
| Rebecca Weekes           | 129,154  | Site Investigator                          | Maureen Edwards          | 134      | Site Investigator                          |
| Elizabeth Coulthard      | 130      | Site Investigator                          | Carrie Ho (Scottish      | 134      | Site Investigator                          |
| Louise Gethin            | 130      | Site Investigator                          | Marie McGill             | 134      | Site Investigator                          |
| Beverley Hayward         | 130      | Site Investigator                          | Mary Porteous            | 134      | Site Investigator                          |
| Kasia Sieradzan          | 130      | Site Investigator                          | Pauline Pearson          | 134      | Site Investigator                          |
| Abigail Wright           | 130,163  | Site Investigator, Language Coordinator    | Sarah Irvine             | 135      | Site Investigator                          |
| Roger A. Barker          | 131      | Site Investigator                          | Peter Brockie            | 136      | Site Investigator                          |
| Deidre O’Keefe           | 131      | Site Investigator                          | Jillian Foster           | 136      | Site Investigator                          |
| Anna Gerritz (nee Di Pietro) | 131  | Site Investigator                          | Nicola Johns             | 136      | Site Investigator                          |
| Kate Fisher              | 131      | Site Investigator                          | Sue McKenzie             | 136      | Site Investigator                          |
| Anna Goodman             | 131      | Site Investigator                          | Jean Rothery             | 136      | Site Investigator                          |
| Susan Hill               | 131      | Site Investigator                          | Gareth Thomas            | 136      | Site Investigator                          |
| Sarah Mason              | 131      | Site Investigator                          | Shona Yates              | 136      | Site Investigator                          |
| Rachel Swain             | 131      | Site Investigator                          | Christian Neumann       | 137      | Site Investigator                          |
| Natalie Valle Guzman     | 131      | Site Investigator                          | Kirsten Patterson        | 137      | Site Investigator                          |
| Jonathan Bisson          | 132      | Site Investigator                          | David Thomson            | 137      | Site Investigator                          |
| Monica Busse             | 132      | Site Investigator                          | Catherine Deith          | 138      | Site Investigator                          |
| Cynthia Butcher          | 132      | Site Investigator                          | Jane Ireland             | 138      | Site Investigator                          |
| Jenny Callaghan          | 132,149  | Site Investigator, Language Coordinator    | Stuart Ritchie           | 138      | Site Investigator                          |
| Rebecca Cousins          | 132      | Site Investigator                          | Pauline Brown            | 139      | Site Investigator                          |
| Stephen Dunnett          | 132      | Site Investigator, REGISTRY Steering       | Liz Burrows              | 139      | Site Investigator                          |
| Catherine Clenaghan      | 132      | Site Investigator                          | Amy Fletcher             | 139      | Site Investigator                          |
| Ruth Fullam              | 132,149  | Site Investigator, Language Coordinator    | Alison Harding           | 139      | Site Investigator                          |
| Name                  | Location | Contribution/Role          | Name                  | Location | Contribution/Role          |
|-----------------------|----------|----------------------------|-----------------------|----------|----------------------------|
| Kaye Harrison         | 139      | Site Investigator          | Charlotte Eddy        | 145      | Site Investigator          |
| Fiona Laver           | 139      | Site Investigator          | Nayana Lahiri         | 145,147  | Site Investigator          |
| Mark Silva            | 139      | Site Investigator          | Meriel McEntagart     | 145      | Site Investigator          |
| Aileen Thomson        | 139      | Site Investigator          | Michael Patton        | 145      | Site Investigator          |
| Carol Chu             | 140      | Site Investigator          | Maria Peterson        | 145      | Site Investigator          |
| Carole Evans          | 140      | Site Investigator          | Sarah Rose            | 145      | Site Investigator          |
| Deena Gallentree      | 140      | Site Investigator          | Thomasin Andrews      | 146,147  | Site Investigator          |
| Stephanie Harmer      | 140,142  | Site Investigator          | Andrew Dougherty      | 146      | Site Investigator          |
| Alison Kraus          | 140,142  | Site Investigator          | Charlotte Golding     | 146,147  | Site Investigator          |
| Ivana Markova         | 140,142  | Site Investigator          | Fred Kavalier         | 146      | Site Investigator          |
| Ashok Raman           | 140,142  | Site Investigator          | Hana Laing            | 146      | Site Investigator          |
| Liz Rowett            | 140,142  | Site Investigator          | Alison Lashwood       | 146      | Site Investigator          |
| Alyson Andrew         | 141      | Site Investigator          | Dene Robertson        | 146      | Site Investigator          |
| Julie Frost           | 141      | Site Investigator          | Deborah Ruddy         | 146      | Site Investigator          |
| Rupert Noad           | 141      | Site Investigator          | Alastair Sanhouse     | 146      | Site Investigator          |
| Jeremy Cosgrove       | 142      | Site Investigator          | Anna Whaithe          | 146      | Site Investigator          |
| Deena Gallantree      | 142      | Site Investigator          | Stefanie Gosling (nee Brown) | 147 | Site Investigator          |
| Emma Hobson           | 142      | Site Investigator          | Stefania Bruno        | 147      | Site Investigator          |
| Stuart Jamieson       | 142      | Site Investigator          | Elvina Chu            | 147,151  | Site Investigator          |
| Mandy Longthorpe      | 142      | Site Investigator          | Karen Doherty         | 147      | Site Investigator          |
| Hannah Musgrave       | 142      | Site Investigator          | Salman Haider         | 147      | Site Investigator          |
| Caroline Peacy        | 142      | Site Investigator          | Davina Hensman        | 147      | Site Investigator          |
| Jean Toscano          | 142      | Site Investigator          | Monica Lewis          | 147      | Site Investigator          |
| Sue Wild              | 142      | Site Investigator          | Marianne Novak        | 147      | Site Investigator          |
| Pam Yardumian         | 142      | Site Investigator          | Aakta Patel           | 147      | Site Investigator          |
| Carole Clayton        | 143      | Site Investigator          | Nicola Robertson      | 147      | Site Investigator          |
| Heather Dipple        | 143      | Site Investigator          | Elisabeth Rosser      | 147      | Site Investigator          |
| Dawn Freire-Patino    | 143      | Site Investigator          | Sarah Tabrizi         | 147      | Site Investigator          |
| Caroline Hallam       | 143      | Site Investigator          | Rachel Taylor         | 147      | Site Investigator          |
| Julia Middleton       | 143      | Site Investigator          | Thomas Warner         | 147      | Site Investigator          |
| Sundus Alusi          | 144      | Site Investigator          | Edward Wild           | 147      | Site Investigator          |
| Rhys Davies           | 144      | Site Investigator          | Oda Ackermann         | 148      | Site Investigator          |
| Kevin Foy             | 144      | Site Investigator          | Sophie Duport         | 148      | Site Investigator          |
| Emily Gerrans         | 144      | Site Investigator          | Adrienne Scott        | 148      | Site Investigator          |
| Louise Pate           | 144      | Site Investigator          | Nicholas Stoy         | 148      | Site Investigator          |
| Urju Anjum            | 145      | Site Investigator          | Jenny Vaughn          | 148      | Site Investigator          |
| Jan Coebergh          | 145      | Site Investigator          | Natalie Arran         | 149      | Site Investigator          |

Additional information on: Site, Investigator, REGISTRY Steering Committee.
| Name                  | Location | Contribution/Role                             | Name                  | Location | Contribution/Role                             |
|-----------------------|----------|-----------------------------------------------|-----------------------|----------|-----------------------------------------------|
| Judith Bek            | 149      | Site Investigator                             | Kathryn Dixon         | 152,156  | Site Investigator                             |
| David Craufurd        | 149      | Site Investigator                             | Richard Armstrong     | 152,156  | Site Investigator                             |
| Marianne Hare         | 149,155  | Site Investigator                             | David Harrison        | 153      | Site Investigator                             |
| Liz Howard            | 149      | Site Investigator                             | Max Hughes            | 153      | Site Investigator                             |
| Susan Huson           | 149      | Site Investigator                             | Sandra Large          | 153      | Site Investigator                             |
| Liz Johnson           | 149      | Site Investigator                             | John O Donovan        | 153      | Site Investigator                             |
| Mary Jones            | 149      | Site Investigator                             | Amy Palmer            | 153      | Site Investigator                             |
| Ashok Krishnamoorthy  | 149      | Site Investigator                             | Andrew Parkinson      | 153      | Site Investigator                             |
| Helen Murphy          | 149      | Site Investigator                             | Beverley Soltsysiak   | 153      | Site Investigator                             |
| Emma Oughton          | 149      | Site Investigator                             | Leanne Timings        | 153      | Site Investigator                             |
| Lucy Partington-Jones | 149      | Site Investigator, Language Coordinator      | Josh Williams         | 153      | Site Investigator                             |
| Dawn Rogers           | 149,163  | Site Investigator, Language Coordinator      | John Burn             | 154      | Site Investigator                             |
| Andrea Sollom         | 149      | Site Investigator                             | Wendy Bailey          | 154      | Site Investigator                             |
| Julie Snowden         | 149      | Site Investigator                             | Caroline Coleman      | 154      | Site Investigator                             |
| Cheryl Stopford       | 149      | Site Investigator                             | Tahir Majeed          | 155      | Site Investigator                             |
| Jennifer Thompson     | 149      | Site Investigator                             | Nicola Verstraelen    | 155      | Site Investigator                             |
| Iris Trender-Gerhard  | 149      | Site Investigator                             | Wendy Barrett         | 156      | Site Investigator                             |
| Nichola Verstraelen   | 149      | Site Investigator                             | Aileen Ho             | 156      | Site Investigator                             |
| (formerly Ritchie)    |          |                                               |                      |          |                                               |
| Leann Westmoreland    | 149      | Site Investigator                             | Oliver Bandmann       | 157      | Site Investigator                             |
| Ginette Cass          | 150      | Site Investigator                             | Alyson Bradbury       | 157      | Site Investigator                             |
| Lynn Davidson         | 150      | Site Investigator                             | Helen Fairtlough      | 157      | Site Investigator                             |
| Jill Davison          | 150      | Site Investigator                             | Kay Fillingham        | 157      | Site Investigator                             |
| Neil Fullerton        | 150      | Site Investigator                             | Isabella Foustanos    | 157      | Site Investigator                             |
| Katrina Holmes        | 150      | Site Investigator                             | Paul Gill             | 157      | Site Investigator                             |
| Suresh Komati         | 150      | Site Investigator                             | Mbombe Kazoka         | 157      | Site Investigator                             |
| Sharon McDonnell      | 150      | Site Investigator                             | Kirsty O’Donovan      | 157      | Site Investigator                             |
| Zeid Mohammed         | 150      | Site Investigator                             | Louise Nevitt         | 157      | Site Investigator, Language Coordinator      |
| Karen Morgan          | 150      | Site Investigator                             | Nadia Peppa           | 157,163  | Site Investigator, REGISTRY Steering Committee |
| Lois Savage           | 150      | Site Investigator                             | Oliver Quarrell       | 157      | Site Investigator                             |
| Baldev Singh          | 150      | Site Investigator                             | Cat Taylor            | 157      | Site Investigator                             |
| Josh Wood             | 150      | Site Investigator                             | Katherine Tidswell     | 157      | Site Investigator                             |
| Caroline Knight       | 151      | Site Investigator                             | Christopher Kipps     | 158      | Site Investigator                             |
| Mari O’Neill          | 151      | Site Investigator                             | Lesley MacKinnon      | 158      | Site Investigator                             |
| Debasish Das Purkayastha | 151    | Site Investigator                             | Veena Agarwal         | 158      | Site Investigator                             |
| Andrea H Nemeth       | 152      | Site Investigator                             | Elaine Hayward        | 158      | Site Investigator                             |
| Gill Siuda            | 152      | Site Investigator                             | Kerry Gunner          | 158      | Site Investigator                             |
| Ruth Valentine        | 152      | Site Investigator                             | Kayla Harris          | 158      | Site Investigator                             |
| Name                  | Location | Contribution/Role                          | Name                  | Location | Contribution/Role                          |
|-----------------------|----------|--------------------------------------------|-----------------------|----------|--------------------------------------------|
| Mary Anderson         | 158      | Site Investigator                          | Tim McLean           | 163      | Site Investigator, REGISTRY Steering Committee |
| Melanie Heywood       | 158      | Site Investigator                          | Susana Pro Koivisto  | 163,167  | Site Investigator, REGISTRY Steering Committee, Language Coordinator |
| Liane Keys            | 158      | Site Investigator                          | Markku Päiväranta    | 168      | Site Investigator, REGISTRY Steering Committee |
| Sarah Smalliey        | 158      | Site Investigator                          | Tereza Uhrova        | 169      | Site Investigator, REGISTRY Steering Committee |
| George El-Nimr        | 159      | Site Investigator                          | Verena Baake (formerly Rödig) | 163      | Language Coordinator, Site Investigator, Language Coordinator |
| Allison Duffell       | 159      | Site Investigator                          | Katrin Barth         | 163      | Language Coordinator, Site Investigator, Language Coordinator |
| Sue Wood              | 159      | Site Investigator                          | Monica Bascuñana Garde | 163      | Language Coordinator, Site Investigator, Language Coordinator |
| Karen Kennedy (nee Smith) | 159 | Site Investigator                          | Kristina Becanovic   | 163      | Language Coordinator, Site Investigator, Language Coordinator |
| Lesley Gowers         | 160      | Site Investigator                          | Tomáš Bernard        | 163      | Language Coordinator, Site Investigator, Language Coordinator |
| Kingsley Powell       | 160      | Site Investigator                          | Sabrina Betz         | 163      | Language Coordinator, Site Investigator, Language Coordinator |
| Pamela Bethwaite      | 160      | Site Investigator                          | Adrien Come          | 163      | Language Coordinator, Site Investigator, Language Coordinator |
| Rachel Edwards        | 160      | Site Investigator                          | Selene Capodarca     | 163      | Language Coordinator, Site Investigator, Language Coordinator |
| Kathleen Fuller       | 160      | Site Investigator                          | Sébastien Charpentier| 163      | Language Coordinator, Site Investigator, Language Coordinator |
| Michelle Phillips     | 160      | Site Investigator                          | Wildson Vieira da Silva | 163      | Language Coordinator, Site Investigator, Language Coordinator |
| Louis Tan             | 161      | Site Investigator                          | Martina Di Renzo     | 163      | Language Coordinator, Site Investigator, Language Coordinator |
| Puay Ngoh Lau         | 161      | Site Investigator                          | Ana Maria Finisterra | 163      | Language Coordinator, Site Investigator, Language Coordinator |
| Emmanuel Pica         | 161      | Site Investigator                          | Camille Genoves      | 163      | Language Coordinator, Site Investigator, Language Coordinator |
| Ida Biunno            | 162      | Site Investigator, REGISTRY Steering Committee | Mette Gilling        | 163      | Language Coordinator, Site Investigator, Language Coordinator |
| Juliana Bronzova      | 163      | Site Investigator, REGISTRY Steering Committee | Olivia J Handley    | 163      | Language Coordinator, Site Investigator, Language Coordinator |
| Joe Giuliano          | 164      | Site Investigator, REGISTRY Steering Committee | Carina Hvalstedt    | 163      | Language Coordinator, Site Investigator, Language Coordinator |
| Olivia J. Handley     | 163      | Site Investigator, REGISTRY Steering Committee | Hasina Hussain      | 163      | Language Coordinator, Site Investigator, Language Coordinator |
| Torsten Illmann       | 165      | Site Investigator, REGISTRY Steering Committee | Kerstin Koppers     | 163      | Language Coordinator, Site Investigator, Language Coordinator |
| Jamie Levey           | 163      | Site Investigator, REGISTRY Steering Committee | Claudia Lamanna     | 163      | Language Coordinator, Site Investigator, Language Coordinator |
| Name                                      | Location | Contribution/Role                  |
|------------------------------------------|----------|-----------------------------------|
| Matilde Laurà                           | 163      | Site Investigator, Language Coordinator |
| Kristina Münkel                         | 163      | Site Investigator, Language Coordinator |
| Lisanne Mütze                           | 163      | Site Investigator, Language Coordinator |
| Martin Oehmen                            | 163      | Site Investigator, Language Coordinator |
| Helene Padieu                           | 163      | Site Investigator, Language Coordinator |
| Laurent Paterski                        | 163      | Site Investigator, Language Coordinator |
| Beate Rindal                            | 163      | Site Investigator, Language Coordinator |
| Niini Raren (formerly Heinonen)         | 163      | Site Investigator, Language Coordinator |
| Ana Salgueiro                           | 163      | Site Investigator, Language Coordinator |
| Pavla Šašinková                         | 163      | Site Investigator, Language Coordinator |
| Catherine Taylor                        | 163      | Site Investigator, Language Coordinator |
| Erika Timewell                          | 163      | Site Investigator, Language Coordinator |
| Marleen R van Walsem                    | 163      | Site Investigator, Language Coordinator |
| Marie-Noelle Witjes-Ané                 | 163      | Site Investigator, Language Coordinator |
| Daniel Zielonka                         | 163      | Site Investigator, Language Coordinator |
| Eugeniusz Zielonka                      | 163      | Site Investigator, Language Coordinator |

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101: Fuenlabrada (Hospital Universitario), Spain
102: Granada (Hospital Universitario San Cecilio, Neurología), Spain
103: Madrid-BTCIEN (Fundación CIEN), Spain
104: Madrid-Clínico (Hospital Clínico Universitario San Carlos), Spain
105: Madrid RYC (Hospital Ramón y Cajal, Neurología), Spain
106: Madrid FJD (Madrid-Fundación Jiménez Díaz), Spain
107: Murcia (Hospital Universitario Virgen de la Arrixaca), Spain
108: Oviedo (Hospital Central de Asturias), Spain
109: Palma de Mallorca (Hospital Universitario Son Espases), Spain
110: Pamplona (Complejo Hospitalario de Navarra), Spain
111: Sevilla (Hospital Universitario Virgen del Rocío), Spain
112: Sevilla (Hospital Virgen Macarena), Spain
113: Sevilla (Residencia Santa Ana), Spain
114: Valencia (Hospital la Fe), Spain
115: Zaragoza (Hospital Clinico), Spain
116: Göteborg (Sahlgrenska University Hospital), Sweden
117: Lund (Dept Neurology, Skånes University Hospital), Sweden
118: Stockholm-Ersta, Sweden
119: Stockholm Karolinska University Hospital, Sweden
120: Umeå (Umeå University Hospital), Sweden
121: Uppsala University Hospital, Sweden
122: Bern (Swiss HD Zentrum), Switzerland
123: Bern (Zentrum für Bewegungsstörungen, Neurologische Klinik und Poliklinik, Universität Bern), Switzerland
124: Lausanne, Switzerland
125: Zürich (University Hospital and University of Zurich), Switzerland
126: Aberdeen (NHS Grampian Clinical Genetics Centre & University of Aberdeen), UK
127: Barnstaple, UK
128: Birmingham (The Barberry Centre, Dept of Psychiatry), UK
129: Blanford Forum, UK
130: Bristol (North Bristol NHS Trust, Southmead hospital), UK
131: Cambridge (Cambridge Centre for Brain Repair, Forvie Site), UK
132: Cardiff (Schools of Medicine and Biosciences, Cardiff University), UK
133: Dundee (Scottish Huntington's Association, Ninewells Hospital), UK
134: Edinburgh (SE Scotland Genetic Service, Western General Hospital), UK
135: Exeter (Department of Neurology Royal Devon and Exeter Foundation Trust Hospital), UK
136: Fife (Scottish Huntington's Association Whyteman's Brae Hospital), UK
137: Forth Valley (Neurology Department, Forth Valley Royal Hospital), UK
138: Gloucester (Department of Neurology Gloucestershire Royal Hospital), UK
139: Exeter (Department of Neurology Royal Devon and Exeter Foundation Trust Hospital), UK
140: Hull (Castle Hill Hospital), UK
141: Launceston (Millaton Court), UK
142: Leeds (Chapel Allerton Hospital, Department of Clinical Genetics), UK
143: Leicester (Leicestershire Partnership Trust, Mill Lodge), UK
144: Liverpool (Walton Centre for Neurology and Neurosurgery), UK
145: London (St. Georges-Hospital), UK
146: London (Guy's Hospital), UK
147: London (The National Hospital for Neurology and Neurosurgery), UK
148: London (Royal Hospital for Neuro-disability), UK
149: Manchester (Genetic Medicine, University of Manchester, Manchester Academic Health Sciences Centre and Central Manchester University Hospitals NHS Foundation Trust), UK
150: Newcastle-upon-Tyne (Centre for Life, Institute of Medical Genetics), UK
151: Northampton (St Andrew's Healthcare), UK
152: Oxford (Oxford University Hospitals NHS Trust, Dept. of Neurosciences, University of Oxford), UK
153: Plymouth (Plymouth Huntington Disease Service, Mount Gould Hospital), UK
154: Poole (Brain Injury Service, Poole Hospital), UK
155: Preston (Neurology Department, Preston Royal Hospital), UK
156: Reading (Royal Berkshire Hospital), UK
157: Sheffield (The Royal Hallamshire Hospital – Sheffield Children’s Hospital), UK
158: Southampton (Southampton General Hospital), UK
159: Stoke on Trent (Bucknall Hospital), UK
160: Swindon (Victoria Centre, Great Western Hospital), UK
161: EHDN’s associate site in Singapore: National Neuroscience Institute Singapore,
162: Institute for Genetic and Biomedical Research, University of Milan, Italy
163: European Huntington's Disease Network (EHDN), Ulm, Germany,
164: CHDI Foundation, Inc., New York, USA
165: 2mt Software GmbH, Ulm, Germany
166: Clinic of Neurology, Charles University and General Teaching Hospital, Prague, Czech Republic,
Czech Republic
167: Center for Rare Disorders, Oslo University Hospital HF, Rikshospitalet, Norway
168: Department of Neurology, Turku University Hospital, Turku, Finland
169: Clinic of Psychiatry, Charles University and General Teaching Hospital, Prague, Czech Republic
### Appendix 3 – Huntington’s disease clinical characteristics questionnaire (HD-CCQ) questions

| Symptom                                | Question                                                                                                                                 |
|-----------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------|
| Motor                                   | Have motor symptoms ever been a part of the subject’s medical history? At what age did the subject’s motor symptoms begin?                  |
| Cognitive                               | Has significant cognitive impairment (severe enough to impact on work or activities of daily living) or dementia ever been a part of the subject’s medical history? At what age did cognitive impairment first start to have an impact on daily life? |
| Apathy                                  | Has apathy ever been a part of the subject's medical history? At what age did apathy begin?                                               |
| Depression                              | Has depression (includes treatment with antidepressants with or without a formally-stated diagnosis of depression) ever been a part of the subject’s medical history? At what age did the depression begin? |
| Perseverative/obsessive behaviours (POB)| Has perseverative/obsessive behaviours ever been a part of the subject's medical history? At what age did perseverative/obsessive behaviour begin? |
| Irritability                            | Has irritability ever been a part of the subject's medical history? At what age did the irritability begin?                                 |
| Violent or aggressive behaviour (VAB)   | Has violent or aggressive behaviour ever been a part of the subject’s medical history? At what age did violent or aggressive behaviour begin? |
| Psychosis                               | Has psychosis (hallucinations or delusions) ever been a part of the subject’s medical history? At what age did psychosis (hallucinations or delusions) begin? |

Questionnaire taken from the European Huntington’s Disease Network’s (EHDN) data dictionary for Registry (Version 3).
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Table 1. Association of validated clinical scores with the HD Clinical Characteristics Questionnaire symptoms (shown in italics), and other covariates. For binary covariates (CCQ symptoms and sex) “effect” is the increase/decrease in the clinical score associated with presence of that covariate. For quantitative covariates (age, CAG, duration), “effect” is the change in clinical score associated with an increase of one unit in the covariate. In addition to having a confirmed onset and pathogenic CAG length (36-93), individuals must have no co-morbid diagnosis of schizophrenia, schizotypy or schizoaffective disorder. Significant associations after Bonferroni correction for 4 phenotypes and 12 covariates are shown in bold ($P < 1.04 \times 10^{-3}$) and nominally significant $P$ values are italicised ($P < 0.05$). CI: confidence interval; TDS: Total depression score from the Hospital Anxiety and Depression Scale; TIS: Total irritability score from Snaith’s irritability scale; SDMT: Symbol digits modalities test; POB: perseverative/obsessive behaviour; VAB: violent or aggressive behaviour; Sex (F): female.
### Table 2. Lifetime prevalence of motor and psychiatric symptoms in males and females with HD. Data from HD Clinical Characteristics Questionnaire at last recorded clinic visit in Registry. Chi-square ($c^2$) tests the difference between prevalence in males and females. Odds ratios (OR) >1 indicates the symptom is more common in females; odds ratios <1 indicates the symptom is more common in males. To be included, individuals must have a pathogenic CAG length (36-93) and confirmed clinical HD onset. Significant $P$ values in bold ($P < 6.25 \times 10^{-3}$, multiple testing correction). CI: confidence interval; POB: perseverative/obsessive behaviour; VAB: violent or aggressive behaviour.

|         | Males Yes | Males No | Males Frequency | Females Yes | Females No | Females Frequency | OR (95% CI) | $P$ value ($c^2$) |
|---------|-----------|----------|----------------|-------------|-------------|-------------------|-------------|-------------------|
| Motor   | 2691      | 28       | 98.97%         | 2859        | 25          | 99.13%           | 1.19 (0.69 - 2.05) | 5.29 x 10$^{-1}$ |
| Cognitive | 1584     | 1132     | 58.32%         | 1688        | 1187        | 58.71%           | 1.02 (0.91 - 1.13) | 7.66 x 10$^{-1}$ |
| Apathy  | 1456      | 1259     | 53.63%         | 1495        | 1374        | 52.11%           | 0.94 (0.85 - 1.05) | 2.56 x 10$^{-1}$ |
| Depression | 1582    | 1135     | 58.23%         | 2025        | 853         | 70.36%           | 1.70 (1.52 - 1.90) | 2.57 x 10$^{-21}$ |
| POB     | 1005      | 1711     | 37.00%         | 1038        | 1834        | 36.14%           | 0.96 (0.86 - 1.07) | 5.04 x 10$^{-1}$ |
| Irritability | 1706   | 1006     | 62.91%         | 1634        | 1240        | 56.85%           | 0.78 (0.70 - 0.87) | 4.03 x 10$^{-6}$ |
| VAB     | 947       | 1769     | 34.87%         | 777         | 2100        | 27.01%           | 0.69 (0.62 - 0.77) | 1.99 x 10$^{-10}$ |
| Psychosis | 319      | 2396     | 11.75%         | 325         | 2549        | 11.31%           | 0.96 (0.81 - 1.13) | 6.06 x 10$^{-1}$ |
Table 3. Variance in age at onset ($R^2$) explained by pathogenic CAG repeat length for eight symptoms in males and females with HD. Ages at onset were logarithmically transformed and plotted against CAG length. $P$ values test difference between male and female $R^2$. Significant $P$ values ($P < 6.25 \times 10^{-3}$; multiple testing correction) are in bold and nominally significant $P$ values ($P < 0.05$) italicised. Individuals had to have a clinical onset of HD, a known sex and a pathogenic CAG length (36-93) to be included. CI: confidence interval; POB: perseverative/obsessive behaviour; VAB: violent or aggressive behaviour.

| Symptom   | Male $R^2$ (95% CI) | N     | Female $R^2$ (95% CI) | N     | N     | $P$ | Both $R^2$ (95% CI) | N     |
|-----------|---------------------|-------|-----------------------|-------|-------|-----|---------------------|-------|
| Motor     | 0.678 (0.657 - 0.697) | 2684  | 0.649 (0.628 - 0.670) | 2844  |       | 5.42 x 10$^{-2}$ | 0.663 (0.648 - 0.677) | 5528  |
| Cognitive | 0.610 (0.579 - 0.639) | 1570  | 0.629 (0.600 - 0.656) | 1681  |       | 3.80 x 10$^{-1}$ | 0.619 (0.598 - 0.639) | 3251  |
| Apathy    | 0.595 (0.562 - 0.627) | 1423  | 0.562 (0.528 - 0.595) | 1462  |       | 1.83 x 10$^{-1}$ | 0.578 (0.554 - 0.601) | 2885  |
| Depression| 0.412 (0.374 - 0.449) | 1551  | 0.351 (0.318 - 0.385) | 1994  |       | 3.50 x 10$^{-2}$ | 0.375 (0.350 - 0.400) | 3545  |
| POB       | 0.539 (0.496 - 0.581) | 973   | 0.440 (0.394 - 0.485) | 1016  |       | 3.67 x 10$^{-3}$ | 0.489 (0.457 - 0.52)  | 1989   |
| Irritability | 0.463 (0.428 - 0.498) | 1670  | 0.547 (0.513 - 0.579) | 1601  |       | 1.25 x 10$^{-2}$ | 0.503 (0.478 - 0.527) | 3271  |
| VAB       | 0.401 (0.341 - 0.524) | 312   | 0.424 (0.426 - 0.528) | 318   |       | 7.29 x 10$^{-1}$ | 0.477 (0.442 - 0.511) | 1688   |
| Psychosis | (0.316 - 0.484)     |       | (0.340 - 0.504)     |       |       | (0.321 - 0.469) |       | 630     |
| Motor (N=1644) | Cognitive (N=1644) | Apathy (N=1643) |
|----------------|-------------------|----------------|
|                | OR (95% CI)       | P              | OR (95% CI)       | P              | OR (95% CI)       | P              |
| Sex (F)        | 0.49 (0.14 - 1.66) | 2.51 x 10⁻¹    | 1.20 (0.97 - 1.49) | 9.75 x 10⁻²    | 1.07 (0.87 - 1.31) | 5.13 x 10⁻¹    |
| CAG            | 0.95 (0.83 - 1.10) | 5.10 x 10⁻¹    | 1.01 (0.98 - 1.03) | 6.64 x 10⁻¹    | 0.99 (0.96 - 1.01) | 2.32 x 10⁻¹    |
| Duration       | 0.91 (0.82 - 1.01) | 8.32 x 10⁻²    | 1.00 (0.98 - 1.03) | 6.99 x 10⁻¹    | 1.00 (0.98 - 1.02) | 8.96 x 10⁻¹    |
| Alcohol        | 1.00 (0.93 - 1.08) | 9.61 x 10⁻¹    | 1.02 (1.01 - 1.04) | 8.78 x 10⁻³    | 1.00 (0.99 - 1.02) | 5.56 x 10⁻¹    |
| Tobacco        | 1.10 (0.96 - 1.26) | 1.54 x 10⁻¹    | 1.01 (0.99 - 1.02) | 3.00 x 10⁻¹    | 1.02 (1.00 - 1.03) | 4.94 x 10⁻²    |
| Education      | 0.89 (0.75 - 1.06) | 1.97 x 10⁻¹    | 1.01 (0.98 - 1.05) | 4.03 x 10⁻¹    | 0.98 (0.95 - 1.01) | 2.02 x 10⁻¹    |
| TFC            | 1.05 (0.75 - 1.46) | 7.85 x 10⁻¹    | 0.78 (0.74 - 0.81) | 1.58 x 10⁻²⁵   | 0.87 (0.84 - 0.91) | 1.14 x 10⁻⁴    |
| TMS            | 1.17 (1.08 - 1.27) | 7.81 x 10⁻⁵    | 1.00 (0.99 - 1.00) | 2.67 x 10⁻¹    | 1.00 (0.99 - 1.00) | 2.59 x 10⁻¹    |

| Depression (N=1645) | POB (N=1641) | Irritability (N=1645) |
|---------------------|-------------|-----------------------|
| OR (95% CI)         | P           | OR (95% CI)           | P           | OR (95% CI)       | P           |
| Sex (F)             | 1.77 (1.44 - 2.17) | 6.98 x 10⁻⁸        | 1.07 (0.86 - 1.32) | 5.68 x 10⁻¹    | 0.75 (0.61 - 0.92) | 5.36 x 10⁻²    |
| CAG                 | 0.96 (0.93 - 0.98) | 1.32 x 10⁻⁴        | 1.00 (0.97 - 1.02) | 6.93 x 10⁻¹    | 0.99 (0.97 - 1.01) | 4.74 x 10⁻¹    |
| Duration            | 1.03 (1.01 - 1.05) | 1.10 x 10⁻²        | 1.03 (1.00 - 1.05) | 1.68 x 10⁻²    | 1.03 (1.01 - 1.05) | 6.84 x 10⁻²    |
| Alcohol             | 0.99 (0.98 - 1.01) | 2.66 x 10⁻¹        | 1.00 (0.99 - 1.02) | 5.14 x 10⁻¹    | 1.01 (0.99 - 1.02) | 4.79 x 10⁻¹    |
| Tobacco             | 1.02 (1.01 - 1.03) | 8.14 x 10⁻⁴        | 1.01 (1.00 - 1.02) | 2.04 x 10⁻¹    | 1.02 (1.01 - 1.03) | 1.02 x 10⁻⁴    |
| Education           | 0.99 (0.96 - 1.02) | 5.83 x 10⁻¹        | 1.00 (0.97 - 1.03) | 8.21 x 10⁻¹    | 1.00 (0.97 - 1.03) | 8.44 x 10⁻¹    |
| TFC                 | 0.90 (0.86 - 0.94) | 7.30 x 10⁻⁶        | 0.89 (0.85 - 0.93) | 1.10 x 10⁻⁶    | 0.93 (0.89 - 0.97) | 8.83 x 10⁻⁴    |
| TMS                 | 0.98 (0.98 - 0.99) | 2.59 x 10⁻⁶        | 0.99 (0.99 - 1.00) | 6.09 x 10⁻⁸    | 0.99 (0.98 - 1.00) | 7.48 x 10⁻²    |

| VAB (N=1645) | Psychosis (N=1642) |
|--------------|-------------------|
| OR (95% CI)  | P                 |
|--------------|-------------------|
| Sex (F)      | 0.75 (0.60 - 0.94) | 1.27 x 10⁻² | 0.81 (0.57 - 1.14) | 2.23 x 10⁻¹ |
| CAG          | 1.00 (0.98 - 1.02) | 9.42 x 10⁻¹ | 0.99 (0.95 - 1.02) | 4.84 x 10⁻¹ |
| Duration     | 1.04 (1.02 - 1.06) | 9.10 x 10⁻⁴ | 1.02 (0.98 - 1.05) | 3.47 x 10⁻¹ |
| Alcohol      | 1.00 (0.99 - 1.01) | 9.29 x 10⁻⁴ | 1.02 (1.00 - 1.04) | 3.35 x 10⁻² |
| Tobacco      | 1.02 (1.01 - 1.03) | 2.08 x 10⁻⁴ | 1.00 (0.98 - 1.02) | 8.38 x 10⁻¹ |
| Education    | 0.99 (0.95 - 1.02) | 3.69 x 10⁻¹ | 0.92 (0.88 - 0.97) | 2.24 x 10⁻³ |
| TFC          | 0.88 (0.84 - 0.93) | 2.07 x 10⁻⁷ | 0.83 (0.77 - 0.89) | 3.33 x 10⁻⁷ |
| TMS          | 0.99 (0.99 - 1.00) | 7.49 x 10⁻² | 0.99 (0.98 - 1.00) | 1.47 x 10⁻¹ |

**Table 4.** Psychiatric and cognitive symptoms are associated with reduced functional capacity. Multiple logistic regression using binary HD-CCQ data for 8 symptoms (0 = no symptom; 1 = reported symptom) and clinical covariates. Significant associations after Bonferroni correction for 8 symptoms and 8 covariates are shown in bold ($P < 7.81 \times 10^{-4}$) and nominally significant associations in italics ($P < 0.05$). With the exception of sex, the odds ratio (OR) indicates the effect on the outcome probability associated with an increase of one unit in the covariate. In addition to having a confirmed onset and pathogenic CAG length (36-93), individuals must have no co-morbid diagnosis of schizophrenia, schizotypy or schizoaffective disorder. CI: confidence interval; Sex (F): female; POB: perseverative/obsessive behaviour; TFC: total functional capacity; TMS: total motor score; VAB: violent or aggressive behaviour.
Figure 1. The initial manifestation of HD varies with age and CAG length. All included individuals had a pathogenic CAG length (36-93) and confirmed HD onset age determined by a rating clinician. (A) Frequency of different onset types in four age groups, chosen to show juvenile HD and then 20 year bins for clarity. Total N=6289; <20 years, N=188; 20-40 years, N=2216; 40-60 years, N=3276; >60 years, N=609. (B) Frequency of different onset types in six CAG length groups, chosen for clarity across the pathogenic range. Total N=6289; 36-39 CAG, N=156; 40-44 CAG, N=3813; 45-49 CAG, N=1735; 50-54 CAG, N=387; 55-59 CAG, N=97; >60 CAG, N=101.
Figure 2. The onsets of cognitive and psychiatric symptoms relative to motor onset in HD. The age at onset of motor symptoms was subtracted from the age at onset of each cognitive/psychiatric symptom when present. Timings of up to +/- 40 years relative to motor onset shown. Only individuals with a rater-confirmed age at onset and CAG length (36-93) were included. Data from HD-CCQ. (A) Cognitive impairment N=3225; (B) Apathy N=2852; (C) Depression N=3495; (D) Irritability N=3235.
Figure 3. Mean ages at onset for motor and psychiatric symptoms at different CAG repeat lengths. Shown are the mean symptom ages as recorded by the HD Clinical Characteristics Questionnaire for apathy (N = 2739), cognitive impairment (N = 3069), depression (N = 3399), irritability (N = 3117) and motor symptoms (N = 4889).
| A | Onset type | Total N | Motor  | Cognitive | Psychiatric | Oculomotor | Other | Mixed |
|---|------------|---------|--------|-----------|------------|------------|--------|-------|
| All | | 6289 | 50.66% | 8.17% | 22.42% | 0.22% | 1.10% | 17.43% |

| B | Onset type | Total N | Motor  | Cognitive | Psychiatric | Oculomotor | Other | Mixed |
|---|------------|---------|--------|-----------|------------|------------|--------|-------|
| <20 | | 188 | 24.47% | 21.81% | 28.19% | 0.53% | 3.19% | 21.81% |
| 20-40 | | 2216 | 46.12% | 8.12% | 26.17% | 0.23% | 0.99% | 18.37% |
| 40-60 | | 3276 | 51.89% | 7.69% | 21.58% | 0.24% | 1.19% | 17.40% |
| >60 | | 609 | 68.64% | 6.73% | 11.49% | 0.00% | 0.33% | 12.81% |

| C | Onset type | Total N | Motor  | Cognitive | Psychiatric | Oculomotor | Other | Mixed |
|---|------------|---------|--------|-----------|------------|------------|--------|-------|
| 36-39 | | 156 | 50.64% | 10.90% | 20.51% | 0.00% | 0.64% | 17.31% |
| 40-44 | | 3813 | 51.25% | 7.92% | 23.29% | 0.21% | 1.08% | 16.26% |
| 45-49 | | 1735 | 50.26% | 7.44% | 22.13% | 0.23% | 1.27% | 18.67% |
| 50-54 | | 387 | 52.20% | 8.53% | 18.86% | 0.26% | 0.26% | 19.90% |
| 55-59 | | 97 | 48.45% | 12.37% | 17.53% | 0.00% | 0.00% | 21.65% |
| >60 | | 101 | 31.68% | 20.79% | 15.84% | 0.99% | 3.96% | 26.73% |

**Table e-1.** The initial manifestation of HD varies by age and CAG length. All included individuals had a pathogenic CAG length (36-93) and confirmed HD onset age determined by a rating clinician. (A) Percentage of different onset types in all individuals. (B) Percentage of different onset types observed in four age groups. (C) Percentage of different onset types observed across six CAG groups. These data are plotted in Fig. 1A-B.
| A | Motor | Cognitive | Psychiatric |
|---|---|---|---|
| **OR (95% CI)** | **P** | **OR (95% CI)** | **P** | **OR (95% CI)** | **P** |
| **Age at onset** | 1.06 (1.04-1.07) | **7.44 x 10^{-22}** | 0.99 (0.99-1.00) | **3.59 x 10^{-2}** | 0.96 (0.95-0.97) | **9.41 x 10^{-16}** |

| Oculomotor | Other | Mixed |
|---|---|---|
| **OR (95% CI)** | **P** | **OR (95% CI)** | **P** | **OR (95% CI)** | **P** |
| **Age at onset** | 1.00 (1.00-1.00) | **6.06 x 10^{-1}** | 1.00 (1.00-1.00) | **6.55 x 10^{-1}** | 0.99 (0.98-1.00) | **2.94 x 10^{-2}** |

| B | Motor | Cognitive | Psychiatric |
|---|---|---|---|
| **OR (95% CI)** | **P** | **OR (95% CI)** | **P** | **OR (95% CI)** | **P** |
| **CAG** | 1.00 (0.96-1.04) | **9.67 x 10^{-1}** | 1.00 (0.98-1.02) | **8.05 x 10^{-1}** | 0.96 (0.93-0.99) | **1.97 x 10^{-2}** |

| Oculomotor | Other | Mixed |
|---|---|---|
| **OR (95% CI)** | **P** | **OR (95% CI)** | **P** | **OR (95% CI)** | **P** |
| **CAG** | 1.00 (1.00-1.00) | **7.93 x 10^{-1}** | 1.00 (0.99-1.01) | **6.07 x 10^{-1}** | 1.01 (0.99-1.04) | **9.98 x 10^{-3}** |

**Table e-2.** Age at onset, but not CAG length, is associated with initial manifestation type in adult-onset HD. (A) Logistic regression of initial manifestation as recorded by the clinician, coded as binary variables (1: initial manifestation of that type, 0: initial manifestation of any other type) on age at onset. (B) Logistic regression of initial manifestation (defined as a binary variable, as above) on CAG length. Significant associations after Bonferroni correction for 12 models are shown in bold ($P < 4.17 \times 10^{-3}$) and nominally significant associations in italics ($P < 0.05$). The odds ratio (OR) indicates the effect on the outcome probability associated with an increase of ten years in age. Only individuals with a confirmed onset ≥20 years, CAG 36-59 and no schizophrenia co-morbidity (ICD-10 F20, F21 or F25) were included. N=6051 for both sets of models. CI: confidence interval.
### Table e-3.

The CAG repeat length of the pathogenic \textit{HTT} allele, but not the wild-type \textit{HTT} allele, is associated with the presence of motor and psychiatric symptoms in HD. Logistic regression of binary symptom data (lifetime prevalence; 0 = no symptom, 1 = reported symptom) on expanded (36-93 CAGs) and wild-type (6-35 CAGs) repeat lengths, with an interaction term. Significant associations are in bold ($P < 2.08 \times 10^{-3}$, correcting for number of covariates and phenotypes), and nominal associations italicised ($P < 0.05$). The odds ratio (OR) indicates the effect on the outcome probability associated with an increase of one unit in the covariate. In addition to having a confirmed onset and pathogenic CAG length, to be included individuals must have a known sex and no co-morbid diagnosis of schizophrenia, schizotypy or schizoaffective disorder. CI: confidence interval; POB: perseverative/obsessive behaviour; VAB: violent or aggressive behaviour.
|                        | Depressed mood (N=1721) | Suicidal ideation (N=1708) | Anxiety (N=1717) | Irritability (N=1727) |
|------------------------|-------------------------|-----------------------------|------------------|----------------------|
| **Effect**             | **(95% CI)**            | **Effect**                  | **(95% CI)**     | **Effect**           |
| **Motor**              | -0.18 (±0.03)           | -0.09 (±0.02)               | -0.02 (±0.01)    | -0.04 (±0.02)        |
| **Cognitive**          | 0.35 (±0.03)            | 0.84 (±0.04)                | 0.60 (±0.03)     | 0.58 (±0.04)         |
| **Apathy**             | 0.22 (±0.03)            | 3.30 (±0.4)                 | 0.54 (±0.04)     | 0.28 (±0.04)         |
| **Depression**         | 0.09 (±0.03)            | 0.58 (±0.03)                | 0.01 (±0.01)     | 0.02 (±0.02)         |
| **POB**                | 0.22 (±0.03)            | 1.63 X 10¹                  | 0.84 (±0.04)     | 0.90 (±0.04)         |
| **Irritability**       | 0.00 (±0.03)            | 9.88 X 10¹                  | 5.58 X 10⁻¹      | 5.58 X 10⁻¹          |
| **VAB**                | 0.05 (±0.03)            | 5.29 X 10⁻¹                 | 5.30 X 10⁻¹      | 5.30 X 10⁻¹          |
| **Psychosis**          | 0.05 (±0.03)            | 1.88 X 10⁻¹                 | 9.80 X 10⁻¹      | -0.06 (±0.05)        |
| **Age**                | -0.00 (±0.02)           | -0.01 (±0.01)               | -0.06 (±0.05)    | -0.04 (±0.02)        |
| **CAG**                | -0.01 (±0.04)           | -0.05 (±0.03)               | -0.07 (±0.05)    | -0.07 (±0.05)        |
| **Sex (F)**            | 0.01 (±0.02)            | -0.47 (±0.03)               | -0.12 (±0.03)    | -0.26 (±0.03)        |
| **Duration**           | 0.02 (±0.03)            | 0.05 (±0.04)                | 0.04 (±0.04)     | 0.04 (±0.03)         |

|                        | Angry or aggressive behaviour (N=1726) | Suicidal ideation (N=1719) | Perseverative thinking/behaviours (N=1722) | Obsessive compulsive behaviours (N=1711) |
|------------------------|----------------------------------------|------------------------------|----------------------------------------------|------------------------------------------|
| **Effect**             | **(95% CI)**                           | **Effect**                   | **(95% CI)**                                 | **Effect**                              |
| **Motor**              | 0.42 (±0.15)                           | 1.03 (±0.24)                 | 1.40 (±2.16)                                 | 0.69 (±1.71)                            |
| **Cognitive**          | 0.35 (±0.03)                           | 0.84 (±0.04)                 | 0.60 (±0.42)                                 | -0.02 (±0.33)                           |
| **Apathy**             | 0.22 (±0.03)                           | 3.30 (±0.4)                  | 0.43 (±0.43)                                 | 0.06 (±0.34)                            |
| **Depression**         | 0.00 (±0.03)                           | 0.58 (±0.03)                 | 0.54 (±0.42)                                 | 0.19 (±0.33)                            |
| **POB**                | 0.44 (±0.03)                           | 1.63 X 10¹                   | 0.84 (±0.4)                                  | 0.84 (±0.39)                            |
| **Irritability**       | 0.52 (±0.33)                           | 9.88 X 10¹                   | 5.30 X 10⁻¹                                  | 5.30 X 10⁻¹                             |
| **VAB**                | 1.51 (±0.34)                           | 1.88 X 10⁻¹                  | 9.80 X 10⁻¹                                  | 7.82 X 10⁻¹                             |
| **Psychosis**          | 0.21 (±0.04)                           | 3.63 X 10⁻¹                  | 5.30 X 10⁻¹                                  | 5.30 X 10⁻¹                             |
| **Age**                | -0.01 (±0.02)                          | 2.21 X 10⁻¹                  | 6.18 X 10⁻²                                  | 6.18 X 10⁻²                             |
| **CAG**                | -0.01 (±0.04)                          | 5.57 X 10⁻¹                  | 1.26 X 10⁻¹                                  | 1.26 X 10⁻¹                             |
| **Sex (F)**            | -0.01 (±0.02)                          | 9.47 X 10⁻¹                  | 3.45 X 10⁻²                                  | 3.45 X 10⁻²                             |
| **Duration**           | 0.02 (±0.03)                           | 1.75 X 10⁻¹                  | 1.84 X 10⁻²                                  | 1.84 X 10⁻²                             |
|                  | Delusions/paranoid thinking (N=1708) | Hallucinations (N=1710) | Disorientated behaviour (N=1701) |
|------------------|-------------------------------------|------------------------|----------------------------------|
| **Effect (95% CI)** | **P** | **Effect (95% CI)** | **P** | **Effect (95% CI)** | **P** |
| **Motor**        | 0.20 (±0.95) | 0.02 (±0.54) | 0.67 (±1.48) | 6.87x10^-1 | 9.31x10^-1 | 3.73x10^-1 |
| **Cognitive**    | 7.16x10^-1 | 8.22x10^-1 | 6.53x10^-4 | 0.01 (±0.10) | 9.44x10^-2 | 0.80 (±0.29) |
| **Apathy**       | 0.00 (±0.18) | 0.09 (±0.11) | 0.20 (±0.29) | 9.85x10^-1 | 9.44x10^-2 | 1.93x10^-1 |
| **Depression**   | 0.16 (±0.18) | 0.05 (±0.10) | 0.08 (±0.29) | 7.10x10^-2 | 3.97x10^-1 | 5.73x10^-1 |
| **POB**          | 0.03 (±0.18) | -0.04 (±0.10) | 0.45 (±0.29) | 7.35x10^-1 | 4.58x10^-1 | 2.13x10^-3 |
| **Irritability** | 0.11 (±0.19) | -0.10 (±0.11) | -0.21 (±0.31) | 2.42x10^-1 | 6.80x10^-2 | 1.79x10^-1 |
| **VAB**          | 0.00 (±0.20) | -0.01 (±0.12) | 0.59 (±0.32) | 9.94x10^-1 | 9.16x10^-1 | 3.44x10^-4 |
| **Psychosis**    | 1.19 (±0.26) | 0.81 (±0.15) | 0.68 (±0.42) | 5.56x10^-1 | 4.67x10^-2 | 1.60x10^-3 |
| **Age**          | -0.01 (±0.01) | 0.00 (±0.01) | 0.03 (±0.02) | 3.08x10^-1 | 5.61x10^-1 | 8.23x10^-4 |
| **CAG**          | -0.01 (±0.03) | 0.00 (±0.02) | 0.03 (±0.04) | 2.81x10^-1 | 6.33x10^-1 | 1.28x10^-1 |
| **Sex (F)**      | 0.07 (±0.16) | -0.08 (±0.09) | -0.07 (±0.26) | 4.19x10^-1 | 9.84x10^-2 | 5.75x10^-1 |
| **Duration**     | 0.02 (±0.02) | 0.00 (±0.01) | 0.05 (±0.03) | 2.81x10^-2 | 2.92x10^-1 | 2.92x10^-4 |

**Table e-4.** Scores for neuropsychiatric symptoms from the short-form Problem Behaviors Assessment questionnaire (PBA-s) correlate with specific responses from the HD clinical characteristics questionnaire (HD-CCQ). Generalised linear models regressed the product of the frequency and severity scores from PBA-s questions against binary lifetime prevalence data on 8 symptoms from the HD Clinical Characteristics Questionnaire (italics, column 1) and other covariates. For binary covariates (CCQ symptoms and sex) “effect” is the increase/decrease in the clinical score associated with presence of that covariate. For quantitative covariates (age, CAG, duration), “effect” is the change in clinical score associated with an increase of one unit in the covariate. In addition to having a confirmed onset and pathogenic CAG length (36-93), individuals must have no co-morbid diagnosis of schizophrenia, schizotypy or schizoaffective disorder. Significant associations after Bonferroni correction for 11 phenotypes and 12 covariates are shown in bold (P < 3.79 x 10^-4) and nominally significant P values are italicised (P < 0.05). CI: confidence interval; POB: perseverative/obsessive behaviour; VAB: violent or aggressive behaviour; Sex (F): female.
Figure e-1. Histogram of pure CAG repeat lengths against frequency for the Registry population analysed in this study. Shown are HTT CAG length frequencies for the largest pathogenic CAG (36-93) in individuals with clinical onset of HD (N=6316).
Figure e-2. The onsets of cognitive and psychiatric symptoms relative to motor onset in HD. The age at onset of motor symptoms was subtracted from the age at onset of each cognitive/psychiatric symptom when present. Timings of up to +/- 40 years relative to motor onset shown. Only individuals with a rater-confirmed age at onset and CAG length (36-93) were included. Data from HD-CCQ. (A) Perseverative/obsessive behaviour (POB) N=1973, skew = -1.54; (B) Violent or aggressive behaviour (VAB) N=1663, skew = -1.30; (C) Psychosis N=619, skew = -0.46. Only individuals with a known age at onset and CAG length (36-93) were included.