Characterisation of Depressive Symptoms in Huntington’s Disease and of the Pharmacological Treatment for Depression: patterns, trends and Statistical Analysis of Enroll-HD Dataset

Ilka Hatakeyama Morishima

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Declaration

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Ilka Hatakeyama Morishima
I would like to dedicate this entire work to my beloved husband, Jun, who was a constant source of support and always encouraged me to pursue my dreams. Thank you for making this possible and for being part of my life.
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Abbreviations

AD+BZD: combination of antidepressant and benzodiazepines
ANCOVA: Analysis of covariance
ANOVA: Analysis of variance
AP: antipsychotics
AP+AD+BZD: combination of antipsychotics, antidepressants and benzodiazepines
AP+BZD: combination of antipsychotics and benzodiazepines
ATC: Anatomical Therapeutic Chemical
BMI: Body mass index
BNF: British National Formulary
BZD: benzodiazepines
CAG repeats: trinucleotides cytosine, adenine, and guanine repetition
COBIT: Control Objectives for Information and Related Technologies
Comb_AD: combination of antidepressants
DSM-III: The Diagnostic and Statistical Manual of Mental Disorders
eCRFs: Electronic case report forms
EDC: Electronic data capture
FAS: Functional Assessment (UHDRS)
FDA: US Food and Drug Administration
GLM: Generalized linear model
GPC: Good Clinical Practice
HADS-SIS: Hospital Anxiety and Depression Scale Snaith Irritability Scale
HD: Huntington’s Disease
HDID: Key variable subjid, labelled as HDID (recoded)
HIPAA: Health Insurance Portability and Accountability Act
HTT: huntingtin gene
HX: History (of symptoms)
ICH: International Conference on Harmonisation
ICMJE: International Committee of Medical Journal Editors
ISO: International Organization for Standardization
LMM: Linear mixed model
MAOI: Monoamine oxidase inhibitors
MTA: Material Transfer Agreement
mHTT: Mutated huntingtin
MHx: Medical history
MMSE: Mini Mental State Examination
NDRI: Norepinephrine and dopamine reuptake inhibitors
NIST: National Institute of Standards and Technology
NMDA: N-Methyl-D-aspartate receptor (blockers)
NSAID: Non-steroidal anti-inflammatory drugs
PBA-s: Problem Behaviours Assessment
PCI DSS: Payment Card Industry Data Security Standard
PHI: Personal Health Information
QA: Quality assurance
QC: Quality control
RCTs: Randomized controlled trials
SARI: Serotonin antagonist and reuptake inhibitors
SC: Sydenham’s chorea
SNRI: Serotonin and norepinephrine reuptake inhibitors
SSRI: Selective Serotonin Reuptake Inhibitors
TFC: Total Functional Capacity (UHDRS)
UHDRS: United Huntington Disease Rating Scale
US – United States
USA: United States of America
WHO: World Health Organisation
WPAI: Work Productivity and Activity Impairment
Summary

Introduction: Huntington’s Disease (HD) is a rare autosomal dominant genetic disorder characterised by motor, psychiatric and cognitive symptoms. Amongst psychiatric manifestations of HD, depression affects patients frequently. It may appear several years prior to motor or cognitive manifestations and the impact on quality of life to both HD patients and their families is significant. Additionally, suicide attributable to depression has been identified in this group as a known cause of premature death. For this reason, it is essential that depression is efficiently diagnosed and treated in this population. Pharmacological treatment of depression is available for HD patients following the same approaches as those used for the general population, due to the lack of HD-specific guidance. Studies undertaken in HD usually involve small sample sizes and the variability in assessment methods and inclusion criteria in studies are also problematic. In recognition of these deficiencies, efforts have been made to collate data in a systematic fashion. Enroll-HD is an observational study aiming to collect information about HD worldwide and contribute to accelerate the discovery and development of new therapeutics.

Aim: This research aims to analyse the Enroll-HD datasets to describe the cohort composed by depressed individuals in Enroll-HD population, the use of evidence-based treatments for these patients and to identify factors that influence the depressive symptoms.

Methods: Data from Enroll-HD study is available to any verified researcher linked to a recognized research organization and was obtained in conjunction with Bloomfield Mental Health Services and Trinity College in order to perform this study. The information provided by Enroll-HD was de-identified and, therefore, ethical approval was not required. The cohort analysed in this research is composed of those HD and non-HD individuals within the Enroll-HD population who presented depressive symptoms and the criteria utilized to distinguish them was the HADS-Depression subscale with a cut-off of 6, based on literature review. This cohort is represented by both male and female, with no limitations regarding age, origin and background. The demographic features, as well as clinical characteristics were evaluated through the statistical methods of One-way ANOVA and the Chi-square test. The description of
the clinical practices that were being used to approach depression in this cohort was performed using a customized Excel tool. Changes in the depression scores over a period of 3 years were analysed by performing a mixed model statistic test. Lastly, the logistic regression method was utilized to identify elements related to improvements in the depression scores. Throughout this study, the HADS-Depression subscale was the chosen rating method to evaluate depression due to its recognised validity of use in the HD population and uncertainties in relation to the use of other scales such as the PBA. The SPSS Software version 26 was utilized to prepare and statistically analyse the data in this study.

Results: Within the Enroll-HD population 3,910 individuals were depressed. The initial evaluation demonstrated that the datasets provided by Enroll-HD contained adequate information for the purpose of this research. The prevalence of depression obtained among the Enroll-HD population (3,910 individuals) was 23.4%, which fits in the overall prevalence found in literature (15-69%). The description of the drug treatments showed differences in the prescribing patterns between affected and non-affected HD participants. In addition, it was highlighted the potential use of alternative drugs such as antipsychotics and their advantages to manage and optimize the treatment of symptoms in HD. The results of the mixed model showed that depression decreased over time and that suicidal ideation, alcohol abuse, anxiety and gender are possible factors linked with this process, which also corroborates with past research found in literature. Finally, a set of characteristics may be potentially linked with improvements in the depression scores: young HD individuals, with absence of involuntary movements and irritability are more likely to bring their depression scores to a better level (less depressed category according to the HADS-Depression).

Conclusion: Although this research was marked by difficulties finding evidence based and clinical guidelines targeting particularly the HD group, the evaluations captured unique and complex aspects of the use of pharmacological agents for the treatment of depression in HD as well as specific factors influencing depressive mood throughout the disease course. This study adds to the existing knowledge about depression in the context of HD and it is hoped that the findings serve the HD community as potential research paths for years to come.
1. Introduction

1.1 Overview

Huntington’s disease (HD) is an autosomal dominant inherited neurodegenerative disorder in which patients present progressive motor symptoms, psychiatric signs, and cognitive decline, resulting in premature mortality within 10-20 years after the onset of initial motor symptoms. Although it is possible for the disorder to manifest at any stage of patient’s life, it is commonly diagnosed in middle-age, between 40 and 60 years, based on the presence of positive family history, detected by genetic testing, as well as apparent and unexplained extrapyramidal motor signs (chorea) (Walker 2007, Beart et al. 2017).

1.2 History

It can be roughly said that the history of HD starts along with HD’s main symptom: chorea. The hyperkinetic movement disorder has its first reports dating from the Middle Ages, coinciding with the period of the Black Death, when many epidemics of both infectious and psychogenic (previously labelled as hysterical) chorea swept through Europe (Vale and Cardoso 2015). Individuals affected by the hysterical “dancing mania” would dance wildly in circles for hours until they dropped from exhaustion (Hecker and Babington 2004, Vale and Cardoso 2015). That would be the reason why to coin the term “chorea”, deriving from the Ancient Greek word “choreia”, that means dance (Vale and Cardoso 2015).

At the first years of the 16th century, Paracelsus (1493–1541) coined the term Chorea Sancti Viti to define the dancing mania and also classified their different forms: chorea imaginativa (arising from imagination), chorea lasciva (arising from sexual desire and associated with passionate excitement), and chorea naturalis (arising from physical or corporeal causes) (Park and Park 1990, Tupper and Dewey 2004, Vale and Cardoso 2015).

Conversely, Thomas Sydenham (1624–1689) studied one specific cause of chorea, which he believed was due to “some humour falling on the nerves, and such irritation causes the spasms” (Donaldson 2012). He contributed with a meticulous clinical description of acute chorea, which he named chorea minor, that later became known as Sydenham’s chorea (SC). From then on, regardless of its cause, the term chorea has been used to characterize
involuntary, purposeless, and rapid distal movements of the limbs (Donaldson 2012, Vale and Cardoso 2015).

In 1894, in his book “On chorea and choreiform affections”, William Osler (1849–1919) recognized chorea major as another important group of choreiform disorders and reported clinical and pathological data on 410 cases of SC treated in Philadelphia since 1876, noticing that SC is an infectious disorder frequently associated with endocarditis, particularly affecting the mitral valve (Goetz and Pappert 1996, Goetz 2000, Lanska 2010). William Richard Gowers (1845–1915) was also one of the pioneers in describing chorea as a syndrome and identifying different varieties and etiologist. After having treated more than 120 children in hospital with SC, he depicted various forms of chorea, one of which is called senile chorea, probably vascular or late-onset HD (Vale and Cardoso 2015).

In the so-called pre-George Huntington’s era, it is possible to find several studies describing disorders very likely to what the HD would have been, such as Charles Oscar Waters did in 1841 (Vale and Cardoso 2015). Even though others reported the condition of HD, it was George Huntington, in 1872, who related the most accurate characterization of the disease, which earned him the eponym “Huntington's disease” (HD), previously known as “Huntington's chorea”. Studying chorea and dementia patterns that ran in families in East Hampton, New York, USA, George Huntington was able to draw several conclusions regarding the disease features, such as its hereditary nature, the wreck of patient’s former self and tendency to insanity, and the certainty of gradual worsening of symptoms culminating in death.

1.3 Genetics

Huntington’s disease genetic mutation starts by an expanded repeat of a sequence of three DNA bases: cytosine-adenine-guanine (CAG), in the huntingtin gene (HTT), located on the short arm of chromosome 4 (van Duijn et al. 2007). HTT encodes for a mutant form of the multifunctional protein huntingtin, resulting in an unusual long polyglutamine sequence with toxic properties that cause dysfunction and damage to neurons (Bates et al. 2015). Non-affected individuals present, on average, 17 to 20 CAG repeats in the HTT gene, whereas patients with HD condition have 40 or more repeats, developing HD in full penetrance, leading to onset of motor signs (Walker 2007, Bates et al. 2015, Dayalu and Albin 2015). With repeats of 36 to 39, there is incomplete penetrance and less than 35 repeats are not associated with
the disorder, although a few exceptions reported symptoms in an intermediate range, from 27 to 35 repeats (Walker 2007, Bates et al. 2015, Dayalu and Albin 2015).

With regards to the manifestation of HD, men and women are affected equally (Dayalu and Albin 2015). However, 28 repeats or more of CAG may result in instability on replication, that increases the repeats and, consequently, the number changes on the following generations. This instability is more expressive in spermatogenesis than oogenesis, in those large expansions of CAG repeats on replication are more prone to happen in males (Trottier et al. 1994, Kremer et al. 1995, Ranen et al. 1995, Walker 2007). This shows a tendency of earlier age of onset and more severe symptoms in offspring, known as anticipation (Walker 2007, Dayalu and Albin 2015).

Accordingly, the hereditary nature of HD is clear. The inheritance means that each affected person usually has an affected parent, with the condition occurring in every generation (Genetic et al. 2009). Furthermore, the dominant characteristic needs only one present copy of the mutation to be expressed. In consequence, every individual who carries the copy of that mutation will have the disease (Genetic et al. 2009).

1.4 Neuropathology

The expansion of trinucleotide CAG in HD culminates in a mutant expression of the polyglutamic tract in the protein huntingtin (HTT). In ordinary amount, this protein is normally produced by neurons throughout the central nervous system (CNS) and has no significant effect or pathological consequence. In HD patients, the excessive size of the CAG tract encodes a long poly-glutamine (poly-Q) sequence, which is toxic and causes dysfunction and death of neurons (Bates et al. 2015).

With regards to the different regions of the brain that are affected, there is pattern to HD, and, despite the fact that deterioration has been identified in various parts of the brain, such as the neocortex, cerebellum, hippocampus, substantia nigra, and brainstem nuclei, major dysfunctions occur specifically in the neostriatum which includes the caudate nucleus and putamen (Goetz 2000, Frank and Jankovic 2010, Lee et al. 2012, Bates et al. 2015). These locations are known as a highly interconnected set of subcortical nuclei, thus, atrophy in one or more regions may cause major effects on the others and spiny neurons of this region seem to be more vulnerable to mutant HTT harm. The striatum receives projections from the entire
cortex and, once it is degenerated, the regions to which it targets, especially the globus pallidus and substantia nigra pars reticulata are also disturbed. Consequently, the highly variable nature of the degeneration in the brain appears to be directly related to the equally irregular range of symptoms in HD, especially in late stages of the disease (Goetz 2000, Frank and Jankovic 2010, Lee et al. 2012, Bates et al. 2015, Dayalu and Albin 2015).

1.5 Signs and symptoms

Symptoms of HD usually occur between the ages of 40 and 60 years, but some can become symptomatic in the range of 1-80 years. Symptoms are characterized by a triad of progressive motor, cognitive and psychiatric signs (Bates et al. 2015, Dayalu and Albin 2015, Ghosh and Tabrizi 2018).

Motor features include a wide variety of involuntary added movements, and chorea is the most remarkable one. It is defined as involuntary, dance-like hyperkinetic movement disorder, which are short-lived and can appear to be semi-purposeful (Gövert and Schneider 2013, Dayalu and Albin 2015, Ghosh and Tabrizi 2018). It can be easily recognized on the distal extremities and face, through fleeting, suppressible, random fidgety movements which spread and become larger in amplitude affecting larger and more proximal muscles (Ghosh and Tabrizi 2018). Different types of movements include facial muscle implication causing saccadic eye movement abnormalities, eye closure, head turning, and tongue protrusion, and involvement of axial muscles causes extension and arching of the back. As a result of chorea progress, it may cause problems with writing and eating, and frequently contributes to falling (Novak and Tabrizi 2010, Nguyen et al. 2016, Ghosh and Tabrizi 2018). Apart from chorea, patients with HD may show evidence of dystonia, which is characterized by slowness of movement, due to increased muscle tone and sustained muscle contractions, leading to atypical postures, like tilting or turning of the neck (torticollis) or arching of the back (opisthotonos) (Novak and Tabrizi 2010, Nguyen et al. 2016, Ghosh and Tabrizi 2018). As HD progresses, hyperkinetic movements diminish, whereas bradykinesia (slowness and reduced scaling of movement), akinesia (delay in initiating movement), and rigidity become more prominent (Novak and Tabrizi 2010, Nguyen et al. 2016). The deterioration of motor skills is a key factor to life-ending complications, as not only do patients have difficulties moving voluntary muscles, but also, they struggle with actions such as swallowing, which usually cause aspiration – noted as the principal cause of pneumonia leading to death (Heemskerk and Roos 2012).
The second element of the triad of symptoms in HD is cognitive decline, in which patients progressively fail to execute activities like organizing, planning, checking, searching for adaptive alternatives and learning new motor skills (Montoya et al. 2006, Walker 2007). With time, memory deficits also become more frequent and involve both short-term and long-term memories, including declarative memory (i.e., episodic memory, working memory) and procedural memory (i.e., implicit memory) (Redondo-Vergé 2001, Montoya et al. 2006). Corresponding to the other features in HD, cognitive decline worsens with time and ultimately dementia will result (Montoya et al. 2006). Dementia in HD, in contrast to Alzheimer dementia, is mainly subcortical and patients show that episodic memory and language function is better preserved than those with Alzheimer’s dementia (Dayalu and Albin 2015).

Finally, the last component of the triad is the psychiatric feature of HD. The main symptoms include obsessive-compulsive behaviours, irritability, outbursts and depression, from which 50% of patients suffer at the time of the disease. Moreover, patients with HD often present apathy, which is also common and causes loss of interest as well as passive behaviour. In contrast to depression, apathy is related to the disease stage (Bates et al. 2015, Dayalu and Albin 2015). These symptoms usually cause more distress to patients and their families than the motor impairment (Bates et al. 2015).

When it comes to HD, it is important to highlight the fact that the diagnosis is made when patients develop extrapyramidal motor symptoms, such as chorea. However, studies have reported that the vast majority of patients, at the point of showing motor signs, had already exhibited psychiatric and cognitive manifestation in the past. This shows that the disease can express itself in an imperceptibly way during the pre-diagnostic period before more apparent and obvious signs, which can be called prodromal phase of HD (Tabrizi et al. 2012, Bates et al. 2015, Dayalu and Albin 2015). The prodromal phase can be associated with the loss of corticostriatal connectivity and striatal atrophy that can lead individuals to become irritable or disinhibited and unreliable at work; multitasking becomes difficult and forgetfulness and anxiety mount (Walker 2007, Tabrizi et al. 2012).
1.6 Depression in HD

Depression is a highly frequent mental disorders in the general population and a major cause of disability, affecting people from different ages, ethnicities, gender and backgrounds (Paulsen 2005, Galts et al. 2019). It is frequently related to other medical conditions, especially terminal and neurodegenerative illnesses, such as HD (Paulsen 2005). In the context of HD, some authors consider that psychiatric symptoms such as depressive mood may be even more distressful and debilitating than the traditional motor symptoms themselves (van Duijn et al. 2007).

The diagnosis of HD is traditionally made based on the presence of motor symptoms; however, it is widely accepted that psychiatric and behavioural symptoms such as depression may manifest several years prior to movement disorders affecting patient’s daily activities, work and quality of life (Paulsen 2005, van Duijn et al. 2007, Tabrizi et al. 2009). Depression in HD can also be correlated with morbidity and early mortality as a result of suicide (Fiedorowicz et al. 2011, Epping et al. 2013), with depression noted as an important predictor of suicidal ideations and behaviours amongst HD patients (Epping and Paulsen 2011, Hubers et al. 2013, Galts et al. 2019). George Huntington, in 1872, described suicidality as a major feature of HD and further epidemiological studies show that suicide rates amongst HD individuals are 4–6 times greater than that in the general population (Rosenblatt and Leroi 2000).

The prevalence rates of psychiatric signs in HD differ greatly according to diverse study populations, different disease stages studied and diverse assessment methods (van Duijn et al. 2014), yet it can be considered that the variation in prevalence for depression in HD is between 33% to 69% (Julien et al. 2007, Dale et al. 2015). Studies also vary hugely when it comes to prevalence of depression in the different stages of the disease. The phases of HD can be assessed by a model commonly used to describe functional decline, involving ranges of Total Functional Capacity (TFC) and scores from United Huntington Disease Rating Scale (UHDRS), which result in a 5 stages model in which patients move from a position of reasonable independence (Stage 1), until they reach a level of severe impairment, with no conditions to perform activities of daily living (Stage 5) (Shoulson and Fahn 1979). However, studies have reported no congruent results regarding critical periods for depression in HD, as some account for depression being more frequent in the prodromal stage of HD (Julien et al. 2007, Kingma et al. 2008, van Duijn et al. 2008, Tabrizi et al. 2009), some report higher rates of depression in
early stage 2 of HD (Epping and Paulsen 2011), whereas other authors found the symptoms to occur more often among stages 4-5 (van Duijn et al. 2014).

Several studies have reported different neuropathological mechanisms for development of depression in HD, for example, the early neuronal loss in the medial caudate and the limbic structures (Paoli et al. 2017). The aetiology of depression in HD, however, is complex and not only does it take into consideration the neurodegenerative consequences of the disease itself, but also the mental pressure of living with a terminal and debilitating disease from which other members of the family are suffering or will suffer in times to come (Shiwach and Norbury 1994, Slaughter et al. 2001, Epping et al. 2013). In addition, several different factors of mental stress contribute to characterize HD mutation carriers as depression prone individuals, such as caregiving for other family members, dealing with the choice of having children, decline in functioning, informing others about genetic risks and anxiety due to the uncertainty of future (Epping et al. 2013). Lastly, depression is conventionally correlated with premature death due to the increase in the risk of suicide in the general population (Nock et al. 2008, Galts et al. 2019). This is not different for patients with HD, whose risk of complete suicide is significantly higher (6.6%) when compared with the global population (1.5%) (Nock et al. 2008, Kachian et al. 2019).

Therefore, it is essential that depression in HD is diagnosed and treated as soon as possible to minimize the psychological and emotional distress as well as to prevent premature death in depressed patients (Galts et al. 2019).

1.7 Management of Symptoms

HD presents with a wide variety of symptoms and, therefore, there are multiple individual mechanisms through which scientists try to explain the neuropathology of the disease. Those include toxic neuronal aggregates, transcriptional dysregulation, excitotoxicity, mitochondrial dysfunction with altered energy metabolism, and changes in axonal transport and synaptic dysfunction, of which more than one may occur at the same time (Frank and Jankovic 2010). Moreover, it is known that symptoms change over the stages of the disease (Mason and Barker 2016). This makes HD a complex condition, that demands tailored treatment to the needs of each single patient, focus on the most bothersome signs that
interfere in daily routine and balancing benefits and potential adverse effects of drugs (Unti et al. 2017).

Pharmacological interventions targeting the motor aspect of HD symptoms are typically focused on the neurotransmitters dopamine, glutamate and γ-aminobutyric acid, (Frank 2014). In 2008, the FDA - US Food and Drug Administration approved tetrabenazine, a synaptic vesicular amine transporter inhibitor, for the treatment of chorea and, even though other medications are constantly being tested (dopamine antagonists, benzodiazepines, and glutamate antagonists), none of them has proven to show significant improvement, thus tetrabenazine has been the only licensed drug for the use in chorea associated with HD so far (Coppen and Roos 2017).

In relation to cognition, despite HD being known as functionally disabling, no drug has shown adequate efficacy at improving this aspect of the disease. A small number of pharmacological agents were tested, including cholinesterase inhibitors (rivastigmine and donepezil), the antidepressant citalopram and the norepinephrine reuptake inhibitor atomoxetine but they failed showing any positive response and were never explored further (Cubo et al. 2006, de Tommaso et al. 2007, Beglinger et al. 2009, Beglinger et al. 2014). The same issue regarding the lack of clinical evidence occurs when it comes to the psychiatric aspects of HD. Treatment of depression, anxiety, irritability, psychosis, among others, include standard antidepressants, benzodiazepines, quetiapine, sodium valproate, carbamazepine, etc (Mason and Barker 2016). Most part of these pharmacological agents are used off-label, according to their rational use on the known neurochemical pathology, the comorbid symptoms or the physician own experience (Mason and Barker 2016, Unti et al. 2017).

Although much progress has been achieved regarding the treatment of HD, successful results in terms of cure or how to slow the progression of the disease are yet to come. In the meanwhile, the treatment consists solely of the multidisciplinary symptomatic management of motor, behavioural and psychiatric disorders, hence the need of carefulness and precaution when choosing the right therapy scheme (Unti et al. 2017). Additionally, several authors emphasize lack of clinical evidence and, consequently, the need of more in-depth studies focusing on symptomatic therapies used in HD which are now becoming possible due to better and larger registries such as Enroll-HD (Dayalu and Albin 2015).
1.8 Management of Depression in HD

When it comes to the aetiology of major depression in HD, the mechanisms mediating the effects of antidepressant therapy involve the activation of signalling cascades that result in higher expression of brain derived neurotrophic factors (Nibuya et al. 1996, Balu et al. 2008, Galts et al. 2019) and enhanced hippocampal neurogenic capacity (Grote et al. 2005, Duan et al. 2008, Galts et al. 2019), (Galts et al. 2019). However, major obstacles arise when it comes to specific drug-based treatments in HD. Firstly, some authors have mentioned that depression is remarkably undertreated, and nearly half of the patients with depressive symptoms do not receive appropriate therapy (Paulsen 2005, Nock et al. 2008, van Duijn et al. 2014, Galts et al. 2019). One of the reasons for this may be the fact that depression is challenging in terms of diagnosis in the HD population once some signs (insomnia, weight loss) can be confounded with manifestations of HD itself, leading to misdiagnosis (De Souza et al. 2010). Secondly, research in this area has been scarce, with small sample sizes, inadequate statistical methods and inappropriate controls for comparative purposes (Moulton et al. 2014, Galts et al. 2019). Additionally, despite several pharmacological agents being tested in small scale trials, they have not been evaluated in more than one trial, preventing meta-analyses to confirm treatment options (Moulton et al. 2014, Galts et al. 2019). For this reason, it is suggested that HD patients with depression should be treated using the same clinical guidelines as those used for depressed individuals in the general population (Epping and Paulsen 2011, Galts et al. 2019)

In general population and primary care, serotonin reuptake inhibitors (SSRIs) are the first-line pharmacotherapy for most patients with depression disorders, once they are safe, effective and well-tolerated, with less frequent adverse reactions when compared to other antidepressants (Chu and Wadhwa 2022) which enhance patient’s adherence to treatment. Despite the self-explained name “serotonin reuptake inhibitor”, the mechanism of action of those drugs cannot be summarized simply by the inhibition of serotonin transporter (SERT). A current theory proposes that a shift in the brain homeostasis happens as a result of the neuronal stress caused by SSRIs, inducing a downregulation of SERTs in some areas of the brain and upregulation in others (Santarsieri and Schwartz 2015). This mechanism may possibly explain the fact that a full therapeutic effect of an SSRI is not expected prior to four to six weeks after initiation, despite significant immediate alterations in serotonin flux (Edinoff et al. 2021). Examples of SSRIs include fluoxetine, sertraline, paroxetine, fluvoxamine, citalopram, escitalopram and vilazodone. The introduction of SSRIs in clinical practice started with the
regulatory approval of fluoxetine in the United States in 1988. Prior to this, monoamine oxidase inhibitors (MAOIs), and tricyclic antidepressants (TCAs) were the only options for pharmacologic intervention in depressive disorders.

Inhibitors of monoamine oxidase function by inhibiting the monoamine oxidase (MAO) enzyme, resulting in the accumulation of its substrates (monoamine and catecholamine neurotransmitters) in the synaptic clefts in the central nervous system (CNS). The antidepressant effect is, therefore, a consequence of the accumulation of serotonin, norepinephrine and dopamine (Sabri and Saber-Ayad 2021). Examples of MAOIs include: isocarboxazid, phenelzine, tranylcypromine, rasagiline and selegiline. Important disadvantages regarding especially the safety profile of this class of drugs made them lose their position as first-choice treatment for depression: MAOIs have a potent hypotensive effect, leading to almost half of their users experiencing dizziness; a potentially fatal side effect is the “cheese reaction” (hypertensive crisis that occurs when taking MAOIs along with sympathomimetic amines such as tyramine found in some fermented foods like cheese) (Sabri and Saber-Ayad 2021) and lastly, the sudden cessation of MAOIs treatment may cause antidepressant discontinuation syndrome, whose symptoms include anxiety, agitation, insomnia, chills, diaphoresis, headache, irritability, malaise, and nausea (Jakubovski et al. 2019).

TCAs act on different neurotransmitter pathways to achieve their effects, blocking the reuptake of serotonin and norepinephrine in presynaptic terminals and increasing the concentration of these neurotransmitters in the synaptic cleft. Additionally, they are competitive antagonists on post-synaptic alpha cholinergic (alpha1 and alpha2), muscarinic and histaminergic receptors (H1) (Moraczewski and Aedma 2021). TCAs have several degrees of receptor affinities and consequently lead to different side effects such as constipation, dizziness, xerostomia, blurred vision, confusion, urinary retention, tachycardia, orthostatic hypotension, increasing risk of seizures in those with epilepsy and mild liver enzyme elevation (Moraczewski and Aedma 2021). Moreover, a common (and alarming) adverse reaction of TCAs is cardiovascular complications, including arrhythmias, QTc prolongation, ventricular fibrillation, and sudden cardiac death in patients with pre-existing ischemic heart disease (Fanoe et al. 2014). For the reason of frequently presenting those unfavourable side effect profiles and consequent poor treatment adherence, the choice of MAOIs and TCAs as first-line treatment for depression was limited. Examples of TCAs include amitriptyline, amoxapine, desipramine, doxepin, imipramine, nortriptyline, protriptyline and trimipramine.
As well as the SSRIs, the SNRIs are a class of drugs that have demonstrated great success treating depression symptoms with reduction of the side effects caused by the MAOIs and TCAs (Dale et al. 2015). SNRIs are serotonin and norepinephrine reuptake inhibitors and bind to 5-HT and norepinephrine transporters to selectively inhibit the reuptake of these neurotransmitters from the synaptic clefts (Shelton 2019). Those drugs have, therefore, have a dual mechanism of action that increases the availability of 5-HT and norepinephrine at the same time within the central nervous system (Shelton 2019). Considering what some authors hypothesized, that a selective action on one or the other of the monoamines (serotonin or norepinephrine) is sufficient for antidepressant activity (Stahl et al. 2005), it was expected that the combined double-action of SNRIs would surpass the efficacy of the SSRIs, as suggested in a meta-analysis conducted in 2002 (Smith et al. 2002). Finding of this study, Smith et al. (2002) showed possible superior efficacy of venlafaxine over fluoxetine and possibly other SSRIs (Smith et al. 2002). On the other hand, a disadvantage of venlafaxine relative to the SSRIs is the potential for dose-dependent (high doses) blood pressure elevation, diaphoresis, tachycardia, tremors and anxiety (Shelton 2019). Also, at low doses, nausea, diarrhea, fatigue or somnolence and sexual side effects may occur such as observed in the adverse effect profile of an SSRI. Examples of SNRIs include venlafaxine, desvenlafaxine (venlafaxine’s active metabolite drug), duloxetine and milnacipran.

Despite the development of new mechanisms of action, that reduce side effects and enhance therapy adherence, important medical needs still remain unmet when it comes to the effectiveness of the pharmacological treatment for depression and those include: the fact that only about 25-35% of patients with major depression disorder achieve symptoms remission with the traditional therapies (Crown et al. 2002); approximately half of the patients with major depression may experience recurrence of episodes, with depression becoming a chronic condition and requiring long-term treatment (Pae et al. 2008); and lastly, 30% of the patients tend to be resistant to standard treatment (Shelton et al. 2010). In this sense it is important that the clinical practices for depression include augmentation and adjunctive strategies to enhance the response rates, target residual symptoms and mitigate adverse effects of the primary antidepressant agents. On this matter, the treatment of depression in the general population may alternatively include benzodiazepine agents, antipsychotic agents, NDRIs, SARIs or atypical antidepressants.
Benzodiazepines are a family of anxiety-reducing and hypnotic drugs whose use in treating depression is justified by the fact that this condition is very often coincides with anxiety. The results of a Cochrane review revealed that the combination of antidepressants and benzodiazepines could be more effective than the use of antidepressants alone in improving depression and reducing symptoms in the early phase of treatment (one to four weeks) (Ogawa et al. 2019).

The alternatives pharmacotherapy for depression may also include antipsychotic agents. Antipsychotics are a class of drugs mainly used to treat psychosis, however, due to the plethora of neurotransmitters and neurotransmission systems in which they act, their use to treat other medical conditions has been largely explored. When it comes to depressive symptoms, the rationale behind the use of antipsychotics, especially the atypical ones, is the fact that they act as antagonists of the serotonin 5-HT2 receptor (DeBattista and Hawkins 2009). As an example, the antagonism of 5-HT2C receptors impacts the dopamine and noradrenergic neurotransmission and may improve, as results, patient’s energy, cognition, interest and motivation (DeBattista and Hawkins 2009). Examples of atypical antipsychotics used for depression are aripiprazole, olanzapine and quetiapine.

Another class of antidepressants that is not part of the first-line choice of physicians but has rather significant importance in the therapeutic arsenal against depression is the norepinephrine and dopamine reuptake inhibitors (NDRIs), whose principal drug is Bupropion. Considering that the comparison of antidepressant medications is generally performed among and within classes, it can be said that bupropion is as effective and safe as the SSRIs (Stahl et al. 2004). An additional mechanism of action of bupropion would include increases vesicular monoamine transporter-2 (VMAT-2) function, which could also play an important role in its antidepressant effect (Foley et al. 2006). Due to the fact that bupropion has different mechanisms of action from the traditional SSRIs, it becomes an important option to treat depression in patients who cannot cope with the serotonergic agents’ side effects (e.g. sexual dysfunction, weight gain and sedation), those who have other medical conditions (e.g. anxiety, seizures) or depression-resistant individuals that require treatment augmentation (Stahl et al. 2004).
Psychotherapy and cognitive behavioural therapy can also be prescribed alongside antidepressants once their benefits in other populations are well recognised, even though those therapies have not been formally studied for HD specifically (Epping and Paulsen 2011).

1.9 Prognosis

HD is yet an incurable condition and, once diagnosed, the course of the disease is typically 15–20 years. As HD proceeds, chorea becomes a safety issue, as patients lose control over their movements and larger amplitude motions may cause injury and poor positioning, resulting in skin wounds, infections, or even fractures and head trauma (Frank and Jankovic 2010). Besides, other symptoms like dementia, mutism, dystonia, and bradykinesia, make patients more prone to develop complications of dysphagia-related aspiration pneumonia in advanced disease, that are known to be ultimately the major cause of death. It is also important to include that 25 % of patients attempt suicide, which is a cause of death in 8–9 % (Frank and Jankovic 2010).

1.10 Medical Registries

One approach to improving the knowledge about neurodegenerative diseases such as HD, is to evaluate how to optimally assess disease progression and identify factors that modify the phenotype of the disease. This can be effectively undertaken by the analysis of data generated by medical registries. In general, clinical registries are of ultimate importance for all types of disease surveillance by providing real world evidence of the impact of treatments and service delivery models (Madhok 2002, Dokholyan et al. 2009, Hoque et al. 2017). Consequently, medical registries contribute to quality improvement in healthcare processes, compliance with the clinical practices guidelines, reduction of costs and research (Hoque et al. 2017). With regards to this later benefit of medical registries, data collected represents real world evidence and may be a powerful source of research hypotheses, facilitates descriptive studies, and reduces time and costs associated with prospective data collection (Sørensen 1997).

In the context of HD, researchers can count on major international studies such as TRACK-HD, PREDICT-HD and Enroll-HD that have been facilitating research through fostering large-scale data collection, data analysis, and data sharing worldwide and have escalated the
data analysis in this area to a global stage (Davies et al. 2020). As an example, TRACK-HD is a multinational prospective observational study that examines clinical and biological findings of HD progression in individuals with premanifest HD and early-stage HD. The study aims to describe phenotypic changes in participants over a period of 36 months and identify baseline predictors of progression. (Tabrizi et al. 2013). As well as TRACK-HD, the Neurobiological Predictors of Huntington’s Disease (PREDICT-HD) is a large, international, multisite, longitudinal observational study. However, the emphasis of the study is mainly on the prodromal stage and to identify biological and clinical features associated with the motor manifestations of HD prior to clinical diagnosis (Paulsen et al. 2006, Paulsen et al. 2008). Overall, over 1,400 participants have been enrolled in the PREDICT-HD study across 32 study sites in six countries (United States, Canada, Australia, Germany, Spain, and the United Kingdom) (Westervelt et al. 2017, PREDICT-HD n.d.). Lastly, Enroll-HD is a unique ongoing observational longitudinal study using a completely integrated clinical research platform. It was designed and implemented to collect and provide detailed information about HD worldwide, in order to contribute to the identification of clinical needs and research in this population and to accelerate the discovery and development of new therapeutics for patients with HD. To date, Enroll-HD includes over 18,895 active participants, individuals who are subdivided into HD patients (manifest HD and pre-manifest HD), and controls (genotype negative and family controls). Written informed consent for participation is mandatory for all participants, to ensure they are fully informed about the study, and also to ensure that each volunteer’s decision is made of their own free will. Standardised data is collected on a global scale and made available for review in compliance with GDPR requirements. To date little research has been published on findings from the data collected. This therefore presented a unique opportunity for this research group to investigate the data collected.

2. Rationale

Although significant improvements have been made with regards to the treatment of HD, it remains as an incurable condition for which the management of symptoms still seems to be the only alternative to provide good quality of life to patients. The disease presents with a
complex array of problems that manifest differently from person to person and, therefore, the heterogeneity requires very specific tailored drug therapy. The lack of trial evidence supporting the use of the drugs in HD results in treatments mostly based on personal physician experience. Since the cure for HD is still under development, it is mandatory to ensure that the drug treatment represents the best alternative that patients have to alleviate the signs and consequences of HD. This study is relevant by reason of the exploration of the Enroll-HD datasets enabled the evaluation of real consented data and present new evidence in terms of drug therapies for depression and prescribing patterns in HD. It may contribute to the development of more assertive practices regarding depressive symptoms in HD in order to maximize quality of life for those sufferers.

Given the dearth of information and clinical guidelines available on the treatment of depression in HD patients, this research project intended to determine the methods of evaluating depressive symptoms in the HD population and describe the pharmacological therapies being utilized by subjects. The findings of this study are thought to contribute to the HD community by providing an initial overview of the principal aspects of depression in HD, once this area faces constant challenges regarding the lack of specific information.

2.1 **Study aim**

The aim of this study was to describe the cohort of patients included in the Enroll-HD dataset, describe the use of evidence-based treatments for HD and non-HD individuals and identify factors that influence the depressive symptoms over time. Specific objectives are addressed in work packages, using different statistical approaches. The conclusions of this work are hoped to serve physicians better on their prescriptions, in order to benefit HD patient’s general health and quality of life.

2.2 **Specific objectives**

- Work package 1: To analyse the data provided by Enroll-HD
- Work package 2: To describe the demographics of patients recorded in the Enroll-HD dataset, those with HD who present with depressive symptoms (HD) and those who do not have HD but who have depressive symptoms (Control). To compare the
demographic characteristics between the two groups (HD and control) using appropriate statistical methods

- Work package 3: To describe the main evidence-based pharmacological treatments prescribed to both cohorts at baseline and at 1st follow-up visit
- Work package 4: To describe depressive symptoms over a three-year period and identify factors that may influence these symptoms in the HD group
- Work package 5: To identify factors that affect depressive symptoms at baseline in the HD group

3. Methodology

3.1 Research structure

3.1.1 Study Design

This is a retrospective observational cohort study.

3.1.2 Enroll-HD

Enroll-HD is an ongoing observational longitudinal study launched in 2012 that incorporated two existing HD registries: The Cooperative Huntington Observational Research Trial (COHORT) based in North America and Australia, and REGISTRY – an observational study of the European Huntington’s Disease Network (EHDN). Enroll-HD also includes centres in Latin America and Asia (Enroll-HD Study Team 2011).

Enroll-HD is executed and funded by the Cure Huntington’s Disease Initiative Foundation (CHDI), a privately funded non-profit biomedical research organization dedicated to HD. The Foundation also funds academic researchers focused on HD, conducts research to develop new treatment ideas, and partners with biotechnology and pharmaceutical companies to develop novel drugs and therapeutics. The main objective of the CHDI is to contribute to the fast goal of the organization is to accelerate the development and testing of new therapies for HD so they can be made available to patients in the fastest possible time (Enroll-HD Website 2020).
Intending to create a rich database for HD research, Enroll-HD consists in a completely integrated clinical research platform, the unique one operating in the neurology area with three main objectives: to provide insights for the development of new pharmacological treatments by enhancing the understanding of HD as it happens from an observational perspective, to collaborate with the design of better, faster and more assertive clinical trials and, lastly, to recognise the best clinical practices in use across all Enroll-HD sites around the world and replicate them to all patients and families (Enroll-HD Website 2020).

Enroll-HD is structured in an open-ended prospective format in which assessments occur annually and interventional procedures (except those of normal clinical care) and experimental therapies are not included in the evaluations. In order to create a large and rich database, the study aims to enrol approximately one-third of the HD affected population in each study region (North America, Latin America, Europe, Asia, Australia and New Zealand) (Enroll-HD Study Team 2011).

On an annual basis, Enroll-HD releases periodic data sets (PDS) containing information about the HD cohort. Every PDS adds up to the last version with up-to-date data from new participants and data from the follow-up visits for the previous participants. Those PDS are characterised by the abbreviation “PDS” which stands for periodic data sets, followed by a number indicating the version (ex. PDS4 – periodic data set version 4). The PDS4 used in this study comprises data gathered during the 6-year period that Enroll has been active (from 2012 to 2018).

**Participants of Enroll-HD study**

The most relevant inclusion criteria in Enroll-HD includes providing informed consent from the participant or legal representative. Individuals 18 years of age and older are asked to participate in all aspects of the study, whereas those under 18 years of age are allowed to enrol when they are clinically and genetically diagnosed with HD (Enroll-HD Study Team 2011). Individuals meeting the inclusion criteria and willing to participate in Enroll-HD are classified into two major categories (Enroll-HD Study Team 2011):

1. Carriers: represents the primary study population and consists of individuals who carry the HD gene expansion mutation (CAG expansion ≥36 on the longer allele).
2. Controls: it is the comparator study population and consists of individuals who do not carry the HD gene expansion mutation.

The category of those who carry the HD gene expansion (CAG expansion ≥36 on the longer allele) classified as (Enroll-HD Study Team 2011):

- Manifest HD: carriers of the HD gene expansion mutation age 18 or older who are deemed to have diagnostic HD clinical features in the opinion of the site investigator (and confirmed at each subsequent visit).
- Premanifest HD: carriers of the HD gene expansion mutation age 18 or older who are deemed not to have diagnostic clinical features of HD.
- Juvenile HDGECs: carriers of the HD gene expansion mutation under the age of 18 years who are clinically diagnosed with juvenile HD.

The control group is composed by individuals who do not carry the HTT gene expansion (CAG expansion <36 on the longer allele) and includes three categories:

- Genotype negative: first or second degree relative of a carrier of the HD gene expansion mutation, who has undergone predictive testing and does not have the CAG expansion.
- Family control: family member or other individual not genetically related to an Enroll-HD carrier of the HD gene expansion mutation participant (e.g., spouses, partners, and caregivers).
- Community control: individual not genetically related to a carrier of the HD gene expansion mutation, who did not grow up in an HD-affected family and does not have a concurrent neurological disorder.

Both men and women from all ethnicities and races are included in this study and Enroll-HD does not differentiate and exclude participants for their social status, age or sexuality. On the other hand, Enroll-HD did establish exclusion criterion, which excluded individuals who presented with movement disorders but a negative test for HD, individuals from the community control group with a history of or concurrent major central nervous system disorder and, obviously, those who could not meet the inclusion criteria (Enroll-HD Study Team 2011).
Recruitment Process

The recruitment of HD affected patients who want to participate in Enroll-HD is undertaken as a result of referrals made from the specialty clinics or community clinics in which the condition is being treated and where support is provided to families affected. Clinicians and the research staff of each site identify potentially eligible participants and inquire as to their willingness to participate in this study. Patients are also encouraged to forward an invitation to their relatives to consider taking part in Enroll-HD. Moreover, another channel to which Enroll-HD receives participants is through website, clinical practices, support groups, advocacy newsletters, etc. and place a direct request to be considered for participation in the study (Enroll-HD Study Team 2011).

On the other hand, individuals belonging to the community control group may become interested in participating by checking information about Enroll-HD disseminated using the Institutional Review Board (IRB)/Independent Ethic Committee (IEC) (approved advertisements, flyers and newsletters) and may get in contact with the study site staff (Enroll-HD Study Team 2011).

Currently, there are over 158 clinical sites worldwide and more than 22 nations participating in this study. Most sites are located in Europe and in the United States, however, clinical sites can also be found in Canada, Australia, New Zealand and Latin America countries such as Colombia, Argentina and Chile (Enroll-HD Website 2020).

In order to become a study site, requirements include, from the patient’s point of view: identification of participants within a geographical area, who are willing to provide information for a non-treatment observational study, recruitment and retention (long term) of a minimum of 50 participants, including at least 20 premanifest/at risk, perform follow up of each participant annually (Enroll-HD Website 2020). In relation to the facilities, it is required the establishment of designated clinic spaces for interview and assessments of participants and their families/carers, for drawing, processing and dispatching blood samples to a central laboratory and access to Enroll-HD web portal for transferring data onto electronic data capture (EDC). Regarding the staff, the clinical site team must be specialized in HD (preferably the primary investigator) and be able to communicate in English. All Enroll-HD study staff must complete training in ENROLL-HD specific assessments and relevant annual motor UHDRS certification. Additionally, sites need a recognised referral path or Standard Operating Procedure (SOP) for mental health issues to a psychiatrist or other mental health care provider,
preferably with HD experience as well as a referral path for participants who wish to undergo genetic testing. Lastly, in terms of institutional structure, clinical sites must have access to a Good Clinical Practice compliant local or regional Ethics Committee, Institutional Review Board (IRB) or equivalent, must have access to and awareness of any other local or regional agency approvals, ability to contract via local institutional (public or private) finance/legal department and accept the CHDI Site Agreement template.

**Informed Consent**

Participants are asked to provide informed consent, which is an unconditional prerequisite for participating in this study. Based on the participants’ competency and age and compliance with the local regulations, requirements, and the Good Clinical Practices, the informed consent form is signed by the individual when they are defined as able to understand the nature and purpose of the study, as well as the procedures, risks and benefits. Additionally, the non-coerced desire of the participant to collaborate in the study is confirmed by the site investigator staff (Enroll-HD Study Team 2011).

Informed consent for underage individuals is obtained from the parents or legal guardian. Assent is obtained and documented, for children below 7 years of age by written parental permission; children between 7 to 12 years of age by parental permission and verbal assent; and for children 13 to 17 of age by parental permission and written/signed assent from the participating child. This procedure, however, may differ from participating site to site to ensure compliance with the local regulations and requirements (Enroll-HD Study Team 2011).

For those individuals with impaired cognitive and mental function and who are therefore unable to consent, consent is obtained from a legally acceptable representative, which may include the spouse, a person specifically appointed to take care of the legal interests of the participant, an individual with guardianship or a health care proxy (when consenting for research studies is within the legal scope of the proxy’s delegated responsibilities). The investigator site has responsibilities over evaluating whether the legal representative has the cognitive and mental capacities that enable them to understand the procedures, risks, and benefits involved with the study (Enroll-HD Study Team 2011).

Once HD is a progressive neurodegenerative condition, the possibility that cognitive function deteriorates over time needs to be considered and, therefore, HD participants of
Enroll-HD are encouraged to discuss their future study participation wishes with their representative.

Participants are free to withdraw from the study at any time, having their data kept in the Enroll-HD database and biosamples stored at the central biorepository (all de-identified), unless they explicitly request them to be deleted (Enroll-HD Study Team 2011).

**Data Collection and Data Quality Control**

Participants of Enroll-HD are assessed on an annual basis, which may coincide with the participant’s routine clinical care visits. During those visits, participants undertake several assessments which are classified as followed (Enroll-HD Study Team 2011):

1. Core Assessments: Mandatory data elements for all participants at all sites.
2. Extended Assessments: Data elements to be collected to the extent possible from all participants at all sites.
3. Optional Assessments (according to participant consent): Participating sites and participants may choose to contribute these data elements.

In the Core Assessments, patients provide information about co-morbid conditions, concurrent medications, and HD clinical characteristics and treatment including pharmaco-therapeutic, non-pharmacologic, nutritional supplements, physiotherapy, etc. These data elements are mandatory for all participants at all sites and are collected at baseline and annual follow-up visits. The Extended Assessments contain elements to be evaluated to the extent possible on all participants at all sites and cover the behavioural (the Hospital Anxiety and Depression Scale, the Snaith Irritability Scale and the Columbia Suicide Severity Rating Scale) and cognitive (the Stroop Interference Test, the Trail Making Tests, the Mini Mental State Examination) domains (Enroll-HD Study Team 2011). Additionally, the following information also compose the Extended Assessments group: physiotherapy outcome measures, the Timed Up and Go test, the Second Chair Stand test, Quality of Life Assessments, Health Economic Assessments, Client Services Receipt Inventory and Work Productivity and Activity Impairment-Specific Health Problem Questionnaire. Lastly, the Optional Assessments contain data to which participating sites and individuals may choose to contribute with and it requires specific
consent from the participants. This group includes information about the family history and is collected through a questionnaire (Enroll-HD Study Team 2011).

The total length of time that participants spend on the visits varies between 45 minutes (completion of core assessments only) and 2.5 hours maximum (completion of core, extended, and optional assessments) (Enroll-HD Study Team 2011).

Enroll-HD ensures that all assessments are performed by trained clinical personnel and provides the participating sites with a variety of training methods (practice videos, test assessments to train and certify raters, training sessions during investigator meetings, on-line using training videos, didactic teaching methods), as well as manuals and written materials detailing instructions for implementing, administering and scoring study instruments. Enroll-HD trained personnel also undergo periodic recertification. The participating sites are asked, to the extent possible, to use the same individual rater to administer study instruments to a particular participant for the duration of the study so as to maximize internal consistency (Enroll-HD Study Team 2011).

In relation to the data collected about the pharmacological treatments, Enroll-HD site staff are asked to update this information on the electronic case report forms (eCRFs) every time a visit is conducted for any participant, in order to capture both current (at the time of visit) and historic medication use. Information regarding supplements is also recorded, however it is captured in a separate spreadsheet by Enroll-HD staff. On the occasion of the visits, the site staff record the medication use at the time of the visit, including any medicines that were stopped since the last visit, however, they are not asked to capture medication changes or temporary medication uses that happened between visits (e.g. antibiotics, pain killers, etc). As part of the monitoring procedure, Enroll-HD ensures that the pharmacotherapy log is checked for 25% randomly selected participants on the monitoring list, meaning that, eventually, most logs are onsite monitored against the medical file or whatever source documentation exist at any given site.

Enroll-HD has implemented data quality checks at multiple levels, from the data entry, through to onsite and remote data monitoring, which are performed regularly throughout the data collection process until the periodic dataset (PDS) is finally released (Enroll-HD Study Team 2011, Enroll-HD Study Team 2020).

With regards to the data entry procedure, in 2018, Enroll-HD released the Guidelines for the Completion of Case Report Forms (CRFs) (Enroll-HD Study Team 2018). This document
provides information on how to correctly complete the data required by Enroll-HD in the assessment forms and also gives further advices and reminders, such as: to always refer to the study protocol before completing forms; the CRF must always be completed by authorised site personnel; the delegation form in the site file must be completed if the staff is new to the study; to always ensure that data entries are consistent with the source data (usually the participant’s medical record); that every page of the case report form must be filled in; discrepancies with source data should be explained and the significance noted in the case report form and/or medical records (Enroll-HD Study Team 2018). Additionally, in order to guarantee compliance with study protocol, Good Clinical Practice, and applicable regulations, Enroll-HD carried out frequent onsite visits (Enroll-HD Study Team 2020). Lastly, remote checks are performed on a monthly basis, in which the participant’s data is subject to cross-sectional checks that evaluates consistency, completeness and plausibility (comprehensive checks for outliers, custom checks for unusual or implausible values, and missing data). Longitudinal quality control checks are also conducted every 6 months and analyses variations within subjects for a subset of variables (e.g., height, TFC score) (Enroll-HD Study Team 2020).

The Webspirit Systems GmbH, located in Neu-Ulm, Germany, maintains the EDC software and the server infrastructure for running the Enroll-HD study. The company carries out supporting and administrative services for the CHDI according to CHDI’s instructions. Webspirit Systems GmbH does not process any identifying patient data and all employees are GDPR trained. Staff, therefore, are not allowed to collect, process or use any personal data without authorization. The Enroll-HD electronic data capture (EDC), the Enroll-HD webpage, and the statistics server used to process the Enroll-HD Periodic and Specified datasets are hosted at a secure third-party data centre (Rackspace) in Frankfurt, Germany and can only be accessed by the Webspirit Systems GmbH's qualified personnel. Webspirit Systems GmbH also acts as IT provider for the Enroll-HD study. Rackspace, which is a renowned provider for top security data centres worldwide, utilizes a high security data storing facility that is HITRUST CSF certified to meet stringent security standards for Personal Health Information (PHI). HITRUST CSF is an accepted set of security and privacy related regulations, standards, and frameworks—including the International Organization for Standardization (ISO), the National Institute of Standards and Technology (NIST), the Payment Card Industry Data Security Standard (PCI DSS), the Health Insurance Portability and Accountability Act (HIPAA), and the Control Objectives for Information and Related Technologies (COBIT). Physical and remote access to each of the
Rackspace servers is highly controlled to ensure limited access. Only Enroll-HD site staff and central Enroll-HD operational staff has access to the Enroll-HD EDC and only the Enroll-HD data management team has access to the Rackspace server used for the storage and preparation of datasets. All datasets are encrypted prior to leaving the Rackspace environment.

On the 25th of May 2018, the European Union (EU) General Data Protection Regulation (GDPR) came into effect and allowed member states to implement further safeguards mechanisms in order to protect personal data, including health data (Kirwan et al. 2021). In Ireland, on the 8th of August 2018, Ireland’s Health Research Regulations (HRRs) was established, introducing additional regulatory requirements for health research in relation to governance, processes and procedures that impacted on several aspects of research (Kirwan et al. 2021). The principal requirement instituted by the HRRs committee was mandatory explicit consent of any individual (data subject) participating in the study. Additionally, guidance mentions good faith as a significantly important factor on the part of the health researcher not only regarding the information provided to the participant but also in relation to the individual’s personal data they then seek from healthcare providers.

As previously mentioned, Enroll-HD is executed and funded by the CHDI and, as a data controller governed by GDPR, CHDI is required to meet specific obligations for data sharing and data security. In order to meet these obligations, the data recipients are required to sign the data use agreement on behalf of their institution, company or organization and to provide justification for the use of such information (description of the research project that is made publicly available on the Enroll-HD website). In the data user agreement, the data recipients agree with what is referred as "Data Protection Legislation", which encompasses all applicable international, national and local laws, rules and regulations relating to the processing of personal data and privacy (Enroll-HD Study Team 2021). Those regulations include the General Data Protection Regulation 2016/679 (GDPR) and any local Member State law giving effect to or implementing the GDPR; the Retained Regulation (EU) 2016/679 (UK GDPR, when applicable) and Data Protection Act 2018 (c.12) and any other rule that may apply depending on the local laws and requirements. Additionally, from the Enroll-HD point of view, the software used to carry out the studies complies with ethical and data protection laws and all data related to the study (pseudonymization of patient identification, demographic and medical data, documents) are transmitted in encrypted form (Enroll-HD Study Team 2021).
Complying with data protection regulations, the identifying medical data is stored pseudonymized with a unique participant identifier. The pseudonym from unique identifying participant data is generated by means of a pseudonymization service. It is collected exclusively on the study site computer, never transmitted to the server or saved either temporarily or permanently and study site personnel reach the system exclusively via a web browser (the web browser running on the client computer communicates with the server). The pseudonymization process is performed only by selected trained users who access the service through the Enroll-HD system (password-protected web page protected by "https" via a secure interface). There is a role-based authorization system that ensures that only authorized users can use this service and initiate the pseudonymization. Once a pseudonymization process is started, identifying data input and calculation an internal pseudonym happens via cryptographic means of a SecureHash algorithm (SHA1), exclusively in the web browser using the technologies HTML and JavaScript without communication to the server. In the next step, the calculation generates an internal pseudonym which (and only this) is encrypted, transmitted to the server and converted into a human-readable 9-digit ID. When the pseudonymization process is finished, the identifying data input is not stored and is no longer available after leaving the pseudonymization page at the study site’s web browser at the study site’s local workstation. In this way, the pseudonymization service is integrated into the application as a module. Therefore, a de facto anonymization of identifying patient data is achieved and made available for the users (Enroll-HD Study Team 2021).

The Transport Layer Security (TLS) standard security protocol on the World Wide Web is used to transmit the data. When using the ordinary web browsers (such as Mozilla Firefox, Google Chrome, Microsoft Edge, and Apple Safari), the data is ultimately encrypted using RC4-128 or AES-256. The participants names are not recorded in any moment and the medical data is stored pseudonymized with a unique participant identifier generated from identifying data by means of a pseudonymization service. The identifying data is never transmitted to the server or stored there (Enroll-HD Study Team 2021).

Prepared datasets are made available for download to verified researchers after they have logged into the Enroll-HD webpage using their EDC credentials (username and password) and have agreed to the Enroll-HD Data Use Agreement. Each dataset release is individually encrypted using AES-256 and requires a 24-character password to extract the data. The
encryption key and notice of the dataset availability is sent to the verified researcher’s confirmed email address. Datasets are removed from the download page after thirty (30) days.

**Participant privacy and identification risk management**

Emerging electronic health records (EHRs) have been playing an essential role in shaping clinical practices and supporting research in all fields (El Emam 2011, He et al. 2015). However, the existence of protected health information (PHI) in medical records requests this data to be de-identified in order to avoid exposure of personal information of the participants (He et al. 2015).

In this sense, for Enroll-HD, participant’s privacy and data protection are matters of great relevance and follow three basic principles: accordance with the EU GDPR rules, US HIPAA rules and the participant’s informed consent; an Enroll-HD Data Use Agreement (DUA) and/or Material Transfer Agreement (MTA) must be signed and honoured; and the risk assessment for participant identification is performed for all participants in the study and steps are taken to mitigate the risk of identification. The risk of identification is defined as the probability that a participant is correctly identified from the full Enroll-HD sample by looking at a specific combination of the key variables (Enroll-HD Study Team 2020).

In order to be added into the periodic dataset, the data obtained from the assessments and visits is subjected to the de-identification process, completed by the Enroll-HD Statistic Team. This process is based on two data safety methods: the “Safe Harbor” method and the “Expert Determination” method, that aim to ensure that the data is HIPAA-compliant and the risk for participant identification is low (Enroll-HD Study Team 2020).

The Safe Harbor method consists of the removal of specific variables that are considered to directly identify the participant, which in the case of Enroll-HD are information regarding the birth date, visit date, site name, and country, for example. In addition, the Expert Determination contributes with the de-identification process once it reinforces the obligation of the responsible organisation to count on professional statistical expert service to perform the identification risk assessment. As a result of the Expert Determination method, the Enroll-HD statistics team identified additional variables that can be considered identification risks. Therefore, some of these variables were suppressed, whereas others were transformed or aggregated. Moreover, as part of the Expert Determination, the probability for participant
identification is calculated based on the combination of potentially identifying variables, which are, in the context of Enroll-HD, HTT CAG size, age, race, sex, educational level (ISCED), and BMI (selected as a result of literature reviews and discussion with HD experts) (Enroll-HD Study Team 2020).

The acceptable risk for identification of a participant in Enroll-HD study is set to 3% and extra techniques are applied in case this percentage is above 3% (e.g., Shifted Delta Cepstrum; further aggregation of variables) to ensure low risk. If these measures are not sufficient to guarantee low risk of identification, the participant is removed from the final released dataset, not meaning though, that they cannot be included in future datasets, as the risk changes when more data is collected. A lower threshold of 1% is attributed for the risk of identification of those participants who are HD family members who do not know if they carry the HD mutation gene, given the delicate situation (Enroll-HD Study Team 2020). Figure 1 provides an overview of the de-identification process implemented for Enroll-HD public dataset releases (Enroll-HD Study Team 2020).
Upon discussion with the Chair of the Level 2, Faculty of Health Sciences Research Ethics Committee, in May 2021 (Trinity College Dublin), ethical approval was not required for this study, considering that the data received from Enroll-HD is already de-identified/anonymised and that this study uses the data for description purposes in a retrospective manner.

Permission to use the Enroll-HD datasets

For the purpose of accelerating HD therapeutic research & development, Enroll-HD gives access to high-quality datasets to any verified researcher linked to a recognized research organization (Enroll-HD Website 2020). The process of requesting access to the databases include (Enroll-HD Website 2020):

1. Creation of an Enroll-HD Clinical Data and Biosamples Access Account
2. Identify the data needed by the researcher
3. Establish the researcher’s eligibility
4. Submit data request form
5. Review and approval of request
6. Preparation of specified datasets
7. Sign Data Use Agreement
8. Delivery of data to the researcher

By signing the Data Use Agreement, the researcher was committing to comply with the terms and conditions that govern the use of the data and consequently with the correct application of GDPR rules, which included warranties and covenants, other good and valuable considerations regarding, for example, additional data protection obligations and publication policies (Enroll-HD Study Team 2012). Some of the terms below illustrate the nature of the document as follows:

- The recipient of the data needs to acknowledge that it is mandatory for CHDI, as the organization funding the Enroll-HD Study and the providing the Data, to safeguard the identity of the research individuals participating in this study.
- The data was collected, processed and transferred to the researcher in accordance with the federal, state, local and international regulations applicable to CHDI and, therefore, the data is provided “as-is” meaning that CHDI makes no warranties or fitness for a particular purpose.
- The recipient agrees to use the data exclusively for research purposes, directed and overseen by him/herself
- The recipient agrees to use the data in compliance with the federal, state, local and international regulations, including health authorities and institutional laws and rules.
- The recipient agrees to maintain, store and treat the data with the same level of care as if it was its own proprietary and confidential information.
- It is strictly forbidden for the recipient to attempt to identify the individuals participating in the study.
- The recipient needs to agree not to transfer or disclose the Data to any third party
- The recipient needs to agree not to publish the data
The recipient agrees to report to CHDI within 48 hours any personal data breach, transfer, disclosure or publication of the data which was not previously allowed by CHDI.

The Data Use Agreement also contains additional protection obligations and those include:

- Assistance Related to Requests by Data Subjects and Supervisory Authorities: the recipient provides assistance whenever requested by the CHDI to comply with the requests from data subjects (exercising their rights under the Data Protection Legislation) or supervisory authorities relating to CHDI’s processing of the Data.
- Requirements Related to Permitted Transfers or Disclosures of the Data: the recipient needs to ensure that any transfer of disclosure of the data to a third party, previously permitted by CHDI, is performed according to the Data Protection Legislation, where the third party has provided appropriate safeguards and on the condition that enforceable data subject rights and effective legal remedies for data subjects are available.
- Destruction of Certain Data upon Request: whenever a participant requests their data to be removed from the database and no longer used for research and, upon notice from the CHDI, the recipient needs to appropriately destroy and discard these data.
- Provision of Data to Third Parties to Replicate Published Research Results: CHDI also agrees to share the data to any third party that desires to attempt to replicate Research Results published by the Recipient Researcher, provided that written request is sent to CHDI and the terms and conditions of the Data Use Agreement are also executed.

As already pointed out, CHDI (as a data controller) and Enroll-HD operate under strict data privacy rules, including the GDPR. This complex piece of legislation was finished in 2016 after a long period of discussion and, as it currently is, encompasses 99 articles and 173 recitals, (which are important for the interpretation of the articles) (van Veen 2018). Examples of how CHDI and Enroll-HD comply with the general principles of GDPR (van Veen 2018) can be observed when:

- The recipients are required to be part of a research institution, provide a description of the research project: in accordance with articles 6 (one should have a legal basis to process
personal data in general) and 9 (one should have a specific legal basis to process sensitive personal data, such as data about health and genetic data (article 9);

- The recipients are required to be transparent about data processing (articles 13 and 14);
- Enroll-HD protocol states that data subjects have rights to their data, such as access, rectification or erasure, restriction of processing, a right to object and data portability (articles 15 and 22) (Enroll-HD Study Team 2011);
- The recipients are required to sign and agree with the Data User Agreement in which Data protection is guaranteed by design and by default (article 25)
- The recipients are required commit with data security while processing the information (article 32).

In addition to those, compliance with GDPR is explicit when observing Enroll-HD’s robust processes in place regarding the de-identification of participants, procedures for collection of data and procedures for informed consent.

The use of Enroll-HD Database for the purposes of this research

Bloomfield Mental Health Services is a psychiatric in-patient facility located in Dublin – Ireland. It is a charity founded in 1812 by Quakers in Ireland rooted in the principle of honouring the dignity of every person who comes through its doors. Allying the neurological and psychiatric domains, Bloomfield Hospital provides care and support for adults and families suffering from mental health conditions such as Alzheimer’s disease, schizophrenia, Parkinson’s disease, and Huntington’s disease (Bloomfield Health Services 2018).

Research, training and education are also key values for Bloomfield Health Services. The hospital is, therefore, committed to engaging in educating the next generation of professionals in providing best practice in the treatment and care of severe and enduring mental health conditions. From this belief, initiations such as the affiliation with Trinity College Dublin and the engagement in transnational research programmes arose (Bloomfield Health Services 2018) As members of the European Huntington's Disease Association, the research team in Bloomfield Hospital had permission to access the Enroll-HD data and went through the registration process, agreed with the Data Use Agreement terms and was allowed to download the datasets.

On the occasion of working part-time in Bloomfield facility, the researcher conducting this study received the invitation to participate in the exploration of the Enroll-HD Database as
part of the Hospital’s interest of developing research in the field of HD and a 16-week and long-term HD residential programme.

Following the data protection rules set by Enroll-HD and CHDI, the datasets from Enroll-HD were obtained by the researcher, stored in a personal device (not provided by the University) protected with password and not transferred to any other third party. It was treated in the same manner, and with the same level of care as if it was the researcher’s own proprietary or confidential information, as to prevent its unauthorized transfer, disclosure or publication. No patient identifiable information was transferred in the file. Upon research termination and according to the Data Use Agreement, data provided by Enroll-HD was retained and used by the researcher only during a sufficient period of time to fulfil the research purposes.

When CHDI provides a license to use Enroll-HD data to an institution under a data use agreement, the institution and the individual researcher are required to keep complying with all terms and conditions contained within the data use agreement while maintaining the data. There is no limit on the term of the license, therefore, as a general orientation from CHDI, if data or any subset thereof will no longer be used after study termination, the data should be appropriately archived in a secure location with limited access to only those who require access to it. However, whenever more conservative internal institutional policies are in place regarding data retention, those are the ones that apply. When it comes to Trinity College as the institutional holder of data, it is recommended in this case that the data used is kept on a secure network in Trinity College Dublin and destroyed 5 years after study completion. Once there is no intend that the data used in this study is archived or stored for reproducibility or future use, upon termination of this research, the data will be kept on a secure network in Trinity College Dublin and destroyed after 5 years.

Enroll-HD in Ireland

In 2015, the Huntington’s Disease Association of Ireland along with the neuropsychologist Niall Pender put resources in place to launch Enroll-HD study in Ireland, which represented the first time the country joined a large-scale international study about HD. According to Dr Pender, who is currently the principal clinical neuropsychologist at Beaumont
Hospital in Dublin, the HD community, patients and their families are extremely willing to participate, since this is the major research project about this condition in Ireland.

Previous research in the HD fields in Ireland involved a few clinicians and insufficient infrastructure to join a study like REGISTRY (prior European observational study before Enroll-HD). At that time, requirements for such large studies could not be satisfied by Irish researchers, such as exigences about tests conduct, data collection and maintenance, staff training and facilities. The Huntington’s Disease Association of Ireland helped get this process off the ground with an initial grant and Dr Pender then handled the administrative aspects of it, such as documentation and systems.

Currently, Ireland has limited specialized services for HD (only one genetic counsellor knowledgeable about the disease and no multidisciplinary clinic that can address the diverse medical needs). For this reason, Enroll-HD is seen as an important opportunity to for Irish people to engage in research, to raise awareness among health professionals about the importance of contributing with research and to improve services for HD in the country. Enroll-HD in Ireland aims to recruit about 100 participants in Ireland.

3.1.3 Rating Scales used to measure Depression

As mentioned previously, the evaluation and diagnosis of depressive symptoms can be especially difficult when it comes to HD. Challenges arise as many somatic signs of HD itself such as sleep disorder, weight loss, psychomotor delay and poor concentration can be confounded with depression, leading to overdiagnosis. In the same vein, depression may be also underdiagnosed if those symptoms are underestimated as being part of the neurodegenerative process of HD or attributed just as a reaction of the diagnosis. Additionally, symptoms related to later stages of HD such as apathy and parkinsonism can overlap with the depression characteristics and result in a misdiagnosis (De Souza et al. 2010). In the Enroll-HD study the evaluation of depressive symptoms is made using two depression rating scales: The Problem Behaviour Assessment (PBA) and the Hospital Anxiety Depression Scale (HADS).

The Problem Behavioural Assessment Short Version (PBA-s) is part of the Core Assessments, in other words, the information is collected as mandatory at every visit. This instrument is originally a 40-item semi-structured interview designed to obtain information about behavioural symptoms relevant to HD. However, the version used by Enroll-HD is a short
one created by the Behavioural Phenotype Working Group of the European Huntington’s Disease Network (EHDN) for use in the REGISTRY study, with the argument that behavioural symptoms were not the primary focus and a shorter instrument was required (Orth et al. 2010). The short version of the PBA-s then contains 11 items, each measuring frequency and severity of symptoms related to altered affect, thought content and coping styles, covering an extensive range of behaviours including: depressed mood, low self-esteem, anxiety, suicidal thought, aggressive behaviour, irritability, perseverance, compulsive behaviours, delusions, hallucinations, and apathy (Enroll-HD Study Team 2011).

The information collected from the PBA is presented in the dataset named “Enrol” which contains data gathered from all annual visits. Following the definitions provided by the Enroll-HD Data Dictionary, each type of behaviour has a specific number (e.g. 1 for depressed mood = pba1) and is evaluated with regards severity (pba1sv) and frequency (pba1fr) rating from a 0-4 scale in which 0 means “absent” symptom and 4 means “severe” (Enroll-HD Study Team 2018). The rater considers frequency and severity of the behaviour over the past month. A variable named “depscore” is also provided by Enroll-HD and it represents the total score resulted from the addition of composite scores for depressed mood + suicidal ideation + anxiety (Enroll-HD Study Team 2018, Enroll-HD Study Team 2020). These composite scores are calculated by multiplying severity by frequency for each symptom, which are then summed to create a composite score. For example: Depression = (severity of depressed mood*frequency of depressed mood) + (severity of suicidal ideation*frequency of suicidal ideation) + (severity of anxiety*frequency of anxiety) (Enroll-HD Study Team 2020).

The Hospital Anxiety and Depression Scale was developed in the early 1980s as an instrument to measure emotional disorders in nonpsychiatric patients within a hospital setting (Zigmond and Snaith 1983). It is composed by a 14-item self-administered questionnaire evaluating the presence and severity of anxiety and depression. Each item scores 0-3 with a total score of 21 for each of the symptoms analysed, seven items for anxiety and seven items for depression (Zigmond and Snaith 1983). In order to reduce the risk of false positive and bias, the scale does not consider signs of anxiety and depression resulting from physical disorders (e.g. fatigue and insomnia), which represents an advantage, once the confounding factor of having physical illnesses may decrease the sensitivity in screening for depression (Brennan et al. 2010). The HADS has been widely used to evaluate psychological distress and has been considered to have satisfactory diagnostic accuracy, as demonstrated in a meta-analysis.
published in 2010, even though in this study it did not demonstrate to be significantly superior to other instruments (Brennan et al. 2010). It has been validated in several languages, countries and settings (Bjelland et al. 2002, Snaith 2003) and it is also one of the National Institute for Health and Care Excellence (NICE) recommended tools for diagnosis of depression and anxiety (Pilling et al. 2011).

Another previous research paper published in 2010 (De Souza et al. 2010) validated the HADS, both sub-scales of depression and anxiety, for the use in HD assessments and reported the high capacity of this method to reduce the influence of the somatic symptoms of HD in the diagnosis. The study also sustained the original intent for the subscales to be used separately to identify casesness (De Souza et al. 2010).

When analysing the best assessment method to be used in this present study, two factors contributed for the choice of the PBA scale to be discarded. Firstly, the total PBA that represents depression (depscore) could not be used, once it refers to a cluster formed by depressed mood, suicidal ideation and anxiety and it would not provide an adequate picture of depressive symptoms alone. Secondly, the PBA subscale that represents depressive mood itself is also subdivided in three aspects: severity (pba1sv), frequency (pba2fr) and worst (pba1wo) which represent different aspects of depression and there was insufficient reference in literature to support the use of those variables alone for the statistical analyses.

In their study, De Souza et al. intended to analyse the criterion validity of three rating scales (the Beck Depression Inventory-II, the HADS, and the Depression Intensity Scale Circles) as screening measures for depression in the HD population when compared to the traditional semi-structured psychiatric interview. To achieve this, fifty HD participants were recruited following the inclusion and exclusion criteria, provided informed consent, completed the three different assessments for depression and had their current psychiatric status assessed using the schedules for clinical assessment in neuropsychiatry (SCAN), and ICD-10 diagnosis as the gold standard (De Souza et al. 2010). Through the statistical analysis of the receiver operating characteristics (ROC) curves the sensitivity, specificity, positive, and negative predictive values were calculated for different cut-off scores on each rating scale (De Souza et al. 2010). Additionally, the calculation of the “area under the curve” (AUC) for each rating scale provided an indication of the discrimination property of the different instruments (De Souza et al. 2010). According to the authors of the study, the optimal cut-off is considered the score at which the scale best distinguishes between depressed and non-depressed individuals in the population,
and this is determined by the cut-off that presents the maximal sum of sensitivity and specificity (De Souza et al. 2010). As a result, HADS-D showed optimal cut-off of 6/7 to maximally discriminate between patients affected and non-affected by depression in the HD population (De Souza et al. 2010). In other words, individuals who presented HADS-Depression above 6 were considered depressed and the ones who scored below 6 were considered not depressed for the purpose of this study.

For this reason, supported by the results of the study presented by De Souza et al. in 2010 and in the absence of a dichotomic variable discriminating depressed and nondepressed patients in the Enroll-HD dataset, the cut-off of 6 was utilised in this research to determine individuals suffering from depression. In Enroll-HD study, the HADS is part of the Extended Assessments, but, despite this, enough data was gathered in order to provide adequate sample size for this research.

Later in this study the HADS-Depression was also utilised to identify the severity of the depressive symptoms for the respective assessments, following the classification provided by Zigmond and Snaith (1983) (Zigmond and Snaith 1983):

0-6: normal
7-10: mild mood disturbance
11-14: moderate mood disturbance
15-21: severe mood disturbance

Despite the well-recognized validity in diagnosing depression and the fact that it is one of the assessment tools validated by NICE for use in primary care, the use of the HADS-D as a method to assess depression severity has been questioned by some authors (Cameron et al. 2011, Mitchell et al. 2011). An important aspect found regarding the use of HADS-D for measuring depression severity related to the possible tendency of this tool to classify the patients in a milder category when compared to other assessment methods, such as the 17-item Hamilton Rating Scale for Depression (HRSD-17), the Patient Health Questionnaire 9 (PHQ-9) and the Beck Depression Inventory, Second Edition (BDI-II) (Cameron et al. 2011). For this reason, some studies raised concerns that the use of HADS-D may confuse physicians, lead to inaccurate classification of patients severity levels and hinder the decision of the more adequate treatment (Mitchell et al. 2011). However, once this study utilizes observational data collected by Enroll-HD, the choices of the pharmacological treatments were already made for
each participant and the factors influencing the decisions as well as the guidelines followed by
the physicians for each patient could not be controlled by the researcher. Additionally, it is
unknown if HADS-D was the assessment method chosen by the physicians to diagnose and
classify depression in each patient. That being considered, the use of HADS-D will not be
considered as a limitation for the characterization of the patients and the analyses of
pharmacological treatments (work packages 2,3 and 4) but will indeed be taken into
consideration for the analysis of improvement of depression scores in which the classification
was made by the researcher using the HADS-D work package 5.

3.1.4 Clinical parameters

The clinical parameters of HD and non-HD participants were analysed in this study
through the data provided by Enroll-HD, which consisted of several data files. The files
contained data items defined by variables. The Enroll-HD periodic dataset files are either
subject-based, meaning that the variables contained in the file describe participant information
that is not specific to a visit (e.g. demographic information), or visit-based, meaning that the
file contains information regarding baseline or follow-up visits (e.g. age, weight) (Enroll-HD
Study Team 2011).

Key variables are also provided by Enroll-HD and consist of variables that are identical
for each visit-based data file, allowing the link and identification of information belonging to
the same participant. Regarding the ‘Profile’ dataset, the ‘Enrol’ dataset and the ‘Pharmacotx’
dataset (the ones used in this research), the key variable linking the information is the ‘subjid’.
This variable relates to the identification of the participant in the Enroll-HD study and it is a
result of a one-way transformation from HDID to recoded HDID in order to comply with the
data protection requirements (Enroll-HD Study Team 2018).

Each work package of this research works with a different set of variables according to
what is provided by the Enroll-HD dataset. A brief description of the content of the three
datasets analysed in this study in terms of variables is provided below:

‘Profile’: Provides general information collected at baseline and updated annually. It contains
62 subject-based variables describing gender, ethnicity, CAG repeats, medical history, etc.
‘Enrol’: Provides information based on follow-up visits and updated information from the baseline visit. There are 303 variables describing age, weight, habits, assessments, etc.

‘Pharmacotx’: For Enroll-HD, pharmacotherapies (e.g. anti-depressants), non-pharmacotherapies (e.g. psychotherapy, physiotherapy) and nutritional supplements (e.g. vitamin C supplements) are recorded in separate logs. ‘Pharmacotx’ provides information about the current pharmacological therapies to which participants are subjected, as well as the history of medication. This information is updated continuously when a visit is conducted and does not contain medication changes and short-term treatments (pain killers, antibiotics). There are 11 variables in this dataset.

Table 17, Table 18 and Table 19 in the Appendix 1 demonstrate all the variables provided by Enroll-HD datasets (‘Profile’, ‘Pharmacotx’ and ‘Enrol’, respectively) and their respective meanings.

In Pharmacotx’, information about all dose regimens is collected, with exception of medication changes or temporary medication uses that happened between. Drug name is coded using WHO-Drug Dictionary. Enroll-HD staff is asked to be precise when entering the indication of drug use. Dose/unit is captured in text format and for dose variations within the day, for example, the staff is asked to adjust the unit dose such that all the information can fit in a single entry. Daily intake is captured coding four digits (in the morning, at noon, in the evening, at night), in which each digit represents the number of doses taken per day (for example, 4 tablets taken at equal intervals = 1111, or a single dose taken at bedtime = 0001) and if frequency is higher than 4 times per day, doses that overlap the same time period are kept together (e.g. 1 dose very early morning and 2 doses mid-morning = 3000). In order to capture the frequency, staff have to choose one of the options: daily, every 2nd day, every 3rd day, weekly, every 2nd week, monthly, every 2nd month, every 3rd month, annually, as needed. Although pro re nata (PRN) medication is also recorded, data regarding this type of medication will not be included in this research and only regular medication will be analysed. For capturing the route of administration, staff is asked to choose one of the options: per oral, per rectum, subcutaneous, intramuscular, intravenous, transdermal, sublingual, inhaler or other (routes provided in abbreviations which are given in full on the EDC and paper CRF. Start and stop dates are captured in date format, however, via de-identification process, this date will be converted in a number that represents the length of time since enrolment (e.g. 100 represents 100 days.
after enrolment, whereas -30 represents 30 days before enrolment). A last variable will indicate whether or not the drug therapy is ongoing (yes or no) (Enroll-HD Study Team 2018).

Data collection and the completion of CRF is performed by trained Enroll-HD site staff, ensuring that data entry is as complete as possible and there are no blank spaces. Guidance is provided in case data are unavailable (e.g. “write unknown, and explain the reason why it is not available” or “if a procedure was not done or not applicable, enter N for not applicable or U for unavailable where appropriate on paper CRFs. Do not write outside of the designated boxes”). However, this type of data collection is inevitably prone to missing data, especially considering the worldwide nature of this study and the enormous number of participating sites and subjects. For this reason, the approach to be considered in this study regarding missing data is to dedicate a significant space of this research analysing the quality of the data and the amount of missing information in order to evaluate whether it will be suitable for the purpose. In this sense, the missing data will be identified and examined according to Enroll-HD Data Handling Manual and will not be considered in the statistical analyses. Some of the statistical methods such as the ones involving regressions will also automatically disregard missing value and consider this in the final N for the analysis.

3.1.5 Statistical Analyses

In this research, different statistical approaches are used to examine depressive symptoms within the Enroll-HD population.

The three datasets provided by Enroll-HD and utilised in this study were evaluated in terms of completeness and accuracy of the information collected by Enroll-HD. At the end, the suitability of the data for the purpose of this study is evaluated. This is achieved by using descriptive statistics to analyse the quality of the data with regards the frequencies of missing data, errors and inconsistencies.

The next sets of analyses consisted in describing the demographic, social and clinical characteristics of the participants and their pharmacological treatments for depression, respectively. The statistical analyses involved in this part of the study include measures of central, and analysis of frequencies The One-way ANOVA and the \( \chi^2 \) test were used to evaluate the differences between HD and non-HD participants with depressive symptoms.
The statistical method chosen to evaluate depressive symptoms over time was the mixed model, and the reason for this lies in the fact that this model is the most adequate to evaluate how fixed and random effects influence the response from a subject. Although there are discrepancies with regards the definitions of fixed and random effects according to the different contexts in which they are used, in summary (and taking into account the objectives of this study), fixed effects are constant across individuals whereas random effects can vary (Gelman 2005). The analysis of the depression scores over time in this research is achieved considering time as a fixed effect and patients as a random effect. By recognizing the influence of fixed and random effects, the mixed model allows a more accurate definition of the factors affecting the depression scores over time, rather than simply observing repeated measurements.

Lastly, the factors that may be related with improvements in depression scores among HD patients. A logistic regression model was chosen to achieve this objective. In this case, the result is represented by the improvement (or not) in depression scores, and which factor may be related with the positive results.

SPSS software version 26 was the statistical tool utilised in all sets of analyses performed in this study.

3.1.6 Period of time evaluated in this study

In this study, different periods of time were used to explore different aspects of depression and antidepressant therapy. The initial set of information gathered at the moment of enrolment of each participant is called “baseline” and then, considering that Enroll-HD study collects data on an annual basis, the following sets of information are considered to represent the period of one year for the purpose of this research and are, therefore, called “year 1”, “year 2”, “year 3”. Since each participant will enrol in a different time, the exact dates will vary, but still represent the same length of time of one year between the visits from baseline.

It is essential to emphasize that Enroll-HD counts on extremely strong data privacy and protection of information procedures (see section 3.1.2) before the release of information. Whatever data that are considered sensitive and may expose or identify the participants are either omitted or transformed, which is the case of dates of any kind within the datasets. For this reason, rather than working with dates, this study will evaluate information gathered annually from the initial assessment of each participant at baseline.
3.1.7 The student’s contribution to the methodology

Throughout this study, the following steps were taken and tasks done in order to contribute to the methodology and structure this work:

![Diagram showing the student's contribution to the methodology]

Figure 2: The student’s contribution to the methodology

3.2 Work package 1

3.2.1 Materials

The Enroll-HD periodic Datasets analysed in this study are part of the 4th Enroll-HD Periodic Dataset (PDS4) released in October 2018. It constituted a collection of 11 different excel files containing several types of data and, from this total, this study was performed by analysing three datasets only: Profile, Enroll and Pharmacotx.
3.2.2 Data Sources

The datafile Profile contains general information, as well as updates stemming from visits that take place in an annual basis. Demographic, medical history, genetic information (trinucleotides cytosine, adenine, and guanine - ‘CAG’ repeats) and mortality data are part of the Profile spreadsheet. The dataset is comprised of 62 variables and each row of the dataset represents the information collected in one annual visit represented by the variable ‘seq’.

Consequently, in this spreadsheet there are 15,301 rows, each one uniquely and exclusively belonging to one participant. The analysis of this dataset consisted in evaluating the frequency of cells with unknown information (9999), missing data (9998), not applicable (9997), wrong information (9996) and the classification ‘Null’ which was applied to count and analyse cells with no information, or blank spaces. These criteria were chosen according to the Enroll-HD Data Dictionary 2018 to examine the proportion of useful data that can be utilised further in this study.

The Enroll file contains visit-depending information collected during the visits made by each participant. Each row of the file corresponds to one visit and participants have different numbers of visits/rows, depending on when they enrolled in the study. In this file, the assessments are made and the data is gathered by filling separate forms as follows:

- Key variables
- Medical history – Main
- Medical history - Group Drug use for non-medical reasons
- General Variable Items I (HD Category)
- Group Vital Signs
- General Variable Items II
- Unified Huntington’s Disease Rating Scale (UHDRS)
- Cognitive Assessments (Cognitive)
- Mini Mental State Examination (MMSE)
- Physiotherapy Outcomes Measures (Physiotherapy)
- Problem Behaviours Assessment – Short (PBA-s)
- Short Form Health Survey – 12v2 (SF-12)
- Hospital Anxiety and Depression Scale Snaith Irritability Scale (HADS-SIS)
• Work Productivity and Activity Impairment-Specific Health Problem Questionnaire (WPAI-SHP)

Finally, the Pharmacotx file records information about drugs and pharmacological treatments of the participants, including variables for dosages, frequency, changes and routes, in a total of 11 variables. More specifically, information was filtered by the indications of the drugs related to depression and those included the following descriptions: depression, agitated depression, antidepressant therapy, depressed mood, depressive symptom, dysthyemic disorder and major depression.

3.2.3 Variables

The variables in the three datasets ‘Profile’ (62), ‘Enroll’ (303) and ‘Pharmacotx’ (11) were evaluated in terms of completeness, accuracy and correctness.

3.2.4 Data Quality Analysis Method

A bespoke Excel tool was utilised to count blank and empty spaces throughout the spreadsheets in order to evaluate the frequency of completeness. The same strategy was used to analyse the percentage of codes 9999, 9998, 9997 and 9996 in all the three datasets. According to the Enroll-HD PSD4 Data Dictionary 2018, the codes mean respectively unknown, missing, not applicable and wrong values, whose percentages were used to interpret the quality of those datasets. The evaluation considered each variable and their specific total (100%) which differed depending on previous questions. Additionally, the Pharmacotx spreadsheet was evaluated with regards to the accuracy for daily doses, units, route, indication and ATC codes. It was intended to evaluate the amount of information that would be suitable for research purposes and entries that were unclear were named “inconsistencies” for the purpose of this study. In this case, only records containing the unit “milligram” were considered, records containing “grams” were converted into “milligrams” and all other units were disregarded, as information such as “1 capsule” or “one tablet” was not considered useful in regard the dose. Moreover, it was observed that some drugs presented more than one ATC code. Once the
rationale behind the use of ATC codes consists of serving as a tool for drug utilization and improve quality of drug use, in this case, the presence of more than one ATC code does not provide assertive information of the indication of such pharmacological agent. For example, the drug ‘prednisone’ has two ATC codes: A07EA03 that refers to its use as a corticosteroid acting locally and also the code H02AB07 that refers to prednisone as a glucocorticoid for systemic use. Since this study handles a significant amount of data, the use of filters is extremely important and, in the case of considering the use of ATC codes, the filters mechanisms would not be accurate finding the correct indication (depression and depressive symptoms) and data would be missed. For this reason and aiming to use as much accurate data as possible, the variable “more than one ATC code” was added to the analysis as an inconsistency, showing that it is no useful information and was disregarded when performing the statistical analyses. Finally, the last parameter for inconsistencies was related to “the use of the drug”, in which the indication for the treatment of depressive symptoms was evaluated. It was observed that some drug agents were identified as for treating depression and depressive symptoms, although there is no reference in the literature or in previous studies for such use. This group consists of an assortment of different pharmacological agents just as first-generation antipsychotics, antihistamines, antimuscarinics, N-Methyl-D-aspartate receptor (NMDA) blockers, dopamine antagonists, herbal preparations, and so on, which will not be considered in this study due to the lack of clinical evidence and literature support.

### 3.3 Work package 2

#### 3.3.1 Study Design

This is a cross-sectional study.

#### 3.3.2 Participants

The first step of this study consisted in the analysis of data from PDS4 (n=15,301) with the intention of identifying individuals presenting depressive symptoms, according to their baseline evaluation in the depression sub-scale of the Hospital Anxiety and Depression Scale
The results showed in a total of 3,910 individuals and from those, 826 belong to pre-manifest group, composed by HD patients who have not manifested motor symptoms yet. Manifest group comprises 2498 HD patients who have already developed motor symptoms. Finally, the family group (318) and the genotype negative participants (268) represent control groups. The classification using the term “pre-manifest” and “post-manifest/manifest” related to the manifestation of motor symptoms in HD, which is one of the clinical signs for HD diagnosis (Walker 2007) and the terms used by Enroll-HD to characterise the participants (Enroll-HD Study Team 2011).

3.3.3 Data Sources

The information analysed in this study originated from the PDS4 provided by Enroll-HD and the datasets analysed were the ‘Profile’, ‘Enroll’, and ‘Pharmacotx’.

3.3.4 Clinical Parameters

The clinical parameters examined were habits (e.g., alcohol, smoking and use of drugs), symptoms (HD motor manifestations, depression, irritability, apathy, cognition, psychosis, anxiety, functionality, independence and suicidal ideation) and the use of antidepressant pharmacological agents.

Habits of alcohol, smoking and use of drugs were examined in terms of whether those habits were present at the moment of assessment, considering that the participant is asked if they currently drink alcohol, if they currently smoke and if they currently use drugs. The history of habits was also evaluated with information captured by Enroll-HD in the same manner as the current habits, but referring to the possibility of the participant having problems in the past (has the participant had alcohol problems in the past, has the participant ever smoked, has the participant ever abused drugs) (Enroll-HD Study Team 2018).

The use of antidepressants in particular, was assessed with information taken from the Pharmacotx spreadsheet. All participants who presented at least one antidepressant in their pharmacological scheme had a positive answer reported to this analysis. The antidepressants were categorised according to the mechanism of action, utilising information from the British
National Formulary (BNF). Table 20 in the Appendix 2 demonstrates the classification of drugs used in this study (Complete 2020):

- SSRI: Selective serotonin reuptake inhibitors
- SNRI: Serotonin and norepinephrine reuptake inhibitors
- NDRI: Norepinephrine and dopamine reuptake inhibitors
- SARI: Serotonin antagonist and reuptake inhibitors
- MAOI: Monoamine oxidase inhibitors
- Atypicals antidepressants
- Tricyclics antidepressants

It is known, however, that the pharmacological treatment of depression may include other agents, such as antipsychotics, benzodiazepines and herbal preparations, as well as antidepressant drugs can be indicated to treat other conditions, such as pain, obsessive-compulsive disorder, anxiety, etc. This practice will be examined and discussed further in the next work packages of this study.

3.3.5 Statistical Methods

This work package described the characteristics of individuals with depressive symptoms (N=3,910). The results for each group (pre-manifest, manifest, family and genotype negative) were divided into four domains: demographics, clinical characteristics, habits and symptoms. In this later analysis of the symptoms, the following manifestations were tested: motor symptoms, depression, irritability, apathy, cognition (utilising the MMSE), psychosis, anxiety, TFC (UHDRS Total Functional Capacity), independence scale (UHDRS) and suicidal ideation.

Subsequently, the characterisation of the cohort was undertaken via statistical analysis, in which aspects such as scores and numerical measures were evaluated using the analysis of variance One-way ANOVA test and subsequent Tukey’s post hoc test was used to evaluate whether differences between the groups were statistically significant. The quantitative
variables analysed were age, age of HD diagnosis, CAG repeats, BMI, motor score, motor score age of onset, depression score, depression age of onset, irritability score, irritability age of onset, apathy score, apathy age of onset, cognitive function score, age of cognitive function decline onset, psychosis score, psychosis age of onset, anxiety score, TFC score, FAS and independence scale.

The $\chi^2$ test was performed to verify potential associations between the variables analysed. The variables analysed were region, marital status, employment status, reason for unemployment, gender, mother with HD, father with HD, use of antidepressants, history of alcohol abuse, alcohol abuse, history of tobacco abuse, current smoking habit, history of drug abuse, drug abuse, history of motor symptoms, history of depression, history of apathy, history of cognitive decline, history of psychosis and history of suicidal ideation.

3.4 Work package 3

3.4.1 Study Design

This study utilises descriptive analyses to characterise the pharmacological treatments used by depressed individuals in the Enroll-HD cohort to manage depressive symptoms. There was an intention to statistically compare the HADS-Depression scores of the groups of individuals taking different pharmacological agents, however, this analysis was not possible due to wide discrepancies in sample sizes. For this reason, this study is mainly exploratory.

3.4.2 Participants

The period of time analysed in this study was one year, represented by the first assessment made at the time of enrolment (baseline) in Enroll-HD study. There is not a fixed year analysed, but a fixed period (as amount of time, which is one year), represented by the first year of enrolment and can be different for each participant. The medicines that were in use during the specified time between baseline and year 1 were included in this study (see section 3.1.6 for more details about time period included in the study). Enroll-HD intends to assess participants annually, with visits that can be face-to-face or phone contact. However, as
the date of the visit depends on each particular individual’s schedule, the period analysed in this study will approximately be 365 days (between first visit baseline and second visit).

The pharmacological treatment was selected according to the mechanisms of action of the drugs, which included SSRIs, SARIs, SNRIs, atypical antipsychotics, Tricyclics, NDRIs, antipsychotics and benzodiazepines, which were classified according to Table 17 presented at Appendix 1. These drugs had their uses in antidepressant therapies supported by literature and clinical practice (Mulder et al. 2018, Galts et al. 2019, Ogawa et al. 2019).

The preliminary evaluation of the data demonstrated that only half of the cohort (1788 individuals) could have their data evaluated in the study. From the remaining 1788 individuals, 463 did not possess records for their medication in the Pharmacotx file and 1325 participants were not taking any of the medicines of interest in the specified period of this study. From the latter group, the majority of 1017 were HD patients. Figure 2 depicts the progression from the total population to the final sample that had their drug treatments analysed.

![Flow chart for the selection of the final sample to be analysed](image-url)
3.4.3 Data Sources

The datasets utilised in this analysis were the ‘Enroll’ and the ‘Pharmacotx’ files. The ‘Enroll’ dataset was used to identify individuals with depression at baseline. Once the identification was done, the ‘Pharmacotx’ dataset was used to examine the pharmacological agents used for depressive symptoms.

3.4.4 Clinical Parameters

The pharmacological treatment for depression was selected according to the mechanisms of action of the drugs, which included SSRIs, SARIs, SNRIs, atypicals, tricyclics, NDRIs, antipsychotics and benzodiazepines, which were classified according to Table 17 presented at Appendix 1. Those drugs had their uses in antidepressant therapies supported by literature and clinical practice (Mulder et al. 2018, Galts et al. 2019, Ogawa et al. 2019).

3.4.5 Statistic Methods

In the first step of this study, the frequencies of the antidepressant therapies were analysed, using a customised Excel tool, and percentages were obtained in order to evaluate which drug treatment was more prevalent in both HD and control groups.

3.5 Work package 4

3.5.1 Study Design

This is a longitudinal study.

3.5.2 Participants

Individuals involved in this study were previously identified with depressive symptoms, following the criteria established in section 3.1.3. The total participants included was 3,910. In the interest of evaluating the way depression manifests throughout the disease course, the HADS-depression scores were examined over a period of 3 years, with the first
assessment made in the beginning of the first year of enrolment (baseline), totaling 4 measurements: baseline, fist year (1\textsuperscript{st} year), second year (2\textsuperscript{nd} year) and third year (3\textsuperscript{rd} year). The total number of individuals who presented such data was N= 2,600.

3.5.3 Groups

In order to compare the different treatments for depressive symptoms, participants had their drug records analysed and groups were formed according to the classification of antidepressants. This step resulted in four groups as showed:

Group 1: Combination – more than one antidepressant agent (N=656)

Group 2: SSRIs only (N=904)

Group 3: Not on any antidepressant agent (N=696)

Group 4: Other – SNRIs, NDRIs, SARIs, atypicals, tricyclics, MAOIs (N=344)

When establishing the criteria to form the groups, it was only considered whether the participants were taking the drugs or not during the period of 3 years. As the objective of this work package was to observe depression scores over time and verify factors linked to this, specific responses to treatments, changes that may have happened during this period and augmentation strategies were not captured in this analysis.

Rather than exploring the use of antidepressants individually, this approach was necessary to ensure the homogeneity of size of the groups, once this aspect has a direct influence on the statistical method utilised (mixed-model). In Enroll-HD dataset, it was observed that SSRIs were the most used class of antidepressants for treating depressive symptoms (904). On the other hand, dataset showed a minimal number of participants (20) using NDRIs and (28) tricyclics antidepressants, for example. This enormous divergence between the sample sizes may interfere at the group level on the accuracy of the estimates.

Moreover, when establishing the criteria to form the groups, it was only considered whether the participants were taking the drugs or not during the period of 3 years. As the objective of this work package was to observe depression scores over time and verify factors linked to this, specific responses to treatments, changes that may have happened during this period and augmentation strategies were not captured in this analysis.
3.5.4 Characterisation of groups

The results of the mixed-model made it possible to identify which of the groups demonstrated better depression scores when compared to the others. The next step consisted in characterising the types of treatment being used within each group and evaluate if those pharmacological approaches are contributing to the reduction of the depression scores.

3.5.5 Data Sources

Information to perform this study was extracted from the ‘Enroll’ and the ‘Pharmacotx’ datasets provided by Enroll-HD.

3.5.6 Statistical Methods and Variables

In order to evaluate the inter-individual and intra-individual changes in depression scores of the groups over a period of 3 years (4 measurements from baseline), a linear mixed-model (LMM) was performed in SPSS. Traditionally, it was common to observe studies in which, instead of the LMM, the generalised linear models (GLM) involving the analysis of variance (ANOVA) and covariance (ANCOVA) were used to examine measurements across time. However, these methods require an accurately balanced repeated-measure design, which was a hard condition to meet and, when not met, could induce the increase of type I errors. Another requirement for GLM is the intrinsic assumption of independence of observations, which is also not easily met when it comes to the evaluation of longitudinal data (Shek and Ma 2011). Furthermore, in a mixed-model, it is expected that the responses from a subject are influenced by fixed and random effects. If an effect has an impact in the whole population, it can be considered as fixed and will affect the covariance of the data simply, whereas a random effect is associated with a sampling procedure and, in addition, often adds correlation between the cases. Therefore, the model requires adjustments in the covariance structure which are not possible in procedures such as GLM, once it assumes independence of observations.

For this reason, the LMM was the chosen method of analysis in this study. Three models were made in SPSS to compare the effects of the variables “antidepressant” and “time” over a
period of 3 years among the groups of patients using different types of antidepressant therapies.

The first step of this analysis aimed to evaluate the HADS-depression score over time, considering the effect of the group only. Next, covariables were included to the model, as to, firstly, examine whether they are significant in the model, and secondly, analyse their influence on the estimated means for HADS-depression scores. The following covariates were included in the model: age, HD category (as per Enroll-HD), BMI, gender, alcohol abuse, drug abuse, number of CAG repeats, motor score (UHDRS), disease stage (as per UHDRS-TFC), independence scale (UHDRS), MMSE, HADs-Anxiety and suicidal ideation. The covariates were chosen according to previous literature review which mentioned the potential influence of these aspects in the manifestation of depression.

Lastly, once the influencer variables were identified, a new mixed-model was performed uniquely including the factors that resulted statistically significant in the previous steps. As a result, the means of HADS-depression could be thoroughly examined as they were adjusted by the model considering the impact of all covariables.

3.6 Work package 5

3.6.1 Study Design

This is a case-control study, in which HD affected individuals were evaluated with regards their improvement in depressive symptoms.

3.6.2 Participants

Depressed and non-depressed participants were selected according to the methodology described in section 3.1.3. For this analysis, in particular, only HD affected participants of Enroll-HD were analysed. The chosen period of time was the first year after enrolment, which was represented by assessments made at baseline and after one year (year 1) (see section 3.1.6 for details about period of time). It is important to note that, although this study analyses the approximate period of one year for each participant, the exact year analysed varies according to when the participant was started in Enroll-HD study. The precise year of enrolment is not
specified due to data privacy reasons. The HADS-Depression was utilised to identify the status of the depressive symptoms for the respective assessments, following the rule provided by Zigmond and Snaith (1983) (Zigmond and Snaith 1983):

0-6: normal
7-10: mild mood disturbance
11-14: moderate mood disturbance
15-21: severe mood disturbance

HD individuals who presented significant improvement (less depressed) within this period were selected for this analysis and by “significant improvement” it was considered those whose score jumped down to a better level of depression, meaning that they were less depressed. Individuals whose score decreased but did not pass to a better level of depression were not considered. Two groups were formed as follows:

- HD affected individuals who demonstrated improvement in depressive symptoms
- HD affected individuals who did not show improvement in depressive symptoms

Once the population was defined, variables originated from the Enroll, Profile and Pharmacotx files were selected in order to represent clinical, demographic, symptomatic and pharmacological characteristics of the participants.

3.6.3 Clinical Parameters

In the first step of the analysis, 38 variables related with clinical parameters and demographic characteristics were initially chosen according to literature review and taking into account their potential influence on depression scores. The variables are HD stage (pre-manifest or manifest regarding motor symptoms), age (which was later grouped due to sample sizes issues), gender, history of suicidal ideation, history of impaired movements, history of depression, history of irritability, history of violence or aggressive behaviour, history of apathy, history of obsessive-compulsive behaviour, history of psychosis, history of cognitive decline, alcohol abuse, drug abuse, CAG repeats, motor score (UHDRS), disease stage (UHDRS-TFC), independence scale (UHDRS), MMSE total, anxiety score (HADS), suicidal ideation (PBA), irritability (PBA), aggressive behaviour (PBA), apathy (PBA), obsessive-compulsive behaviour
(PBA), perseverative thinking (PBA), paranoid thinking (PBA), hallucinations (PBA), disoriented behaviour (PBA), polypharmacy, use of SSRIs, use of SARIs, use of atypical antidepressants, use of tricyclic antidepressants, use of NDRIs, use of antipsychotics for treating depression, use of benzodiazepines for treating depression.

### 3.6.4 Statistical Methods

The statistical test chosen for this analysis was the logistic regression in order to verify which factors contribute to the decline of the HADS-depression.

The logistic regression method was proposed in the late 1960s and early 1970s as an alternative to previous techniques such as the ordinary least squares regression and the linear discriminant function analysis, that had too strict statistical assumptions for handling dichotomous research questions (Chao-Ying Joanne et al. 2002, Lei and Koehly Laura 2003).

In this study, the logistic regression was used to explain the possible relationship between the dependent variable (decline in the HADS-depression, indicating patients that became less depressed) and other independent variables. By describing this relationship, it was intended to obtain a possible set of characteristics that a patient may have that facilitate the clinical improvement of depression.

A sample size calculation was not carried out, once this study utilized observational data provided by Enroll-HD and data was not collected by the researcher. The study started by verifying the frequencies of the variables chosen, in relation to the dependant variable. Part of the data had to be excluded due to the lack of values for the variables being tested. The next step consisted in selecting variables using the stepwise method and calculating the odds ratios and respective p-values through the simple logistic regression test. The level of significance adopted for this analysis was p<0.05. Once potential variables were identified in a univariate manner, the existence of possible correlation/multicollinearity was tested to avoid increased standard errors and inaccurate estimation results. In this study, considering the variance inflation factor <10, no linear relation was identified between the variables. Then, a multivariate logistic regression model was performed to eventually generate odds ratios and respective p-values for the chosen variables. By calculating the odds ratios and the adjusted
odds ratios, it was possible to take into consideration all the influence the variables have on each other. In this step, level of significance p<0.05 was considered once again.

4. Results

4.1 Work package 1

Profile: Details were analysed for a total of 15,301 participants. The quality analysis of the dataset showed a low proportion of user-defined missing values (2.02%) and, more importantly wrong data corresponded to 0.02% of the dataset only. Table 1 demonstrates the quantities for blank spaces in the Profile spreadsheet and respective reasons for the absence of information.

<table>
<thead>
<tr>
<th>Table 1: Data Quality analysis of the Profile Dataset</th>
</tr>
</thead>
<tbody>
<tr>
<td>Count</td>
</tr>
<tr>
<td>Unknown (9999)</td>
</tr>
<tr>
<td>Missing (9998)</td>
</tr>
<tr>
<td>Not Applicable (9997)</td>
</tr>
<tr>
<td>Wrong (9996)</td>
</tr>
<tr>
<td>Null</td>
</tr>
</tbody>
</table>

Enroll: The results of the data quality analysis of Enroll dataset are depicted in Table 2. Enroll dataset contains information from the Enroll-HD study gathered during baseline visit and follow-up visits. Primary forms for key variables, medical history, vital signs and use of drugs for non-medical reasons presented a small proportion of missing data, errors and blank spaces with no specific justification, ranging from 0.0 to 7.8%. The Unified Huntington’s Disease Rating Scale (UHDRS) assessments for motor, total functional capacity and independence scale, as well as the cognitive assessments showed insignificant percentages for missing data (0.08 to 0.2%) and errors (0.02 to 0.09%), and less than 10% for blank spaces. All the Problem Behaviour Assessments had extremely low percentages for missing data (0.0 to 1.3%) and wrong (0.01%), and slightly higher rate for blank spaces (9.7%). Lastly, the forms Mini Mental State Exam, Physiotherapy Outcomes, Short Form Health Survey, Hospital Anxiety and Depression Scale and Work Productivity and Activity Impairment also demonstrated high quality in terms of
completeness and errors. Those forms, however, presented with higher percentages of blank spaces, respectively 38.4%, 58.67, 33.3%, 43.4% and 59.5%.
<table>
<thead>
<tr>
<th>Key variables</th>
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<th>Missing (9998)</th>
<th>Not Applicable (9997)</th>
<th>Wrong (9996)</th>
<th>Null (%)</th>
</tr>
</thead>
<tbody>
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<td>Form: Medical history – Main</td>
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<td>0.00</td>
<td>0</td>
<td>0.00</td>
</tr>
<tr>
<td>Form: Group Drug use for non-medical reasons</td>
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<td>111</td>
<td>0.73</td>
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<tr>
<td>Form: Variable Items - General Variable Items I (HD Category)</td>
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<td>0.13</td>
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<td>1893</td>
<td>311</td>
<td>0.02</td>
</tr>
<tr>
<td>UHDRS Total Functional Capacity (TFC)</td>
<td>0</td>
<td>0</td>
<td>205</td>
<td>97</td>
<td>0.04</td>
</tr>
<tr>
<td>UHDRS Independence Scale (Function)</td>
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<td>0</td>
<td>1316</td>
<td>993</td>
<td>0.09</td>
</tr>
<tr>
<td>Cognitive Assessments (Cognitive)</td>
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<td>Mini Mental State Examination (MMSE)</td>
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<td>0</td>
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<tr>
<td>Physiotherapy Outcomes Measures (Physiotherapy)</td>
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<td>11</td>
<td>0.01</td>
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<tr>
<td>Short (PBA-s) - Group Domain scores</td>
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<td>0</td>
<td>0</td>
<td>0</td>
<td>0.00</td>
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<tr>
<td>Short (PBA-s) - Depressed mood</td>
<td>0</td>
<td>0</td>
<td>287</td>
<td>391</td>
<td>0.32</td>
</tr>
<tr>
<td>Short (PBA-s) - Suicidal Ideation</td>
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<td>0</td>
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<td>10508</td>
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<tr>
<td>Short (PBA-s) – Anxiety</td>
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<td>0</td>
<td>1493</td>
<td>10446</td>
<td>8.43</td>
</tr>
<tr>
<td>Short (PBA-s) – Irritability</td>
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<td>0</td>
<td>1380</td>
<td>10156</td>
<td>8.20</td>
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<tr>
<td>Short (PBA-s) - Aggressive behaviour</td>
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<td>0</td>
<td>1328</td>
<td>10065</td>
<td>8.12</td>
</tr>
<tr>
<td>Short (PBA-s) – Apathy</td>
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<td>0</td>
<td>1462</td>
<td>10433</td>
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</tr>
<tr>
<td>Short (PBA-s) - Perseverative thinking or behaviour</td>
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<td>0</td>
<td>1641</td>
<td>10609</td>
<td>8.56</td>
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<tr>
<td>Short (PBA-s) - Obsessive-Compulsive Behaviours</td>
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<td>1459</td>
<td>10312</td>
<td>8.32</td>
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<tr>
<td>Short (PBA-s) - Delusions paranoid thinking</td>
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<td>0</td>
<td>1530</td>
<td>10500</td>
<td>8.47</td>
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<tr>
<td>Short (PBA-s) – Hallucinations</td>
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<td>0</td>
<td>1622</td>
<td>10622</td>
<td>3.21</td>
</tr>
<tr>
<td>Short (PBA-s) - Disoriented Behaviour</td>
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<td>0</td>
<td>1531</td>
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<td>0</td>
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<td>HADS-SIS</td>
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<td>0</td>
<td>0</td>
<td>0.00</td>
</tr>
</tbody>
</table>
Pharmacotx: The results of data analysis of Pharmacotx dataset are presented in Table 3, and demonstrated an extremely low percentage of errors, missing data or irrelevant information. All results showed minimal percentages ranging from 0% to 0.8% (depicted in Table 3).

![Table 3](image)

Table 3: Data Quality Analysis of the Pharmacotx Dataset (N=11088)

<table>
<thead>
<tr>
<th>Count</th>
<th>Percentage (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unknown (9999)</td>
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<tr>
<td>Missing (9998)</td>
<td>908</td>
</tr>
<tr>
<td>Not Applicable (9997)</td>
<td>55</td>
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<td>Wrong (9996)</td>
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</tr>
<tr>
<td>Null</td>
<td>72</td>
</tr>
<tr>
<td>Zero for dose</td>
<td>12</td>
</tr>
</tbody>
</table>

Low percentages for imprecise information about units (1.9%), route (0.02%) and preparations with combined or unspecified drugs (0.1%). There were 562 (5%) records of drugs with more than one ATC code, that may restrict the power of interpretation of the data by a statistical software package once the specific indication in those cases is uncertain. In addition, 4.8% of the drugs analysed for depressive symptoms are not traditional pharmacological agents for this purpose and do not present either proven effectiveness, clinical evidence or literature support. Results are depicted on Table 4 below:

![Table 4](image)

Table 4: Inconsistencies in the Pharmacotx Dataset (N=11088)

<table>
<thead>
<tr>
<th>Count</th>
<th>Percentage (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Units</td>
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<td>Route &quot;other&quot;</td>
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</tr>
<tr>
<td>Ingredients combined or unspecified</td>
<td>15</td>
</tr>
<tr>
<td>More than one ATC code</td>
<td>562</td>
</tr>
<tr>
<td>Dose range</td>
<td>0</td>
</tr>
<tr>
<td>Use of the drug</td>
<td>539</td>
</tr>
</tbody>
</table>
4.2 Work package 2

The first step of this study included data from PDS4 of the entire population of Enroll-HD compared pre-manifest, manifest and control groups with the intention of verifying the prevalence of individuals presenting depressive symptoms. It is known that the prevalence of depression in HD varies considerably from study to study and it is thought to range from 33-69% (Julien et al. 2007, Dale et al. 2015). Results are depicted in Tables 5 and 6.

Table 5: Prevalence of Depression Enroll-HD (N=15,301)

<table>
<thead>
<tr>
<th>Count</th>
<th>Percentage (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>11,725</td>
</tr>
<tr>
<td>Yes</td>
<td>3576</td>
</tr>
<tr>
<td>Total</td>
<td>15,301</td>
</tr>
</tbody>
</table>

Table 6: Prevalence of depression per group in Enroll-HD population PDS4

<table>
<thead>
<tr>
<th>Depression</th>
<th>NO</th>
<th>YES</th>
<th>Percentage of depressive patients (%)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-manifest</td>
<td>2938</td>
<td>601</td>
<td>16.9</td>
<td>3539</td>
</tr>
<tr>
<td>Manifest</td>
<td>5742</td>
<td>2301</td>
<td>28.6</td>
<td>8043</td>
</tr>
<tr>
<td>Genotype negative</td>
<td>1643</td>
<td>283</td>
<td>14.6</td>
<td>1926</td>
</tr>
<tr>
<td>Family</td>
<td>1402</td>
<td>391</td>
<td>21.8</td>
<td>1793</td>
</tr>
<tr>
<td>Total</td>
<td>11725</td>
<td>3576</td>
<td></td>
<td>15301</td>
</tr>
</tbody>
</table>

A higher proportion of HD patients (28.6%) showed depressive symptoms compared the other patient groups (Table 6). Followed by the family controls (21.8%), then the Pre-manifest HD patients (16.9%) and finally the e showed 16.98%, and genotype negative (14.6%) and family groups demonstrated respectively 14.6% and 21.8% of individuals with depressive symptoms. Results demonstrated a study sample consisting of individuals with depressive symptoms N=3,910, which was used as the population to be described.

Demographic characteristics: Figures 3 illustrates the results χ2 test performed to assess demographic characteristics and the regions where participants are from (p<0.001). Results showed the largest proportion of participants as being from Europe in all groups. The second most popular region from which participants are from is represented by Northern America.
Significant differences were observed for the marital status and were depicted in Figure 4. Larger part of HD patients all groups are in a partnership, however, with regards the proportions for married and divorced status, 16.5% (p<0.001) of the pre-manifest sample were married and 7.2% (p<0.001) were divorced, whereas 5.6% (p<0.001) of the manifest individuals were married and 13.7% (p<0.001) were divorced.
The χ² test provided an analysis of the employment status of participants (p<0.001), which were demonstrated in Figure 5. It could be seen that among pre-manifest patients, the greatest proportion is full-time employed (45.6%), whereas within manifest patients, the vast majority is not employed (80.2%, p<0.001). Enroll-HD then, inquired the reason if not employed (Figure 6), and the total of individuals who were not working was N=2,545. The principal answer among pre-manifest patients was unemployed (36%, p<0.001), though among manifest patients, the main reason is retirement (50.4%, p=0.011). Genotype negative group showed mixed results with reasons varying between retirement (19.6%, p<0.001), working in the home (27.2%, p<0.001) and unemployed (33.7%, p=0.004). Family control group’s main reason for being away from work was also retirement (59.3%, p<0.001).
Clinical Features: Starting with the clinical features presented in Table 7, the analysis demonstrated that female individuals were the majority in all groups. The pre-manifest group presented lower average age (40.2%, p<0.001) when compared to manifest group (52.1%, p<0.001), genotype negative group (42.1%, p=0.023) and family group (55.4%, p=0.022). The average age of HD diagnosis for pre-manifest and manifest groups were similar, 41.6 and 47.9 respectively, as well as the means for number of CAG repetitions of 42.6 and 43.8. The body mass index (BMI) was also evaluated, once overweight and obesity can be considered risk factors for developing depression (Pereira-Miranda et al. 2017), and results demonstrated
that control groups showed higher BMIs (28 – genotype negative group and 28.8 – family group) than HD patients (27.0 – pre-manifest and 25.3 - manifest). The use of antidepressants was 29.6% (p<0.001) among pre-manifest patients and this percentage decreased slightly when it comes to manifest individuals (28.2%, p<0.001). Genotype negative individuals demonstrated lower percentages of the use of antidepressants (13.7%, p<0.001), as well as individuals in family group, the use of antidepressants was 13.8%.

Table 7: Clinical characteristics of the group in the Enroll-HD population PDS4

<table>
<thead>
<tr>
<th></th>
<th>Pre-manifest</th>
<th>Manifest</th>
<th>Genotype negative</th>
<th>Family</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (female)</td>
<td>58.6%</td>
<td>51.4%</td>
<td>66.8%</td>
<td>60.4%</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>Age (±SD)</td>
<td>40.2 (±11.2)</td>
<td>52.1 (±12.2)</td>
<td>42.1 (±14.2)</td>
<td>55.49 (±12)</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>Age of HD Diagnosis (±SD)</td>
<td>41.6 (±12.2)</td>
<td>47.9 (±12.0)</td>
<td>NA</td>
<td>NA</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>CAG repeats (±SD)</td>
<td>42.6 (±2.9)</td>
<td>43.8 (±3.6)</td>
<td>20.37 (±3.7)</td>
<td>19.89 (±3.3)</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>BMI (±SD)</td>
<td>27 (±6.3)</td>
<td>25.3 (±5.3)</td>
<td>28.00 (±7.5)</td>
<td>28.82 (±6.1)</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>Mother HD positive</td>
<td>54.8%</td>
<td>47.7%</td>
<td>48.4%</td>
<td>NA</td>
<td>0.010</td>
</tr>
<tr>
<td>Father HD positive</td>
<td>44.3%</td>
<td>47%</td>
<td>39%</td>
<td>NA</td>
<td>0.033</td>
</tr>
<tr>
<td>Antidepressants</td>
<td>29.6%</td>
<td>28.2%</td>
<td>13.7%</td>
<td>13.8%</td>
<td>p&lt;0.001</td>
</tr>
</tbody>
</table>

NA= not applicable; SD=standard deviation; BMI=body mass index; HD=Huntington’s Disease

Habits: χ² test was used to evaluate associations between the prevalence of habits (alcohol abuse, smoking and use of drugs for non-medical reasons) and the history of habits among the groups. Results are depicted in Table 8 and demonstrate percentages for the use of alcohol among the groups ranging from 34.6% in manifest group to 50.9% in pre-manifest, with rates for other groups being in the middle (43.4% in genotype negative and 48.6% in family group). The proportions for smoking habit were also very close to each other, around 30%, apart from family group which demonstrated 26.3% of frequency for the smoking habit.
Drug abuse was the less prevalent habit, with the lowest frequency in manifest group (3%) and the highest in genotype negative (9.9%).

Table 8: Differences between groups in terms of history and habits of alcohol, tobacco and drug consumption assessed by the χ² test at baseline

<table>
<thead>
<tr>
<th></th>
<th>Pre-manifest N=601</th>
<th>Manifest N=2301</th>
<th>Genotype negative N=283</th>
<th>Family N=391</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>History of alcohol abuse</td>
<td>11.3%</td>
<td>10.7%</td>
<td>8.9%</td>
<td>5.6%</td>
<td>0.012</td>
</tr>
<tr>
<td>Alcohol abuse</td>
<td>50.9%</td>
<td>34.6%</td>
<td>43.4%</td>
<td>48.6%</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>History of tobacco abuse</td>
<td>52.6%</td>
<td>51.6%</td>
<td>51.6%</td>
<td>50.8%</td>
<td>0.953</td>
</tr>
<tr>
<td>Smoke habit</td>
<td>32.6%</td>
<td>30.1%</td>
<td>33.1%</td>
<td>26.3%</td>
<td>0.138</td>
</tr>
<tr>
<td>History of drug abuse</td>
<td>20%</td>
<td>9.3%</td>
<td>21.3%</td>
<td>9%</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>Drug abuse</td>
<td>8%</td>
<td>3%</td>
<td>9.9%</td>
<td>2.3%</td>
<td>p&lt;0.001</td>
</tr>
</tbody>
</table>

Symptoms: Finally, the symptomatology of the individuals with depression in the Enroll-HD population was assessed. In this analysis, the following symptoms were analysed in terms of frequency of occurrence (presented as mean values) and frequencies: motor symptoms, depression, irritability, apathy, cognition (utilising the MMSE), psychosis, anxiety, TFC (UHDRS Total Functional Capacity), independence scale (UHDRS) and suicidal ideation. Table 9 demonstrates the results for this evaluation.
Table 9: Symptomatology differences between groups assessed by the One-way ANOVA and χ2 tests at baseline

<table>
<thead>
<tr>
<th></th>
<th>Pre-manifest</th>
<th>Manifest</th>
<th>Genotype negative</th>
<th>Family</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=826</td>
<td>N=2498</td>
<td>N=318</td>
<td>N=268</td>
<td></td>
</tr>
<tr>
<td>Motor signs (±SD)</td>
<td>4.1 (±5.5)</td>
<td>36.5 (±19.7)</td>
<td>2.5 (±4.1)</td>
<td>1.8 (±3.0)</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>Hx Motor</td>
<td>27.7%</td>
<td>98.6%</td>
<td>6%</td>
<td>Nav</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>Motor symptoms - Age of onset (±SD)</td>
<td>41.7 (±12.9)</td>
<td>45.5 (±11.6)</td>
<td>NA</td>
<td>NA</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>Depression (±SD)</td>
<td>8.6 (±2.68)</td>
<td>8.4 (±3.04)</td>
<td>8.2 (±2.36)</td>
<td>8.2 (±2.52)</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>Hx Depression</td>
<td>76.8%</td>
<td>79.9%</td>
<td>55.8%</td>
<td>5%</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>Depression - Age of onset (±SD)</td>
<td>31.5 (±12.51)</td>
<td>42.6 (±13.72)</td>
<td>33.2 (±14.14)</td>
<td>Nav</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>Irritability (±SD)</td>
<td>3.9 (±5.0)</td>
<td>4.2 (±5.4)</td>
<td>2.8 (±4.5)</td>
<td>2.0 (±3.3)</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>Hx Irritability</td>
<td>57.5%</td>
<td>72%</td>
<td>33.2%</td>
<td>Nav</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>Irritability - Age of onset (±SD)</td>
<td>35.2 (±12.7)</td>
<td>44.3 (±13.0)</td>
<td>32.6 (±15.4)</td>
<td>Nav</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>Apathy (±SD)</td>
<td>2.9 (±3.7)</td>
<td>4.8 (±4.6)</td>
<td>1.6 (±2.9)</td>
<td>1.1 (±2.5)</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>Hx Apathy</td>
<td>53.2%</td>
<td>73.7%</td>
<td>24.7%</td>
<td>Nav</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>Apathy - Age of onset (±SD)</td>
<td>35.5 (±12.2)</td>
<td>47.4 (±12.5)</td>
<td>33.3 (±15.2)</td>
<td>Nav</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>Cognition (±SD)</td>
<td>28.3 (±1.9)</td>
<td>24.8 (±4.3)</td>
<td>28.8 (±1.4)</td>
<td>28.6 (±1.8)</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>Hx Cognitive</td>
<td>19.2%</td>
<td>61.1%</td>
<td>5.7%</td>
<td>Nav</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>Cognition impairment - Age of onset (±SD)</td>
<td>40.1 (±10.9)</td>
<td>47.1 (±12.2)</td>
<td>36.53 (±18.0)</td>
<td>Nav</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>Psychosis (±SD)</td>
<td>0.3 (±1.6)</td>
<td>0.4 (±1.9)</td>
<td>0.4 (±2.1)</td>
<td>0.04 (±0.4)</td>
<td>0.003</td>
</tr>
<tr>
<td>Hx Psychosis</td>
<td>6%</td>
<td>12.5%</td>
<td>4.6%</td>
<td>Nav</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>Psychosis – Age of onset (±SD)</td>
<td>33.0 (±10.6)</td>
<td>46.1 (±13.2)</td>
<td>28.3 (±13.7)</td>
<td>Nav</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>Anxiety (±SD)</td>
<td>9.1 (±4.0)</td>
<td>8.0 (±4.2)</td>
<td>8.6 (±4.2)</td>
<td>8.1 (±3.9)</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>TFC (±SD)</td>
<td>12.31 (±1.3)</td>
<td>8.0 (±3.3)</td>
<td>12.7 (±0.9)</td>
<td>12.7 (±0.6)</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>FAS (±SD)</td>
<td>24.3 (±1.5)</td>
<td>18.0 (±6.0)</td>
<td>24.7 (±1.0)</td>
<td>24.7 (±0.7)</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>Independence (±SD)</td>
<td>97.5 (±5.7)</td>
<td>77.0 (±15.6)</td>
<td>99.0 (±3.7)</td>
<td>99.3 (±2.6)</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>Hx Suicidal ideation</td>
<td>38.3%</td>
<td>36.9%</td>
<td>23.3%</td>
<td>Nav</td>
<td>p&lt;0.001</td>
</tr>
</tbody>
</table>

Hx=history; SD=standard deviation; TFC=total functional capacity; FAS= Functional Assessment (UHDRS)
As expected, the analysis of the motor symptoms (UHDRS at baseline) showed poorer results for the HD manifest group, which were dramatically higher (36.5) than the other groups. Pre-manifest patients demonstrated worse motor score (4.1) than the control groups genotype negative and family (2.5 and 1.8, respectively) showing that even before chorea manifests in HD patients, those are susceptible to impaired movements than the normal population. Among HD affected participants, the mean age of onset of motor symptoms for HD pre-manifest patients was 41.7, whereas for manifest patients it was 45.5. Although the mean ages appear similar, the post-hoc test showed statistical differences between them.

The evaluation of depression (HADS at baseline) showed that participants had statistically different scores, even though the numbers appear very similar according to the HADS test. The frequency of past depressive signs is superior in HD patients, ranging from 76-79%, whereas in control groups this frequency is 50-55%. Additionally, the post-manifest group demonstrated the manifestation of depressive symptoms later in life, with mean age of 42.6 years, while the pre-manifest and genotype negative groups showed means, of 31.5 and 33.2, respectively. For the last group of family members, data was not available to perform the analysis.

Signs of irritability (PBA at baseline) were also evaluated through the PBAs and results indicated worse scores for HD patients when compared to control groups. HD patients scored means of 3.9 and 4.28 in pre-manifest and post-manifest groups respectively, and control groups scored 2.8 (genotype negative) and 2.0 (family group). In addition, HD patients also experienced irritability more frequently in the past than control groups, and this could be observed on the percentages of history: 57.5% in pre-manifest groups, 73.7% in post-manifest groups, against 24.7% in genotype negative individuals. Irritability seems to have started earlier in life for pre-manifest and genotype negative groups (35.2 and 32.6), and, in the post-manifest group the mean age of onset was 44.3. The family group did not present enough data to support the analysis of irritability for this group.

With regards to apathy, the scores were very similar to the results obtained when analysing irritability. HD affected individuals presented the worsened results with 53.2% for pre-manifest group and 73.7% for post-manifest group, whereas control group of genotype negative participants were only 24.7% apathetic. The family group again did not present enough data to support the analysis of apathy.
The cognitive function of participants was assessed using the MMSE at baseline and participants were also asked about previous disabilities at baseline evaluation. The results showed that, at baseline, cognitive function scores were very similar for all groups, ranging around 28. The age of onset was lower for the control group (36.5) than for the HD patients varying from 40.1-47.1. However, when analysing the history of cognitive impairment, post-manifest group demonstrated a strikingly higher percentage of 61.1% when compared to other groups (pre-manifest 19.2% and genotype negative 5.7%).

The cluster called ‘psyscore’ used by Enroll-HD is a sub-score calculation (PBA at baseline) that comprises delusions, paranoid thinking and hallucinations. Throughout the evaluation of symptoms in this study, ‘psyscore’ remained very low and poorly prevalent. The highest frequency is presented by motor manifest HD patients (12.5%), followed by 6% in the pre-manifest group and 4.6% in the genotype negative group. The mean ages of onset for psychosis were between 28.3 and 46.1 years.

For the parameters of Anxiety (HADS at baseline), Total Functional Capacity (UHDRS at baseline), Functional Assessment (UHDRS at baseline), Independence Scale (UHDRS at baseline) and History of Suicidal Ideation, data collected allowed the evaluation of the scores at baseline and frequency uniquely.

When analysing data for anxiety, the pre-manifest group showed the highest anxiety scores of (9.1), in relation to the other groups. Surprisingly, post-manifest group had the lowest score (8.0), followed by control groups - family group (8.1) and genotype negative (8.69).

Participants were examined with regards their functionality were assessed using the TFC and Functional Assessment (UHDRS). Both tests depicted similar results, in which, as expected, functional capability was superior in non-HD individuals. Likewise, patients affected with HD, whose movements have not been yet impaired by the disease, were also considerably functional. On the other hand, post-manifest HD patients had the poorest scores and were, therefore, the least functional when compared to the other groups. Following the same reasoning, the level of independence was worse in the post-manifest group (77.0%), while the others appeared to be fully independent (97.5-99.35%).
Lastly, the frequency of suicidal ideation was examined, and for pre-manifest group, post-manifest group and genotype negative group were, respectively 38.3%, 36.9%, 23.3%. The family control group did not present available data to support analysis. Surprisingly, the pre-manifest group showed higher rates of suicidal thoughts compared to the manifest group and the control groups.

All parameters were considered statistically significantly different according to the One-way ANOVA and the Chi-Square test results (level of significance 0.05), which indicate that at least one of the groups being compared had different result. Those distinctions will be more deeply considered in terms of clinical significance further at the discussion section. Once it was identified that the groups were different when comparing the means of the quantitative variables, Tukey post-hoc was performed to evaluate specifically the comparisons between the groups one-to-one.

4.3 Work package 3

Table 10 depicts the comparisons between those percentages for HD patients and control group.

Results showed that SSRIs are indeed the first-line treatment and the most frequently prescribed type of antidepressant for depression on both control (33.1%) and HD (20.7%) groups. SNRIs represent the second more frequent type of serotoninergic antidepressants used as monotherapy for both HD (5%) and control group (9.8%), followed by atypicals (HD – 3.3% and control – 2.5%). The lowest percentages were observed for tricyclics (HD – 1.7% and control – 3.7%) and SARI (HD – 0.6% and control – 1.2%). Moreover, antipsychotics and benzodiazepines were also prescribed as monotherapy for depression in the Enroll-HD cohort. The antipsychotics alone were present in 3.1% of the control group whereas in the HD groups these drugs were much more prevalent (15.1%). Benzodiazepines were observed as a monotherapy in 5.7% of the HD group and 12.9% in the control group. Subsequently, proportions for combinations were analysed and the results demonstrated that a considerable percentage of participants were receiving a combination of antidepressants and antipsychotics (20.1%) in the HD group, while in the non-HD group this proportion was much lower (3.1%). Another type of combination of drugs included different types of serotoninergic
antidepressants, and this particular treatment approach was identified in 5.4% of the HD individuals and 9.2% of the control group. Then, other participants demonstrated to be taking both antidepressant drugs and benzodiazepines, with this combination representing 11% in the HD group and 17.2% in the control group. The next type of drug treatment for depressive symptoms included antipsychotics and benzodiazepines, which were identified in 2.5% of the HD group and 1.2% in the control group. Finally, the last combination consists in the use of these drugs all together, antidepressants, antipsychotics and benzodiazepines, and this treatment was frequent in 8% of the HD group and only 1.2% of the control group.

<table>
<thead>
<tr>
<th>HD</th>
<th>Drug</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>20.7%</td>
<td>SSRI</td>
<td>33.1%</td>
</tr>
<tr>
<td>0.6%</td>
<td>SARI</td>
<td>1.2%</td>
</tr>
<tr>
<td>5.0%</td>
<td>SNRI</td>
<td>9.8%</td>
</tr>
<tr>
<td>3.3%</td>
<td>Atypical</td>
<td>2.5%</td>
</tr>
<tr>
<td>1.7%</td>
<td>Tricyclic</td>
<td>3.7%</td>
</tr>
<tr>
<td>1.1%</td>
<td>NDRI</td>
<td>1.8%</td>
</tr>
<tr>
<td>15.1%</td>
<td>AP</td>
<td>3.1%</td>
</tr>
<tr>
<td>5.7%</td>
<td>BZD</td>
<td>12.9%</td>
</tr>
<tr>
<td>20.1%</td>
<td>AP+AD</td>
<td>3.1%</td>
</tr>
<tr>
<td>5.4%</td>
<td>Comb_AD</td>
<td>9.2%</td>
</tr>
<tr>
<td>11.0%</td>
<td>AD+BZD</td>
<td>17.2%</td>
</tr>
<tr>
<td>2.5%</td>
<td>AP+BZD</td>
<td>1.2%</td>
</tr>
<tr>
<td>8.0%</td>
<td>AP+AD+BZD</td>
<td>1.2%</td>
</tr>
</tbody>
</table>
Enroll-HD provided information about the depression scores evaluated by the HADS method, however, the comparison of the means of depression by pharmacological treatment was not attempted, due to the heterogeneity of the groups sample sizes.

### 4.4 Work package 4

The first analysis resulted in a mixed-model in which both time and group were statistically significant (p<.0001). Subsequently, the covariates were added to the model in order to verify their influence on the depression scores. The results showed that out of all the covariables evaluated, gender (p=0.0129), anxiety (p<.0001), alcohol abuse (p<.0001) and suicidal ideation (p=0.0022) were considered statistically significant.

Once the covariables were identified, a final mixed-model was executed comprising the evaluation of HADS-depression over time, with time as a fixed effect, the individuals as random effect and gender, alcohol abuse and anxiety as covariates. The variable ‘suicidal ideation’ could not be included in this analysis as a covariate for the reason that the number of observations was minimum, leading to an unbalanced “n” for this variable. It could have led to excessive adjustments by the statistical software and, consequently, erroneous interpretation of the data. Despite this, it is well accepted that suicidal ideation and depression are closely related, especially when it comes to neurodegenerative and terminal conditions such as HD (Kachian et al. 2019) and, hence, this aspect will be explored further in this study.

The initial result provided by the mixed-model relates to the performance of the HADS-depression throughout the period of three years. Results demonstrated that depression in both control group and HD individuals decreased over this time. At baseline, HD patients showed a depression score estimated mean of 10.37 which decrease to 9.57 after the third year. At the same time, control group started at baseline with a depression score estimated mean of 9.46 and, at the third year, reduced to 7.85. The mixed-model also demonstrated statistical significance for the comparisons between the assessments made at baseline and at year 3 for both control group (p<.0001; CI (95%) = 0.8047-2.415) and HD group (p<.0001; CI (95%) = 0.4777-1.1177).

The line graph in Figure 7 below depicts these results:
Figure 8: HADS-Depression means for HD affected and non-affected individuals at baseline and year 3 (after 3 years of observation)

Table 12 shows the percentages of those reductions:

<table>
<thead>
<tr>
<th>Group</th>
<th>N</th>
<th>Difference</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>656</td>
<td>0.6</td>
<td>7%</td>
</tr>
<tr>
<td>2</td>
<td>904</td>
<td>1.1</td>
<td>12.4%</td>
</tr>
<tr>
<td>3</td>
<td>696</td>
<td>1.4</td>
<td>16.6%</td>
</tr>
<tr>
<td>4</td>
<td>344</td>
<td>0.7</td>
<td>8.22%</td>
</tr>
</tbody>
</table>

Results of the mixed-model also demonstrated that the depression scores measured at baseline and at the third year were statistically and significantly different in the control group (p<.0001; [CI (95%) = 0.8047-2.415]) and HD group (p<.0001; [CI (95%) = 0.4777-1.1177]).

More results from the mixed-model showed differences between the means of HADS-depression of HD affected and non-affected individuals. In this analysis, HD patients demonstrated depression score estimated mean of 9.7, whereas in the control group, the estimated mean for depression score was 8.1. Not only was the mean higher for HD affected
individuals, but also the difference between those groups was statistically significant (p<.0001; [CI (95%) = -2.2555 to -0.09323]).

The next results of the mixed model represent gender distinctions for depression scores among HD and non-HD subjects. It could be seen that, in this cohort, men demonstrated higher depression score estimated mean (9.3) than women (8.6) and this difference was also considered statistically significant (p=0.0129; [CI (95%) = -0.9633 to – 0.1142]). It is well-known in literature that women are more likely to develop depressive symptoms than men (Dale et al. 2016), however, in terms of severity, male showed to have worse depression than female, in general.

Last, but not least, the mixed-model provided information about the differences between the groups of medication that the participants were taking. The primary results for this evaluation are general means for the groups, which are represented in Table 13:

<table>
<thead>
<tr>
<th>Group</th>
<th>N</th>
<th>Estimated Means</th>
<th>Standard Error</th>
<th>CI (95%) Lower</th>
<th>Upper</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>656</td>
<td>9.3</td>
<td>0.2</td>
<td>8.7</td>
<td>9.8</td>
</tr>
<tr>
<td>2</td>
<td>904</td>
<td>8.5</td>
<td>0.2</td>
<td>8.0</td>
<td>9.0</td>
</tr>
<tr>
<td>3</td>
<td>696</td>
<td>8.4</td>
<td>0.2</td>
<td>7.9</td>
<td>8.8</td>
</tr>
<tr>
<td>4</td>
<td>344</td>
<td>9.4</td>
<td>0.3</td>
<td>8.8</td>
<td>10.1</td>
</tr>
</tbody>
</table>

When comparing the HADS-depression between the groups, it could be seen that groups 1 and 4 had the greatest scores at baseline and, after a period of 3 years, they remained with the higher scores, followed by group 2 and group 3 eventually, with the lowest score. Group 1 is representing patients using a combination of traditional antidepressants; Group 2 is formed by patients using SSRIs only; in Group 3 patients are not under treatment with traditional antidepressants; and Group 4 is a mixed group with patients taking other types of antidepressants (SNRIs, NDRIs, SARIs, atypical, tricyclics). The line graph in Figure 8 depicts the estimated means of the groups over a period of three years.
Figure 9: Estimated means of HADS-Depression by groups at baseline and after 3 years of observation.

*Figure 8* demonstrates that the estimated means of depression scores in all groups decreased after a period of 3 years.

*Table 14* shows information about the difference in means of depression score between the different groups analysed and the respective p-values demonstrating whether this comparison is statistically significant. The mean values of depression scores of the participants in each group of the second column were subtracted from the mean values of depression scores of the participants in each group of the first column and the result is represented in the third column. Positive values shown in the third column demonstrate that the mean of depression score in the first group was higher than the one in the second group, whereas negative values result from the mean of depression score in the second group being greater than the one in the first group.
According to the mixed-model, the following results could be observed, with statistically significant differences:

- Individuals taking SSRIs are likely to see their HADs score fall by 8.7% compared to those taking combination.

- Depression scores of individuals treating depressive symptoms with other drugs than traditional antidepressants were 10% (0.9) lower than the depression scores of those individuals taking combinations of traditional antidepressants.

- Depression scores of individuals taking SSRIs were approximately 10% (-0.9) lower than the depression scores of those individuals taking traditional antidepressants, such as SNRIs, NDRIs, SARIs, atypical, tricyclics and MAOIs.

- Depression scores of individuals treating depressive symptoms with other drugs than traditional antidepressants were approximately 11% (-1.0) lower than the depression scores of those individuals taking traditional antidepressants, such as SNRIs, NDRIs, SARIs, atypical, tricyclics and MAOIs.

### 4.5 Work package 5

In this analysis, two groups were evaluated: HD individuals who presented significant improvement in their depression score (less depressed – details of the classification presented on the methods section 3.6.2) and those who did not demonstrate improvement.
Table 15 depicts the clinical parameters (selected by the stepwise method) with respective odds ratios and p-values calculated by the univariate logistic regression. In the group of patients who did not show improvement in their depression scores, 12.4% were aged 39 years or younger, 20.9% were between 40 and 49 years of age, 29.8% were between 50 and 59 years of age and 36.7% were between 60 and 80 years of age. Additionally, 87% of those individuals demonstrated past experiences with motor symptoms and the following frequencies for the history of psychiatric symptoms: depression – 82.6%, irritability – 74.5%, apathy – 74.2%, obsessive-compulsive behaviour – 56.8% and cognitive decline 56.5%. The percentages for the motor scores of those subjects concentrated between the mild (52.6%) and moderate (34.3%) levels of severity. Lastly, the apathy prevalence for this group was 70.9%.

Then, regarding the group in which HD individuals did demonstrate some improvement in depression scores, the results of the descriptive analysis indicated that, similarly to the other group, 23% were pre-manifest patients, while 76.9% had already manifested motor symptoms. In this group, 16.6% were younger than 39 years old, 22.4% were in between 40 to 50 years of age, 25.6% were between 50 and 60 years of age and 35.2% were older than 60. As expected, a high percentage of the individuals (81.1%) presented a history of involuntary movements, whereas the following frequencies were observed for psychiatric symptoms: depression – 77.8%, irritability – 68%, apathy – 67.4%, obsessive-compulsive behaviour – 50.9% and cognitive decline 50.8%. As well as the previous group, the greater parts of the patients presented mild (52.9%) and moderate (34.3%) motor symptoms, and the frequency of apathy among this group was 64.5%.

The univariate logistic regression provided results of odds ratios and p-values taking as reference p<0.05. The first significant variable was related to the manifestation of motor symptoms, in which pre-manifest patients had 18.6% increase in the odds of improvement of depression score when compared to manifest patients (OR=1.186, [CI (95%) = 0.931–1.511]; p= 0.167). HD patients younger than 39 had 177% increase in the odds of improving their depressive symptoms in relation to persons in their 50’s (OR=2.779, [CI (95%) = 1.24 6.226]; p=0.0231), while those with age between 40 and 49 had 73.7% increase in the odds of improving depression than persons in their 50’s (OR=1.737, [CI (95%) = 0.807-3.736]; p=0.0231). Individuals who did not experience motor symptoms prior to their diagnosis of HD indicated 56.5% increase in the odds to improve the severity of depression when compared
to those who had a history of involuntary movements (OR=1.565, [CI (95%) = 1.19-2.058]; p=0.0013). The history of depression was also considered significant and individuals who did not experience depression before the diagnosis were had 35% increase in the odds of improving depressive symptoms than those with a previous diagnosis (OR=1.359, [CI (95%) = 1.058-1.746]; p=0.0164). Individuals who did not present history of irritability presented 37.3% increase in the odds of improving depressive symptoms than those who had already shown this symptom in the past (OR=1.373, [CI (95%) = 1.101-1.7112]; p=0.0049). The history of apathy was also considered significant and those who did not present apathy before diagnosis showed 38.7% increase in the odds of improving the severity of their depressive symptoms when compared to those who did (OR=1.387, [CI (95%) = 1.114-1.728]; p=0.0035). The absence of prior episodes of obsessive-compulsive behaviour were also associated as potential protective factor for depression, as those who did not have this feature had 26.8% increase in the odds of ameliorating their depressive symptoms than those who did OR=1.268, [CI (95%) = 1.037-1.549]; p=0.0205). No history of cognitive decline was associated with better depression scores and individuals with no records of previous cognitive decline had 26% increase in the odds of bringing depressive symptoms to a better level when compared to those who presented history of some decline (OR=1.261, [CI (95%) = 1.032-1.542]; p=0.0232). The UHDRS motor score was also significant and, in relation to individuals presenting severe and very severe motor disability (p=0.0116), those who had moderate symptoms had 75.9% increase in the odds of improving depression (OR=1.759, [CI (95%) = 1.108-1.792]) and those who did not present movement impairment at all had an even higher increase in the odds (167%) to improve depression scores (OR=2.674, [CI (95%) = 1.496-4.779]). Lastly, individuals who did not show current apathy had 34% increase in the odds of improving depressive symptoms than those who did have this characteristic (OR=1.341, [CI (95%) = 1.083-1.662]).
Table 14: Variables selected by the stepwise method and results of the univariate logistic regression evaluating potential factors for improvement in depression scores

<table>
<thead>
<tr>
<th>Variable</th>
<th>No improvement</th>
<th>Improvement</th>
<th>OR</th>
<th>CI (95%)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
<td>n</td>
<td>%</td>
<td></td>
</tr>
<tr>
<td><strong>Depression</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;=39 years</td>
<td>113</td>
<td>12.4</td>
<td>111</td>
<td>16.6</td>
<td>2.779</td>
</tr>
<tr>
<td>40-49 years</td>
<td>191</td>
<td>20.9</td>
<td>150</td>
<td>22.4</td>
<td>1.737</td>
</tr>
<tr>
<td>50-59 years</td>
<td>272</td>
<td>29.8</td>
<td>171</td>
<td>25.6</td>
<td></td>
</tr>
<tr>
<td>60-80 years</td>
<td>335</td>
<td>36.7</td>
<td>235</td>
<td>35.2</td>
<td>0.695</td>
</tr>
<tr>
<td><strong>Hx Motor</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>118</td>
<td>12.9</td>
<td>126</td>
<td>18.8</td>
<td>1.565</td>
</tr>
<tr>
<td>Yes</td>
<td>793</td>
<td>87.0</td>
<td>541</td>
<td>81.1</td>
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</tr>
<tr>
<td>Missing = 1</td>
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<td></td>
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<tr>
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<td>17.3</td>
<td>148</td>
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</tr>
<tr>
<td><strong>Hx irritability</strong></td>
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<td></td>
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<td></td>
</tr>
<tr>
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<td>213</td>
<td>31.9</td>
<td>1.373</td>
</tr>
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<td>454</td>
<td>68.0</td>
<td></td>
</tr>
<tr>
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</tr>
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<td>32.5</td>
<td>1.387</td>
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<tr>
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<td>454</td>
<td>68.0</td>
<td></td>
</tr>
<tr>
<td><strong>Hx OC behaviour</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>676</td>
<td>74.2</td>
<td>450</td>
<td>67.4</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>393</td>
<td>43.1</td>
<td>327</td>
<td>49.0</td>
<td>1.268</td>
</tr>
<tr>
<td>Yes</td>
<td>518</td>
<td>56.8</td>
<td>340</td>
<td>50.9</td>
<td></td>
</tr>
<tr>
<td><strong>Hx cognitive decline</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>395</td>
<td>43.4</td>
<td>328</td>
<td>49.1</td>
<td>1.261</td>
</tr>
<tr>
<td>Yes</td>
<td>515</td>
<td>56.5</td>
<td>339</td>
<td>50.8</td>
<td></td>
</tr>
<tr>
<td>Missing = 1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Motor score (UHDRS)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>51</td>
<td>5.6</td>
<td>57</td>
<td>8.5</td>
<td>2.674</td>
</tr>
<tr>
<td>Mild</td>
<td>480</td>
<td>52.6</td>
<td>353</td>
<td>52.9</td>
<td>1.759</td>
</tr>
<tr>
<td>Moderate</td>
<td>313</td>
<td>34.3</td>
<td>229</td>
<td>34.3</td>
<td>1.75</td>
</tr>
<tr>
<td>Severe / Very severe</td>
<td>67</td>
<td>7.3</td>
<td>28</td>
<td>4.2</td>
<td></td>
</tr>
<tr>
<td><strong>Apathy (PBA)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
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<td>264</td>
<td>29.0</td>
<td>235</td>
<td>35.4</td>
<td>1.341</td>
</tr>
<tr>
<td>Yes</td>
<td>645</td>
<td>70.9</td>
<td>428</td>
<td>64.5</td>
<td></td>
</tr>
</tbody>
</table>

Hx: History of the symptom; HD=Huntington’s Disease; OC=obsessive compulsive; UHDRS= United Huntington Disease Rating Scale; PBA= Problem Behaviours Assessment
The results of the multivariate analysis are demonstrated in Table 16. In this test, four variables were identified as a good fit to potentially be related with the improvement in the depression scores. The unadjusted odds ratios (UnAOR) appearing in Table 16 illustrate the odds ratio of one that particular independent variable for predicting the possible improvement in depression score, whereas the adjusted odds ratio (AOR) holds the other relevant variables constants and provides odds ratios that consider the collective effects of the other independent variables included in the model. In this way, the test found the best model that considered the variables and the collective influence they have on the improvement of depression.

The results of the logistic regression revealed that age, motor score, history of motor score and irritability were variables that, when considered together, produced a conjunct effect in the improvement of depression scores of the individuals involved in this study. As the individuals analysed in the univariate model were the same of those analysed in a multivariate manner, the frequencies and proportions remained the same. However, the multivariate logistic regression provided more information on how the variables influenced each other. Regarding the age, the test showed an extremely slight difference from the univariate test, in which individuals younger than 39 years of age showed 2.4 times increase in the odds of improvement of depression score than those on around 50 years of age (AOR=2.497, [CI (95%) = 1.104-5.649]). The UHDRS motor score also demonstrated minimal differences in the adjusted odds ratios, as, in relation to severe/very severe motor disability, individuals who presented moderate motor score showed 1.7 times increase in the odds of improvement of depression scores (AOR= 1.76, [CI (95%) = 1.095-2.831]); individuals with mild motor scores showed 1.62 times increase in the odds of improvement of depression scores (AOR=1.624, [CI (95%) = 1.016-2.594]) and individuals with no movement disturbances showed 1.82 times increase in the odds of improvement of depression scores (AOR=1.829, [CI (95%) = 0.955-3.505]).
### Table 15: Results of the multivariate logistic regression investigating potential factors related to the improvement in depression scores (N=1,578)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Depression</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>No improvement</td>
<td>Improvement</td>
<td>UnAOR CI (95%)</td>
<td>AOR CI (95%)</td>
</tr>
<tr>
<td></td>
<td>n</td>
<td>%</td>
<td>n</td>
<td>%</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;=39</td>
<td>113</td>
<td>12.41</td>
<td>111</td>
<td>16.64</td>
<td>2.779</td>
</tr>
<tr>
<td>40-49</td>
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<td>20.97</td>
<td>150</td>
<td>22.49</td>
<td>1.737</td>
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<td>50-59</td>
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<td>60-80</td>
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<td>36.78</td>
<td>235</td>
<td>35.23</td>
<td>0.695</td>
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<td></td>
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<tr>
<td>Motor Score (UHDRS)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>51</td>
<td>5.6</td>
<td>57</td>
<td>8.55</td>
<td>2.674</td>
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<tr>
<td>Mild</td>
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<td>52.92</td>
<td>1.759</td>
</tr>
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<td>229</td>
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<td>1.75</td>
</tr>
<tr>
<td>Severe/Very severe</td>
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<td>7.35</td>
<td>28</td>
<td>4.2</td>
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</tr>
<tr>
<td></td>
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</tr>
<tr>
<td>Hx Motor</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
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<td>12.95</td>
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<td>793</td>
<td>87.05</td>
<td>541</td>
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<td>Hx Irritability</td>
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<td>213</td>
<td>31.93</td>
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<td>74.53</td>
<td>454</td>
<td>68.07</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>911</td>
<td>100</td>
<td>667</td>
<td>100</td>
<td></td>
</tr>
</tbody>
</table>

*Hx= History of the symptom; UHDRS= United Huntington Disease Rating Scale*
5. Discussion

Medical registries such as Enroll-HD have become more and more important over recent years, due to the progress healthcare has achieved in terms of technology and the increasing need for accountability. In order to provide useful and reliable data, participatory centres must ensure to follow robust quality assurance and quality control procedures (Arts et al. 2002). When evaluating whether the data obtained was suitable for research, what is understood by ‘data quality’ varies greatly and the definitions can be sometimes imprecise or not available. However, it is accepted that the data has good quality once it meets the expectations for the intended uses and shows data consistency (Arts et al. 2002).

The initial results provided demonstrated that, apparently there was no explanation for missing data. However, when exploring the reasons for the high percentage of null spaces, it could be seen that the new version of the Enroll-HD Data Dictionary 2018 contains an update regarding the user-defined missing values. The latest version of the document provides new codes which can be applied when there is no answer for the corresponding variable or question. This fact could possibly explain the high percentage of missing values, once all the data collected prior to the creation of this coding does not count on those alternative answers, and the fields were, consequently, left blank.

According to Enroll-HD Protocol, assessments at baseline and annual follow-up visits are subdivided into three different categories: Core Assessments, Extended Assessments and the Optional Assessments (further information provided in section 3.1.2.4). There is considerable variability from site to site in terms of whether they conduct the extended assessments or not and which ones of the extended assessments they focus on. This may result in blank spaces within the datasets in greater amount which, however, cannot be considered as “missing data” since it is optional for the sites to participate. This may justify the high percentages of blank spaces in the forms Short Form Health Survey, Hospital Anxiety and Depression Scale Snaith Irritability Scale, Work Productivity and Activity Impairment-Specific Health Problem Questionnaire, Mini Mental State Examination and Physiotherapy Outcomes Measures.

The forms “Medical History Main” provides information about the abuse of substances such as alcohol, drugs and the habit of smoking, whereas the “Medical History Group Drug
use for non-medical reasons” provides information about the use of substances that are not part of the medical assortment, for example, marijuana, heroin, cocaine, etc. Those two forms also showed elevated percentage of blank spaces making it unclear whether this data was not recorded or the participant simply did not make use of it. This lack of information may be due to the fact that this questionnaire is completed only once at baseline visit and re-evaluated and updated at subsequent annual visits only when necessary. In other words, once this information is recorded in the first visit and remains unchanged on the follow-up visits, the data collector may find it appropriate to leave it as a blank space. Secondly, when it comes to a participant who do not use such substances (alcohol, drugs, etc), the following questions aiming to specify the habit (which type of drugs the participant uses, for example) are pointless and therefore, once again it might feel adequate for the data collector to leave this information as a blank space. Those hypotheses may serve as possible explanations for the high percentage of spaces in the dataset with no information but could have been avoided if the code 9997 (not applicable) was more often utilised, in such manner to become obvious the record of that specific data is not applicable.

The analysis of Pharmacotx dataset also demonstrated high quality with regards to completeness and missing data. However, some aspects must be considered; firstly, 539 (4.8%) drugs were identified as for treating depression and depressive symptoms, although there is no reference in literature or previous studies for such use. This group consists of an assortment of different pharmacological agents just as first-generation antipsychotics, antihistamines, antimuscarinics, NMDA blockers, dopamine antagonists, herbal preparations, and so on. Some studies have reported the use of unusual drugs such as non-steroidal anti-inflammatory drugs (NSAID), statins and angiotensin agents for the treatment of depression, highlighting the hypothesis of an inflammatory process as part of depression and the link between angiotensin-converting enzyme polymorphisms and the serotonin and dopamine neurotransmitter systems affecting mood. Although it must be considered that physicians have their own prescribing practices and personal experience, the unconventional drugs found in the Pharmacotx dataset were considered unfavourable for the for the purpose of this study, as those correlations are yet to be confirmed. Moreover, due to the lack of evidence, the possibility of error when populating the system with data or collecting the data must be considered, which may, in this case, represent an aspect for improvement not only for the process of collecting data, but also for the quality control system.
Sørensen, Sabroe et al. (1996) classified errors into two groups: systematic errors or type I and random or type II. Type I errors are cause by programming errors, unclear definitions for data items or violation of the data collection whereas type II errors are due to inaccurate data transcription and typing errors or illegible handwriting in the patient medical record (Arts et al. 2002). Just as any other medical registry, Enroll-HD study is susceptible to both type I and II errors, as observed in this analysis. For example, the use of “other” as an item of classification may be the result of an unclear definition. Errors may occur in certain instances, especially when the study proposes to assemble data worldwide, facing all kinds of obstacles, such as intensive training for participatory centres, different languages, audits and the exhaustive task of filling the extensive forms. Despite that, the proportions in Enroll-HD datasets can be considered minimal when analysing the unprecedented number of participants in an HD study, and the judgement on the quality of the data will depend on whether the research question is satisfied or not.

Despite clear definitions of “data quality” are ambiguous or scarce in literature, the requirements for good quality data are determined by its intended use (Arts et al. 2002). In this sense, Enroll-HD provided adequate data for all the statistical analysis and interpretation of results of this study, and this aspect did not affect the ability to explore the clinical scenario of depression in HD. As it is unrealistic to admit that a registry database can be totally free of errors, and also considering the challenges that Enroll-HD faces regarding the management of data coming from multiple centres around the world and concerns with data protection, it is possible to say that Enroll-HD is a reliable platform and a robust data provider. The results of the following analyses in this study highlighted the severe lack of clinical evidence, therefore, the importance of Enroll-HD as a worldwide platform supplying HD-specific data is unquestionable.

Specific objectives of this study target the description of demographic characteristics of participants of Enroll-HD who presented with depressive symptoms and the comparison of those features between HD and non-HD individuals.

Depression is a highly frequent psychiatric disorder and leading cause of disability in general population (Paulsen 2005). It is also associated with other comorbidities, especially neurodegenerative, progressive and terminal illnesses such as HD (Epping et al. 2013). So it is, that literature have reported that patients with previous medical conditions are twice as likely to develop depression when compared to those with no other medical condition (Luber
et al. 2000, Paulsen 2005). Some authors suggest that the prevalence of depressive symptoms varies between 15-69% (Slaughter et al. 2001, Paulsen 2005, Julien et al. 2007, van Duijn et al. 2007, Galts et al. 2019). The results of this study corroborate with these previous findings, as the percentage of depressed HD patients (45.58%) is higher than the proportion of individuals in control groups (36.49%). However, an important limitation in this evaluation lies in the fact that the studies referenced differ greatly in terms of assessment tools (UHDRS, DSM-III, Beck Depression Inventory, PBA, HAM-D) and also in terms of population size, which makes it difficult to compare studies in this field (Galts et al. 2019).

Literature analysing the aspects that motivate people to participate in registry studies is limited. However, some authors have reported that older women are indeed more willing to engage in research, taking into consideration the frequent personal contact with the staff and the benefits stemming from the study (Crystal et al. 2018). This could be observed in the analysis of the gender of participants, in which the majority in all groups is represented by women around their 40’s-50’s.

A result worth discussing when evaluating the clinical aspects is the one obtained for the body mass index (BMI). While genotype negative and family groups showed respectively 28.00 and 28.82 means for BMI, HD pre-manifest and post-manifest groups showed lower means (27.09 and 25.35). Although important guidelines such as the National Heart, Lung and Blood Institute guidelines of 1998 suggest that the BMI values presented can be all considered under the same “overweight” category (NHLBI 1998) which might appear that the results show no clinical significance, past authors have highlighted that both the widths and actual boundaries of the intervals should not be strictly used to guide weight loss recommendations and analysis, once these classifications do not correspond to meaningful risk thresholds (Strawbridge et al. 2000, Gronniger 2006, Stommel and Schoenborn 2010). Instead, this study emphasizes the consistence of the results with previous research in which authors underline the significant weight loss in HD patients when compared to general population (Djoussé et al. 2002). It was suggested that this phenomenon may occur due to higher energy expenditure originated from involuntary movement (Pratley et al. 2000). However, this would not be a suitable explanation for the weight loss in early stages of HD in which involuntary movements are more subtle. Therefore, what other authors propose is that the HTT gene may cause a metabolic fault, leading to a systemic response of generalised loss of body mass (Djoussé et al. 2002). Further studies are necessary to fully understand the physiologic reasons for the
weight loss. Finally, with regards to the clinical aspects of HD, the use of antidepressants was evaluated. It was expected that participants would show high frequencies for the use of antidepressants, once the study population comprises individuals with depressive symptoms. However, demonstrated that small percentages of those patients (ranging around 30%) are being treated with conventional first-line serotoninergic antidepressants. The percentages are even lower when it comes to control groups (13%). It can be argued that the remaining participants were either being treated with alternative approaches or were not at all being treated. The latter case is a worrying situation already mentioned by previous studies in which a significant part of HD affected individuals with depressive symptoms remains untreated (Paulsen 2005, van Duijn et al. 2014). This gap can be in parts attributed to the fact that the underdiagnosis of depression in HD can be common and may occur if affective signs are interpreted simply as a result of the somatic and cognitive aspects of HD itself or as a consequence of the diagnosis and the degree of the disability (De Souza et al. 2010). On the other hand, when considering that depressed patients may be taking unconventional drug treatments other than traditional antidepressants, it is interesting to discuss the use of other pharmacological agents and their role in improving depressive symptoms which may include different agents, such as benzodiazepines, antipsychotics and anxiolytics.

Habits of alcohol, drugs and cigarette consumption were analysed subsequently. The fact that pre-manifest individuals abused alcohol more frequently (50.9%) than manifest individuals (34.6%) may be due to two distinct factors: independence and depression. As it could be seen by the other independence parameters such as ‘independence scale’, for example, pre-manifest patients are highly able to perform daily living activities self-sufficiently, which could include the access to alcohol, rather than manifest patients, whose independence had already stated to be impaired by more advanced stages of the disease. On the other hand, many studies have reported greater frequency of depressive symptoms at the early stages of HD, which may be related to the increased consumption of alcohol among patients of this group (Paulsen 2005, Epping and Paulsen 2011). It is necessary to highlight that, in general population, there is a propensity for depression and alcohol to co-occur, leading to increased severity of depressed mood and, poorer health-related consequences and higher risk of suicide (Regier et al. 1990, Nunes and Levin 2004), which must be carefully considered when evaluating HD patients, who already have to cope with the burden of HD itself.
When analysing the socio-demographic aspects of depressive participants of Enroll-HD, it could be seen that the majority of participants of all groups come from Europe and Northern America and this is simply due to the fact that these are the regions where Enroll-HD has based the studies and where the program started. There is an intention of expanding the study to other sites, including other continents and countries (Enroll-HD Website 2020). Further and more specific information regarding locations, participant centres and number of participants are considered by Enroll-HD as sensitive information that may facilitate the identification of participants and, for this reason, such kind of data is not provided.

The results for ‘marital status’, ‘employment’ and ‘reason if not employed’ demonstrated the major impact that the manifestation of motor symptoms implies in HD patient’s lives, being also confirmed by the poorer capability of working that HD-manifest patients presented: only 12.3% of manifest patients are employed in a full-time job, whereas the other groups showed significantly higher proportions (ranging from 43.3% to 50.4%). These results indicated that the transition through the stages of HD produce major impacts in peoples’ activities of daily living and one can hypothesize that this can be aggravated by psychiatric symptoms, such as depression (Paulsen et al. 2001, Dale et al. 2016). As well as in HD, depression is well-recognised as a leading cause of disability, contributing to medical morbidity, early mortality and personal suffering (Lisa et al. 1994, Hays et al. 1995, Paulsen 2005). Moreover, manifest group also had elevated rates of divorced status when compared to the other groups. Further research is needed in order to evaluate whether the distress caused by HD could influence negatively social relationships. However, this can be hypothesized if considered that, at early stages of HD patients still present elevated independence (as can be seen in the discussion of ‘independence scale’ ahead) and, as HD progresses, especially with the manifestation of motor symptoms (HD affected patients), their autonomy plummets drastically while dependency rockets, representing a severe burden to those providing health care (who are commonly the closer members of the family – spouse). These results demonstrated the huge impact of the manifestation of motor symptoms and the set of socio-demographic and neuropsychiatric stresses that may be contributing for those individuals to worse depressive symptoms and suicidal ideation (Dale et al. 2016).

The examination of the symptomatology showed higher percentages of psychiatric background for HD patients when compared to control groups, regarding all symptoms. As mentioned in previous studies, psychiatric manifestations in HD could be more related to the
neuropathology of the condition itself than the probability of having those symptoms in general population (Peyser and Folstein 1990, Slaughter et al. 2001). In addition, and more specifically, the group composed by HD motor manifest patients was considerably more impaired concerning overall evaluation of the symptoms, in which they demonstrated worse scores for the most part of motor-functional assessments, cognitive performance and psychiatric symptoms. Prior studies have reported no direct association between motor symptoms and depression, as well as other psychiatric signs (Weigell-Weber et al. 1996, Zappacosta et al. 1996, Paulsen 2005) that would explain why manifest patients are more disabled. Although depression is not directly related to the manifestation of involuntary movements, the substantial fall in functionality and independence lead is thought to display a negative impact in mood (Galts et al. 2019). It may be the case, again, that the disease stage and progression of the neurodegeneration is playing great influence in most functional and psychiatric aspects of those individuals. Furthermore, when analysing depression, it could be seen that pre-manifest group had slightly worse depression (8.54) when compared to manifest group (8.42). This fact is also discussed in previous studies, in which it is said that depression decreases with the disease progression (Paulsen 2005).

A particularly interesting result was observed when analysing suicidal ideation: pre-manifest patients were slightly more frequent at demonstrating suicidal thoughts when compared to the manifest group. A recent systematic literature review showed conflicting findings in relation to the manifestation of motor symptoms as a risk factor for suicide and suicidal behaviour (Kachian et al. 2019). The results of the study published in 2019 pointed out another research in which suicidal ideation was correlated with the movement disorder (Anderson et al. 2016), yet it also mentioned several other authors who could not find a connection between motor symptoms and suicidal ideation (Orth et al. 2010, Wetzel et al. 2011, Hubers et al. 2012). Due to the great number of contradictory findings of the previous research, it is evident that additional studies are needed in order to confirm those results.

When describing the main evidence-based pharmacological treatments prescribed to both cohorts at baseline and at 1st follow-up visit, the initial result of this analysis arose from the selection of the data used in this study and 1017 HD individuals who were not taking medicines for depression also could not have their data analysed and represented 28.5% of the cohort comprised of subjects with depressive symptoms. One important discussion concerning this group relies on the fact that depression in HD has been greatly
underdiagnosed with some authors mentioning that up to 50% may remain untreated (Paulsen et al. 2005, van Duijn et al. 2014). One aspect that may contribute to this situation relates to the complexity of diagnosing depression in HD, once some traditional signs of depression are, as well, part of the HD clinical picture and can be considered as somatic and cognitive manifestations of the condition, leading to the minimization of depression (De Souza et al. 2010).

Considering the lack of specific guidelines for the treatment of symptoms in HD, the management of depression in this population includes the same pharmacological approaches as the guidelines for general population (Killoran and Biglan 2014, Galt et al. 2019). These guidelines usually recommend the use of serotonergic antidepressants such as SSRIs as first choice treatment for depressive symptoms (Jakobsen et al. 2017). In that way, it is understandable that SSRIs would emerge as the most prescribed drugs for this purpose in both HD and non-HD groups. However, interesting findings demonstrated high frequencies for the use of other agents rather than traditional serotonergic drugs.

There was a higher prevalence of benzodiazepine drugs among HD patients when compared to control groups. The combination of anxiety and depression symptoms is frequent in primary care (Möller et al. 2016), but in the context of HD this fact is even more evident, with some authors suggesting that this symptoms can manifest in up to 71% of the individuals affected with HD (Dale and van Duijn 2015). Despite not recommended as a first-line treatment for depression due to the potential side effects, toxicity, dependency and also to the fact that those drugs do not present with antidepressant action, benzodiazepines agents prescriptions are justified by the high prevalence of anxiety in this context (Möller et al. 2016). Apart from the indication for anxiety and as depression treatment augmentation, benzodiazepines are mentioned in the article “International guidelines for the treatment of Huntington’s Disease, published in 2019, as alternatives for involuntary movements or emergency situations (e.g. midazolam) (Bachoud-Lévi et al. 2019). However, due to the context of depression approached in this study, these indications will not be thoroughly examined.

Another interesting result indicated the use of antipsychotic drugs as widely prevalent among HD individuals, when in comparison to control group. The use of antipsychotics to treat depressive symptoms has been supported since their discovery in the 1950s (Mulder et al. 2018) and has been intensified by the development of the second generation of
antipsychotics, once the efficacy of the traditional SSRIs has been considered limited and also due to their high risk of pharmacokinetic interactions (Möller 2005). The justification for the use of antipsychotics to treat depression relies on those drugs acting as antagonists at serotonin receptors 5-HT 1A and 2 and partial agonists at dopamine receptors (DeBattista and Hawkins 2009). Although authors of a Cochrane review published in 2010 emphasized that clinical evidence and trials are insufficient to state antipsychotics agents as efficient drugs for treating depression in both HD and general population, it is of ultimate importance to explore alternative options considering that up to 30% of the depressive patients may show resistance to the conventional serotoninergic drugs or cannot tolerate its side effects (Shelton et al. 2010).

Moreover, when taking into account HD as a progressive and neurodegenerative disease, depression is only one piece of a complex array of interconnected symptoms that commonly co-occur and, ultimately, add to a poorer quality of life for the affected individuals. In this context, antipsychotics agents may represent an alternative in which more than one symptom can be ameliorated with the action of one drug. The different properties and actions of antipsychotics have been separately evaluated not only to target regular psychosis but also to treat HD-specific manifestations, such as chorea, sleep disturbances and weight loss (Schultz et al. 2019) (Hamilton et al. 2003, Trejo et al. 2004, Fasano et al. 2008, Mulder et al. 2018, Schultz et al. 2019). One can hypothesize that the “multi-task” ability of antipsychotic drugs may benefit HD patients in terms of reduction of side-effects, drug interactions, polypharmacy, enhancing medication compliance and preserving cognitive function by reducing the anticholinergic burden in the long term. For this reason, these drugs deserve further attention for future and deeper research that provide support for its use in clinical practice.

Last but not least, another finding worth mentioning is the proportions for the combination of all antidepressants, benzodiazepines and antipsychotics, which, in HD, was nearly 8 times more prevalent than that of the control group. It is known that psychiatric manifestations may occur at any stage of HD, including the period prior to motor signs (Anderson and Marder 2001) but, more importantly, they may occur concomitantly. Several studies have reported significant associations between anxiety and depression (Morgan L. Levy et al. 1998, Anderson and Marder 2001) and how this combination of symptoms may increase the risk of suicide and suicidal ideation (Kachian et al. 2019). Additionally, psychosis
is not a very prevalent symptom in HD and appears to happen as an isolated phenomenon (van Duijn et al. 2014) that would not fully explain the use of antipsychotics. Instead, as mentioned earlier, a more suitable reason for the large use of antipsychotics may rely on the fact that a considerable part of depressive patients shows resistance to the conventional serotoninergic antidepressants (Shelton et al. 2010). These aspects can justify the higher prevalence of the combination of antidepressants, benzodiazepines and antipsychotics in HD when compared to control group. Moreover, this finding suggests that psychiatric symptoms in HD such as depression and anxiety may be worse in terms of severity when compared to non-HD population, hindering the management with monotherapy. Further research is needed in order to verify this hypothesis, however, if confirmed, it may provide evidence to develop new approaches for the drug treatment of depression and anxiety in HD that may include, for example, extra concern with polypharmacy, the anticholinergic burden and consequences with the deterioration of cognitive function over time.

It is important to emphasize that the period of time chosen to evaluate the pharmacological treatments for depression may represent a factor that clinically influence the results once therapeutical changes made midway (during the period of one year) affect the duration of the treatment. However, for the purpose of this analysis, this factor does not represent a significant impairment since the specific objective was to describe the pharmacological treatments in order to obtain an overview of the principal clinical practices. Considering that the period of time analysed in this study is first year of enrolment, which can be different for each participant, a limitation consists in the fact that different prescribing guidelines could have been in place depending on the time period. Future research may find convenient to explore these aspects further, with appropriate control for variables and period of evaluation.

The comparison of the means of depression scores for the different groups of pharmacological treatments was intended, yet not possible, once the groups presented with inherent imprecision regarding the sample sizes. This highlights that the examination of the efficacy of drugs for such a complex condition that is depression in HD requires powered and thorough analysis such as well-designed clinical trials. Moreover, it must be considered that the evaluation of the effects of pharmacological treatments involves the sophistication of an in-depth anamnesis, consideration of many other clinical, demographic, social, economic
aspects and the physicians’ own experience that could not be incorporated in this investigation.

The next set of analyses intended to describe depressive symptoms over a three-year period and identify factors that may influence these symptoms in the HD group using a statistical instrument named mixed-model.

The primary result of the mixed model showed that anxiety, alcohol abuse and gender are singled out as significant covariates, which means that those factors have a statistical relationship with the dependant variable (HADS-depression). Several reports have shown that depression correlates with anxiety (Morgan L. Levy et al. 1998, Anderson and Marder 2001) and, despite the possibility of a two-way relationship, anxiety appears to precede depression (Beesdo et al. 2010). Additionally, anxiety is also thought to have an independent association with suicidal ideation when it comes to HD (Hubers et al. 2013). All those factors considered, although anxiety has received little attention in clinical studies and literature reviews so far, it is important that anxiety is efficiently detected and treated within HD population, in order to improve symptoms related, such as depression, and achieve better results in the overall clinical picture of the patients.

The mixed-model results also pointed the alcohol abuse as a significant factor that influences the depression scores in HD. This relationship is well-known in the scientific community as numerous studies have documented the greater risk of depression among alcoholics when compared with non-alcoholics (Merikangas and Gelernter 1990, Hämäläinen et al. 2001). Alcoholism and major depression have been largely described in literature as comorbidities and the consequences for both mental and physical health are notorious, with some authors additionally suggesting that individuals may exhibit a specific clinical profile and present other comorbidities more frequently (Carton et al. 2018). Similar to anxiety, alcohol abuse also correlates with increased suicidal thoughts and sleep disturbances which raises awareness for the cluster of psychiatric manifestations that may be linked to attempted and completed suicide (Chioqueta and Stiles 2003, Turecki 2005). In HD, particularly, findings of an up-to-date systematic review confirmed that HD patients are more susceptible to suicidal ideation and behaviour than the general population and patients suffering from other clinical conditions (Kachian et al. 2019). Nevertheless, the same study also emphasized that further
research is needed in order to thoroughly explore the causes of this increased risk and eventually develop new interventions that better approach suicide in HD (Kachian et al. 2019).

Lastly, with regards to the covariates, gender was surprisingly found to be statistically significant. Although the mechanisms by which sex influences other neurodegenerative conditions such as Alzheimer’s Disease is well-understood, conflicting evidence is presented by previous studies regarding HD. The results of this study corroborate the findings of a great deal of the previous works which indicate that gender does influence depression, just like in general population (Kessler et al. 1994, World Health 2004), and additionally, suggest a hypothesis that may explain such phenomenon (Galts et al. 2019). On the other hand, the results of this study are contrary to previous authors who suggested that other factors rather than gender would affect psychological distress and the depression symptomatology (van Duijn et al. 2014, Dale et al. 2016).

Another important finding in this analysis and depicted in Figure 8, was that depression scores decreased over time. These results differ from previous studies which found that, as HD and its classic symptomatology progresses, so does depression (Dale et al. 2016). However, there are similarities between the attitudes expressed by HADS-depression in this study and those described by other past research, in which the percentage of HD patients suffering from significant depressive symptoms reduced over a period of time (Paulsen 2005). A number of distinct factors are suggested to explain this data behaviour, with the first being the resources utilised by the patient to cope with the distress caused by HD and the fact that, since diagnosis, the patient had time to accept their chronic, progressive and untreatable situation (Galts et al. 2019). Another cause that may (additionally) explain the decline of depression scores over time is the inability of the current methods to accurately assess depression, once the progressive characteristic of the disease implies in more impaired verbal fluency and poorer insight of the actual condition (Paulsen 2005). Last but not least, one last and further interpretation suggests the influence of the neurodegenerative process itself: the deterioration of certain parts of the brain may hinder patient’s ability to experience depression and the severity of their disability (Paulsen 2005). Recent imaging studies have reported microstructural alterations in several parts of the brain, including the frontal cortex and left superior frontal cortex of individuals with HD (Sprengelmeyer et al. 2014), which are the same regions targeted by the Americans Walther Freeman (neurologist) and James Watts
(neurosurgeon) in their prefrontal lobotomy procedures in 1936. Although controversial, these techniques achieved relative success at diminishing refractory depression and demonstrated that those particular cerebral areas could be linked to the manifestation of psychiatric symptoms (Staudt et al. 2019). Thus, following the same reasoning as of the lobotomy strategy, it may be proposed that the deterioration of the frontal cortex and surroundings resulting from the neurodegenerative process of HD could be associated with the progressive reduction of awareness of the patient, which would consequently decrease the levels of depression.

These results must be interpreted with caution, once not necessarily the statistically significant decreases in depression scores represent clinical significance. A study published in 2017 explored the differences between statistical and clinical significance and the authors reported that in order to determine whether the results are clinically relevant, the statistical significance must be followed by the patients’ perspective of improvement (Harris et al. 2017). In the case of the present research, the results did not show unquestionable improvement, nor could the patients’ satisfaction be confirmed and, therefore, the clinical relevance of the decrease in depression scores are not clear. Nevertheless, the findings of this analysis may serve as basis for future research with more powerful control for variables that aim to further explore this topic.

The differences between the groups were demonstrated by taking one group as reference and subtracting the means of depression scores. In this sense, positive results shown in Table 15 represent that the mean of depression of the group taken as reference was greater than the other, whereas the opposite interpretation is valid for the negative results presented in the table. The fact that the mean of depression in a certain group is higher than in the other group may not reflect clinical significance, as mentioned previously. However, if those means are significantly different from the statistical point of view, this may represent a start point for future research to further explore this aspect. The results of the mixed-model demonstrated a high estimated mean of depression scores for patients in the group using combinations and other antidepressants excepting SSRIs. These worse rates of depression in groups 1 and 4 may justify the need of another class or the combination of different classes of antidepressants. According to the rationale provided by a recent review published in 2014, SSRIs (group 2) are a widely accepted class of antidepressants used as first line treatment,
due to its side effects and safety profile (Annie et al. 2014). However, in cases of persistent symptomatology even after dose optimization, the change in antidepressant or the addition of an adjunct drug may be considered (Annie et al. 2014, Gautam et al. 2017). In conclusion, it can be suggested that groups 1 and 4 demonstrated worse depression scores as they may represent those individuals who are refractory to SSRIs as first line treatment.

Additionally, in this analysis group 2 showed better scores than groups 1 and 4, and it’s represented by individuals taking SSRIs only. Due to the lack of HD-specific data for tailoring pharmacological treatments, depressive symptoms in HD have been managed with standard clinical approaches (Epping and Paulsen 2011, Galts et al. 2019), which makes it suitable to state that SSRIs are also the first choice when choosing an antidepressant agent for an HD patient (Annie et al. 2014), as mentioned previously. It can be hypothesized that this group would show lower levels of depression as it is formed by individuals whose condition is at the initial stages.

Lastly, one interesting finding was those depressed individuals who were not taking traditional antidepressants as pharmacological treatment (group 3) and presented the lowest scores for depression, indicating that the symptom in these participants was less severe. One assumption that would explain such results is that those individuals have not come to the point of needing pharmacological interventions. In cases of mild to moderate depressive disorder, psychotherapy may be considered as an initial approach (Gautam et al. 2017). Another possibility would consider that the subjects in group 3 were not under antidepressant therapy with the traditional antidepressants, however, other psychotropic agents may be used when it comes to depression management and they can include, for example, antipsychotics, benzodiazepines and others (Mulder et al. 2018, Ogawa et al. 2019).

Although not recommended as a first-line treatment for depression due to the potential side effects, toxicity, dependency and also to the fact that those drugs do not present with antidepressive action, benzodiazepines agents seem to be commonly prescribed by physicians, as the combination of anxiety and depression symptoms is highly prevalent in primary care (Möller et al. 2016). In the context of HD, anxiety has not received adequate attention in terms of research, even though it can manifest in up to 71% of the individuals affected with HD (Dale and van Duijn 2015) The results of this study corroborate with those evidences, showing anxiety as an important factor that affects depression symptoms and as a covariate that influences the behaviour of the depression scores. Therefore, the individuals
in group 3 who are not under the treatment with traditional antidepressants may benefit from the treatment with benzodiazepines to manage both anxiety and, ultimately, depressive symptoms.

Another class of drug worth discussing is the antipsychotic agents that were also observed as treatment for depression in individuals of group 3. Conventionally, antipsychotics are used for patients manifesting psychotic symptoms, however, new observations in the beginning of the year 2000 began a series of randomized clinical trials to evaluate the efficacy of antipsychotic as adjunctive therapy for treatment resistant depression. Eventually, in 2010 the US Food and Drug Administration (FDA) approved the use of fluoxetine and olanzapine, aripiprazole and quetiapine for major depression (Mulder et al. 2018). The rationale behind the use of antipsychotics to manage depressive symptoms consists on those drugs acting as antagonists at serotonin receptors 5-HT 1A and 2 and partial agonists at dopamine receptors (DeBattista and Hawkins 2009).

The major limitation of this part of the study relies on the fact that the examinations of drug treatments require powerful trials, with well-established inclusion/exclusion criteria, strong control of influencer factors and, preferably randomization, in order to avoid bias and confusion. These aspects could not be considered in this study, as data provided by Enroll-HD was used with exploration purposes. Notwithstanding those limitations, the analysis provided by this study focused on giving a preliminary idea of the HD scenario over a certain period of time, that may be useful for future research that wish to address those issues.

Last but not least, the analysis had the purpose of identifying factors that affect depressive symptoms at baseline in the HD group via the logistic regression. In the univariate analysis, it could be observed that the absence of previous psychiatric symptoms, such as depression, irritability, apathy, obsessive-compulsive behaviour and cognitive decline, was a prevalent and meaningful feature for improving from depressive episodes when analysed individually. Due to the fact that, frequently there are associations between the significant variables in the univariate analysis, it is common to observe that those variables do not appear in the multivariate analysis. Age, history of involuntary movements, the UHDRS motor score and history of irritability represented the significant variables resulted from the multivariate analysis that may be related with the improvement in depression scores as a result of the influence that they have on each other. In other words, the results indicated that younger subjects, with no history of involuntary movements or
irritability and absence of motor manifestations were most likely to improve their depression scores. These findings suggest that there could be an association between good depression scores and higher functionality in those individuals who were able to reduce their depressive symptoms. Previous authors have already mentioned the association between functionality and depression and the way one aspect influences the other throughout the disease progression (Helder et al. 2001, Paulsen 2005). Despite the results appear to describe an early stage of HD, it must be stressed that, in the context of this particular disease, the diagnosis may occur at different ages, as well as the manifestation of motor symptoms are more correlated with the genetic modification and, additionally, the illness seem to progress differently from person to person (Walker 2007). For this reason, future research might find convenient to further explore this link, as the results may be helpful finding specific characteristics that, when preserved or stimulated, facilitate good depression levels among HD patients.

Although literature is not very abundant in terms of ‘improvement’ of symptoms in HD, the topic should be further explored by future research more research is indeed needed in order to confirm causality. One important limitation in the multivariate analysis relates with the possibility of errors when interpreting the estimates, once, the multivariate models that consider only principal effects (and no interactions between the factors) are prone to bias for showing strong assumptions that are not all the time valid. In a complex context as depression in HD, several different factors might be acting together, and the interactions are important part of the understanding process (Hosmer DW 1989).

An important limitation of this part of the study regards the uncertainty surrounding the quality of the HADS-depression as method to assess severity. In 2011, Cameron et al. conducted a study in which the findings showed a tendency of the HADS-depression of placing the individuals in a milder category when compared to other assessment methods, such as the 17-item Hamilton Rating Scale for Depression (HRSD-17), the Patient Health Questionnaire 9 (PHQ-9) and the Beck Depression Inventory, Second Edition (BDI-II) (Cameron et al. 2011). This means that patients may be judged to be less depressed than they are in fact. From the medical practice point of view, this limitation of the method is significant and may directly impact the clinical understanding of the patient’s condition and consequently lead to the wrong choice of pharmacological approach, subject patient to ineffective
treatments or raise the chances of patient remaining untreated. However, despite this limitation and the significant impact that it may cause in clinical practice, for the purpose of this research, the use of HAD-depression was considered adequate firstly because it is an assessment method validated for the measurement of depression in HD (Brennan et al. 2010, De Souza et al. 2010), there was insufficient literature references that supported the use of separate subscales (severity) of the alternative assessment methods provided by Enroll-HD (e.g. PBA, see section 3.1.3) and lastly, the analysis performed in work package 5 considered the decrease in the depression scores and the factors that could be influencing this tendency, regardless their initial status. In other words, the study evaluated the transition from a more depressed to a less depressed level, rather than using severity levels as a status of the patient that would impact a decision (choice of pharmacotherapy, for example). Notwithstanding these limitations, previous authors have mentioned that, for example, greater suicidal rates are associated with critical periods in HD where the patient start losing their functional abilities (Paulsen et al. 2005). For this reason, the concept of better functionality being linked with the improvement in depression scores is an important finding that requires further studies to fully understand this correlation.

It is understood that the depression is a complex condition in which several personal, clinical, demographic, social and economic aspects influence the fluctuations of mood in a constantly dynamic manner and, therefore, the use of observational data is indeed insufficient to draw any conclusions and attribute causality. Nevertheless, the aim of this study was to start a discussion about the factors that may be influencing good depression levels in HD, as a large and growing body of literature has been investigating the opposite (causes of depression, risk factors, suicide).

6. The impact of findings on clinical pharmacy practice in Ireland

The pharmacist plays a role in hospital and community settings that used to be traditionally related to dispensing medication and providing guidance regarding the health aspect. However, in recent times, the profession has achieved a much more prestigious space as an essential part of the healthcare team (Halvorsen et al. 2011, Ronan et al. 2020). The clinical pharmacist acts together with other healthcare professionals to provide
pharmacotherapy interventions that reduce the incidence of drug-related problems and enhance drug therapy’s effectiveness and safety (Harris et al. 2014). One example of the interventions performed by the clinical pharmacist is the medication review, which is defined by the NHS Cumbria Clinical Commissioning Group as “a structured, critical examination of a patient’s medicines with the objective of reaching an agreement with the patient about treatment, optimizing the impact of medicines, minimizing the number of medication-related problems and reducing waste” (REF). Apart from ensuring a secure drug treatment, such interventions are also thought to contribute with cost reduction and consequently provide economic benefit to the institution (Gallagher et al. 2014). For these reasons, clinical pharmacists are increasingly becoming essential members of multidisciplinary teams (Ronan et al. 2020).

In Ireland, the policy document “A Vision for Change” described the multidisciplinary team practice as the preferred model for mental health practice (Expert Group on Mental Health et al. 2006), which, in the context of HD can be considered especially relevant. Considering HD as a complex condition with a plethora of different signs and symptoms that differ from patient to patient, it is reasonable to imagine that HD requires a multidisciplinary approach (Nance 2007, Novak and Tabrizi 2010).

In this sense, the findings of this study may be of interest to the clinical pharmacy field in Ireland once, as an example, chapter 6 suggests a further exploration of the use of antipsychotics to treat not only depression in HD, but also other symptoms that are part of the clinical manifestations of HD (insomnia, weight loss, etc). In general terms, clinical pharmacists may be encouraged to develop lean treatment suggestions based on drugs with different receptor profiles, focusing on the management of more than one symptom at the time. Possible benefits of this approach may include decrease in polypharmacy, reduction in drug interactions and adverse effects and improved treatment compliance. In addition, another aspect to be taken into account is medication provision: residents in the Republic of Ireland can obtain prescribed medications through three different community drug schemes (General Medical Services – GMS, Drug Payment Scheme – DPS and the Long-Term Illness Scheme - LTI) (REF). Consequently, the possibility of reducing the number of drugs used by HD patients as a result of the optimization of the treatment may ultimately contribute to reduce government spending.
Ideally, further investigation is needed to confirm the results of this study. Nevertheless, the concept of optimization may represent a potential research path in future and has the clinical pharmacist as a central point.

7. Strengths and Limitations

This study, derived from Enroll-HD registry, is of an observational nature, in which some sources of weakness could have affected the results and the evaluation of the depression scores. Those limitations are due to the observational nature of the study and relate specially with the fact that the exposure was not controlled by the investigator.

Firstly, as a fundamental limitation of observational studies, no randomization process could be implemented in this analysis in order to distribute risk factors equally, and, therefore, the results provided are unable to attribute any causal relationship between depression in HD and other factors. Secondly, analysing the evidence-based treatments used was challenging. This is because some of the medicines prescribed were used at dosages that were unlicensed for the clinical indications for which they were prescribed, or the medicines used might have been entirely unlicensed. Justifications for choice of medicines or doses were not provided in the database in these instances. These medicines were excluded from analyses, as the primary aim of this study was to investigate evidence-based use of treatments in this cohort. In retrospect, noting the unlicensed nature of medicines prescribed could have added some value to the study. Treatment decisions for patients with HD are based on the extrapolation of evidence from clinical trials of patients without HD in most scenarios. Therefore, capturing the unlicensed use of medicines in this patient cohort would have been of value to describe what currently happens in clinical practice in the absence of clinical trials.

Additionally, observational studies are prone to bias, which may occur in six domains: the selection of participants, the classification of interventions, deviations from intended interventions, result of missing data, measurement of outcomes and the selection of the reported result (Gueyffier and Cucherat 2019). Whilst there was no intervention involved and therefore the assessment of the risk of bias for the classification of interventions, deviations from intended interventions is not relevant, there are three relevant domains that might have
introduced bias. These include, the selection of participants, result of missing data, measurement of outcomes and the selection of the reported result. The researcher of the current study had no way of controlling for those. However, very few missing data points were noted throughout the analyses, all results reported were measured using validated scales, all measures noted in the data collection tool were reported. There is a clear, documented pathway for how HD patients are selected for the study, in that all patients diagnosed with HD are recommended to take part in the study. The recruitment of non-HD patients to the Enroll-HD database is less clear, and therefore might not be generalisable to the non-HD population.

As this was a study undertaken using an existing dataset, the researcher did not have any control over how variables were collected and what variables were collected. This is a common limitation seen with analyses of databases used for research purposes, and one which could not be avoided in this research.

Lastly, it is necessary to mention that the results of this study need prudence when interpreted, particularly with regards the different pharmacological treatments, as due to the mechanisms of data protection and de-identification and the global aspect of the Enroll-HD database, specific features regarding guidelines for depression, provision, availability and licensing of drugs and discrepancies in culture and ethnicity of each region of the world could not be captured in this study. This may have affected the ability of analysing particular characteristics of certain regions, which will need to be addressed in future studies. As a result, the findings of this study cannot be considered as generalized to all HD patients worldwide.

Notwithstanding these limitations, it is important to emphasize that depression in HD is an area that severely miss evidence-based data, adequate sample sizes, standardized assessment methods and powered randomized controlled trials. Regarding this last point, not only does observational research like the present one, address important clinical questions in the absence of more controlled tests, but it may also add positive collaboration even when clinical trials have already been conducted, tackle questions that are not suitable for those types of study and exposures that are not under the control of the researcher and, last but not least, it provides preliminary data to justify the performance of a clinical trial (Boyko 2013).
Secondly, the literature on depression in HD has highlighted the issue about research with insufficient sample sizes that hindered the possibility of integrating the findings into robust clinical recommendations (Galts et al. 2019). In this sense, this study has made a step forward analysing a database of a significant size that allowed some effects to be observed as both statistically and clinically significant, once matched with existing findings in literature.

In addition, the present study permitted the evaluation of depression in HD from an international point of view, considering the global nature of the database provided by Enroll-HD. Further studies are needed to design specific clinical practices to each region affected by HD, however, in the light of the generalized lack of data and research for this particular population, the characterisation of a worldwide scenario of HD may represent an opening move to more individualised therapies in future.

Lastly, the findings of this study, in particular the ones obtained in the analysis of the pharmacological treatments for depression used by subjects, provide preliminary ideas that, if confirmed afterwards by more robust research, may not only benefit the HD community itself, but also the health system overall, in a collaborative and optimized manner by reducing costs and enhancing the quality of life of HD sufferers and their families.

In conclusion, observational studies like this are indeed prone to several biases that make them impossible to completely master reliability and, therefore, cannot be utilised as the unique source of information for clinical decisions. However, many factors contribute for them to be as important as the other trials (Gueyffier and Cucherat 2019). Future research using data from registries and data warehouses around the world, such as Enroll-HD study, will be able to illustrate the limitations of this type of research, but they will also allow better prediction of risk factors impact, of prognosis and, eventually, adjustment of drug therapy (Gueyffier and Cucherat 2019).
8. Future studies

The findings of this study have a number of important implications for future practice:

- There is no gold-standard procedure for assessing depression in general population, which makes the comparison between the studies more complicated and prone to bias and confounding.
- There is a necessity to develop new HD-specific scales to measure psychiatric manifestations, such as depression, according to the HD particular clinical picture.
- The review of current guidelines of diagnosis and follow-ups of psychiatric patients in order to include the measurements of the psychiatric symptoms and, consequently, generate further information and specific data for certain groups of the population.
- Continuous efforts are needed to evaluate the efficacy of pharmacological agents in ameliorating depressive symptoms particularly in the HD population.
- Novel approaches regarding the drug treatment of symptoms in HD should consider a deeper exploration of the ability of such drugs to hit multiple receptors and, consequently, act on more symptoms at once, avoiding polypharmacy, undesirable side effects and the increase of the anticholinergic burden.
- Future research is needed in order to thoroughly evaluate functionality in HD and develop new clinical practices that enhance and prolong functional capacity in HD patients, as this appeared in this study as an important aspect that influences the perspective of patients in relation to their quality of life and, if not supported, may ultimately facilitate premature death by suicide.
9. Conclusion

Throughout the development of this study, many challenges were encountered, especially those regarding the scarcity of HD-specific research, lack of standardization in assessment methods and absence of clinical guidelines targeting particularly the HD group. In addition, the nature of the data obtained allowed this study an observational characteristic only, that hindered the ability to attribute causality to the findings and draw any definite conclusions.

Notwithstanding those difficulties, this study presented several findings summarized below:

- Depression in HD decreased with time, and this was consistent with past research (Paulsen 2005).
- Suicidal ideation, alcohol abuse, anxiety and gender as covariates that influence the depression scale over time.
- Younger subjects, with no history of involuntary movements or irritability and absence of motor manifestations were most likely to improve their depression scores.

This study also suggests, with regards the pharmacological treatments of depression in HD, that the use of antipsychotics is further explored in order to benefit patients in terms of reduction of side-effects, drug interactions, polypharmacy (enhancing medication compliance) and preserving cognitive function by reducing the anticholinergic burden in the long term.

The present study has gone some way towards enhancing our understanding of depression in Huntington’s Disease and providing preliminary ideas and starting points to the development of further and stronger clinical trials. Patients suffering with HD have multiple needs, that distinguish from person to person and, consequently, require multifaceted tailored care (Mestre et al. 2016). Although HD and depression in HD remain as complex topics in the scientific community and still face several challenges, the hope that new clinical approaches significantly improve the consequences of HD in patients’ activities of daily living and ultimately maximize their quality of life, motivates studies like this present one.
10. References


11. Appendices

Appendix 1: Variables of the datasets provided by Enroll-HD (Complete list)

Table 16: Variables of ‘Profile’ dataset (PDS4)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Information</th>
</tr>
</thead>
<tbody>
<tr>
<td>subjid</td>
<td>Participant’s ID (de-identified)</td>
</tr>
<tr>
<td>region</td>
<td>Region</td>
</tr>
<tr>
<td>hdcat</td>
<td>HD category (pre-manifest, manifest, genotype negative, family member)</td>
</tr>
<tr>
<td>sex</td>
<td>Gender</td>
</tr>
<tr>
<td>race</td>
<td>Ethnicity</td>
</tr>
<tr>
<td>handed</td>
<td>Handedness</td>
</tr>
<tr>
<td>hxsid</td>
<td>Previous suicidal ideation or attempts?</td>
</tr>
<tr>
<td>dssage</td>
<td>Age of death</td>
</tr>
<tr>
<td>dsplace</td>
<td>Place of death</td>
</tr>
<tr>
<td>dsend</td>
<td>Cause of death</td>
</tr>
<tr>
<td>cagh high</td>
<td>Larger research CAG allele determined from DNA</td>
</tr>
<tr>
<td>caglow</td>
<td>Smaller research CAG allele determined from DNA</td>
</tr>
<tr>
<td>momhd</td>
<td>Mother affected</td>
</tr>
<tr>
<td>momagesx</td>
<td>Age at onset of symptoms in mother</td>
</tr>
<tr>
<td>dadhd</td>
<td>Father affected</td>
</tr>
<tr>
<td>dadagesx</td>
<td>Age at onset of symptoms in father</td>
</tr>
<tr>
<td>fhx</td>
<td>Family History</td>
</tr>
<tr>
<td>ccmtr</td>
<td>Have motor symptoms compatible with HD ever been a part of the participant’s medical history?</td>
</tr>
<tr>
<td>ccmtrage</td>
<td>At what age did the participant’s motor symptoms begin?</td>
</tr>
<tr>
<td>sxsubj</td>
<td>Symptoms first noted by participant</td>
</tr>
<tr>
<td>sxsubjm</td>
<td>Initial major symptom noted by participant</td>
</tr>
<tr>
<td>sxsm</td>
<td>Initial major symptom noted by participant – Motor</td>
</tr>
<tr>
<td>sxsc</td>
<td>Initial major symptom noted by participant – Cognitive</td>
</tr>
<tr>
<td>sxsp</td>
<td>Initial major symptom noted by participant – Psychiatric</td>
</tr>
<tr>
<td>sxso</td>
<td>Initial major symptom noted by participant – Oculomotor</td>
</tr>
<tr>
<td>sxfam</td>
<td>Symptoms first noted by family</td>
</tr>
<tr>
<td>sxfamm</td>
<td>Initial major symptom noted by family</td>
</tr>
<tr>
<td>sxf_m</td>
<td>Initial major symptom noted by family – Motor</td>
</tr>
<tr>
<td>sxf_c</td>
<td>Initial major symptom noted by family – Cognitive</td>
</tr>
<tr>
<td>sxf_p</td>
<td>Initial major symptom noted by family – Psychiatric</td>
</tr>
<tr>
<td>sxf_o</td>
<td>Initial major symptom noted by family – Oculomotor</td>
</tr>
<tr>
<td>hddiagn</td>
<td>Date of clinical HD diagnosis</td>
</tr>
<tr>
<td>sxest</td>
<td>Can you, as a rater, estimate the time of symptom onset</td>
</tr>
<tr>
<td>sxrater</td>
<td>Rater’s estimate of symptom onset</td>
</tr>
<tr>
<td>sxraterm</td>
<td>Rater’s judgement of initial major symptom</td>
</tr>
<tr>
<td>sxreas</td>
<td>Please specify why you, as a rater, can not estimate symptom onset (without additional external information) at the moment</td>
</tr>
<tr>
<td>sxgs</td>
<td>What is your best guess of how many years ago symptom onset took place</td>
</tr>
<tr>
<td>sxgsdy</td>
<td>Day of data entry</td>
</tr>
<tr>
<td>sxr_m</td>
<td>Rater's judgement of initial major symptom - Motor</td>
</tr>
<tr>
<td>-------</td>
<td>---------------------------------------------------</td>
</tr>
<tr>
<td>sxr_c</td>
<td>Rater's judgement of initial major symptom - Cognitive</td>
</tr>
<tr>
<td>sxr_p</td>
<td>Rater's judgement of initial major symptom - Psychiatric</td>
</tr>
<tr>
<td>sxr_o</td>
<td>Rater's judgement of initial major symptom - Oculomotor</td>
</tr>
</tbody>
</table>

Has depression (includes treatment with antidepressants with or without a formally-stated diagnosis of depression) ever been a part of the participant’s medical history?

<table>
<thead>
<tr>
<th>ccdep</th>
<th>At what age did the depression begin?</th>
</tr>
</thead>
<tbody>
<tr>
<td>ccdepage</td>
<td>Has irritability ever been a part of the participant’s medical history?</td>
</tr>
<tr>
<td>ccirb</td>
<td>At what age did the irritability begin?</td>
</tr>
<tr>
<td>ccirbage</td>
<td>Has violent or aggressive behaviour ever been a part of the participant’s medical history?</td>
</tr>
<tr>
<td>ccvab</td>
<td>At what age did violent or aggressive behaviour begin?</td>
</tr>
<tr>
<td>ccap</td>
<td>Has apathy ever been a part of the participant’s medical history</td>
</tr>
<tr>
<td>ccapage</td>
<td>At what age did apathy begin?</td>
</tr>
<tr>
<td>ccpob</td>
<td>Has perseverative obsessive behaviour ever been a part of the participant’s medical history</td>
</tr>
<tr>
<td>ccpobage</td>
<td>At what age did perseverative obsessive behaviour begin?</td>
</tr>
<tr>
<td>ccpsy</td>
<td>Has psychosis (hallucinations or delusions) ever been a part of the participant’s medical history</td>
</tr>
<tr>
<td>ccpsyage</td>
<td>At what age did psychosis (hallucinations or delusions) begin?</td>
</tr>
<tr>
<td>ccpsyfh</td>
<td>Does the participant have a family history of a psychotic illness in a first degree relative</td>
</tr>
<tr>
<td>cccog</td>
<td>Has significant cognitive impairment (severe enough to impact on work or activities of daily living) or dementia ever been a part of the participant’s medical history</td>
</tr>
<tr>
<td>cccogage</td>
<td>At what age did cognitive impairment first start to have an impact on daily life?</td>
</tr>
</tbody>
</table>

Additional GWAS data

Additional biosamples available

Additional phenotypic data available

Additional morphometric data available

Raw images available
### Table 17: Variables of 'Pharmacotx' dataset (PDS4)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Information</th>
</tr>
</thead>
<tbody>
<tr>
<td>subjid</td>
<td>HDID (recoded)</td>
</tr>
<tr>
<td>cmtrt__modify</td>
<td>Drug name – Modified Term (coded by WHO-DD)</td>
</tr>
<tr>
<td>cmtrt__decod</td>
<td>Drug name - Code (coded by WHO-DD)</td>
</tr>
<tr>
<td>cmtrt__ing</td>
<td>Ingredient – Modified Term</td>
</tr>
<tr>
<td>cmtrt__atc</td>
<td>Ingredient – Code (coded by ATC)</td>
</tr>
<tr>
<td>cmindc__modify</td>
<td>Indication – Modified Term (coded by MedDRA)</td>
</tr>
<tr>
<td>cmindc__decod</td>
<td>Indication - Code (coded by MedDRA)</td>
</tr>
<tr>
<td>cmdostot</td>
<td>Total daily dose</td>
</tr>
<tr>
<td>cmdose__cmdosu</td>
<td>Unit (unit of one intake)</td>
</tr>
<tr>
<td>cmdosfreq</td>
<td>Frequency</td>
</tr>
<tr>
<td>cmroute</td>
<td>Route</td>
</tr>
<tr>
<td>cmstdy</td>
<td>Start day</td>
</tr>
<tr>
<td>cmenrf</td>
<td>Ongoing</td>
</tr>
<tr>
<td>cmendy</td>
<td>End day</td>
</tr>
</tbody>
</table>

### Table 18: Variables of 'Enroll' dataset (PDS4)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Information</th>
</tr>
</thead>
<tbody>
<tr>
<td>subjid</td>
<td>Participant's ID (de-identified)</td>
</tr>
<tr>
<td>studyid</td>
<td>Study ID</td>
</tr>
<tr>
<td>seq</td>
<td>Sequence</td>
</tr>
<tr>
<td>visit</td>
<td>Visit</td>
</tr>
<tr>
<td>visdy</td>
<td>Visit day</td>
</tr>
<tr>
<td>visstat</td>
<td>Visit status</td>
</tr>
<tr>
<td>age</td>
<td>Age</td>
</tr>
<tr>
<td>hdcat</td>
<td>Participant category</td>
</tr>
<tr>
<td>hxalcab</td>
<td>Has the participant had alcohol problems in the past</td>
</tr>
<tr>
<td>hxtobab</td>
<td>Has the participant ever smoked</td>
</tr>
<tr>
<td>hxtobcpd</td>
<td>Cigarettes per day</td>
</tr>
<tr>
<td>hxtobynos</td>
<td>Years of smoking</td>
</tr>
<tr>
<td>hxpacky</td>
<td>Packyears</td>
</tr>
<tr>
<td>hxdrugab</td>
<td>Has the participant ever abused drugs</td>
</tr>
<tr>
<td>hxmar</td>
<td>Marijuana</td>
</tr>
<tr>
<td>hxmarfrq</td>
<td>Frequency</td>
</tr>
<tr>
<td>hxher</td>
<td>Heroin</td>
</tr>
<tr>
<td>hxherfrq</td>
<td>Frequency</td>
</tr>
<tr>
<td>hxcoc</td>
<td>Cocaine</td>
</tr>
<tr>
<td>hxcocfrq</td>
<td>Frequency</td>
</tr>
<tr>
<td>hxclb</td>
<td>Club drugs (Ecstacy, GHB, Roofies)</td>
</tr>
<tr>
<td>hxclbfreq</td>
<td>Frequency</td>
</tr>
<tr>
<td>hxamp</td>
<td>Amphetamines</td>
</tr>
<tr>
<td>hxampfrq</td>
<td>Frequency</td>
</tr>
<tr>
<td>hxrit</td>
<td>Ritalin</td>
</tr>
<tr>
<td>hxritfrq</td>
<td>Frequency</td>
</tr>
<tr>
<td>hxhal</td>
<td>Hallucinogens</td>
</tr>
<tr>
<td>Acronym</td>
<td>Description</td>
</tr>
<tr>
<td>-------------</td>
<td>-----------------------------------</td>
</tr>
<tr>
<td>hxhalfrq</td>
<td>Frequency</td>
</tr>
<tr>
<td>hxinh</td>
<td>Inhalants</td>
</tr>
<tr>
<td>hxinhfrq</td>
<td>Frequency</td>
</tr>
<tr>
<td>hxopi</td>
<td>Opioium</td>
</tr>
<tr>
<td>hxopifrq</td>
<td>Frequency</td>
</tr>
<tr>
<td>hxpak</td>
<td>Painkillers</td>
</tr>
<tr>
<td>hxpakfrq</td>
<td>Frequency</td>
</tr>
<tr>
<td>hxbar</td>
<td>Barbiturates sedatives</td>
</tr>
<tr>
<td>hxbarfq</td>
<td>Frequency</td>
</tr>
<tr>
<td>hxtrq</td>
<td>Tranquilizers</td>
</tr>
<tr>
<td>hxtrqfrq</td>
<td>Frequency</td>
</tr>
<tr>
<td>height</td>
<td>Height (cm)</td>
</tr>
<tr>
<td>weight</td>
<td>Weight (kg)</td>
</tr>
<tr>
<td>bmi</td>
<td>BMI</td>
</tr>
<tr>
<td>alcab</td>
<td>Does the participant currently drink alcohol?</td>
</tr>
<tr>
<td>alcunits</td>
<td>Units per week</td>
</tr>
<tr>
<td>tobab</td>
<td>Does the participant currently smoke?</td>
</tr>
<tr>
<td>tobcpd</td>
<td>Cigarettes per day</td>
</tr>
<tr>
<td>tobyos</td>
<td>Years of smoking</td>
</tr>
<tr>
<td>packy</td>
<td>Packye years</td>
</tr>
<tr>
<td>cafab</td>
<td>Current caffeine use?</td>
</tr>
<tr>
<td>cafpd</td>
<td>Do you drink more than 3 cups of coffee, tea and cola drinks combined per day?</td>
</tr>
<tr>
<td>drugab</td>
<td>Does the participant currently use drugs?</td>
</tr>
<tr>
<td>mar</td>
<td>Marijuana abuse</td>
</tr>
<tr>
<td>marfrq</td>
<td>Marijuana Frequency</td>
</tr>
<tr>
<td>her</td>
<td>Heroin abuse</td>
</tr>
<tr>
<td>herfrq</td>
<td>Heroin Frequency</td>
</tr>
<tr>
<td>coc</td>
<td>Cocaine abuse</td>
</tr>
<tr>
<td>cocfrq</td>
<td>Cocaine frequency</td>
</tr>
<tr>
<td>clb</td>
<td>Club drugs (Ecstasy, GHB, Roofies) abuse</td>
</tr>
<tr>
<td>clbfrq</td>
<td>Club drugs (Ecstasy, GHB, Roofies) frequency</td>
</tr>
<tr>
<td>amp</td>
<td>Amphetamines abuse</td>
</tr>
<tr>
<td>ampfraq</td>
<td>Amphetamines frequency</td>
</tr>
<tr>
<td>rit</td>
<td>Ritalin Abuse</td>
</tr>
<tr>
<td>ritfrq</td>
<td>Ritalin Frequency</td>
</tr>
<tr>
<td>hal</td>
<td>Hallucinogens abuse</td>
</tr>
<tr>
<td>halfrq</td>
<td>Hallucinogens frequency</td>
</tr>
<tr>
<td>inh</td>
<td>Inhalants abuse</td>
</tr>
<tr>
<td>inhfrq</td>
<td>Inhalants frequency</td>
</tr>
<tr>
<td>opi</td>
<td>Opium abuse</td>
</tr>
<tr>
<td>opifrq</td>
<td>Opium frequency</td>
</tr>
<tr>
<td>pak</td>
<td>Painkillers abuse</td>
</tr>
<tr>
<td>pakfrq</td>
<td>Painkillers frequency</td>
</tr>
<tr>
<td>bar</td>
<td>Barbiturates sedatives abuse</td>
</tr>
<tr>
<td>barfrq</td>
<td>Barbiturates sedatives frequency</td>
</tr>
<tr>
<td>trq</td>
<td>Tranquilizers abuse</td>
</tr>
<tr>
<td>trqfrq</td>
<td>Tranquilizers frequency</td>
</tr>
</tbody>
</table>
Any changes to the following General Variable Items:

- Marital status
- Residence
- ISCED education level
- Employment
- Status (if employed)
- Have you had to stop or reduce work due to your health?
- How many days in the last 6 months have you been off work because of HD?
- How many fewer hours per week have you worked because of HD?
- Reason (if not employed)
- Retired due to (if retired)
- If retired or unemployed Do you receive social security or disability benefit?
- If retired or unemployed Do you intend to return to work?
- If retired or unemployed Since when have you been unemployed retired?
- Since the last visit have there been Any changes to participant’s medication?
- Since the last visit have there been Any changes to participant’s comorbid conditions?
- Since the last visit have there been Any updates to the clinical characteristics and or onset of HD?
- Motor score (TMS)
- Motor score (TMS) incomplete
- Ocular pursuit horizontal
- Ocular pursuit vertical
- Saccade initiation Horizontal
- Saccade initiation vertical
- Saccade velocity horizontal
- Saccade velocity Vertical
- Saccade velocity Dysarthria
- Tongue protrusion
- Finger taps Right
- Finger taps left
- Pronate supinate-hands right
- Pronate supinate-hands left
- Luria
- Rigidly-arms right
- Rigidly-arms left
- Bradykinesia – body
- Maximal dystonia Trunk
- Maximal dystonia RUE
- Maximal dystonia LUE
- Maximal dystonia RLE
- Maximal dystonia LLE
chorface  Maximal chorea Face  
chorbol  Maximal chorea BOL  
chortrnk  Maximal chorea Trunk  
chorrue  Maximal chorea RUE  
chorlue  Maximal chorea LUE  
chorrle  Maximal chorea RLE  
chorlle  Maximal chorea LLE  
gait  Gait  
tandem  Tandem walking  
retropls  Retropulsion pull test  
diagconf  Diagnostic confidence level (DCL)  
tfcscore  Functional score  
occupatn  Occupation  
finances  Finances  
chores  Domestic chores  
adl  ADL  
carelevl  Care level  
fascore  Functional assessment score  
fiscore  Functional score incomplete  
emplusl  Could subject engage in gainful employment in his/her accustomed work?  
emplany  Could subject engage in any kind of gainful employment?  
volut  Could subject engage in any kind of volunteer or nongainful work?  
fafinan  Could subject manage his/her finances (monthly) without any help?  
grocery  Could subject shop for groceries without help?  
cash  Could subject handle money as a purchaser in a simple cash (shop) transaction?  
supchild  Could subject supervise children without help?  
drive  Could subject operate an automobile safely and independently?  
housewrk  Could subject do his/her own housework without help?  
laundry  Could subject do his/her own laundry (wash/dry) without help?  
prepmmeal  Could participant prepare his/her own meals without help?  
telephon  Could subject use the telephone without help?  
ownmeds  Could subject take his/her own medications without help?  
feedself  Could subject feed himself/herself without help?  
dress  Could subject dress himself/herself without help?  
bathe  Could subject bathe himself/herself without help?  
pubtrans  Could subject use public transport to get to places without help?  
walknbr  Could subject walk to places in his/her neighbourhood without help?  
walkfall  Could subject walk without falling?  
walkhelp  Could subject walk without help?  
comb  Could subject comb hair without help?  
trnchair  Could subject transfer between chairs without help?
bed  Could subject get in and out of bed without help?
toilet Could subject use toilet/commode without help?
carehome  Could subject's care still be provided at home?
indepscl  Subject's independence in %
  Did the participant complete the assessment in their native language and with normal or corrected-to-normal vision and hearing?
gen1  Did the participant complete the assessment in their native language?
gen2  At what age did the participant learn the language used?
gen3  Did the participant have normal corrected-to-normal hearing and vision?
gen4  Was vision uncorrected (e.g. no glasses during visit)?
gen5  Was hearing uncorrected (e.g. no hearing aid worn)?
sdmnt  Symbol Digit Modality Test completed
sdmt1  Total correct
sdmt2  Total errors
sdmtnd  Justification for errors
verfct  Verbal Fluency Test (Category) completed
verfctd  Category
verfct5  Total correct (1min)
verfct6  Total intrusion errors
verfct7  Total perseverative errors
verfctnd  Justification for errors
scnt  Stroop Colour Naming Test completed
scnt1  Total correct
scnt2  Total errors
scnt3  Total self-corrected errors
scntnd  Justification for errors
swrt  Stroop Word Reading Test completed
swrt1  Total correct
swrt2  Total errors
swrt3  Total self-corrected errors
swrtn  Justification for errors
sit  Stroop Interference Test completed
sit1  Total correct
sit2  Total errors
sit3  Total self-corrected errors
trl  Trailmaking Test completed
trla1  Part A: time to complete
trla2  Part A: total correct
trla3  Part A: total errors
trlb1  Part B: time to complete
trlb2  Part B: total correct
trlb3  Part B: total errors
verflt  Verbal Fluency Test (Letters) completed
verflt05  Total correct (3 min)
verflt06  Total intrusion errors
verflt07  Total perseverative errors
mmsetotal  MMSE score
tug  Timed "Up and Go" performed
tug1  Total time
scst  30 second chair stand test performed
scst1  Number of times the participant stands in 30 seconds
depscore  PBAs Depression
irascore  PBAs Irritability aggression
psycore  PBAs Psychosis
aptscore  PBAs Apathy
exfscore  PBAs Executive function
pbas1sv  Depressed mood severity
pbas1fr  Depressed mood frequency
pbas1wo  Depressed mood worst
pbas2sv  Suicidal ideation severity
pbas2fr  Suicidal ideation frequency
pbas2wo  Suicidal ideation worst
pbas3sv  Anxiety severity
pbas3fr  Anxiety frequency
pbas3wo  Anxiety worst
pbas4sv  Irritability severity
pbas4fr  Irritability frequency
pbas4wo  Irritability worst
pbas5sv  Aggressive behaviour severity
pbas5fr  Aggressive behaviour frequency
pbas5wo  Aggressive behaviour worst
pbas6sv  Lack of initiative (apathy) severity
pbas6fr  Lack of initiative (apathy) frequency
pbas6wo  Lack of initiative (apathy) worst
pbas7sv  Perseverative thinking or behaviour severity
pbas7fr  Perseverative thinking or behaviour frequency
pbas7wo  Perseverative thinking or behaviour worst
pbas8sv  Obsessive-Compulsive Behaviours severity
pbas8fr  Obsessive-Compulsive Behaviours frequency
pbas8wo  Obsessive-Compulsive Behaviours worst
pbas9sv  Delusions paranoid thinking severity
pbas9fr  Delusions paranoid thinking frequency
pbas9wo  Delusions paranoid thinking worst
pbas10sv  Hallucinations severity
pbas10sm__1  Modality of hallucinations - auditory
pbas10sm__2  Modality of hallucinations - visual
pbas10sm__4  Modality of hallucinations - tactile
pbas10sm__3  Modality of hallucinations - olfactory
pbas10sm__5  Modality of hallucinations - gustatory
pbas10fr  Hallucinations frequency
pbas10wo  Hallucinations worst
pbas11sv  Disoriented Behaviour severity
pbas11fr  Disoriented Behaviour frequency
Disoriented Behaviour worst
Is informant a relative?
Is informant a household member?
Online scoring
Physical Functioning
Role-Physical
Bodily Pain
General Health
Vitality
Social Functioning
Role-Emotional
Mental Health
Physical Component
Mental Component
Hospital Anxiety and Depression Scale Snaith Irritability subscore
HADS-SIS Depression subscore
HADS-SIS Irritability subscore
HADS-SIS Outward irritability subscore
HADS-SIS Inward irritability subscore
Problem Questionnaire (WPAI-SHP) Work time missed due to HD
Impairment while working due to HD
Overall work impairment due to HD
Activity impairment due to HD
Suicidal Ideation – For Lifetime, rate the period when the participant felt the most suicidal. Have you wished you were dead or wished you could go to sleep and not wake up?
Have you actually had any thoughts of killing yourself?
Have you been thinking about how you might do this?
Have you had these thoughts and had some intention of acting on them?
Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?
Intensity of Ideation – Most Severe Type
Intensity of Ideation – Most Severe How many times have you had these thoughts?
Intensity of Ideation – Most Severe When you have the thoughts, how long do they last?
Intensity of Ideation – Most Severe Could/can you stop thinking about killing yourself or wanting to die if you want to do?
Intensity of Ideation – Most Severe Are there things – anyone or anything (e.g. family, religion, pain of death) – that stopped you from wanting to die or acting on thoughts of committing suicide?
Intensity of Ideation – Most Severe What sort of reasons did you have for thinking about wanting to die or killing yourself?

Suicidal Behavior Actual attempt
Suicidal Behavior Total # of attempts
Suicidal Behavior Has subject engaged in Non-Suicidal Self-Injurious Behavior?
Suicidal Behavior Has there been a time when you started to do
something to end your life but someone or something stopped you before you actually did anything?
Suicidal Behavior Total # of interrupted
Suicidal Behavior Has there been a time when you started to do
something to try to end your life but you stopped yourself before you actually did anything?
Suicidal Behavior Total # of aborted
Suicidal Behavior Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?
Suicidal behaviour was present during the assessment period?
Completed Suicide was present during the assessment period?
Answer for Actual Attempts Only - Day of most recent attempt
Answer for Actual Attempts Only - Actual Lethality/Medical Damage
Answer for Actual Attempts Only - Potential Lethality
Answer for Actual Attempts Only - Day of most lethal attempt
Answer for Actual Attempts Only - Actual Lethalit/Medical Damage
Answer for Actual Attempts Only - Potential Lethality
Answer for Actual Attempts Only - Day of Initial/First attempt
Answer for Actual Attempts Only - Actual Lethality/Medical Damage
Source of information
Reason for missed follow-up visit
Level of care required
Days since full-time dependency
## Appendix 2: Classification of the drugs

### Table 19: Classification of the drugs in Pharmacotx file according to the mechanism of action (Complete list)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mechanism of Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Agomelatine</td>
<td>Atypical Antidepressant</td>
</tr>
<tr>
<td>Alprazolam</td>
<td>Benzodiazepine</td>
</tr>
<tr>
<td>Amisulpride</td>
<td>Antipsychotic</td>
</tr>
<tr>
<td>Amitriptyline</td>
<td>Tricyclic</td>
</tr>
<tr>
<td>Amitriptyline hydrochloride</td>
<td>Tricyclic</td>
</tr>
<tr>
<td>Aripiprazole</td>
<td>Antipsychotic</td>
</tr>
<tr>
<td>Asenapine maleate</td>
<td>Antipsychotic</td>
</tr>
<tr>
<td>Bromazepam</td>
<td>Benzodiazepine</td>
</tr>
<tr>
<td>Bupropion</td>
<td>NDRI</td>
</tr>
<tr>
<td>Bupropion hydrochloride</td>
<td>NDRI</td>
</tr>
<tr>
<td>Chlorprothixene</td>
<td>Antipsychotic</td>
</tr>
<tr>
<td>Chlorprothixene acetate</td>
<td>Antipsychotic</td>
</tr>
<tr>
<td>Chlorprothixene hydrochloride</td>
<td>Antipsychotic</td>
</tr>
<tr>
<td>Citalopram</td>
<td>SSRI</td>
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<tr>
<td>Citalopram hydrobromide</td>
<td>SSRI</td>
</tr>
<tr>
<td>Citalopram hydrochloride</td>
<td>SSRI</td>
</tr>
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<td>Tricyclic</td>
</tr>
<tr>
<td>Clomipramine hydrochloride</td>
<td>Tricyclic</td>
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<td>Clonazepam</td>
<td>Benzodiazepine</td>
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<td>Clorazepate dipotassium</td>
<td>Benzodiazepine</td>
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<td>Clozapine</td>
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<tr>
<td>Clozapine</td>
<td>Antipsychotic</td>
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<td>Cyamemazine</td>
<td>Antipsychotic</td>
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<tr>
<td>Desipramine</td>
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<tr>
<td>Desipramine hydrochloride</td>
<td>Tricyclic</td>
</tr>
<tr>
<td>Desvenlafaxine</td>
<td>SNRI</td>
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<tr>
<td>Desvenlafaxine succinate</td>
<td>SNRI</td>
</tr>
<tr>
<td>Diazepam</td>
<td>Tricyclic</td>
</tr>
<tr>
<td>Dosulepin</td>
<td>Tricyclic</td>
</tr>
<tr>
<td>Dosulepin hydrochloride</td>
<td>Tricyclic</td>
</tr>
<tr>
<td>Doxepin</td>
<td>Tricyclic</td>
</tr>
<tr>
<td>Doxepin hydrochloride</td>
<td>Tricyclic</td>
</tr>
<tr>
<td>Duloxetine</td>
<td>SNRI</td>
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<tr>
<td>Duloxetine hydrochloride</td>
<td>SNRI</td>
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<tr>
<td>Escitalopram</td>
<td>SSRI</td>
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<tr>
<td>Escitalopram oxalate</td>
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<tr>
<td>Estazolam</td>
<td>Benzodiazepine</td>
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<tr>
<td>Etizolam</td>
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<tr>
<td>Fluoxetine</td>
<td>SSRI</td>
</tr>
<tr>
<td>Fluoxetine hydrochloride</td>
<td>SSRI</td>
</tr>
<tr>
<td>Flupentixol</td>
<td>Antipsychotic</td>
</tr>
<tr>
<td>Flupentixol decanoate</td>
<td>Antipsychotic</td>
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</tbody>
</table>
Flupentixol dihydrochloride
Flupentixol dihydrochloride, Melitracen hydrochloride
Fluspirilen
Fluvoxamine
Fluvoxamine maleate
Haloperidol
Haloperidol decanoate
Imipramine
Imipramine hydrochloride
Ketazolam
Levomepromazine
Levomepromazine hydrochloride
Levomepromazine maleate
Levomilnacipran
Levosulpiride
Lofepramine
Lorazepam
Lormetazepam
Lurasidone
Lurasidone hydrochloride
Maprotiline hydrochloride
Mianserin
Mianserin hydrochloride
Milnacipran
Milnacipran hydrochloride
Mirtazapine
Moclobemide
Nefazodone hydrochloride
Nortriptyline
Nortriptyline hydrochloride
Olanzapine
Opipramol
Opipramol hydrochloride
Oxazepam
Paroxetine
Paroxetine hydrochloride
Perazine dimaleate
Perazine dimalonate
Perphenazine
Pimozide
Pipamperone hydrochloride
Prazepam
Quetiapine
Quetiapine fumarate
Reboxetine
Reboxetine mesilate
Risperidone
Selegiline

Antipsychotic
Antipsychotic
Antipsychotic
SSRI
SSRI
Antipsychotic
Antipsychotic
Tricyclic
Tricyclic
Benzodiazepine
Antipsychotic
Antipsychotic
SSRI
Antipsychotic
Tricyclic
Benzodiazepine
Benzodiazepine
Antipsychotic
Antipsychotic
Tricyclic
Tricyclic
Tricyclic
SNRI
SNRI
Atypical Antidepressant
MAOI
Atypical
Tricyclic
Tricyclic
Antipsychotic
Atypical
Atypical
Benzodiazepine
SSRI
SSRI
Antipsychotic
Antipsychotic
Antipsychotic
Antipsychotic
Antipsychotic
Benzodiazepine
Antipsychotic
Antipsychotic
SNRI
SNRI
MAOI
Sertraline  
SSRI

Sertraline hydrochloride  
SSRI

Sulpiride  
Antipsychotic

Temazepam  
Benzodiazepine

Thioridazine hydrochloride  
Antipsychotic

Tianeptine  
Atypical Antidepressant

Tianeptine sodium  
Atypical Antidepressant

Tiapride  
Antipsychotic

Tiapride hydrochloride  
Antipsychotic

Trazodone  
SARIs

Trazodone hydrochloride  
SARIs

Trimipramine  
Tricyclic

Trimipramine maleate  
Tricyclic

Trimipramine mesylate  
Tricyclic

Venlafaxine  
SNRI

Venlafaxine hydrochloride  
SNRI

Vilazodone  
Atypical Antidepressant

Vilazodone hydrochloride  
Atypical Antidepressant

Ziprasidone hydrochloride  
Antipsychotic

*SNRI* = Serotonin and norepinephrine reuptake inhibitors; *SSRI* = Selective Serotonin Reuptake Inhibitors; *MAOI* = Monoamine oxidase inhibitors; *SARI* = Serotonin antagonist and reuptake inhibitors