"I hope that it's okay for everybody": Exploring understanding of Neural Cell Transplantation (NCT) as an Intervention for Huntington's Disease (HD). An Interpretative Phenomenological Analysis.

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Abstract

Background

Huntington's Disease (HD) is a debilitating and ultimately fatal progressive neurological disorder. It is a genetically inherited disease with each person affected having a 50 per cent chance of transmitting the disease to their children. At the time of writing, there is no cure.

People with pre-manifest HD are due to be approached to participate in clinical trials of Neural Cell Transplantation (NCT) as a potential new therapy for the disease. This thesis sought to uncover their beliefs, concerns, and perspectives, surrounding this trial intervention, so that their insights could be available to health service decision makers and clinical trials teams.

Understanding the lived experience and giving voice to people with HD is critical to the development of person-centred practice. It is important that these experiences are embedded in activities and guidelines surrounding the potential therapeutic use of NCT.

Aim

To explore the lived experience of people with pre-manifest Huntington's Disease (HD) during a time when NCT is being developed as a novel potential therapy.

Method

The thesis was conducted using Interpretative Phenomenological Analysis (IPA). It sought to uncover how the participants made sense of their lived experience of premanifest HD and the meaning that they attribute to NCT within the context of their own future lives.

Semi-structured interview data was collected from six people with pre-manifest HD. Four of their partners were present at interview and these partners also participated. The interview data was analysed, and the discussion framed using Ashworth's (2015) Lifeworld model.

Findings

The thesis found that participants view HD is a pervasive disease which impacts on multiple dimensions of their lifeworld, beyond physical and cognitive health. However, NCT appears to provide a sense of hope that pervasiveness of HD can potentially be alleviated, and sense of agency restored. However, caution needs to be maintained in creating a sense of over optimism with regard to the benefits of NCT.

The thesis also uncovered how people with pre-manifest HD form Secret Circles which can incorporate Healthcare and Researchers Workers (HRs) and, it suggested that, if HRs are trusted enough to be a member of the circle, then this can facilitate engagement with research amongst people with pre-manifest HD.

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Glossary of Terms

Bradykinesia- Slow movement and progressive reduction of frequency and/or amplitude of repetitive movements.
CAG repeat- People with HD have the same genetic mutation. There is an expansion of a normal repetitive piece of genetic information on chromosome number 4. All humans have this but in people with HD there is a repetitive stretch of genetic code Cytosine, Adenine and Guanine (CAG). In people without HD this repeat occurs fewer than 35 times. In people who have HD the CAG repeats 36 times or more.
Chorea- Involuntary, short, abrupt, irregular and unpredictable abnormal movement. Chorea can affect multiple parts of the body and interfere with speech, posture, gait and swallowing.
Clinical Trial- Any research that prospectively assigns human participants to one or more interventions in order to evaluate their impact(s) on health.
Double Hermeneutic- Making sense of someone's situation via that person's own interpretations of their experiences.
Huntington's disease (HD)- An inherited and devastating neurodegenerative disease which is characterised by progressive cognitive, psychiatric and motor symptoms.
***HTT*-** HD is caused by a CAG trinucleotide repeat expansion in the *HTT* gene.
Idiographic- How a particular person makes sense of a phenomenon within a context.
Interpretative Phenomenological Analysis (IPA)- A qualitative research approach which draws upon the theoretical traditions of phenomenology, hermeneutics and idiography. It is concerned with how people understand and make sense of their lived experience.
Juvenile HD- Similar the adult disease, however, the children and young people affected by this form of HD are less likely to experience the involuntary movements and more likely to experience muscle contractions and stiffness. Epilepsy is more common in Juvenile HD.
Feelings- An emotional state or reaction to phenomena.
Neural Cell Transplantation-Transplantation of neural stem/pre-cursor cells from a donor into a host with the aim of combatting neurodegenerative disease. In the case of the current trial, foetal cells will be used.
Neurodegenerative- Degeneration of the nervous system, especially the neurons within the brain.
Neuron- Neurons are the electrically excitable cells which are the fundamental units of the brain and nervous system
Parkinson's Disease (PD)- PD is a condition whereby parts of the brain become progressively damaged resulting in motor and psychological symptoms. The disease is characterised by a loss of neurones within the substantia nigra of the brain resulting in decreased production of dopamine. The cause is unclear but thought to be a combination of genetic and environmental factors.
Perceptions- The way in which phenomena are regarded and the surrounding beliefs. Beyond the cognitive to the sense making.
Pre-manifest - Relating to the early stages of the disease when symptoms have not yet manifested.
Prodromal- The early stages of a disease when symptoms start to manifest.
Understanding-Comprehension of phenomena.

Prologue

I am a registered nurse currently working in higher education. Prior to commencing my nurse education in the late nineties, I began, but did not finish, a degree in psychology and biology. As the first in my immediate family to go to university, I was originally interested in biological structure and function, however, my areas of interest evolved after witnessing the illness and death of my great-grandmother (Nan).

As was not uncommon in a post-industrial town in South Wales in the 1980s, I spent a vast amount of time as a child with my Nan, eventually living with her for several years in her later life. I vividly remember returning home one night to the house I shared with her only to be greeted by my great aunt who informed me that Nan had been taken ill and had had a stroke. When I visited her, it became apparent that the stroke had been severe. It had left her with profound paralysis and she would not be returning home. She initially moved between hospital wards and eventually was moved to a nursing home where she remained until her death around six months later. I visited her a great deal in the nursing home and remember feeling an immense sense of loss. I felt angry that illness had taken her independence, her ability to communicate effectively, and, essentially, the capacity to be my Nan. Shortly after her death, I moved to England to begin my studies but increasingly knew that I wanted to pursue a career applying science to working with people and, after a year, returned home to study nursing.

Upon entry into the nursing profession and following a long period working within critical care medicine, I moved on to a role where I was employed in early phase clinical trials within a research facility. During my time in this post, I worked on several firsts in human drug trials aimed at treating a range of conditions from cancers to neurological conditions such as multiple sclerosis (MS). Many of the patients had exhausted their treatment options; many were near the end of life. As a result, I initially had a simplistic notion of what motivated people to participate in clinical trial research. The motivation was to stay alive. However, as my time with and exposure to this patient group grew, I recognised that there was greater complexity in why people consent to participate. Amongst the many patients I worked with, two stand out in particular.

The first was a gentleman in his late fifties who had a diagnosis of terminal haematological cancer. He had volunteered to participate in the trial of a Phase I clinical trial drug. His treatment involved multiple visits, undergoing blood tests, and often spending long hours receiving an intravenous infusion of the experimental medication. As a result, I spent a great deal of time with him and, outside of conversations about sport and the news, I once asked why he had decided to participate in such a

seemingly arduous regime. He answered that illness had cut his career short and he had to do something. He could not sit at home and just wait to die. He continued that, up until his illness, he had worked all his adult life as a plumber and he needed to occupy his day. The clinical trial was now his job.

The second was a woman who was in her early forties and only a few years older than me. She had advanced multiple sclerosis (MS) with pronounced symptoms. The disease had had a notable effect on her movement and during visits, she described the impact that it had on her whole life, particularly in her role as a parent to two young children. I remember her describing how she was prepared to try anything which could help her get better as she wanted to be a "proper mum".

The interactions with my patients, combined with my own personal experiences, increased my questioning surrounding illness and self. I developed an intense interest in what clinical trials meant to people within the context of their own lives. As a result of this curiosity, I began a professional doctorate and was consequently given the opportunity to undertake this thesis exploring people's lived experience of Huntington's disease in an era of new and emerging therapies.

Coincidentally and whilst undertaking this study, I have personally experienced events such as the birth of my own children and the death of two immediate family members. One died from cancer and the other from rapid-onset dementia. I was heavily involved in their care and felt challenged to understand how they made sense of their situation so that I could best facilitate their wishes. Consequently, this has augmented my desire to ensure that people's voices are heard and that healthcare professionals consider them.

Organisation of Thesis

The thesis is divided into four parts.

Part 1: This section offers the background and justification and identifies the research question. The context for the thesis is also set.

Part 2: The research process is described. This section presents the design, research methods, and data collection process used. The use of interpretative phenomenological analysis (IPA) is also justified.

Part 3: The stories of the people recruited are presented. They are described and analysed using IPA, identifying individual and shared experiences with cross-case patterns explored.

Part 4: The participants' experiences are located within the theoretical framework of Ashworth's Lifeworld (2016) model. The conclusions are presented alongside how this thesis could potentially impact healthcare practice, education, and future research.

The background for the thesis is now presented.

Part One

1.0: Background

Huntington's disease (HD) is a debilitating and ultimately fatal progressive neurological disorder. It is an inherited disease with each person affected having a 50 per cent chance of passing on the genetic predisposition to disease to their children, regardless of sex (Harper 2005). Progression of HD, for most people, results in cognitive and physical decline, with an increased reliance on care provision escalating to complete dependency and ultimately death. There is no cure for HD but there has been growing scientific interest in neural cell transplantation (NCT) as a potential therapy. There are plans to undertake further clinical trials, recruiting people with pre-manifest and prodromal HD, using foetal-derived cells derived from elective abortions. The clinical trial has a recruitment base in Cardiff and will look to recruit people from mid and South Wales alongside people from the Southwest of England.

Throughout this thesis, these human foetal ganglionic eminence cell transplants will be referred to as NCT.

NCT, as a treatment for neurological disorders, has been a topic for experimental and clinical research over the past two decades (Dunnett and Björklund 2017). The process involves surgically implanting cells from donor tissue into the central nervous system of people affected by neurodegenerative diseases. The aim is to repair the normal neural networks and to re-establish function. It is thought that NCT has the possibility for stabilisation and possible remission for those affected by HD (Precious et al. 2017). To date, however, there have been a limited number of clinical trials undertaken involving a small number of HD participants.

A clinical trial of NCT is currently being undertaken in Cardiff. The TRIal designs for DElivery of Novel Therapies in neurodegeneration (TRIDENT 2021) aims to recruit a cohort of between 18-30 gene-positive, pre-manifest or early stage (prodromal) individuals with HD. The primary objective is to evaluate the safety of transplantation surgery using human foetal neuronal tissue for the treatment of patients with HD. People will be recruited to the trial from a database of people who attend a clinic in Cardiff.

To date, the limited research which has been undertaken surrounding NCT in HD has tended to focus on the procedure itself and not yet examined the views of people with HD. The European Consortium for Communicating Stem Cell Research (2022) encourages patient consultation and argues that it is of primary importance to involve patients and the public in healthcare and research strategy

development. People with HD have valuable insights and their perceptions and understanding could be of benefit to future research and healthcare planning.

This thesis sought to explore the lived experience of people with pre-manifest HD who live in a time where NCT is being investigated as a potential, albeit experimental therapy. It examined the thoughts, feelings, and understanding of NCT amongst people who might be asked to participate in TRIDENT (2021).

Understanding within the context of this thesis means awareness of NCT and its potential impacts for people with HD within the context of their own lives and experiences.

The research question is now presented followed by the aims.

1.1: The Research Question

It appears that limited research has been undertaken surrounding NCT in HD and there are areas which have not yet been addressed. Research has yet to explore the perceptions and understanding of NCT amongst people living with HD who might be approached to participate in clinical trials or ultimately receive NCT as a therapy. The aim of this thesis was to redress this gap in knowledge and to explore understanding amongst adults who have pre-manifest HD. Consequently, the research question is:

- What is it like to have a lived experience of pre-manifest HD in a time where NCT is being proposed and developed as a potential therapy?

It was not intended to be an overall exploration of the lived experience of pre-manifest HD.

1.2: The Research Objectives

To achieve this, the following was done:

- A systemised literature review was undertaken to gain insight into the lived experience of people with HD and to identify how they view NCT. The literature review suggested that there is a dearth of available research surrounding the topic.
- To find out more about the intervention and associated procedures, a novel approach was taken and I interviewed professionals identified as being experts within the field of NCT for HD. The aim of this was to gain greater insight into the background, procedure, and targeted population for the clinical trials.
- The focus of the research was to look at the lived experience of people with HD within a new era of NCT using interpretative phenomenological analysis (IPA). Specifically, the aim of the research was to critically explore the thoughts, feelings and understanding of NCT in people

with pre-manifest HD within the context of their own lives and to explicitly give a voice to them.

- To make recommendations for healthcare practice, education, and future research based on the findings.
- To discuss any limitations and quality issues.

1.3: The Research within the Context of a Professional Doctorate

This research has been undertaken as part of a professional doctorate. Prior to undertaking this thesis, a series of level eight modules were undertaken to enhance research knowledge and understanding. Professional doctorates have become a prominent method of accessing doctoral-level study over the last three decades (Kot and Hendel 2012). They can be viewed as an alternative to a PhD which is an academic degree where the original research, data analysis, and the evaluation of theory seek to generate new knowledge (Fulton et al. 2021).

Arguably, the term professional doctorate can be viewed as an umbrella term covering a range of delivery methods which focus on applying research to practical problems, formulating solutions to complex issues, and designing effective professional practices within a given field (Fulton et al. 2021).

Prior to undertaking this research, NCT technology existed as a prospective therapy for HD but, as healthcare professionals, we did not know what the people, who could be asked to participate in clinical trials, thought about NCT within the context of their own lives.

Now these have been explored, there is the potential to develop practices, procedures, and an environment which truly embraces the HD population as the principal interest in novel interventional research. The Welsh Government's Genomics for Precision Medicine Strategy (2017) commits to engaging with patients to drive service developments. To achieve this, the strategy argues that researchers and health services within Wales must capture patient experiences to improve service delivery. This research seeks to action this commitment.

1.4: Conclusion

This section has presented the focus of the research, which is to explore the lived experience of people with pre-manifest HD where NCT is now being proposed as a therapy. The organisation of the thesis has been set out and the research question aims have been outlined. Chapter 2 will outline, in detail, the context of this research exploring HD and NCT.

2.0: Setting the Scene

The following section sets the context in which the thesis was undertaken. It outlines the historical context of the disease and the contemporary scientific understanding of HD and genetics before moving on to current management strategies. This is followed by an overview of NCT and its potential place as a therapeutic option.

2.1: The Historical Context

Although the symptoms associated with HD have been documented for centuries, it was George Huntington who described the choreiform movements which seemed to be prevalent in some families. Huntington observed a disorder of movement which was accompanied by personality changes and a "tendency towards insanity" (Bates 2005). In his seminal paper "On Chorea", Huntington (1872) outlined its autosomal-dominant pattern of inheritance and described the disease as not being a dangerous or serious affliction despite it being potentially distressing to the person who has it.

Diseases with similar presentations identified throughout history have often been associated with societal persecution. Coon and Hassan (2015) outlined how Charlotte Bronte's novel Jane Eyre depicted the character Bertha Mason as having HD-like symptoms. Bronte described "the mad woman in the attic" as having a hereditary, progressive psychiatric illness, "movements of the wild beast", and cognitive decline.

As early as the 17th Century, families presenting with similar symptoms and disease characteristics in New England, United States of America were labelled using derogatory terms, including "magrum" or "megrim". The individuals, with their uncontrollable movements, were viewed by local inhabitants as mocking the sufferings experienced in Christ's crucifixion, and subsequently labelled as witches. There were instances where these individuals were burnt to death as both they and their families were seen as cursed. It is also widely believed that choreic movements and abnormal behaviour resulted in executions during the Salem Witch Trials (1692-1693) as it was thought that the characteristics indicated possession by the devil (Bhattacharyya 2016).

Further abuses continued throughout the 20th Century, with suggestions that those identified as having HD were forcibly sterilised and might have been executed by the Nazis during World War II (Harper 1992).

Discrimination still appears to exist in contemporary society. In Canada, a survey of 233 asymptomatic individuals at risk of HD, of whom 70 per cent had undergone predictive genetic testing, demonstrated that 40 per cent of respondents had experienced some degree of discrimination. This prejudice

manifested in the form of discrimination from mortgage companies, life insurance, and disability insurance providers, predominantly in the form of insurance rejection and increased requests for applicants to undergo genetic testing (Bombard et al. 2009). Penziner et al. (2008) also identified stigmatisation and discrimination among individuals who had undergone predictive testing for HD. The perceptions of 15 pre-symptomatic participants who had tested positive for the expanded *HTT* gene were examined regarding differential treatment they had experienced post-testing. Although most participants revealed their test results to their employers, nearly all declared that, in future, they would not repeat this with any future employer due to negative experiences surrounding gaining promotion and feeling "stuck" in current employment. More positively, most participants did openly disclose results within their families and social networks, with two participants reporting that they revealed their genetic status in a public forum. This was due to a sense of feeling responsible to advocate and support HD causes and is pertinent to this study with regard to participants' understanding of and motivation towards research participation.

Within the United Kingdom (UK), there are legal moratoria providing protection from discrimination for people with the HD gene. This prohibits employers from discriminating against people with manifest HD. However, currently, there is no legislation which protects asymptomatic individuals who are carriers of the HD mutation (Edge 2010).

2.2: Contemporary Understanding of Huntington's Disease

HD is a progressive, ultimately fatal, autosomal dominant, and genetically inherited neurodegenerative disease. There is no cure at present. It is caused by an abnormal and expanded cytosine, adenine, guanine (CAG) repeat in chromosome four. This results in the production of the damaging *HTT* protein (Ross and Tabrizi 2011). Post-mortem examinations, as well as the use of animal models, have identified that numerous pathologic mechanisms are unleashed due to the disease process. Studies have shown atrophy and loss of mass in multiple areas of the brain including 57 per cent in the caudate, 64 per cent in the putamen in moderately affected cases, and losses in the cerebral cortex and thalamus (de la Monte et al. 1988). Microscopic changes in HD are most severe in the striatum where the medium spiny neurons become damaged by the disease, resulting in associated symptoms (Graveland et al. 1985).

HD is characterised by neuronal dysfunction and selective neuronal cell death within the brain. The areas of the brain affected by HD are the striatum and, in particular, the caudate nucleus and putamen. The medium spiny neurones are particularly impacted by HD. Although the striatum is the most profoundly affected region of the brain, degenerative changes have also been reported as occurring within the cortex, thalamus, and sub-thalamic nucleus. The precise mechanism via which the neurons

die in the disorder remains unknown (Leegwater-Kim and Cha 2004). The neuronal damage results in distinct motor, behavioural, and cognitive symptoms associated with HD (Imarisio et al. 2008).

2.2.1: Diagnosis and Symptoms

People who have a parent with the expanded *HTT* gene have a 50 per cent risk of inheriting the disease and if they do, it is inevitable that they will then go on to develop the associated symptoms. The disorder affects both sexes equally (Dunnett and Rosser 2007). HD does not skip generations (Dawson et al. 2004).

Diagnosis of HD is based on positive genetic testing, (often) identification of a family history of the disease, and, as the disease progresses, expression of the unequivocal motor signs of HD. These signs include extrapyramidal motor signs of chorea, dystonia, bradykinesia, and a lack of coordination (Ross and Tabrizi 2011). The majority of those affected by the gene appear healthy throughout childhood and adolescence but gradually develop signs and symptoms of HD, often resulting in diagnosis during middle age (Stout et al. 2011). Following positive genetic testing but prior to symptom development, people are considered to be pre-manifest.

A prominent symptom of HD is involuntary, unwanted movements which often start with fingers, toes, and facial muscles. These then progress and walking becomes unstable, often leading to the misconception that people are drunk (Roos 2010). This lack of muscle control then progresses to all the person's skeletal muscle. Choreic movements become prominent with continuous facial movements including the lifting of eyebrows, eye closing, and tongue protrusion. The most prominent are the extension movements of the long back muscles (Roos 2010). This chorea is usually present in the early stages of the disease, however, those affected go on to develop progressive bradykinesia, further lack of coordination, and rigidity. As the disease progresses, there is an increase in disabling functionality, for example, the ability to perform self-care. Many patients have substantial cognitive or behavioural disturbances before the onset of diagnostic motor signs (Rosenblatt et al. 2012). The Track-HD study also identified volumetric changes in brain size, even in people who were pre-manifest (Tabrizi et al. 2011)

Psychiatric symptoms are often present in the early stage of the disease, frequently before the development of motor symptoms. The most common of these is depression. Apathy, guilt, and anxiety are also common amongst people with early symptoms and people who are pre-manifest gene carriers. Progressive cognitive decline is another notable symptom of HD and can be present prior to motor symptoms appearing. People with advanced HD may lose the ability to plan and control their own lives. Memory also becomes severely impaired (Cleret de Langavant 2013). Other prevalent

symptoms of HD can include unintended weight loss, sleep and circadian rhythm disturbances, and autonomic nervous system dysfunction (Roos 2010).

Signs and symptoms of the disease tend to emerge between the ages of 30 and 50 in most of the HD population, however, as outlined, the disorder can manifest at any point during a genetically positive individual's lifetime (Walker 2007). The mean duration between symptoms emerging to death is 17-20 years (Roos 2010).

Progression of HD eventually results in loss of independence and function, leading to increased reliance on care provision, escalating to complete dependency. Death usually occurs due to complications of the disease, including aspirational pneumonia and nutritional deficiencies (Walker 2007), however, suicide is also a predominant cause of death (Roos 2010).

The stages of HD are presented in Table 1 below.

Table 1: The Stages of Huntington's disease

Staging	***Characteristics at this stage***
Person at risk of having disease	Uncertainty
	Potentially witnessing and caring for family
Identified that carrier person is in pre-manifest stage	➢ Confirmation of disease
	➢ Uncertainty about onset
Transition phase	➢ Anxiety about changes in cognition
	➢ Changes in behaviour
	➢ Changes in motor activity
Clinical staging	
Clinical stage I	➢ Neurological, cognitive, or psychiatric changes begin
	➢ Chorea becomes a prominent symptom
	➢ Can still remain independent
Clinical stage II	➢ Motor disturbances more notable
	➢ Physical dependence begins
Clinical stage III	➢ Severe motor disturbance
	➢ Can be completely dependent
	➢ Death

Adapted from Roos (2010)

2.2.2: The Genetics of Huntington's Disease

As stated previously, HD is an inherited disorder, therefore, an explanation of the underpinning genetics is now presented. HD is a progressive, ultimately fatal, autosomal dominant and genetically inherited neurodegenerative disease. Autosomal dominant disorders occur when only a single copy of a defective gene is required to cause disease (Mahalingham and Levy 2013). The inherited gene can affect males and females equally, with offspring having a fifty per cent chance of inheriting the disease if one parent is affected (Novak and Tabrizi 2010).

The responsible HD gene (IT15) was discovered in 1983 (Walker 2007). In the following decade, the specific deoxyribonucleic acid (DNA) mutation, or expanded *HTT* gene, which results in the production of the damaging *HTT* protein, was discovered on chromosome four. Scientists identified that the gene contains a region where the triplet nucleotide, cytosine, adenine, guanine (CAG), is repeated several times (Dunnett and Rosser 2007). This damaging expanded *HTT* protein results in the degeneration of cells within the mid-brain associated with HD and with the resultant expression of HD-associated symptoms (Rosenblatt et al. 2011).

Additionally, it was identified that the number of CAG repeats determines whether an individual develops the disorder, with longer CAG repeats being utilised to predict earlier onset. These cannot, however, reliably predict the rate of onset (Rosenblatt et al. 2006).

It was discovered that individuals with six to 35 CAG repeats remain unaffected, however, individuals with 36-39 repeats will go on to develop HD. The average CAG tract length in the general population is 16 to 20 repeats (Prinsheim et al. 2012). Individuals with 40 or more CAG repeats are, however, certain to develop the disorder (Bates 2005). It was identified that the gene expression is ubiquitous throughout the body but primarily impacts specific areas of the central nervous system (CNS) (Li et al. 1995). The damaging expanded *HTT* protein, as described by DiFiglia et al. (1995), results in the degeneration of cells within the mid-brain with the resultant expression of HD and its associated symptoms. These include abnormal muscle tone, cognitive deterioration, and behavioural abnormality and are relentlessly progressive and ultimately fatal (Walker 2007).

2.2.3: Prevalence

Worldwide prevalence estimates vary considerably depending on the population under study. Pringsheim et al.'s (2012) systematic review and meta-analysis identified an overall worldwide prevalence of HD of 2.71 per 100,000 people. A further meta-analysis of subgroups from North America, Europe, Australia, and Asia also revealed a disparity in prevalence globally. In North America, Europe, and Australia, an overall prevalence of 5.7 per 100,000 was identified compared to an overall prevalence of 0.4 per 100,000 in Asia.

Jones et al. (2016) state that approximately 9,000 people in the United Kingdom (UK) are affected by HD and this is associated with economic as well as human cost. Data for patients within the UK in 2013 was extracted from the European Huntington's Disease Network (EHDN) registry study and national unit costs were applied to health and social care services. Data from 131 people were examined and it was identified that the mean annual cost/investment per person with HD was £21,605. Mean annual costs per person in Stage I of the disease were noted to be £2,250, rising to £89,760 in later stages.

2.2.4: Juvenile Huntington's Disease

Juvenile HD is a less common subset of HD in which symptoms present before the age of 20. Juvenile HD accounts for approximately 5-10 per cent of all HD cases (National Institute for Health 2019). As with the more common form of the disease, it is a progressive disorder with behavioural disturbances and learning difficulties presenting first. Motor disorder, including bradykinesia and hypokinesia, emerges, with a tendency for chorea to develop in the second decade. Epileptic fits are common, with the CAG repeat length being more than 55 in most cases. Most people with Juvenile HD do not survive more than 10 to 15 years following the onset of symptoms (Roos 2010).

There are no plans to use NCT for Juvenile HD at present. Therefore, young people with this condition will not be explored in further detail.

2.3: Management of Huntington's Disease

The previous section outlined HD within the context of history and society and described the current understanding of HD. As stated previously, there is no cure at present. Current management strategies, including pharmacological and nonpharmacological approaches, are addressed. Finally, experimental approaches, including NCT, are discussed.

Traditionally, there has been a focus on pharmacological treatment to improve the symptoms and quality of life in patients affected by this currently incurable disease (Sharma and Deogaonkar 2015).

Following the onset of disabling and movement-related symptoms, people are generally started on pharmacologic therapies where the aim is to improve their quality of life. This can include drugs such as antidepressants, GABA agonists, and neuroleptics (both typical and atypical). These decrease the action of the neurotransmitter dopamine and are intended to decrease hyperkinesia symptoms, for example, unsteady gait and facial grimaces. Both the management and titration of these medications can be difficult, with resultant side effects including bradykinesia, depression, and sedation (Adam and Jankovich 2008). The European Huntington's Disease Network (EHDN) recently commissioned a task force with the aim of identifying global evidence-based recommendations for the everyday clinical management of HD. The objectives were to standardise pharmacological, non-

pharmacological, and surgical therapies to improve the care and quality of life of people with HD (Bachoud-Levi et al. 2019).

Due to the complex nature and progression over time, people with HD require the input of multiple healthcare professionals, the coordination of services, and regular reassessments so that their changing needs are met (Phillips et al. 2008). These teams can include, but are not limited to, the following in Table 2:

Table 2: Healthcare professionals and their roles

Professional	***Role in HD management***
Genetic counsellor	Genetic counsellors enable people and their families to understand their HD risks. They can identify and discuss reproductive options.
Neurologist	A medical doctor who specialises in the treatment of diseases of the nervous system, including HD.
Specialist HD nurse	Specialist HD nurses provide a pivotal coordination role, supporting people and their families. They provide a readily accessible point of contact.
Social worker	Social workers can coordinate assistance within the community and provide advice surrounding disability benefits, the power of attorney, home care, and issues including wills and advanced directives, etc. In the UK, the NHS and Community Care Act 1990 legislates for assessment and assistance by social services.
Palliative care team	Palliative care teams aim to improve the quality of life of people with life-threatening illnesses. They offer care and advice surrounding pain and other distressing symptoms. Palliative care teams can also address spiritual and psychological needs. For people with HD, palliative care can be provided at any time but is likely to be more focused near the end of life.
Dietician	Dieticians can address weight loss, obsessions, and eating habits. They can address issues such as dysphagia and regurgitation, along with providing advice on supplements and the consideration of enteral feeding.

Physiotherapist	Physiotherapists aim to improve mobility and motivation. They can assist with the provision of a stimulatory environment for people with HD.
Occupational therapist (OT)	OTs assess and address safety issues, particularly in the home, and provide aids to support daily living activities.
Speech and language therapist (SALT)	SALTs can address communication issues which often compound the behavioural and psychiatric symptoms of HD. Alongside dieticians, they undertake dysphagia assessments and advise on swallowing food and enteral feeding.

Adapted from Phillips et al. (2008)

Phillips et al. (2008) also suggest that the role of the general practitioner (GP) is also pivotal alongside support from families and charitable HD organisations.

As there is no cure for HD, current management tends to focus on the alleviation of symptoms, however, there is a huge scientific interest in preventing the disease process from manifesting, along with neuroprotection and cellular repair. There are several clinical trials currently being undertaken worldwide. They are pharmacological and interventional but non-pharmacological. Table 3 provides some examples of these non-pharmacological, interventional trials. The table includes the interventions being adopted and the intended mechanism of action.

Table 3: Examples of current clinical trials

Trial name	***Intervention/mechanism of action***	***Target population***	***Intervention***
TRIDENT	Foetal cell transplant	Early-stage HD	Non-pharmacological
HD-DBS	Deep brain stimulation	Moderate HD with chorea	Non-pharmacological
No name – registration ID: NCT04244513	Deep brain stimulation	HD with chorea	Non-pharmacological
ADORE-EXT	Intravenous stem cell therapy	HD	Non-pharmacological
SAVE DH	Intravenous stem cell therapy	HD	Non-pharmacological
HD-DBS	Deep brain stimulation	HD with chorea	Non-pharmacological

BMAC HC	Bone marrow transplant	HD with chorea	Non-pharmacological
No name – registration ID: NCT02252380	Extracranial stereotactic radioablation	HD, essential tremor, Holmes tremor, Parkinson's disease, Wilson's disease, dystonia, tardive dyskinesia, or orofacial dyskinesia	Non-pharmacological
Select-HD	Allele-selective antisense oligonucleotide	Early HD	Pharmacological
AMT-130	rAAV-miHTT -non allele selective miRNA	Early HD	Pharmacological
No name – registration ID: NCT04713982	Deutetrabenazine- non allele selective miRNA	HD with chorea	Pharmacological
No name – registration ID: NCT04826692	Metformin- antihyperglycemic/ AMPK activator	Early and moderate HD	Pharmacological
No name – registration ID: NCT04514367	ANX005- C1q inhibitor	Early HD	Pharmacological
No name – registration ID: NCT04421339	Melatonin- melatonin receptor agonist	Early and moderate HD	Pharmacological
No name – registration ID: NCT04400331	Valbenazine- VMAT2 inhibitor	Early and moderate HD	Pharmacological
No name – registration ID: NCT04301726	Deutetrabenazine- VMAT2 inhibitor	HD with dysphagia	Pharmacological

HUNTIAM	Thiamine and biotin-B vitamins	HD	Pharmacological
No name – registration ID: NCT04201834	Risperidone-dopamine antagonists	Early and moderate HD with chorea	Pharmacological
No name – registration ID: NCT04071639	Haloperidol, risperidone, sertraline and coenzyme Q10- multiple (dopamine antagonists, selective serotonin	Early and moderate HD	Pharmacological
KINECT-HD	Valbenazine- VMAT2 inhibitor	HD with chorea	Pharmacological
No name – registration ID: EUCTR2019	WVE-120102- Allele-selective antisense	HD	Pharmacological
GEN-PEAK	RG6042- Non allele selective miRNA	HD	Pharmacological
GEN-EXTEND	RG6042- Allele-nonselective antisense oligonucleotide	HD	Pharmacological
GENERATION-HD1	RG6042-Allele-nonselective antisense oligonucleotide	HD	Pharmacological
No name – registration ID: NCT03515213	Fenofibrate- PPARα agonist	HD	Pharmacological
Tasigna HD	Nilotinib- selective Bcr-Abl tyrosine kinase inihbitor	HD	Pharmacological
PRECISION-HD1	WVE-120101- allele-selective antisense oligonucleotide	HD	Pharmacological

TRIHEP 3	Triheptanoin-anaplerotic therapy	HD	Pharmacological
No name – registration ID: NCT02509793	Tetrabenazine- VMAT2 inhibitor	HD	Pharmacological
SIGNAL	VX15/2503-Anti-semaphorin 4D monoclonal antibody	Late premanifest or early HD	Pharmacological
OSU6162Open1309	(-)-OSU616-Monoaminergic stabilizer	HD, PD, brain trauma, stroke, myalgic encephalomyelitis and narcolepsy	Pharmacological
UDCA-HD	Ursodiol-Bile Acid	HD	Pharmacological

Adapted from: Estevez-Fraga et al. (2022)

2.4: Neural Cell Transplantation

Amongst the approaches being explored within clinical trials is NCT. Cell transplantation, as a treatment for neurological disorders, has been a topic of experimental and clinical research over the past two decades (Dunnett and Bjorklund 2017). As well as HD, NCT has been used with varying success in Parkinson's disease (PD).

With regard to HD, Dunnett and Rosser (2007) suggest that NCT is intended to reform and repair the normal neural networks damaged by HD and to re-establish normal nerve cell function. The neural cells are derived, with consent, from elective abortions and it is thought that NCT has the possibility to provide stabilisation and possible remission for those affected by HD (Peschanski et al. 2004). However, to date, there have been a limited number of clinical trials undertaken involving a small number of HD participants.

There are concerns surrounding NCT in that intra-cranial surgery is associated with significant morbidity and mortality (Karhade et al. 2017). Complications can include bleeding and surgical site infections. These have a reported incidence of between one and eleven per cent and can be devastating for patients (Karhade al. 2017). The use of foetal cells and immunosuppression also has the potential for a manifestation of disorders such as tumorigenesis (Hess 2009) and graft versus host disease (Trounsen et al. 2011). A total of 51 patients with HD across Europe have had transplants using human foetal cells in open-label pilot trials. Clinical and follow-up data are available for 30 of the

recipients. These studies were primarily designed to assess safety and feasibility; however, signs of long-term efficacy have been reported in four out of 30 individuals. There were, however, differences in tissue preparation, surgical procedure, immunosuppression treatments, and clinical and imaging assessments, making it difficult to define the optimal process for NCT (Bachoud-Levi et al. 2017)

Future exploration of NCT is now planned via the phase I TRIDENT (2021) study. This trial aims to recruit a cohort of between 18-30 genetically positive, pre-manifest or early-stage individuals with HD with the primary objective being to evaluate the safety of transplantation surgery using human foetal ganglionic eminence cells for the treatment of patients with HD.

The neural grafting procedure has been adapted from previous trials involving individuals with a diagnosis of Parkinson's disease as well as five HD patients (Bachoud-Levi et al. 2017). The procedure involves:

- Pre-transplantation: Clinical evaluation was undertaken and participants were approached with regard to a possible trial with entry three months before the procedure. Relatives were also supported and were offered counselling.
- Potential cell retrieval donors were identified and screened for latent viral infections and a history of neurological disease. Neural cells were removed from aborted foetuses who were 7-9 weeks post-conception. Cells were then prepared for transplantation in a laboratory.
- Transplantation: Co-ordinates for the target area of the recipient's brain were calculated using magnetic resonance imaging (MRI) and the cells were injected into the recipient's brain along multiple needle tracts in an operating theatre.
- Postoperatively: Patients were monitored for any potential surgical complications and started on immunosuppressive drugs intended to prevent rejection of the transplant.
- Response measurement: Recipients were then followed up over a period of one year to measure response and identify any adverse reactions.

In this early clinical trial of NCT involving patients with HD, Bachoud-Levi et al. (2000) outlined how the procedure elicited some concern amongst participants and their families but a detailed account of this is not provided in the published literature.

As stated, both previous and planned clinical research surrounding the use of NCT for the treatment of HD has focused on procedural safety and the exploration of physical and cognitive efficacy (Rosser and Dunnet 2006), however, an understanding of the procedure and concept of NCT amongst people with HD has yet to be investigated. Ramos-Zúñiga et al. (2012) argued that extensive and constant discussion is required about the role of biotechnology and its ethical implications with regard to NCT,

however, it seems that the voices of potential recipients have yet to be heard in any detail. The aim of this thesis was to redress this.

2.5: Conclusion

This aim of this chapter was to set the context for the thesis. An overview of HD was provided alongside a discussion of HD through history, the contemporary understanding of HD, and current management strategies and NCT.

3.0: Literature Review

The previous sections provided context for the thesis. However, to establish knowledge surrounding the topic area and then to identify the knowledge gap in which this thesis sits, a review of the literature surrounding HD and NCT was undertaken.

Smith et al. (2009) suggested that this is not always necessary, based upon the Husserlian suggestion that it helps avoid preconceptions about a phenomenon. The literature review provided an opportunity to inform my exploration of the topic further, gain a greater understanding of the lived experience of HD, and identify a gap in the evidence base which had not yet been explored. It also helped me to develop sensitivity for questioning the participants.

There are multiple approaches to undertaking a literature review (Aveyard 2020). For this study, a comprehensive context-setting review was undertaken using a systematic approach.

As is consistent with the research approach adopted in this thesis, lived experience was the primary area of interest. Therefore, the two aims of the literature review were to:

1. Explore the lived experiences of people with HD to gain an insight into how the disease impacts them.
2. Examine what impact the emergence of NCT has had on people's experiences and perceptions of their lives, both with and beyond their HD.

As there were two aims, two searches were completed independently of each other.

3.1: Search Strategy

A systematic approach to literature searching and appraisal was adopted for both searches. Although not in the detail of a systematic review, quality was assured via the adoption of a comprehensive strategy (Aveyard 2020).

When devising a search strategy, a research project should consist of at least one person with methodological expertise in conducting reviews and at least one person with knowledge of the topic area (Rethlefsen et al. 2015). Therefore, expertise, with regard to the development of the search strategy, was sought from an experienced healthcare librarian whose role was fundamentally to identify subject and keyword search terms and develop a robust search strategy (Harries 2005).

3.1.1: Review Strategy

Firstly, it was essential that the literature review had a clear focus and reflected the aims stated (Rethlefsen et al. 2015). Cooke et al. (2012) argued that utilising a research question tool enables researchers to focus the research aims, laying the pathway for a systematic search strategy. Therefore,

to structure the search, the sample, phenomena of interest, design, evaluation, and research type (SPIDER) were utilised (Cooke et al. 2012). Tools including population, intervention, comparison, and outcome (PICO) and setting, perspective, intervention, comparison, and evaluation (SPICE) were considered. The PICO is commonly used to identify clinical evidence for systematic reviews in evidence-based practice, however, terms such as "control group" and "intervention" are very infrequently relevant to qualitative research since traditionally qualitative studies do not use these (Methley et al. 2014).

As stated, the aim of the review was to explore people's lived experiences, therefore, a tool more consistent with qualitative research was utilised. The addition of design and the research type categories to the SPIDER tool is intended to further increase the ability of this tool to identify qualitative articles. It also results in the removal of irrelevant PICO categories such as the comparison group (Methley et al. 2014).

Table 4: Aim 1

Aim 1	Explore the lived experiences of people with HD to gain an insight into how the disease impacts them.
Sample	Huntington*
Phenomena of interest	Lived experience*
Design	Qualitative design, mixed methods
Evaluation	Lived experience, understanding, feelings, perceptions
Research type	Qualitative, mixed methods

Table 5: Aim 2

Aim 2	Examine what impact the emergence of NCT has had on people's experiences and perceptions of their lives with neurodegenerative conditions.
Sample	Neurodegen*
Phenomena of interest	Stem cell, transplant*
Design	Qualitative design, mixed methods
Evaluation	Lived experience, understanding, feelings, perceptions
Research type	Qualitative, mixed methods

Medline was explored to identify and refine search terminology. This allowed for the formation of subject headings to ensure that relevant papers were identified following a comprehensive search.

This stage also involved ensuring that the terms were compatible across each of the databases used. Then a search for relevant literature was conducted across EBSCO CINAHL, OVID Medline, OVID EMBASE, APA PsycINFO, and SCOPUS. There is inadequate empirical evidence to suggest that a particular number or type of databases should be searched in a review. Subsequently, a broad search across multiple databases can add validity; therefore, this was undertaken (the Joanna Briggs Institute (JBI) Reviewers Manual 2020).

The terms were combined using the Boolean operators "AND", and "OR", with a proximity indicator distance of three words to provide focus and to reduce the capture of inappropriate titles. The search was limited to the English language, qualitative or mixed methods, and human-only studies. No date restrictions were included in order that the maximum number of papers could be captured.

Inclusion and exclusion criteria were applied. The inclusion criteria included studies subjected to peer review which explored the lived experiences of HD from any environment. No time restrictions were applied to the search to capture as much of the literature as possible. Exclusion criteria removed studies exploring Juvenile HD for reasons stated previously. Studies not published in English were also excluded.

The inclusion and exclusion criteria are summarised in Table 6.

Table 6: Summary of inclusion and exclusion criteria

Inclusion	***Exclusion***
Peer-reviewed studies	Juvenile HD
Lived experience of HD	Non-English language publications

The results were then subject to screening, firstly based on title then on abstract. Duplications were also removed. The task of retrieving full-text papers was then undertaken utilising electronic databases. Online access to full-text papers was achieved using an institutional subscription.

Once the appropriate literature had been identified, a process of assessing reliability, rigour, and relevance was identified (Greenhalgh, 2014). To ensure this, I reviewed the papers using the critical appraisal skills programme (CASP) (2014) (Appendix I) tool for qualitative research.

It is recognised that ideally, papers identified for potential inclusion should be assessed for methodological quality independently by two reviewers prior to inclusion, however, due to limited

resources and the nature of this research being part of a professional doctoral thesis submission, only I reviewed the papers. Zetoc alerts were also set up until March 2022 to capture new and significant literature

The final stage of searching included back and forward chaining to identify any additional relevant literature.

Table 7: Summary of Aim 1 search

Aim 1: Explore the lived experiences of people with HD to gain an insight into how the disease impacts them.		
Identification	**Records identified from:** **EBSCO CINAHL (n=151)** **Ovid Medline (n=242)** **Ovid EMBASE (n=311)** **APA PsychINFO (n=123)** **SCOPUS (n=62)** **Total: 888**	**Duplicates removed (n=364)**
Screening	**Papers left following title and abstract review (n=110)** **Papers remaining following subjection to CASP quality assurance (n=75)**	**Reasons excluded:** **Non-HD studies** **Laboratory/Biochemical studies** **Opinion pieces and not empirical research**
Included	**Studies included in review (n=53)**	

3.2: Aim 1: Exploring the Experiences of Living with Huntington's Disease

This research seeks to explore NCT within the context of a lived experience of HD, therefore, it is important to understand more widely what it is like to live with the disorder. This allowed me to consider the lived experience of HD before the emergence of NCT.

Rather than present the literature review thematically, I present the literature to reflect how HD is experienced throughout the course of an individual's life. The studies presented suggest that HD can be experienced throughout the life course and influences the individual and family experiences.

As will be presented later, the interviewees in this study also describe how HD has punctuated their life events from an early age and continues to influence perceptions of their own past, present, and future.

The following literature review will be presented in chronological order from childhood to the end of life.

3.2.1: Early Life in a Family with HD

As stated previously, HD is a genetic disease where people have a 50 per cent chance of inheriting the condition from an affected parent. If a person has the expanded *HTT* gene, it is certain that they will go on to develop symptoms. Some people become aware of the disease early on in life through being in a family where HD is present, however, there are numerous ways in which people develop knowledge about their own HD status.

Due to the hereditary nature of HD, people often become aware of HD in their families long before discovering their own genetic status. Forrest Keenan et al. (2009) outlined the problematic nature of initial family communication surrounding hereditary illness. How people first become aware of HD in their families can have a long-standing impact resulting in people being inadequately informed about the disease and, therefore, unaware of associated risks moving into adulthood and later life. Forrest Keenan et al. (2009) initially described how previous studies had explored barriers and facilitators surrounding the family communication of genetic risk, however, questions remained about when what and how or indeed even whether to inform younger relatives.

As a result, Forrest Keenan et al. (2009) aimed to explore young people's (aged 9-28) experiences surrounding their discovery of a family history of HD. They used in-depth qualitative interviews. The research was underpinned by grounded theory. The interviews revealed four types of disclosure experiences.

The first was having known about HD from a young age after living with an older relative directly affected by the disease. The second was when the participants were gradually informed about HD throughout their childhood and adolescence, however, these interviewees revealed that they knew something was wrong but were informed incrementally, usually by a female relative. The third was a situation whereby HD was kept secret and, despite having contributed to the care of an impacted relative, they only found out the truth in adulthood. These interviewees understood that this was intended to be a protective measure, however, for some this led to a sense of resentment when looking back on their childhood. Finally, some participants discovered HD as a new diagnosis. They had witnessed the illness of a loved one but with no awareness that it was HD and described a sense of shock and panic about their own diagnosis.

This study highlighted that the timing and method of disclosure, alongside the stage of awareness, were fundamental to the structure of participants' accounts of HD. Forrest Keenan et al. (2009) concluded that people use a range of methods to cope with knowledge of HD and these include denial,

avoidance, minimisation, or assimilation but how and why they develop these strategies remained unclear. Forrest Keenan et al. (2009) suggested that people's self-beliefs can protect them from anxiety at discovering they are at risk of HD, whilst others can suffer from senses of loss or even grief. The research demonstrates the difficulties that both families and individuals have. From the outset and often prior to diagnosis, adverse feelings which can manifest include considerable anxiety, emotional distress, and, sometimes, physical harm. This study is, however, limited to the experiences of the information-receivers and does not explore the experience of the information-givers.

The experiences of affected parents disclosing HD to their children were, however, explored in more depth by Holt (2006). Holt (2006) initially suggested that predictive genetic testing provides information which can allow people to make decisions about their futures. However, when people undergo predictive genetic testing, this acquisition of knowledge requires decisions to be made regarding disclosure to their families. Holt (2006) used IPA and semi-structured interviews to explore the contrasting choices between two sets of parents surrounding the disclosure of their genetic risk status to their children.

The children, who were interviewed in adulthood, discussed growing up with contrasting disclosure experiences as well as their current views regarding predictive genetic testing for themselves. The primary finding of this study was that all the participants declared a preference for the early disclosure of genetic risk underpinned by an open and supportive communication style regarding HD. However, why they preferred early disclosure and if there were any tangible emotional, psychological, or social benefits to finding out early in life remained unclear. Also, being interviewed years later might have resulted in a degree of memory bias and inaccurate recall.

This was further explored by Williams et al. (2010) who concluded that the discovery of a family history of HD need not always be entirely bleak. They identified how receiving the results of HD predictive genetic testing can impact individual well-being, family relationships, and social interactions in both positive and negative ways. Having the ability to develop knowledge and understanding was perceived as the most common benefit. Connecting with others and achieving life meaning and the ability to plan life based on this knowledge were also significant for people. The study participants also reported that being older in age, as opposed to early childhood disclosure, was beneficial.

A recent IPA study by Kjoelaas et al. (2021) was an in-depth exploration of the adverse childhood experiences (ACEs) of 36 people who grew up with a parent with HD. As well as uncovering the adversity suffered, the authors explored perceptions of caregiver support using semi-structured qualitative interviews.

Analysis of the data uncovered a range of adverse events which occurred frequently during participants' childhoods. These included a persistent sense of fear due to parental mood changes, a lack of stability and support growing up due to the symptoms that their parents expressed, including apathy and irritability, as well as the sense of loss of a parent due to the disease process. They also recalled a sense that there was a lack of support and recollected that they often felt overwhelmed by feelings of stress. However, in some instances where external support was offered, such as from areas outside the nuclear family, it appears that these adverse experiences could be mitigated by buffering these ACEs.

Resilience to ACEs linked with growing up in a family with HD was also explored by Idarraga-Cabrera et al. (2021). They assessed the resilience levels of a group of children and adolescents whose parents had HD, in contrast to a control group of children and adolescents at risk of poverty. They recruited 63 children, between seven and 18 years with an average age of 12.67. The participants completed a questionnaire exploring three factors: internal protective factors, external protective factors, and empathy.

Analysis suggested that both groups had higher levels of resilience than a predicted theoretical median. Resilience levels in children and adolescents did not increase when they were exposed to adverse circumstances such as having a parent with HD.

In an earlier study, Lewit-Mendez et al. (2018) attempted to explore the nature of this childhood adversity (of having a parent with HD) using an online anonymous questionnaire. The questionnaire contained mostly forced choice questions with the results suggesting that most participants provided care and assistance to a family member, with 46 per cent wishing that they did not have to. Eighty-two per cent reported anxiety about being at risk themselves, with 64.9 per cent expressing that this anxiety was a barrier to them in their life. Many of the participants stated that they did not have support, despite 85.5 per cent stating that they needed it and that ongoing follow-up is of upmost importance.

Lewit-Mendez et al. (2018) concluded that young people in families with a history of HD endure practical, social, and emotional burden and an absence of support services likely to have a long-term impact on their wellbeing.

This need for support was also emphasised by Van Der Meer (2016), who explored ACEs, alongside the psychological characteristics developed in adulthood, in people from families with an HD-affected parent. Seventy-four participants were recruited with people from families with HD who reported increased childhood adversity due to parental physical and psychiatric dysfunction compared to non-affected controls. The participants from HD families had lower psychological wellbeing in adulthood

compared to controls and, having had experience of a parent's disease before age 16, appeared to be associated with a higher number of adverse childhood events. The study concluded that people with HD who have young children should be offered specialised care and support to prevent attachment anxiety.

Sparbel et al. (2008) wanted to specifically explore the key developmental stage of the teenage years in families with HD. They conducted a qualitative study exploring the experiences of 32 teens using six focus groups in the US and Canada.

HD appeared to cast a shadow over the lives of the participants, with four themes being identified. These were “watching and waiting”, “being alone in the midst of others”, “family life is kind of hard”; and “having to be like an adult”. Sparbel et al. (2008) described how recognising patterns of teen experiences can help healthcare providers develop strategies to support teens in HD families.

Afridi et al.’s (2016) later study also suggested that living in a family where a member has established HD can result in emotional and psychological stress amongst adolescents and young adults. This results in them having a poor quality of life. They argued that there is an assumption that social support can, however, decrease the negative consequences of this stress. This study aimed to explore the role of social support across throughout the various stages of development with this underpinning assumption that that social support plays various roles across different age ranges in relation to stress.

They recruited 30 participants, ranging from 14-27-years-old, who were at risk of developing HD due to familial genetic inheritance. Alongside collecting demographic information and information on academic success, participants completed the Social Support Questionnaire, Depression, Anxiety, and Stress Scale (DASS) and WHO-QOL (BREF). In contrast to Sparbel et al.’s (2008) study, the findings showed that lower levels of social support are beneficial for adolescents whilst higher levels of social support are beneficial for adults. Afridi et al. (2016) conclusions were that social support for adolescents can have negative consequences regarding their developing a sense of autonomy but is important for and valued by adults.

The research surrounding HD in early life demonstrates that from the beginning, the disease can have indirect adverse impacts. Despite not being individually impacted by symptoms, the presence of HD in a family can lead to negative experiences throughout childhood and adolescence. The devastating physical and psychosocial symptoms of the disease impact, not just the affected individual, but close family members and, importantly, the young people who potentially carry the risk of inheriting the disease. Finding out about HD early on in life, however, has positives for some people. The ability to take HD into account when planning life appears to be beneficial for some people.

3.2.2: Finding Out

The previous section explored the family impact of HD in early life. For young people entering adult life, there comes a period where an individual must decide whether to find out whether they carry the expanded *HTT* gene. Once people discover that they have a genetic risk, then the decision of whether to take the test or not is a personal one. Taking the test is a complex and personal decision; discovering the results could lead to personal and familial changes.

Typically, genetic testing for HD becomes available in early adulthood (Duncan et al. 2008). They also stated that, despite guidelines recommending that predictive genetic testing for HD should be deferred until the age of 18 , some clinicians argue that testing before this age might be beneficial. The authors, therefore, explored the experience of predictive genetic testing for HD from the young person's perspective and documented the impact that this has on their lives. They interviewed eight young people who had been tested for HD between the age of 17 and analysed using thematic analysis.

Three themes emerged related to the time prior to the test being performed. They were “living as though gene-positive”, involved in “risk behaviours”, and had experienced “complex pasts”. Two themes emerged relating to the post-test period: experiencing “identity difficulties” and “living again”.

The participants also discussed their experiences of predictive testing within the broader context of growing up in a family where HD was present. Uncertainty surrounding their own genetic status appeared to create a barrier in their lives and prevented them from moving on. The testing process appeared to alleviate these barriers and, in some cases, helped them move forward with their lives and adapt. None of the participants expressed regret in undergoing predictive testing.

With regard to genetic testing, Etchegary (2009) highlighted gaps in understanding surrounding people’s responses to genetic threats and how they cope with them. Etchegary (2009) utilised psychological theory to understand genetic testing decisions and outcomes, drawing on Lazarus and Folkman’s (1984) seminal work. The transactional model of stress and coping suggests that response to stress involves primary appraisals about a threat including perceived susceptibility, perception of severity, and personal relevance. Following this, secondary appraisals are undertaken, which explore the resources available for coping with problems generated by the threat. The strategies adopted are based upon individual responses to these primary and secondary appraisals (Lazarus and Folkman 1984).

Etchegary (2009) conducted an IPA study using interviews with people at risk of or living with HD and the research suggested that coping strategies were both varied and dynamic. However, Etchegary (2009) did identify that coping with HD primarily included seeking information about HD genetics and

contemplating potential solutions to life with HD, including the adaptation of lifestyle practices and monitoring adverse emotions such as anxiety.

Important distinctions were observed amongst those who had undergone genetic testing and those who had received a test result. Also, differences in coping strategies were identified for those who were genetically at risk for HD and for those vicariously affected as caregivers.

The participants' coping strategies included appealing to luck or fate in a spiritual sense, attempts at rationalisation, seeking social support, and having faith in science. This trust in the scientific community suggested that science would find a cure – if not for them, for their children. Even if a cure could not be found, there was hope that science would plug the therapeutic gap. Although vague, this belief in science allowed some people to engage in positive thinking surrounding their HD, whilst more negative thinking emerged for some participants who dismissed science's ability to find a cure.

Gargiulo et al. (2009) conducted a cross-sectional study on the long-term outcome of pre-symptomatic predictive testing for HD. Their study sought to compare the psychological well-being and social adjustment of carriers and non-carriers of the HD mutation, alongside identifying the psychological determinants which could improve the care and support of people tested. Gargiulo et al. (2009) used structured interviews as well as five self-report scales and the MINI (Mini International Neuropsychiatric Inventory) to identify any psychopathologies or problems with social adjustment in 351 people who had undergone pre-symptomatic testing approximately 3.7 years post testing.

Depression was identified as common in asymptomatic carriers, however, they also noted how 27 per cent of non-carriers did not cope well with a favourable result, with 24 per cent noted to be suffering from depression during follow-up. The consequences of the study suggest that psychological support is required for all people tested, both carriers and non-carriers, regardless of the result of their pre-symptomatic test.

Brinkman et al. (2009) also explored the psychological consequences of predictive testing over a period of seven years. They used questionnaires of standard measures of psychological distress (the General Severity Index of the Symptom Check List-90-Revised), depression (the Beck Depression Inventory), and general well-being (the General Well-Being Scale) and a significant reduction in psychological distress was observed at two years and at five years. There was an overall improvement in psychological wellbeing and Brinkman et al. (2009) proposed several hypotheses as to why this was the case. These included the self-selection of individuals for testing being more capable of coping with 'bad' news and the possibility that predictive testing is only one of multiple experiences which impact the way people experience their lives within the context of HD.

Duff et al. (2009) identified that, despite stress having been studied in HD areas such as genetic testing, there has been limited research exploring the daily stressors associated with the period before diagnosis, otherwise called pre-HD. As a result, they examined the psychosocial life stressors, reactions to stressors, and substance use patterns in people who had yet to have a positive genetic test. Baseline data were used from 774 gene-expanded pre-HD participants and 198 people who discovered that they did not have HD gene expansion. Duff et al. (2009) measured the number of psychosocial stressors (from the Life Experiences Scale), reactions to stressors (from the Life Experiences Scale and Perceived Stress Scale), and self-reported substance use patterns (from the Substance Use Form).

In comparison to non-gene-expanded people, the pre-HD participants did not report any more psychosocial stressors but the stressors reported tended to be seen as more negative and unmanageable in the pre-HD group. Although people with pre-HD perceive life events to be more negative and stress as more unmanageable, they did not use strategies such as substance misuse to cope. Why this transformation existed, however, remained unexplored and the use of deeper, more expansive exploratory methods, such as interviews, might have uncovered this.

The impact on mental health surrounding the testing process was also explored by Lickleder et al. (2009), who suggested that predictive genetic testing for HD has the potential to cause severe short-term psychological reactions in patients with already established poor mental health. They, therefore, aimed to compare mental health and quality of life (QoL) in people who were waiting on the result of the genetic test.

Lickleder et al. (2009) recruited 121 participants for this study; 52 were non-carriers of the expanded *HTT* gene, 54 were carriers of the expanded *HTT* gene, and 15 were carriers suffering from HD symptoms. Data was collected by self-report questionnaires.

Four variables were identified that predicted increased levels of depression and low QoL. These were “low perceived social support”, “lack of an intimate relationship”, “being female”, and “being younger in age”. For the participants who were gene carriers, three predictors were found. These were “low perceived social support”, “an expectation of an unfavourable genetic test result before the testing procedure” and, finally, “being childless”.

In response to their findings, Lickleder et al. (2009) suggested that, to prevent the detrimental effects of HD testing on mental health and QoL, attention needs to be focused on people with limited social networks during genetic counselling. Also, assessment of expectations in relation to genetic testing could help identify gene carriers at risk of coping poorly following an unfavourable test result.

Exuzides et al. (2020) explored the burden of genetic testing (for HD) on people as well as on their partners. Using a cross-sectional, web-based survey, health-related quality of life (HRQoL) was measured using the EQ-5D tool, depression severity using the PHQ-9 tool, and HD-related quality of life using the HD-PRO-TRIAD. The couples with someone who had received a positive test result reported close and strong relationships and described feeling that they will always have each other for support. However, people with HD experienced severe depression and relatively low QoL but testing positively impacted people in relationships where HD was present. Exuzides et al. (2020) suggested that is important to ensure that appropriate mental health services are available for people with HD and their partners. Exuzides et al. (2020) highlighted that, for many, HD is not just a disease of the individual but that partners experience adversity because of the disease. Any HD-related activity can impact both people with HD and their partners, therefore, it is arguable that their views on therapy development should also be sought.

Hagberg et al. (2011) conducted a qualitative study using semi-structured interviews to explore the long-term experiences of people who carry the mutated HD gene. Their findings suggested that there is a lack of available knowledge surrounding how the experience of being a mutation carrier of HD impacts the lived experience. They also indicated a variety of impacts on the participants' lives, both positive and negative. The most prominent findings were an enhanced appreciation of life and bringing the family closer together. Some participants, however, expressed regret at being tested and described the negative effect that this had on their psychological wellbeing.

Overall, they described that knowledge of their genetic status acted as either a motivator or an obstruction when pursuing life goals such as continuing their education or a career. The study concluded that a more in-depth understanding of reactions to a positive genetic test result is required as the certainty that they will become affected by HD might result in the need for future professional support.

Oliveira et al. (2020) explored how transgenerational families deal with information about HD once a positive diagnosis had been made. The qualitative study focused on how families acquire knowledge about HD and management of the condition within the family and in their social relationships. They undertook semi-structured interviews with 10 participants from families with HD and analysed them thematically. The finding indicated that families started with the search for a diagnosis in an affected family member and that diagnosis resulted in a process of "making sense of HD in the family". This activated a transgenerational process to understand HD within a family context, which improved awareness and different ways family members manage their situation.

Zingales-Browne's (2019) study demonstrated that humour also serves as a form of coping, a brief distraction from the disease, and, in a sense, hope for the future amongst families impacted by HD. Cognitive reframing using humour can turn negative perceptions into more optimistic views. Caregivers who believe they can change their perceptions have improved well-being and confidence to face the challenges posed by HD.

Helder et al. (2001) systematically assessed the impact of HD on people's health-related quality of life (QoL). They interviewed 77 people with a clinically confirmed diagnosis of early manifest HD and additional data were gathered on patients' motor and cognitive performances by means of standardised, validated testing. They identified that HD has a significant impact on people's physical and psychosocial well-being, with the latter being more severely affected.

In a later study, Helder et al. (2002) described the illness perceptions and coping mechanisms and their role in wellbeing amongst people with HD in the Netherlands. Using a single group, cross-sectional study, 77 individuals with a clinically confirmed diagnosis of HD were asked via questionnaire-guided interviews about their illness perceptions, coping mechanisms, motor and cognitive performance, and wellbeing.

The results demonstrated that people with HD experience a strong illness identity with strong beliefs about a long duration of HD. They also have perceived negative consequences for their daily lives and little hope for cure or improvement. The coping strategies that the participants reported to deal with their disease were comparable with the general population dealing with everyday stressful situations. However, illness perceptions and coping mechanisms were significant predictors of patients' wellbeing.

Gong et al. (2016), in a qualitative study, explored the views of 14 people who had undergone HD predictive genetic testing and had received a positive result at least six months prior to their study enrolment. Utilising telephone interviews and a combination of grounded theory and thematic analysis, they sought to explore the impact that discovering a positive genetic status for HD has on attitudes towards life goals as well as the challenges that pre-symptomatic adults face.

Many of the participants expressed a greater appreciation of time following the positive test results specifically identifying clearer priorities, living in the moment, and letting go of trivial worries. However, they also expressed negative experiences surrounding the diagnosis and their relationships. They suggested that their gene-positive status and developing HD symptoms in the future would be a burden on partners. These results, like the studies presented earlier, suggest that receiving gene-positive results impacted life goals, attitudes towards relationships, family planning, education, and

career choices. The study highlighted the need for flexible and tailored genetic counselling to address the unique needs of people with HD.

The evidence presented suggests that genetic testing and receiving a positive or negative result can be associated with complex psychology and emotions. However, for some, it offers the opportunity to gain knowledge and incorporate HD into their future life plans. The outcome of the test can determine and influence a range of life decisions going forward.

3.2.3: Living with a Diagnosis

The previous section explored how people discover their own genetic status and how that can impact them, their partners, and their families. However, once a positive HD diagnosis has been identified, people then must navigate their lives with this knowledge. Wieringa et al. (2021) explored the experience of ten people in the UK who were in the pre-manifest stage of HD. To explore the topic in detail and to ascertain the impact of HD within the context of people's lives, they used IPA and semi-structured interviews.

Three themes emerged from the interviews and these included feeling limited by time, the perception of stalling time, and making the most of time. Being able to manage anxiety related to future deterioration was key to both wellbeing and the ability to achieve one's life goals. These goals included careers, education, and when and if to have children.

Quaid et al. (2010) sought to determine whether discovering that someone is a carrier of the HD mutation can change their decision to start a family or to have more children. This qualitative study examined reproductive decision-making in a sample of people at risk for HD who had chosen not to pursue genetic testing. They explored reproduction decision-making in three groups including 1) people who knew of their risk and decided to have children, 2) people who had children before they knew of their risk, and 3) those who chose not to have children based on their risk.

In group one, they identified four main themes, "hoping for a cure", "feeling guilty", "just another something", and "magical thinking". Participants appeared to convince themselves that it would be safe to have children because they believed that research is progressing rapidly and a cure, or at least a treatment, would be found in the near future.

In the second group, people for whom the risk of HD was unclear at the time they had their children expressed regret that they may have already unknowingly passed on the disease.

Group three were aware of their risk of developing HD and had deliberately made the decision not to have children. In extreme cases, this decision extended to self-imposed restrictions to having any intimate relationships. It appeared that members of group three based their decision on their personal

experiences with an affected parent. They either did not want to pass on the gene or did not want to have their children go through a similar experience to what they had.

A restricted life was also addressed by Gog et al. (2013), who explored the various elements of genetic discrimination among 60 genetically positive but clinically asymptomatic people with the expanded *HTT* gene living in Australia. Their participants completed a survey to capture their experiences of unfair treatment as well as their knowledge of the legality surrounding genetic discrimination.

The results demonstrated that 68 per cent of the participants experienced a "great benefit" from knowing their genetic test results, including allowing them to plan for the future, make decisions, and find personal meaning through active participation in the HD community, which facilitated their drive to participate in research. However, the results also demonstrated that 33 per cent of participants had perceived experiences of genetic discrimination, with more participants reporting incidents of discrimination than gene-negative respondents. Multiple incidents of discrimination were reported relating to obtaining insurance, gaining employment, and with regard to relationship satisfaction.

Following a longitudinal study, Boileau et al. (2020) also suggested that people with HD experience stigma due to their gene status. To achieve this, they used data from the HDQLIFE study, which included 479 participants at baseline, 315 participants at 12 months, and 277 participants at 24 months. A multilevel model was utilised to examine the effect of physical, emotional, cognitive, and social health on perceived stigma with the findings indicating that physical, emotional, and cognitive health were all associated with perceived stigma but not social health and demographics. The research suggested that an individual's sense of stigma is influenced by physical, emotional, and cognitive health, which may be treated with interventions including physical therapy, emotional counselling, and cognitive rehabilitation, thereby potentially lowering a sense of stigma.

Erwin et al. (2010) explored a similar topic using data from the United States, Canada, and Australia from the records of 433 individuals who have tested either positive or negative for the expanded *HTT* gene. In total, 46.2 per cent of the participants reported discrimination or stigma based on either a family history of HD or genetic testing for the condition. These specifically related to obtaining insurance, gaining employment, and forming relationships.

However, it was noted that there was a higher incidence of worrying about discrimination compared to the actual experience of discrimination yet despite this, the cumulative burden of genetic discrimination across all domains of life represented a challenge to those who were at risk of HD.

Genetic testing, as well as having an impact on the individual, can have an impact on partners. Richards (2004) conducted a qualitative study, based on family systems theory, to obtain a greater understanding surrounding the impact of predictive testing and of living with the risk of HD in couples.

Data was collected using semi-structured interviews with 14 couples; nine with an at-risk partner who had undergone testing and five where a member of the couple was already affected with HD.

The interview transcripts were analysed thematically. Most couples reported that receiving a predictive test result had little or no adverse effect on their relationship but for two of the couples who separated after the at-risk partner received a non-carrier result, the emotional factors associated with years of living with the HD risk were viewed as having caused irreparable damage to the relationship. These separations were attributed to emotional distancing and to the obsessive behaviour of the affected partner.

For two of the couples who stayed together since the positive diagnosis of one partner, loyalty was viewed as the main factor contributing to the maintenance of the relationship. The findings of this study emphasised the complexity of psychological effects on the relationships of couples who live with the risk or reality of HD.

Mariscal (2009) explored the personal experiences of 18 people with regard to the rejection of predictive genetic testing for people at risk of HD alongside the psychological consequences of refusing a test. They were compared to people who did take the test. They utilised a prospective, cross-sectional, mixed-methods, multi-centre study design based in Spain. They measured anxiety, depression, and health-related QoL using the Hospital and Depression and EuroQoL scales. They also used a multi-method approach and collected qualitative data via focus groups. Factors which influenced people's decisions to take a test, however, included the quality of medical information, psychological counselling received prior to the test, and the experience of living with relative with HD.

McGonigal-Kenney (2011) suggested that the experiences of the intimate partners of people who had undergone testing for HD had not adequately been explored and that knowledge surrounding genetic predisposition to future illness and disability can create uncertainties which influence life decisions about reproduction, health behaviour, careers, and the need for care. In a qualitative hermeneutic-phenomenological approach, the researcher interviewed 10 intimate partners of persons in the prodromal phase of HD. Analysis revealed an intangible reality characterised by anticipation with ebbing and flowing disquietude, dwelling upon HD, inner turmoil, a subdued presence but freeing possibilities.

The lived experience was also explored by Vishnevetsky et al. (2016) who sought to explore the determinants of QoL quantitatively and qualitatively in people with HD. Participants with HD, alongside their familial caregivers, were recruited and asked to complete a socio-demographic questionnaire, the Total Functional Capacity scale (TFC), and standardised HD-specific questionnaires (HDQOL and HDQOL-c). Face-to-face semi-structured interviews were also used and the primary

themes from the qualitative analysis were: dealing with the economic insecurity resulting from HD, misinformation about the genetics of HD, loss of the productive role in family and work, as well as fearing the future. The overall conclusions suggest that interventions should focus on easing the economic burden for people with HD as well as their caregivers, thereby avoiding a one-size-fits-all approach.

Leontini's (2006) single case narrative also explored the impact of receiving a positive genetic test for HD. They explored the experiences of one woman. The author described how testing results in the production of new ways of viewing various aspects of life. Receiving a positive result can result in changing perspectives towards the body as well as altering perceptions of relationships towards family members and a sense of the future. Leontoni (2006) described how the woman searched for 'signs' of disease, including ways to accommodate her new 'status'. The narrative explored how the participant made sense of the anticipation of illness, how they experienced their body in relation to that possibility, and how they managed or coped with their newfound status.

Hagen (2018) explored the intersections between genetics, the body, and lived experience of having a genetic disease such as HD. The IPA interview study explored how people affected by HD experience their everyday life and resulted in the production of two themes which represented and captured the experiences of affected individuals. These themes were "noticing symptoms in everyday life" and "neither health nor disease".

Hagen (2018) developed these two themes and discussed them framed around Leder's (1990) phenomenological absent body perspective. Leder (1990) suggested that, as individuals, we have parts of our bodies of which we have no direct sensory experience as they are hidden in corporeal depths and are, therefore, phenomenological null points. These hidden areas include our genes. Hagen (2018) suggested that whilst most of the population is generally not exposed to these phenomenological null points, they emerge into everyday existence in people with HD. The expanded *HTT* gene becomes visible and, therefore, its abstract qualities are reconfigured within a person's lived experience. Therefore, Hagen (2018) suggests that there is often complexity and great difficulty in creating a stable lived experience with HD.

Downing et al. (2012) also examined perceived stress and its relationship to depressive symptoms, life changes, and functional capacity amongst people who were gene-positive for HD but were prodromal. They classified their participants by estimated proximity to HD diagnosis into one of three categories; near, mid, and far, then compared them with a non-gene-expanded comparison group. They noted that people in the prodromal mid-group (nine to 15 years since diagnosis) experienced the highest stress scores and that there was a significant interaction between age and time since HD genetic

testing. Downing et al. (2012) stated that this was unexpected and a possible explanation was that ambiguous signs of HD might be presenting, resulting in increased levels of distress. They suggested that people in the near to diagnosis group (fewer than nine years) might receive greater support, have a greater degree of apathy post testing, or simply do not endorse their own negative emotions. The study left several questions open, however, including why distress does not seem to correlate with a linear path when compared to time.

Ho et al. (2011) described how there has been little empirical data examining what people are most concerned about across the progression of the disease. They conducted semi-structured interviews with 31 people living at different stages of HD. These stages included being pre-clinical gene carriers right through to the advanced stages of the disease. They explored how often participants raised issues and concerns regarding the impact of HD on their lives. At the pre-clinical stage, physicality/functionality was not significant, but it emerged significantly, even at the early stages of manifestation and rose steadily and peaked at the advanced stages of the disease.

Across all stages of the disease, there were no significant changes in emotional, social, and self-themes, and the more rarely mentioned financial and legal themes also remained similar across stages. Concerns about cognition rarely featured at all in the pre-clinical and advanced stages of the disease.

The transition from being asymptomatic to symptomatic can be distressing and Eddy et al. (2012) described how factors such as altered movement, emotions, and cognitive function are, therefore, likely to affect patients' QoL. They investigated the relationships between cognitive and emotional factors and self-reported QoL in HD. Sixteen outpatients with HD were recruited from the Queen Elizabeth Psychiatric Hospital, Birmingham, UK, with QoL being was measured using the SF36. A range of executive tasks, including measuring verbal fluency, working memory and inhibition, apathy disinhibition, and executive dysfunction were also measured.

QoL scores did not appear to be related to motor symptom scores or scores on specific executive tasks, however, it was lower for people who exhibited greater apathy with a greater degree of executive dysfunction in their everyday behaviour. Additionally, it was noted that disinhibited behaviour was associated with reduced empathic concern. Overall, the findings suggest that deterioration in mood and cognitive function impacted QoL to a greater degree than movement disorder in HD.

Sherman et al. (2020) explored movement disorder, or chorea, as one of the dominant characteristics of HD. They described how it can interfere with day-to-day functioning and have a negative impact on health-related QoL. They examined data from focus groups of individuals with manifest HD, people at risk of or with premanifest HD, family carers, and professional providers with experience treating HD.

Dominant themes emerged across all groups and included anticipation of disease progression, associated adverse consequences, concern over the stigma of HD, the negative effect on independence, interpersonal relationships and mental health, and potential coping strategies. The participants at risk of or with premanifest HD expressed concern over HD onset and wished to proactively manage the disorder. Participants with early-stage HD described the requirement to adapt to the increasing role that HD played in their lives, as well as the development of strategies which could potentially maintain their current lifestyle. Contrastingly, the participants with late-stage HD expressed concern about decreased autonomy and social engagement and the potential progression of their HD. The caregivers expressed their desire to monitor changes in the person they cared for and to ensure they remained as healthy as possible. The healthcare providers' primary concerns were their patients' social roles and they also expressed particular concern surrounding patient safety. Arran et al. (2013) also recognised that people with HD experience a range of emotional, behavioural, psychological, and social consequences.

Arran et al. (2013) utilised Leventhal's (1980) self-regulation model with the aim of uncovering the factors which have adverse psychosocial impacts in people with HD. They also examined the relationships between perceptions of illness, coping mechanisms, and psychological distress.

They utilised the Illness Perceptions Questionnaire, which is a 57-item, Likert style tool which assesses illness identity, timeline, consequences, and control/cure. The experiences of 87 people with a diagnosis of HD were explored. Data on both demographic and clinical variables previously found to be associated with psychological distress were also collected by Arran et al. (2013). Utilising hierarchical multiple regression analyses, they demonstrated that perceptions of illness, identity, and disease timeline could be used as predictors of anxiety.

Their findings suggest that individuals' perceptions of their HD play a significant role in the psychological distress experienced. As a result, the authors suggested that a focus on interventions which change illness perceptions could potentially reduce psychological distress and should, therefore, be a focus for future research. It is of interest in the present study as to whether the emergence of NCT does change illness perceptions.

Gunn et al. (2020) also recognised that mental health difficulties are prominent in people with HD, however, these problems are weakly associated with HD progression. Instead, they suggested that the causes are multifactorial rather than simply related to the disease process itself. As previously stated in this review, evidence suggests that genetically unaffected family members also experience mental distress due to multiple factors. They aimed to evaluate quantitative and qualitative similarities and differences between people with HD and those without the gene to identify the systemic and

environmental contributions to HD-related mental health problems. They recruited 5,294 individuals from four groups – those with manifest or premanifest HD, family controls, and those who were genotype negative. Four factors emerged across all groups including depression, anxiety, temper, and self-harm.

They identified that people with HD did not report significantly different anxiety scores to control groups but the manifest HD group suffered from significantly higher depression, temper, and self-harm compared to the genotype-negative group. The findings suggest greater similarity in the severity of mental health symptoms between people both with and without HD than previously believed – potentially related to family structure.

Fritz et al. (2018) examined the relationship between variables of apathy, functional status, physical function, cognitive function, behavioural status/emotional function, and health-related QoL. They used clinician-rated measures of physical, cognitive, and behavioural functioning, as well as clinician-rated apathy and self-reported measures of physical function, QoL, emotional, cognitive, and social function in 487 people at various stages in the HD disease trajectory. The data revealed greater apathy related to reduced independence, increased motor impairment, and problems such as irritability and anger. Also, poorer self-reported health-related QoL, advancing chorea, increased speech and swallowing problems, as well as worsening anxiety, depression, lack of personal control, increasing cognitive dysfunction, and reduced satisfaction with social roles all contributed to increased apathy. The authors concluded that physical, cognitive, and behavioural dysfunction throughout the disease trajectory were all linked to apathy and that research should explore if clinical interventions which target specific functional domains could potentially lead to a reduction in apathy in people with HD.

As was noted in the first part of the literature review, other family members, other than those with HD, feel the impact of the condition. Cox (2012) set out to identify the factors which impact the QoL of family carers of people with HD to provide insight into how the burden could be alleviated. To achieve this, they recruited 31 HD carers who completed the 34-item Huntington's Disease Quality of Life Battery for Carers (HDQOL-C) questionnaire with analysis demonstrating that 55 per cent of the participants had a mid-level QoL. Equally, an inverse relationship was noted between the hours spent caring and reduced QoL. However, the number of times a carer socialised per month was positively related to QoL. The study indicated that participants felt that access to affordable care programmes for the HD-affected person, more time for themselves, and social support would have a positive impact on their own QoL, and that respite provision might help.

Read et al. (2013) studied the specific life domains which impact QoL in people with HD and in a subgroup of gene-negative partners. They recruited 355 participants who completed standardised

self-report measures of QoL, underwent assessments of capacity and motor function and semi-structured interviews assessing neuropsychiatric symptoms, and completed paper and computerised cognitive tasks and assessment of behaviours which are associated with damage to the frontal brain.

The HD group scored statistically lower than a gene-negative sibling control group in areas including general health, neuropsychiatric symptoms, and executive function. Also, those with Stage II HD reported statistically significantly lower QoL than gene-negative controls across physical, emotional, and social life domains. People with manifest partners also reported lower QoL. They concluded that understanding the nature and timing of disruption to QoL in people who are pre-manifest and diagnosed with HD, as well as their gene-negative partners, can potentially result in informing the development of appropriate strategies and interventions.

Ho and Schwenke (2009) also explored people's quality of life and carer burden as part of the European REGISTRY study. People with HD across Europe completed the generic health-related quality of life questionnaire, SF-36, which provides physical summary and mental summary scores. Carers completed the Caregiver Burden Inventory (CBI), which was intended to capture their experiences of caring for someone with HD.

Ho and Schwenke (2009) examined the data in relation to the various stages of HD and the results indicated that the SF-36 mental summary score is significantly poorer than the physical summary score in the early stages of the disease but the pattern reverses at Stages 4 and 5. The CBI increased significantly as the disease progressed but plateaued at Stage 4. The scores relating to social burden and emotional burden remained static across disease stages, with the development of burden increasing significantly between the first two earliest stages. However, the physical burden subscale increased more significantly only later – between Stages 3 and 4. Ho and Schwenke's (2009) research further underlined the impact of disease on carers of people with HD as well as patients themselves across the stages of the disease.

Roscoe et al. (2009) recognised that HD poses particular challenges to patients and families, therefore, 17 family caregivers were interviewed and completed scales measuring stressors, appraisals, protective factors, and outcomes.

Analysis of the data showed that there was no direct relationship between stress and caregiver well-being and that the impact of possible stressors was mediated by appraisals and protective factors. Mastery of care was significantly positively correlated with the life satisfaction of carers and negatively correlated with depressive symptoms.

Decruyenaere et al.'s (2005) study focused on the psychological distress and coping strategies in the partners of people five years following diagnosis. They recruited 16 couples where the gene was identified, alongside 17 noncarrier-couples.

Self-report questionnaires were administered to both groups which assessed depression levels, anxieties, and psychological impacts such as intrusive and avoidance thoughts, as well as coping strategies. Analysis revealed how the partners of carriers experience as much distress as the gene carriers themselves and they clearly experience greater psychological distress than partners of non-gene people.

Having children prior to predictive testing was an additional distress factor in both gene carriers and their partners. Decruyenaere et al. (2005) concluded that partners have at least as much psychological distress as carriers but that partners may be 'disenfranchised' or not have their worries and concerns socially recognised.

The studies presented suggest that HD has severe and adverse effects on individuals even before the commencement of symptoms. HD, and even testing for HD, can also have consequences for the families and partners of affected people. Anxiety and distress can manifest at the discovery of HD. The process of testing has impacts on psychosocial wellbeing and perception of self. As stated, it is important to this thesis to explore how people's perceptions and understanding of NCT impact their perceptions of their HD. The above has demonstrated how HD can severely and adversely affect QoL, mental health, and wellbeing in people diagnosed with the condition, as well as have profound negative impacts on partners and family members, and this seems to continue as the disease progresses.

3.2.4: Progressing HD, the Need for Care, and End of Life

The previous section described the impact of genetic testing and the impact that it has for affected people, their partners, and their families. The disease progression will now be explored.

The purpose of Januario et al.'s (2010) study was to assess the health-related quality of life (HrQOL) in an HD patient department. The study was a non-randomised clinical study of 23 consecutive outpatients of people with genetically confirmed HD. The study included 10 women and 13 men with a mean age of 42.43 +/-12.67 years. Januario et al. (2010) used the Short-Form (SF)-36 and Unified Huntington's Disease Rating Scale (UHDRS) and compared both scores of the sample with the scores of a sample of non-HD Portuguese people. The results showed a decrease in both mental and physical dimensions of health amongst people with HD as well as that the HD patients' perceptions of their QoL are decreased, particularly by functional ability.

Kaptein et al. (2006) assessed whether people with chronic illnesses perceive their illnesses differently to their partners. They proposed that these differences negatively impact QoL. Utilising an illness perception questionnaire, the study assessed whether the perceptions of people with HD were different from those of their partners and examined whether spousal illness perceptions were important for the QoL of the couples recruited.

The partners in the study reported that their spouses with HD suffered more symptoms and experienced less control over their lives than the patients themselves reported. The partners also had less belief in a cure. However, the authors themselves recognised that further research needs to be undertaken, utilising qualitative methods, to deepen understanding of this topic area

Williams et al. (2009) also described how the emotional aspects of caregiving can contribute to mental health risks for family members of people with HD. They conducted a qualitative study using focus groups with 42 adult carers of people with HD in Canada and the US. The data was analysed using descriptive coding and thematic analysis with all participants reporting multiple aspects of emotional distress. Being a carer was described as experiencing the disintegration of one's life and it appeared that carers attempted to cope by seeking comfort from particular family members, anticipating the time when the care recipient will die, and using prescription medications.

Dorey et al. (2010) also explored the poor QoL for people with HD and their caregivers but wanted to explore the drivers for this deficit. This was done as part of the European HD burden study (Euro-HDB), a cross-sectional survey of people with HD and their caregivers in six countries (France, Italy, Germany, the UK, Sweden, and Spain). Dorey et al. (2010) utilised a previously validated questionnaire – the Huntington's disease Quality of Life Battery for Carers (HDQoL-C) short-version. The deficit drivers measured among patients were clinical characteristics. These included voluntary movement disorders, chorea, depression/anxiety, psychotic disorder, cognition, and temper. The driving determinants of deficits in caregiver QoL were studied by regression and adjustments were made based on age, sex, and occupational categories.

The authors recruited 201 caregivers in France and 124 in Italy initially, with early results indicating that 12 per cent experienced complete dissatisfaction with their QoL and only five per cent were totally satisfied. Drivers of caregiver's QoL were the disease-associated symptoms, including involuntary movement disorders, depression/anxiety, psychotic disorders, and declining cognition. This QoL also worsened as the clinical manifestations increased.

Spousal carers were particularly distressed by the loss of their relationship and coped by ceasing to view themselves as having an intimate partner. All carers were concerned about the disease risk for the children in their families and all hoped for a cure. Also, Urbinati et al. (2012) conducted a study as

a part of an international survey, investigating the QoL of family carers of people with HD. They provided participants with two self-reported questionnaires; one for the person with HD and one for their caregivers.

The caregivers were asked to answer sociodemographic questions and complete the short version of the HD Quality of Life Battery for Carers (HDQoL-C) – a previously validated questionnaire. It was identified that caregivers' QoL worsens as patients' motor symptoms and functional capacity deteriorate.

The specifics of how HD continually and incrementally impacts life and relationships were researched by Kolenc et al. (2017), who identified that HD can have a significant impact on female sexual function, which progressed with patients' functional decline and impaired patients' QoL They argued that this sexual dysfunction might be caused by HD progression itself or the side effects of medication or comorbidities like depression or dementia.

Kolenc et al. (2017) collected data using the Female Sexual Function Index (FSFI) questionnaire, the Unified Huntington's Disease Rating Scale (UHDRS), and the Total Functional Capacity (TFC). Thirty female patients with established HD and eight pre-symptomatic HD mutation carriers responded to an invitation to complete questionnaires. They identified that HD patients had more problems with sexual arousal, lubrication, orgasm, and sexual satisfaction. However sexual desire remained normal. Sexual dysfunction appeared to worsen in parallel with disease progression.

Sexuality was also investigated by Hulter (2012), who recognised the variety of physical, mental, and social disabling impairments that can impact the expression of sexuality among people with HD. The most prevalent is reduced sexual desire, but conversely, sexual interest and paraphilia have also been noted. Hulter (2012) suggested that specific brain lesions might be associated with changes in expression of sexuality, but also that psychosocial factors such as depression and anxiety might be a factor and that these changes might cause suffering for spouses and other family members such as children.

Zielonka et al. (2018) compared whether biological sex differences in motor, cognitive, and behavioural symptoms affect functioning and the impact that this has on QoL. They recruited 2,191 subjects from the REGISTRY database that provides personal data, HD age of onset, visit date, and CAG mutation from at least one visit. They identified how motor, cognitive, and behavioural factors contributed significantly to function and independence and that decline in functional abilities correlated significantly with a reduction in QoL. They concluded that motor symptoms correlated more with functional ability and influenced function variability more in women than in men and that

these symptoms affect female function and independence more than male function and independence.

Harding et al. (2012) explored the perceptions of QoL of people with HD, held amongst healthcare workers employed in a specialist HD unit in a UK hospital. They also explored their perceptions of how they felt both they and others contribute to the QoL of their service users.

Eight participants were recruited using opportunity sampling. The participants were nursing, dietetic, occupational therapy, physiotherapy, psychology, and speech and language therapy staff. They utilised semi-structured interviews and the data analysis was guided by grounded theory.

Eight main themes emerged from the analysis which highlighted the perceived quality of life amongst service users with HD and these included the quality associated with the unit, the staff, effective communication, hopes, fears and behaviour, family involvement, ongoing support, and future directions for enhancement of QoL. It was hoped that the research could be a foundation for further exploration of QoL issues amongst people with HD and that the study could highlight the challenges faced when providing appropriate care.

Telarovic and Sarac (2012) aimed to evaluate the degree of anxiety, depression, and general QoL in caregivers of people with HD. They recruited 17 people with HD, alongside 22 family and partner caregivers and they analysed the demographic variables of the participants including age, sex, marital status, relationships, employment status, and duration of HD. Statistical analysis indicated a high incidence of anxiety amongst caregivers, as well as depression, with an overall reduction of QoL in the caregivers of people with HD.

Dale et al. (2014) recognised that most of the care for people with HD is provided by family members and primary partners. They argued that the partner relationship is also the most sensitive to any impacts of disease progression. Therefore, Dale et al. (2014) explored the experiences of partner carers of people with HD, highlighting the psychological impact of participating in the caring process. They used qualitative interviews with six partner carers and conducted analysis and interpretation using IPA as the research approach.

Dale et al. (2014) identified five super-ordinate emergent themes: “collective vs. individual care”; “the invisible partner”; “the emotional roundabout”; “struggling in the present”; and “ways of being”. These were alongside various sub-themes which Dale et al. (2014) stated provided an exploration of the similarities and differences between respondents within these broader super-ordinate themes.

They concluded that the themes reflected challenges for carers, which both affirmed and disempowered the participants, particularly isolation, absence of reciprocity in their relationships, and wider impacts on other family members.

Using a qualitative semi-structured discussion design, Carreon et al. (2018) explored their participants' experiences in caring for patients with HD across the disease trajectory and adopted a semi-structured discussion guide. Analysis suggested that five interrelated themes were central to HD care. These were that the patient is the biggest teacher, that multidisciplinary care can be both a help or hindrance, that they frequently had to support patients through a series of bereavements, the importance of a good death, and that HD is a complex disease with which to cope.

Overall, the caregivers identified a need for practical support alongside better training and education to meet the health needs of HD patients. The study concluded that healthcare providers need to focus on identifying the needs of HD caregivers, to offer emotional support to families, and to help caregivers with their coping strategies. The research suggests that fostering these approaches could improve the continuity of care as well as improve QoL in people with HD.

Aubeeluck and Buchanan (2005) also undertook an exploratory study to describe the experiences of family carers of HD patients, specifically in relation to QoL. They utilised visual representations of QoL which were collected by carers using disposable, 27-exposure, colour film cameras, and were given a corresponding dialogue sheet. The participants were also given a written description and verbal explanation of Cummins' (1997) definition of QoL:

"Quality of life is both objective and subjective, each axis being the aggregate of seven domains: material well-being, health, productivity, intimacy, safety, community, and emotional well-being. Objective domains comprise culturally relevant measures of objective well-being. Subjective domains comprise domain satisfaction weighted by their importance to the individual".

The participants were then asked to take photographs of things which reflected a compromise or enhancement in their QoL.

Aubeeluck and Buchanan (2005) utilised content analysis and nine themes were identified. Positive themes did emerge but negative themes, including "sense of loss", and "neglected needs", were more prevalent in relation to QoL, suggesting that QoL is negatively affected for these spousal carers.

As with the previous study, they suggested that family caregivers of people with HD are exposed to a unique series of problems. These can be linked to the complex nature of the disease. Responding to a dearth in research which explicitly focused on the impact of HD on the QoL of family caregivers, Aubeeluck et al. (2012) explored the issues for family carers of people with HD, utilising six semi-

directed focus groups for data collection. IPA, again, was used as a method of analysis. The use of focus groups within IPA does not have the same status as interviews and it can be argued that theory and practice cannot remain unchanged when applying this method of data collection within IPA (Tomkins and Eatough 2010). The main issue is the negotiation of part-whole relationships and how to manage the interplay between real-time discursive as well as later thematic sense-making. Although it is possible to adjust the IPA focus groups, questions exist surrounding group and individual dynamics as well as the individual construction of experience. Arguably, focus groups move too far away from ideography to be considered "true IPA" (Tomkins and Eatough 2010). The participants were recruited from the Huntington's Disease Association (HDA) and four superordinate themes were developed. The first theme was "Levels of Support", whereby people felt let down by health and social care systems. The second theme was "Dissatisfaction with Caregiving Role", whereby the carers stated that they had had to deal with several personal burdens due to their role of caring for a loved one with HD. Many felt that they had an overwhelming 'duty of care' placed upon them. The "Practical Aspects of Caring" were also identified as a burden, with many citing a lack of support, respite care, and tiredness. Finally, the "Feelings and Emotional Well-being" of family carer givers were universally and detrimentally impacted. Aubeeluck et al. (2012) described how carers experienced a range of emotions including depression, guilt, anger, and frustration. They also experienced a strong sense of loss in relation to their caregiving role. Positives were noted including the bringing together of families surrounding HD, however, the research suggested that overall, QoL is compromised in multi-faceted ways for HD family carers. Aubeeluck et al. (2012) concluded that family carers often negate their own needs, with the caregiver role becoming overwhelming and taking over their lives.

Fernandez et al. (2012) explored the link between the QoL of people with HD and their demographic, clinical, and psychopathologic characteristics using the Short Form Health Survey (SF-36). They recruited 24 HD patients alongside 24 demographically matched people without HD and uncovered statistically significant reductions in HD patients' QoL across all the explored dimensions except bodily pain. This decrease in QoL was significantly related to the severity of psychopathological symptoms but modest links were found with other demographic and clinical variables. Fernandez et al. (2012), therefore, stressed that recognising depressive symptoms in people with HD is of upmost importance in relation to their QoL and reinforcement is needed for an integrated and multidisciplinary clinical approach amongst the HD population. The literature identified suggests that HD is far from a personal or individual disease. The presence of HD impacts family units and can result in social instability.

Brun (2018) undertook a phenomenological study which examined the lived experiences of seven participants diagnosed with HD. This study utilised semi-structured interviews. They used convenience

sampling, recruiting from a HD patient organisation, recorded, transcribed, and then analysed the data, producing ten themes.

The study indicated that people with HD experience multiple difficulties from both within society and that they are confronted by multiple existential dilemmas. The themes included "Mortality and Finitude", "Suffering", "Limitations and Possibilities", "Unplanned Change", "Redefining One's Identity", and "Finding Meaning and Hope".

Scerri (2015) explored the experiences of Maltese family caregivers in caring for individuals with advanced-stage HD using grounded theory principles. Eight in-depth semi-structured interviews were undertaken with the carers of people who were living at home or in a healthcare facility. The results indicated that the experiences of the carers were determined by the psychological impact of the caregiving experience and that health professionals and policymakers can enhance the psychological wellbeing of HD family caregivers by improving the available policies and services leading to the development of better coping strategies.

Røthing et al. (2015) also explored the experiences and expectations of family caregivers for people with HD, focusing on collaboration with healthcare professionals. They conducted an explorative, qualitative interview study with 15 adult participants experienced in caring for family members in all stages of HD and they found that family caregivers approached healthcare professionals in the hope of understanding the disease course and to share their experiences with trustworthy professionals. Family caregivers viewed healthcare professionals as important factors in improved health services, and they also felt that the clarity surrounding the roles and responsibilities of professionals was crucial to collaboration. Røthing et al. (2015) argued that family caregivers need to be acknowledged for their knowledge and experience and should be viewed as valuable contributors in partnerships with healthcare professionals.

What is clear from the evidence presented is that HD has significant impacts on families and caregivers, particularly as the disease progresses. As well as slowly losing their loved ones, there appears to be an inverse relationship between the amount of care that they give and an increased association with decreased wellbeing for carers. It is clear from many of the studies presented that increased help is required for carers, and advice and care are often sought from specialist HD professionals

Wilson and Aubeeluck (2016) used interviews and observations with 33 people living with HD, their family members, and key healthcare staff to explore the role of the specialist HD nurse. Patients and carers described the importance of the role, in particular, recognising their knowledge of the disorder. The participants understood that HD was a rare and complex condition about which many general

practitioners know very little. The specialist nurses also had knowledge and advice that was highly valued and considered to be an essential aspect of care by participants, and specialist nurses were seen to be a vital resource for people with HD. Families will often work with their HD professionals for many years as HD has a long trajectory with people having a prior awareness of what their future will bring.

Dawson et al. (2004) suggested that this presents an opportunity to plan and direct care and supportive services for individuals and families impacted by HD. Consequently, they conducted a study to explore the needs for palliative care service provision of people with HD. They recruited six people with the disease alongside 19 family/informal carers and seven healthcare workers working within the field of HD. They used a semi-structured interview approach and analysed the data thematically. The themes which emerged from the interviews included adjusting to the impact of the illness, surviving the search for essential information, gathering practical support from many sources, bolstering the spirit, choreographing individual care, and fearing the future. Dawson et al. (2004) concluded that palliative care services for people with HD and their informal carers need to adapt to provide targeted psychological and practical support but they need to be adequately planned and choreographed to reflect the needs of individuals and their families.

Downing et al. (2018) explored the notion of end-of-life (EoL) planning in HD. The aim of the study was to determine the prevalence of EoL plans, including advance directives (ADs) among persons across three lived stages of HD. To achieve this, they collected data from 503 participants in the HD Quality of Life study. This was done via an online health-related quality-of-life survey which include questions about EoL planning and self-reported HD symptoms. In total, 38.2 per cent of participants stated they had ADs and but less than half had other EoL plans. Factors which appeared to be significant in whether ADs had been formulated included being older, being in a more advanced stage of HD, increased levels of education, reduced anxiety, increased problems with swallowing, and having a higher meaning and purpose. Downing et al. (2018) suggested that the prevalence of ADs within the study was similar to the general US population, but surprisingly low when the severity and long disease are considered.

3.2.5: Conclusion

HD, unlike many diseases, does not begin with the diagnosis of a person. For many, HD is present from the start of their lives due to being born into families with the condition. Children often take on carer roles and growing up in the presence of HD can have adverse impacts such as loneliness and the feeling that they have already lost a parent.

As people reach early adulthood, they reach a phase where they can decide whether to find out their own genetic status. To some degree, the discovery of genetic status, whether positive or negative for HD, can be positive and allow for planning for future life. Conversely, however, testing can be anxiety-provoking and have adverse psychosocial impacts. This is not just for the person being tested but also their families and partners. HD, to some extent, can have an equally devastating impact on the partners of genetically positive people. Not only do they often transition into a caring role but often experience the loss of their partner across multiple dimensions of life as the disease progresses.

This caring role is also fraught with difficulties and, just as wellbeing and QoL diminish for people with a genetic diagnosis, the life quality of those caring for them can, and usually does, deteriorate over time. As stated earlier, to some extent, HD can be viewed as a vicarious disease for the families and partners.

3.3: Aim 2

After exploration of the literature to explore the lived experience of HD, to explore what impact novel therapies such as NCT might have within the context of participants' lives, a second search was undertaken. The search indicated that there was a dearth of literature specific to HD. Therefore, as NCT has been trialled within similar neurodegenerative disorders such as PD, the search was expanded to include these. The second line of enquiry was, therefore:

- Examine what impact the emergence of NCT has had on people's experiences and perceptions of their lives with neurodegenerative conditions.

Despite this expanded search, there remained a lack of research exploring the impact of emerging therapies on people's lives as demonstrated in the table below:

Table 8: Summary of Aim 2 search

Aim 2: Examine what impact the emergence of NCT has had on people's experiences and perceptions of their lives with neurodegenerative conditions.		
Identification	**Records identified from:** **CINAHL (n=0)** **Ovid Medline (n=602)** **Ovid Emcare (n=95)** **Embase Classic+Embase (n=973)** **Total: 1670**	**Duplicates removed (n=364)**
Screening	**Papers left following title and abstract review (n=25)** **Papers remaining following subjection to CASP quality assurance (n=2)**	**Reasons excluded:** **Non-HD studies** **Laboratory/Biochemical studies** **Opinion pieces and not empirical research**
Included	**Studies included in review (n=2)**	

The two papers are now presented.

Cleret de Langavant et al. (2015) undertook a longitudinal study surrounding the consent of HD patients during the Multicentre Foetal Cell Intracerebral Grafting Trial in Huntington's Disease (MIG-HD) clinical trial within Belgium and France. Consent questionnaires (CQ-HD) were given to patients and their proxies at inclusion, prior to consent to the trial, and at one year of follow-up, before randomisation and transplantation. The CG-HD questionnaire was used to assess understanding of the protocol, examine satisfaction with the information delivered by trial staff, and obtain their reasons for participating in the trial as well as expectations regarding the transplant. Initially, 46 HD patients and 27 proxies completed the initial questionnaire, with 27 HD patients and 16 proxies completing the second, one year later.

However, the study suggested that HD patients had a good understanding of the protocol at month zero and they largely understood the consequences of randomisation and recognised the purpose of

the trial (37 patients, 80.4 per cent). The patients also had a relatively good recollection of risks. At this time point, the proxies' comprehension scores were similar to those of the patients. At the second time point a year later, the patients and proxies had similar comprehension scores and their understanding of randomisation, the research purpose of the trial, and risks.

In terms of motivation to participate, their reasons for consenting to participation in the trial seemed to be based on altruism rather than hope for a personal cure but there was no deep exploration undertaken. Simple statements such as "for scientific progress", "for my children", and "helping others" were simply agreed with or not, meaning there was no deep exploration of people's thoughts within the context of their own lives. Again, this thesis hopes to redress this.

Lundin et al. (2016) explored the viewpoints of people with HD surrounding participation and exerting influence in a phase I clinical trial of gene therapy, although they did not study transplantation. The study recruited 16 participants via the Swedish National Association for HD and utilised a focus group approach. Mailed questionnaires were also used to explore affected individuals' views of exerting influence surrounding clinical trial activity. Thematic analysis from the focus groups and mail responses was undertaken, resulting in the development of three main themes which expressed people's rationales for taking part in the clinical trial. These were participation as a "last resort", as an "activity of hope", and as "a means of taking responsibility for the development of a cure that will benefit future generations".

The authors suggested that there was no clear and single reason for people agreeing to participate in clinical trials, however, the lack of existing treatments for HD resulted in a sense of vulnerability and no real choice but to participate. Participants also emphasised that their lived experience of HD meant that they were informed enough to make well-considered choices with regard to clinical trial participation. A pragmatic attitude was also noted, with participants suggesting that even if the research failed to produce an effective treatment, useful information would still be gathered.

The participants also expressed a sense of powerlessness and the desire for a greater degree of control over their lives. This links to the vulnerabilities and lack of control addressed in the previous aim. Participants also described a lack of options which could change their life situation and said that participation in medical research at least provides hope. Participation in clinical trials also acted as a strategy to counteract involuntary passivity and inactivity with regard to their circumstances. Extremely pertinent to this thesis was the stated desire by some participants not only to be active in combatting HD but also in the desire to seek out treatments not yet approved by clinical trials. Participants discussed the purchase of stem cell treatments despite the lack of evidence of their effectiveness, with one participant describing how they would travel abroad and purchase stem cell

therapies in an attempt to be treated or cured of HD. Finally, participants described faith in medical research and expressed an understanding that researchers were not able to develop novel treatments for HD without partnership and participation from people with HD. The affected individuals expressed that they were united with medical researchers in combatting HD. They knew their value in the research and, therefore, felt an obligation to assist.

3.3.1: Conclusion

NCT has the potential to alleviate symptoms and disease burden, however, there is an obvious gap. Research has been undertaken surrounding the lived experience of HD in an era of potential new therapies such as NCT. In fact, there is a dearth of in-depth, qualitative literature which explores the understanding surrounding any novel therapy, however, the exception is the work undertaken by Lundin et al. (2016). Although the research addressed gene therapy and not NCT, it does explore similar areas of interest including the potential impact on the lived experience of HD.

From the literature presented in research question one, it is clear that HD has a profound impact across the lifespan, including prior to genetic diagnosis. It impacts gene-positive individuals, family members, partners, and children, and genetic status influences important life decisions and opportunities. Some of the literature presented suggests a lack of hope, the desperation for a treatment, and the desire to help others. However, it remains unclear what impact, if any, the emergence of new therapies might have on people's perceptions of HD and of how it might impact their lives.

Currently, the progression of HD across the life stages is managed palliatively but new treatment options are emerging, such as gene therapy and NCT. For many patients, they offer limited hope for themselves but offer the possibility of active therapeutic options for future generations including their families.

It remains unclear what impact, if any, the emergence of new therapies might have on people's perception of HD, how it might impact their lives, how the ethical sensitivities might be ameliorated, and how clinical trials can be supported ensuring a person-centred approach. This thesis seeks to address the gap in knowledge by exploring the research question outlined earlier:

- What is it like to have a lived experience, as an adult with pre-manifest HD, in a time where NCT is being proposed and developed as a potential therapy that seeks to offer an active therapeutic option?

4.0: Further Knowledge Acquisition

As stated, despite there being a wealth of research surrounding the lived experience, there is a gap in the literature exploring what the impact of emerging therapies like NCT might have on people's perceptions. As stated, this offers justification for the research topic, however, arguably, a lack of literature does not mean a lack of available information. To further my understanding of NCT, a novel approach was adopted and three experts within the field were interviewed about the topic. All interviews were undertaken after obtaining Cardiff University ethical approval.

This stage was intended to benefit the project in multiple ways including:

- To build on the literature review to identify contemporary topics of interest.
- To help ensure that the thesis was underpinned by contemporary, professional intelligence which enhanced the researchers' understanding of the NCT process and the aims of NCT.
- To access clinicians' experience of the HD population and any challenges faced when interacting with those impacted by HD.

The three professionals were identified via professional networking, published literature, and their online profiles. I approached them via email with a standardised letter (Appendix-II), gained consent (Appendix-III), and interviewed them to explore their past involvement with the procedure. The recorded interviews also addressed their recollections of the participant experience and understanding alongside the questions, queries, and concerns posed by individuals approached with regard to NCT. This was intended to increase my depth of understanding surrounding any future clinical applications of NCT and address issues such as neurosurgical risk. As stated, this process complemented the literature review and improved my subject knowledge acquisition.

All interviews were undertaken on Cardiff University premises. The interviews were recorded utilising an audio recorder and all data, whether audio or digital/written, was stored safely as per CU policy. Real-time notes were also recorded. A loose structure was applied to the interviews and the schedule is supplied. (See Appendix IV).

Anonymity was maintained by omitting actual names. Anonymised biographies are also not provided due to the potential of recognition due to the limited number of professionals working in this area. A brief thematic analysis of these interviews was undertaken and this information was utilised to further inform and provide the background questions for the main interviews.

This type of analysis can be described as a qualitative, descriptive approach which is "a method for identifying, analysing and reporting patterns within data" (Braun and Clarke 2006). Holloway and Todres (2003) argue that thematic analysis should be considered as the foundational method of

qualitative analysis and that by undertaking this, researchers develop core skills which can be utilised in other forms of qualitative analysis. This exploratory process did indeed increase my confidence with the interview process as well as aid my familiarity with handling research recording equipment and data.

I do, however, recognise that thematic analysis has been described as having an absence of clear and concise guidelines. It can be viewed as an "anything goes" approach to qualitative research (Braun and Clarke 2006). However, to combat this, a robust process was undertaken to ensure rigour.

This five-stage step is presented in Table 7 below.

Table 9: Five-stage approach

1. Familiarisation with the data

   Data transcription – an iterative process of reading and re-reading the data and identifying initial ideas.
2. Generating initial codes

   Identifying features of data across the set and collating data according to each code.
3. Searching for themes

   Collating codes into potential themes and identifying all data relevant to each theme.
4. Reviewing themes

   Re-checking if the themes relate to the coded extract.
5. Defining and naming the themes

   Generating clear definitions and names for each theme.

Adapted from Braun and Clarke (2006)

4.1: Professional Theme-Making Sense via Contrast

It emerged from the professional interviews that there was a perception that people make sense of their illness, circumstances, and NCT by comparing themselves with others. For example, an illness trajectory might be compared to that of their parent or sibling. This appeared consistent with the literature review section, which explored how people found out about HD and what impact this had on them.

It was, therefore, deemed important to understand where people source their knowledge from and what is key to their understanding.

Illustrative Quotes-Making Sense via Contrast

"There are a number of diseases where cell replacement therapy is being used; skin, eyes and things like that – obviously the brain's a lot more complex because the organ is more complex…"

"So, in Parkinson's I think that there is quite good evidence that, if you get the right sort of cell at the right time and put it into the brain of a Parkinson's animal and actually, there's good evidence now in the Parkinson patient that you can improve symptoms…"

"Huntington's is several years behind Parkinson's and it's a more complex biological problem. Because, in Parkinson's, if you put the cells into the brain and they produce dopamine, just literally produce the neurotransmitter, you should expect to see some improvement. With Huntington's, the neurons need to connect up."

4.2: Professional Theme-Chronological Risk

A recurrent theme identified across the three interviews was that attitude towards risk is influenced by the chronology/trajectory of the disease. Asking people "to take a hit" now for symptoms which might occur five years down the line might differ from undergoing an intervention where deterioration is imminent. There is also the risk of failing to act now when HD will inevitably impact future generations. This complements the literature presented surrounding altered perceptions of time.

Illustrative Quotes-Chronological Risk

"It is always difficult or ethically challenging to, well, it is always challenging for patients to come to terms with the idea of taking a risk up front for a potential gain further on down the line."

"…essentially, we know about Huntington's that, once you have the gene, you're going to get the disease and it's fatal. So, to a certain extent, it's easier for them than it is other diseases where the outcome is not so drastic".

"They still have to grapple with the fact though that they may be taking the risk of early morbidity upfront so, if they have a haemorrhage, or get an infection or an abscess, they may die or be left severely neurologically compromised".

This theme appeared important due to the question as to whether potential participants are aware of the risk that novel neurological therapies might bring. Also, by having the gene for HD, does this influence the way that they perceive risk? As suggested, the thought of taking a risk now for symptoms which might not occur for decades leads to the consideration of questions surrounding mortality and attitudes to risk.

4.3: Professional Theme-Ethical Dissonance

It was initially felt that the use of foetal tissue in NCT might be a contentious issue because the cells are from post-abortion foetal tissue. Lo and Parham (2009) stated that many people object to abortion but, under multiple national legislations, research with these cells is permitted provided that the donation of tissue for research is considered only after the decision to terminate pregnancy has been made. This, therefore, minimises the chances that a woman's decision to terminate pregnancy can be influenced by researchers looking to obtain tissue. However, for many, including Volaveric et al. (2009), the fundamental question remains – is it morally acceptable to pursue novel therapies for curing illnesses at the expense of a destroyed human embryo? They also argue that the pluripotency of stem cells is a double-edged sword. Arguably, the same plasticity that facilitates the formation of new tissue also makes them difficult to control post transplantation, thereby increasing the risk of tumour growth.

However, the professional interviews indicated that the ethics surrounding the use of foetal tissue is driven by the scientific/societal ethical community and might not be important to the HD population. It was the view, however, that the individual ethics of the people recruited might be vastly different or even unaddressed since they have this life-limiting illness. However, as Heydal et al. (2020) suggest, by the time people are asked to consent to research participation, other parties have already decided most of the issues, including those of ethics. The direction of research, the design of the study, and the overall risk-benefit analysis are usually determined without exploring and incorporating the views of possible research participants and future patients. Again, this provides further justification for exploring peoples' views.

Illustrative Quotes-Ethical Dissonance

"I'm not sure that it is, I think when I speak to patients, they are not really fussed where they (neural cells) came from".

"It would be my experience that they've got a lethal disease and I think that the ethical concerns are driven by the ethics community. And in real true life, people don't have the same ethical concerns".

"…think if you're in a position where you have a life-threatening untreatable condition, your view of the ethics is rather different to someone who's perfectly well".

Exploration of this concept in the HD interviews, therefore, felt appropriate. A question was, therefore, devised which addressed whether their lived experience of the gene had influenced their perceptions surrounding the use of foetal tissue alongside wider experimental issues.

4.4: Professional Theme-Familial Drivers and Brakes

The desire to undergo the intervention which might or might not be driven by the familial or community context of HD was also a theme that emerged throughout these interviews. Intentional or unintentional coercion was a factor thought worthy of exploration alongside whether families might facilitate or stymie recruitment.

Illustrative Quotes-Familial Drivers and Brakes

"I've also seen situations where you know you're asking someone if they're interested, not necessarily transplantation but any therapy and the patient is a little bit iffy and the carer's going 'oh no you should do this, no you definitely should, no this is really important'".

"…then you're in a position of trying to safeguard the patient because there's a very keen carer who's for the trial. So, it can work both ways and equally you can have patients who's quite keen and a carer who's sort of I don't know".

It was, therefore, felt that exploring the individual's role within the context of their family and how this influences their understanding and perceptions of NCT would be an important line of enquiry.

It is important to note that in undertaking the interviews with professionals, the aim was not to develop fixed topics for discussion but instead to develop an overview of NCT which could underpin a schedule which allowed the participants to provide a detailed account of their experience and understanding. Within IPA, it is essential to create a schedule which is open and refrains from making too many assumptions regarding participants' experiences (Smith et al. 2009). The schedule formed, following the professional interviews, simply served as a guide and participants were encouraged to take the lead.

4.5: Conclusion

This additional step to the traditional literature review provided an increased awareness of NCT as well as professional perceptions of the target population. This helped remedy the lack of subject-specific literature whilst also having the originally unintended consequence of building my confidence at interviewing, increasing familiarisation with equipment and data, as well as helping to build a foundation in analysis skills which would be used later. The data collected was, however, recognised as being a deep and a potential source of further inquiry outside of the scope of this thesis and I intend to return to it in greater detail.

The interview helped reinforce some of the findings in the literature review whilst also further justifying exploration of people with HD's thoughts and understanding surrounding NCT within the context of their own lives.

Both the literature review and these professionals did, however, reinforce gaps which have yet to be researched adequately. These specifically are that, nobody has undertaken an inquiry into the thoughts, feelings and understanding of people due to be approached to participate in clinical trials of NCT and no-one has asked this population how the emergence of NCT might influence their lived experience. There is an obvious absence of an in-depth experiential exploration of this topic.

Part Two

5.0: Introduction to the Research Method, Design, and Procedures

Part two of the thesis outlines the research approach, study design, and the research methodology used. The research process is presented, addressing ethical approval and data collection with a discussion of the issues of quality and limitations. I will discuss my reasons for choosing interpretative phenomenological analysis (IPA) for this study in preference to alternative research methodologies. The literature search confirmed that no studies into the lived experience of HD exist during a time period when they might be offered participation in potential therapeutic/curative therapies such as NCT.

This research aimed to specifically explore if and how the advent of research trials and therapies had impacted the lives of people with HD. The research also sought to gain insight into how they perceived NCT within the context of their own lives.

To achieve this, I chose to use an experiential, qualitative approach. The rationale as to why this approach was taken will now be explained.

5.1: Arriving at IPA

Initially, a range of approaches were considered to ensure that the research questions could be addressed. It was important to understand the spectrum of philosophical and methodological approaches which could have been potentially used (Snape and Spencer 2003).

This also meant that I could undergo a process of introspection (Durant-Law 2005) surrounding my own beliefs about what I constituted reality to be and how I can learn about it. I, therefore, confronted my own ingrained ontological assumptions surrounding how existence is attributed to phenomena and how I felt reality can be perceived. Bailey (2008) argued that “basic beliefs” can potentially misguide enquiry and it is, therefore, important that researchers participate in self-enquiry to reveal personal biases.

I was aware that the acquisition of knowledge within medicine and healthcare has been undertaken within the positivist paradigm, using quantitative methods, which exert that truth is derived from an objective reality. It is frequently referred to as “the scientific method” (Mackenzie and Knipe 2006). Emerging from Aristolean philosophy and developed by empiricist thinkers including Francis Bacon and Auguste Comte, positivism asserts the presumption that truth or fact exists independently of human consciousness (Mack 2010). As a result, positivist researchers believe that social observations

should be studied with the same approach that physical phenomena are and that quantitative methodological approaches are desirable (Burke-Johnson and Onwuegbuzie 2004).

The aim of this thesis was to explore and understand the lived experience, but positivism deals with the objective. Instead, I wanted to adopt an approach which recognises and embraces that people have sentience, agency, and will, all of which allow them to make conscious decisions within the context of their own lives (Buchanan 1998). Qualitative approaches embrace the experiences, judgements, individual perceptions, moral choices, and personal values held by participants, and understanding all of these was crucial to this thesis (Mack 2010). This is why a qualitative approach was used.

As stated previously, a qualitative approach was deemed appropriate for this project because this perspective argues that truth and reality are embodiments of the human consciousness and, therefore, people's lifeworld (Ashworth, 2015)

The central premise of qualitative research is that individuals construct the social world and that, therefore, multiple versions of reality exist (Court, 2013). I understood that the people taking part in this study have a lived experience of HD which impacts their perceptions and understanding of phenomena. Therefore, I wanted to use an approach that captured this.

There are many approaches within the qualitative paradigm which focus on gaining insight or understanding into the experiences of people (Bryman 2008). There are, however, fundamental differences which impacted their appropriateness for this research. I will now briefly outline my reasons for choosing IPA instead of these other approaches.

5.3.1: Phenomenology

Phenomenology can be described as the attentive exploration of human experience and that knowledge acquisition happens when individuals realise their own experience of a given phenomenon (Ashworth and Greasely 2009). Phenomenology is, therefore, the philosophical exploration of 'being' (Smith et al. 2009).

Although he might not have been the first to use the term, Edmund Husserl is considered to be the founder of phenomenology (Larkin 2020). Husserlian phenomenological research essentially seeks to transcend everyday suppositions and objectively identify the essence of a given experience (Tufford and Newman 2010). Essentially, it is the experience of a phenomenon which is stripped of all conscious filters and to do that, researchers must strip aside their own preconceived ideas. However, with prior experience within healthcare, alongside my considerable contemplation of the topic, it could be argued that the process of bracketing filters off would not have been extremely difficult. I was also

interested how people with pre-manifest HD view NCT within the context of their own lives so, essentially, this "stripping away" would have been undesirable.

Heidegger built on the work of Husserl but instead argued that phenomenological enquiry requires interpretation due to observation being contextual (Smith et al. 2009). Heideggerian phenomenologists argue that the researcher's human understanding and interpretation, through culture and language, results in "embodied" knowledge, therefore, exploration cannot be done without referencing past experience (Brown et al. 2011).

A Heideggerian approach suggests that participants' interpretation and experience are embodied in language and culture and can only be understood and interpreted by the researcher 'being-in-the-world' and that the removal of our prejudices is not achievable or even desirable (Lowes and Prowse 2001). Gadamer (2014) argued that our interpretative skills are grounded in our experiences and pre-suppositions and suppression of these can hinder the communication process and, in fact, impede interpretation.

As with these other phenomenological approaches, IPA, developed by Smith (1996), seeks to uncover the lived experiences of participants, however, it recognises the inherent subjectivity offered by the researcher (Smith et al. 2009). When using IPA, the researcher makes sense of the participant making sense of their world (Smith et al. 2009). Research utilising IPA typically considers important, life-transforming or threatening events, conditions, or decisions (Smith 2004). It gives an opportunity for researchers to get an intimate and detailed understanding of what an experience is like for somebody, as well as how they make sense of it (Smith and Nizza 2022).

Unlike other forms of phenomenology, IPA also encourages researchers to understand and embrace the frames of reference they bring to an inquiry, such as their gender and cultural influences (Larkin et al. 2006). Having been employed within the field of healthcare and with extensive clinical experience of neurosurgery alongside working with people with life-limiting illness, the removal of my preconceptions and prejudices would have proven difficult. By utilising IPA instead of dismissing pre-formed ideas, the approach embraces researcher biases. Experience is laid bare and can add to the transparency of the research being undertaken.

Whilst IPA has a deep connection to earlier forms of phenomenology in focusing on individuals' direct experience, participants are encouraged to explore their own individual experiences, with the researcher being encouraged to be open to the disclosures of each participant.

Researchers using IPA should also accept that experience is not only grounded in individual biographies but is context dependent. It is also based upon relationships with others, society, and culture (Eatough and Smith 2008). IPA assumes that individuals self-interpret the people, objects, and

events in their lives to make sense of their reality (Pietkiewicz and Smith 2016). HD impacts families, communities, employment, and more, as outlined in the introduction. Therefore, people's own situations and ideas about NCT will be influenced by these factors. In addition, NCT with its potential benefits and dangers and the use of foetal material are just two factors which could be viewed as being dependent, not just on the individual, but wider institutions including culture and spirituality.

This period of time where NCT has the potential to transform the lives of people with pre-manifest HD is arguably the most promising period of treatment and potential cure in the history of the disease. For this research, it was important to capture people's views of this potentially transforming time and gain a detailed understanding of what it meant to people with pre-manifest HD within the context of their own lives. It requires decisions to be made such as whether to participate in trials or even accept it as a therapy in future. Understanding of HD and the consequent associations will be made by people with unique lived experiences but who happen to have a shared disease profile. The core theoretical underpinnings of IPA reflect this (Smith and Nizza 2022).

5.3.2: Hermeneutics

Hermeneutics is central to IPA. Hermeneutics is concerned with making meaning understood, and rather than adopting a linear approach, an iterative process towards understanding is adopted (Pietkiewicz and Smith 2012). This approach is intended to facilitate a changing relationship with the data and is arguably more pragmatic (Smith et al. 2009). The hermeneutic circle is concerned with dynamic relationships between the part and the whole (Smith et al. 2009). Essentially it allows the researcher to re-examine, reconsider, and explore areas of interest. This type of analysis requires the dismantling of the experience in multiple ways in order to make sense of and then rebuild the experience.

When exploring appropriate methodologies to use, I noted the similarity between the hermeneutic cycle and the nursing process. The iterative nature of assessment, planning, intervention, and review of interventions appeared to be reflected in the hermeneutic cycle. An initial act of listening (assessment) is followed by careful consideration and sense-making. This allows the researcher to consider what to question next (planning and intervention) and is followed by sense-making (review) before the cycle starts again. As a novice researcher, comfort in a process that I am familiar with meant that using a methodology with similar components was an attractive option.

This further cemented the argument for me to use IPA, as the hermeneutic cycle emphasises the need for participants' voices to be heard comprehensively and their sense-making to be understood, all within the context of their own lives

5.3.3: Idiography

Idiography is another core component of IPA whereby in-depth analysis of single cases within their unique contexts is undertaken (Pietkiewicz and Smith 2012). Within a study, exploration of each individual case and the associated perspectives is undertaken prior to more universal conclusions being made. It is the opposite of the nomothetic approach whereby conclusions are drawn at a group level. This means that a focus on the particular is maintained, rather than the general (Smith et al. 2009). The resultant effect is that specific statements could be made about study participants. Again, this resonates with me as a nurse as it reflects the concept of person-centeredness. There are multiple definitions of patient-centeredness but they all essentially revolve around the concepts of respect, acknowledging human dignity, treating people as individuals, and uncovering what is important to them (Godfrey 2018).

Within the process of analysis, an IPA researcher commences with the detailed examination of a single case prior to moving onto the next. This allows the generation of themes within each individual case narratives and facilitates comparing and contrasting between participants.

5.3.4: Conclusion

There are multiple approaches available to answer research questions and I considered the diversity of paradigms and methodologies available. The origins of IPA are in psychology, however, the approach is increasingly being used more widely across healthcare research and when exploring the lived experience, it appeared to be a very suitable approach.

Using IPA would go on to allow the people recruited to this study to be given a voice and make sense of their own thoughts, feelings, and understandings surrounding NCT within the context of their own lives (Larkin et al. 2006), and it allowed for the uncovering of deep meaning.

The idiographic focus enabled a deep and person-centred exploration of each person's experience whilst also allowing for the identification of patterns and shared meaning.

Finally, unlike the more descriptive forms of phenomenology, IPA recognises that interpretation is inevitable, and that a researcher's preconceptions cannot be bracketed off. As stated previously, I have a great deal of experience in neurosurgery, clinical trials, and patient care and it would be both impractical and, arguably, undesirable to not recognise this. IPA was, therefore, considered to be the most appropriate approach for this thesis.

6.0: The Research Process

The previous section outlined the theoretical underpinnings and choice of research methodology and justified the use of IPA.

This section will now describe the process of how the research was undertaken.

6.1: Ethical Approval

Following the literature review, professional interviews, the identification and justification of an appropriate methodological approach, National Health Service (NHS) ethical approval was obtained prior to any research activity being undertaken.

It has been suggested that traditionally there has been a minimal emphasis on ethics in qualitative health services research (Richards 2002). This could be because of the belief that, unlike clinical trials, the approach is unlikely to cause harm to the people who wish to participate. IPA research is, however, a dynamic process which seeks to uncover meaning and the lived experience. Therefore, I was concerned that the research process could involve the exploration of potentially upsetting topics including family members impacted by HD and the use of foetal tissue. Arguably this could constitute emotional and psychological harm (Smith et al. 2009) and, consequently, full ethical approval was sought.

All research utilising human participants, biological material, and personal data is obliged to undergo formal ethical review and approval before any activity can commence. All protocols and recruitment materials were submitted and the study was approved following minor amendments.

The Health and Care Research Wales Ethics Service stipulates that ethical approval should be sought from an NHS Research Ethics Committee (REC) when research involves NHS patients and service users.

Since the United Kingdom adopts a universal approach to healthcare, it could be argued that there is ambiguity surrounding what constitutes an NHS service user. Essentially anyone who resides in the UK could be argued as being an NHS service user.

Participants were recruited from a Cardiff University clinic, and this was also where they saw their named NHS physicians. Also, all potential participants accessed NHS services and would need to in future as their HD progressed. I did not access any direct data from medical records but I also understood that the interviews created the potential for participants to divulge information related to their NHS care.

Finally, all other research undertaken at the recruitment centre undergoes full NHS review.

At the REC meeting, concerns were raised related to supportive attendance from a third party (partner, spouse, friend, or family member) at the interviews. It was recommended by the committee that all present at the interview should have consented as there was the potential for them to divulge sensitive information. Whilst appreciative of this point, I understood that research methods and design have the potential to be influenced by the ethics process itself. This unintended consequence did, however, lead to an enhancement of the project by increasing the amount of lived experience which could be explored. The partners also helped foster a relaxed atmosphere and sometimes appeared to facilitate the uncovering of experiences

As the literature review demonstrated, HD can be considered a shared disease within families, even by those who do not have the gene. The inclusion of partners and spouses arguably led to a richer pool of data and a greater understanding of experience. When partners were present, at times, it did appear that they acted as a further conduit which helped me uncover and understand situations, relationships, and circumstances.

6.2: Data Collection Method

The participants were originally approached in the clinic and received the patient information sheet (PIS) and consent form. All were given all documents relating to consent and their data were stored in accordance with Cardiff University Governance and Compliance procedure and Data Protection Policy (2018).

The aim of qualitative research is to gain access to the feelings, perceptions, and lived experiences of participants. Consequently, this requires a flexible method of data collection.

The exemplary method for data collection and the predominant approach in IPA studies is the interview (Smith and Osborn 2003). Therefore, I felt that this would be the most appropriate data collection method.

There is a range of interview approaches which can be adopted within qualitative research. They range from fully structured to completely unstructured (Bryman 2008). Hefferon and Gil-Rodriguez (2011) argue, however, that researchers should be mindful not to produce overly extensive, prolonged, and detailed schedules as these can be constraining.

Instead, IPA requires a more open-ended interview approach which is mindful of the balance of guiding and leading (Smith et al. 2009). The interviews started with general questions which allowed the participant to set the parameters of the interview and facilitate an uncovering of their lived experience. In retrospect, the interview structure also appeared to allow the participants to relax, build confidence, and create a rapport between us.

Once they had consented, the people recruited were individually interviewed in the presence of their primary support provider (partner, spouse, family member) if they so requested. I gave the participants the option as to where the interview took place, as comfort within their environment seemed essential. This offer did, however, have the caveat that the environment they chose would be a confidential setting and in accordance with the Cardiff University Lone Worker document. All chose to be interviewed within their homes.

Interviews were used as the data collection method. IPA requires that the data transcription be undertaken verbatim (Smith et al. 2009). For practical and financial purposes, audio recording was undertaken using a Dictaphone. To limit distraction, I did not take notes during the interview. This was noted by one of the participants who, on reflecting on previous research interview experiences, positively commented:

"…because she sat and talked to us, she didn't sit there [like you] and looked at a piece of paper [pointing at me, raising finger up and down] and asked you the questions off the piece of paper, she needed that piece of paper in front of her…".

As a novice researcher, I did not find it too difficult to adhere to the semi-structured schedule, as in nursing practice, questioning and assessment usually relies on adherence to models. Also, having clinical experience meant that the establishment of rapport came naturally, seemingly allowing the interviewees to express themselves across a range of topics.

To add context and recognise interaction, I also took field notes after each interview as an aide memoir.

Once the method of data collection had been identified, the process of constructing an interview schedule was undertaken.

6.3: Developing the Interview Schedule

The literature review and interviews with the professionals helped underpin a schedule which was intended to allow the interviewees an opportunity to provide a detailed account of their lived experience, thoughts, and feelings. Within IPA, it is essential to create a schedule which is open and refrains from making too many assumptions regarding participants' experiences (Smith et al. 2009). The schedule formed (Appendix VI) simply served as a guide and interviewees were encouraged to take the lead.

6.4: Public Involvement

Smith et al. (2009) suggested that the phrasing of a question can often appear abstract to participants and consequently numerous prompts are often required. A danger of this is, however, that the prompts themselves can appear abstract. As a result, consultation around phrasing is desirable.

Alongside utilising the supervisory team attached to this thesis, the schedule was also kindly reviewed by a member of the public identified via BRAIN Involve at Cardiff University and who is linked to Health and Care Research Wales Public Involvement and Engagement Involving People Network. The reviewer was from a family impacted by HD and brought this experience into the interview by adjusting the language and framing of the questions into a more accessible format for the participants.

The initial interview schedule was adapted following review by a member of the public and is included in Table 10.

Table 10: Reviewed questions

- **I realise that this isn't easy for you, but can you tell me how it feels to be gene-positive?**

  Prompts-holistic impact, changed attitude to life, positive and negative thoughts, physical and mental health, who do you share your concerns with? Feelings at diagnosis, have feelings changed?

- **So, you have had the information I gave you about this potential new therapy. Do you think that you can tell me what you understand about it?** Prompts surgery/cells
- **How do you feel about this potential intervention?** Prompts, hopes, fears, anxieties, impacts, excited, trust surrounding clinic.
- **What would you think if the study was offered to you?** Prompts – what would be important? Family/people/care providers, career, job, finances, study.
- **If it were offered to you, what do you think that the uncertainties or risks would be?**
- **Does the fact that HD runs in families affect how you think about things like this?**

I recognise that activity of this kind can be viewed as tokenistic by some (Brett et al. 2009), however, the reviewing of the questions and prompts resulted in the adoption of more participant-friendly format.

6.5: Recruitment

The identification of the total population of interest is not a concern within qualitative research. Too large a population can lead to a general analysis and this was not the aim of this study. Instead, the

aim was to recruit people who could potentially provide rich sources of data. Consideration of the strategy was, therefore, essential (Bryman 2008). Pietkiewicz and Smith (2014) state that there are no rules with regard to the population size within an IPA study. The focus should be on the depth of analysis and the richness of the individual cases.

The strategy adopted was to purposively identify a group of individuals who were gene-positive for HD. Smith et al. (2009) suggest that, for a professional doctorate study, between four and ten participants is acceptable. Six people who were gene-positive for HD agreed to participate.

As HD is a rare disease (Roos 2010), accessing the population for this research could have been problematic, however, as stated, the specialist HD clinic within Cardiff University was used as the recruitment site. The Cardiff HD centre is a specialist clinic and a Registry/ENROLL-HD (https://www.enroll-hd.org/) site for the European Huntington's Disease Network (EHDN). Many patients attending the HD clinic are already enrolled in the EHDN Registry/ENROLL-HD study (04//WSE05/89) where the symptom progression of participants is followed over. a number of years. Patients who are at the pre-manifest stage, the target population for this study, are also registered on the EHDN registry.

The EHDN Registry/ENROLL-HD study is a full clinical dataset, including the full medical history and medication history. One of the benefits of using the EHDN Registry/ENROLL-HD study is that those on the database have already given permission to be contacted about other additional and affiliated HD research projects. In consenting to be enrolled in the Registry study, participants also give their permission for their coded data to be accessed by researchers conducting other HD-related research.

To identify participants, I attended the clinic in person for two months. At the clinic, potential participants, receiving routine HD clinical care or attending a REGISTRY/ ENROLL-HD research assessment, were identified by the clinician responsible for care. The patients were then highlighted to me and I approached them in the waiting room to ask if they would like to receive an invitation letter (Appendix VII), the participant information sheet, and a consent form (Appendix VIII).

To add to the robustness of the study and to ensure an ethical approach to recruitment, I used the process of gatekeeping. This was intended to ensure that vulnerable or inappropriate individuals were not inadvertently targeted for recruitment. Guillemin et al. (2017) suggested that physician gatekeepers prioritise clinical status over research meaning that the best interests of the patients are maintained. Physicians can also make significant and beneficial recruitment decisions based on knowledge of patients' personal, behavioural, and attitudinal characteristics. This is often grounded in long-standing relationships with their patients. I acknowledge, however, that this strategy had the potential for recruitment bias.

Although the process of purposive sampling was employed, on reflection, a concurrent snowballing approach might have been incorporated into the study and family networks could have been accessed (Bryman 2008). During two of the six interviews, the participants offered to introduce family members.

All interested people were given greater than 48 hours to consider the study participation before being contacted via telephone. They were also offered the opportunity to ask any questions and discuss any issues with potential involvement.

6.6: Undertaking the Interviews

The interviewees were given the option to choose an acceptable time, date, and venue. Most of the interviews took place in people's homes, with the exception of one which was undertaken via Skype. The lone worker policy, previously stated, was adhered to.

Following consent, the participants were invited to express their experiences and informed that there were no right or wrong answers and that the research was concerned with their story.

The audio interviews were recorded using two digital recorders due to my anxiety about equipment failure. Recordings were stored on a password-protected storage device which ensured data protection. The interview lengths varied as per the table below. Pietkeiwicz and Smith (2012) offered guidance that interviews should be around an hour long. I was aware that I needed to allow the interview to be of a length which allowed for the interviewee's story to be explored but not too long that the process became tiring or distressing. I also noted that the initial interview was shorter than the others and potentially the lengths of the interview increased due to my own confidence.

Table 11: Length of interviews

Interview 1	Interview 2	Interview 3	Interview 4	Interview 5	Interview 6
29 mins	40 mins	59 mins	45 mins	60 mins	78 mins

I transcribed the interviews verbatim, giving me the advantage of immersion into the data. I made no attempt to correct grammar, wording, or anything which might change the interviewees' spoken words. I attempted to match the written transcription to the audio as closely as possible.

The process was time-consuming, taking approximately four to six hours per interview. I recognised that alternative approaches were available, including the hiring of a professional transcriptionist. This is, however, costly, and it might have resulted in the omission of key non-verbal interaction such as pauses, laughter, and over-emphasising of words and phrases which are important when using IPA.

Professional transcription might also have possibly led to the correction of grammar thereby losing meaning and reducing the rigour of the study (Rodham et al. 2015).

Anonymity was attempted in accordance with the Data Protection Act (1998) by requesting that the participants use pseudonyms to describe themselves and others, however, this was of varying success. Often people forgot to use their pseudonyms and I have learned that they could even be interpreted as being distracting for the participants. As a result, I allocated pseudonyms during the transcription process.

6.7: Conclusion

When undertaking research using IPA, it is important that there is depth of exploration which captures the lived experience of people and explores emotion, beliefs, understanding, and interpretation. By using minimally structured interviews, focus could be maintained, which allowed for the safe exploration of the interviewees' understanding of NCT. Self-transcription led to an increased sense of immersion within the data meaning that the findings presented are grounded in the words and experiences of the people interviewed.

The next section will outline how the data was managed alongside presenting the analysis and findings of this thesis.

Part Three

7.0: Introduction

The aim of this section is to describe and justify the process of data analysis used. Reflexivity is also included within the analysis, as it is consistent with IPA. I recognise that my thoughts and attitudes will have shaped the coding and analysis. Excerpts of data have been incorporated to provide greater transparency surrounding the coding structure which was applied as well as the finer detail of the analysis.

The computer software programme NVivo was initially considered to organise and assist with the data analysis, however, the interface made me feel detached from the data. I felt that sufficient organisation was achieved via Word and by hand. I adopted a systematic approach to the analysis which composed of six steps (Smith et al. 2009). These steps are summarised in the table below:

Table 12: Six-step approach (Smith et al. 2009)

Step	Action
1	Read and re-read each transcript
2	Initial noting
3	Development of themes
4	Search for connections across the themes
5	Move onto the next case
6	Look for patterns across cases

7.1: Analytic Process

The first step of IPA analysis should involve immersion within the data (Smith et al. 2009). Initially, I listened to and re-read the audio recordings several times on an individual basis. I reflected on the atmosphere and made notes regarding the interview experience and my thoughts and reflections. The transcripts were later annotated with these thoughts and reflections, and interpretations and links were then used to form models of emerging themes alongside their relationships to one another. This process adopted allowed for immersion in the data as well as deep consideration of the coding structure.

I then undertook a meticulous line-by-line analysis of the individual transcripts with, initially, each interviewee being treated as a single case, to understand their lived experience. An example of this can be found in Appendix IX.

Initially, I asked the interviewees to choose their own pseudonyms but this proved impractical as they often forgot and referred to their actual names. Consequently, the names displayed are fictional and are not linked to the interviewees in any way. To aid reading, where there are dyad interviews, the individual with the HD gene is named first.

Prior to the presentation of the interviews, a brief biographical description of the participants is offered to add context. I have attempted to leave them vague enough to prevent identification by third parties. This is because the population of people with HD is relatively small, thereby increasing the risk of identification.

As stated, a fundamental aspect of IPA is idiography. Idiography is an in-depth analysis of individual cases which explores the perspectives of study participants within the context of their own, unique lives. The aim is to examine every single case prior to the production of more general statements. This is in contrast with other approaches in research whereby the aim is to predict cause and effect (Pietkiewicz and Smith 2014). IPA can, therefore, be said to focus on the particular rather than the universal (Smith et al. 2009).

An account of the individual interviews is then provided, which describes the interviewee's own perceptions, understanding, and lived experience in their own words.

The language and other linguistic devices, such as metaphor, utilised by the interviewees are also described throughout. Smith et al. (2009) describe language and content as being interrelated and that attention to the way in which in which thoughts, ideas, and experiences are expressed adds meaning. An example from the interviews presented in this thesis includes:

"It goes way too fast once you let the handbrake off. It's gone and gathers speed. Sometimes just sit there hold it quietly". **Eirian**

Differences in tone, emotion, word choice, and linguistic tools can indicate similarities as well differences between individual experiences of the same phenomena. Focusing solely on words alone is restrictive and fails to encompass the full extent of expression (Derrida 1973). Instead, analysis should also explore the way things are said as analysis of linguistic strategies can allow for exploration of both the literal meaning and that which is hidden (Smith and Nizza 2022). For example, one of the interviewees, Jean, spoke about one of her family's approaches to dealing with HD:

"Cos my family is very prone to talk about it, we take the mick out of it and everything else like that."
Jean

These words alone did not match the sentiment in which they were said. The literal meaning is that they find the topic humourous, but the underlying message, when considered alongside the tone, is that her family is scared and needs mechanisms to cope.

Following an exploration of each participant's story, a conceptual phase of analysis is presented. Rather than focusing on the explicit accounts offered by the participants, the focus is instead on overarching understanding (Smith and Nizza 2022). This stage draws on my own experience and pre-understandings, however, it remains grounded within the dialogue between myself and the participant.

Lastly, in relation to the individual interviews, themes are discussed which emerged following analysis. Patterns and connections between the themes are identified and presented in a table alongside illustrative quotes.

7.2: Jean

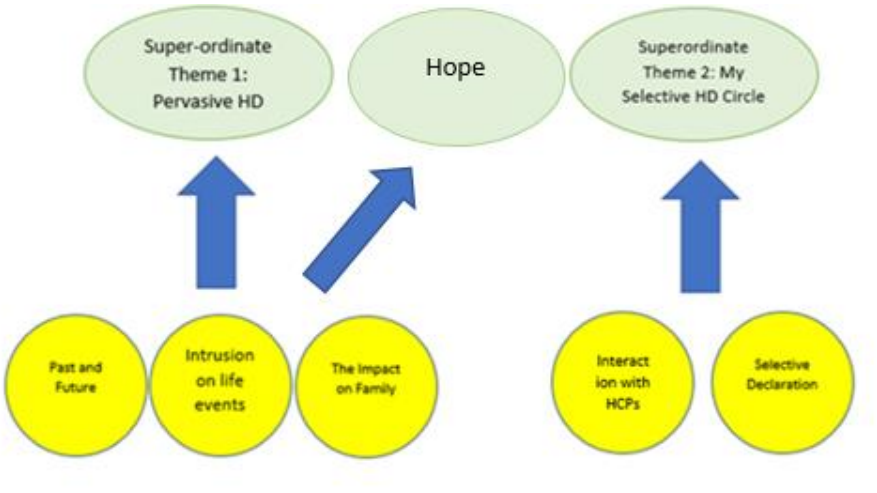
Jean was my first interviewee. She is in her early thirties, married with two young children, and lives in a small town in the Welsh Valleys. Her mother passed away due to complications of HD a few years ago.

Jean was interviewed in her home whilst her husband was at work. At the time of the interview, Jean was caring for her two young children. Apart from a brief introduction and one minor interruption, she asked them to remain in their bedrooms. Before we commenced the interview, Jean informed me that she works in healthcare as a non-registered medical professional within the field of mental health. She told me that she had previously and currently works with patients with advanced HD.

The interview was characterised by long monologues with little need for prompting. At times, Jean changed the direction of the interview but, through a combination of apprehension to interrupt as well as wanting Jean to discuss what was important to her, I did not interject.

The themes from the interview are summarised in the diagram below.

Figure 1: Jean's themes



Jean began the interview by telling me the story of how she had first become aware that she had HD. Although she appeared uncertain about the age at which she discovered her mum had HD, Jean was very specific about her own diagnosis.

"Uhm, I got tested when I was 23 just after I got married".

Throughout the interview, Jean referred to specific life events and suggested that HD had been a presence in her thoughts at all stages. She appeared to mark HD against her life events. As well as marriage, Jean openly discussed becoming pregnant and having children. Jean described the impact on her attending university and how HD seemed to intrude everywhere. HD appeared to lurk in the background in her thoughts when making decisions about her life but it was not always the most significant factor when a commitment had to be made. Intrusion into life events became a subordinate theme.

"We were going to go to London to do the IVF, where you have the kids with testing positive with them, but because I've got polycystic ovaries uhm, it took years and years and years for me to get pregnant anyway and I kept having miscarriages. So, by the time I was pregnant with (XXXX), it was just like, shall we get him tested and then we thought, no we've waited this long."

What was notable at the time of the interview, transcription, and reading was that Jean very rarely used labelling terms, including Huntington's or HD, and instead used non-direct phrases such as "it". This could have been a conscious or subconscious decision to avoid associated terms and appeared to contrast with her apparent openness in discussing it.

"Cos my family is very prone to talk about it, we take the mick out of it and everything else like that."

Here, the apparent self-protective use of the idiom, "take the mick", suggests a degree of self-deprecation in recognising that both she and her family have a serious disorder. This emotion was not

ubiquitous throughout her story, however. Adopting a humorous stance appeared at odds with many of the distressing memories recalled by Jean and, as the interview went on, she went on to describe a tapestry of reactions to HD amongst her family including guilt and fear.

This impact on family formed a second subordinate theme and throughout the interview, Jean referred to her family and described a shared experience of HD and how they had found difficulty in coping.

"…it's never just one person in the family, it affects all of them even the ones who are positive, uhm I mean aren't positive. Like my brother, I mean was gutted because he was the only one who wasn't married, no kids, absolutely gutted you know, really, really gutted and he went through a phase of setting fire to his skin and things like that."

This extract demonstrates a deep emotional and empathetic connection with her brother, suggesting that all her family experience HD despite their gene-positive or negative status. The use of "gutted" indicates a deep, painful, and sorrowful reaction which is confirmed by the description of her brother's actions.

Jean described how, together, the family had cared for Jean's mother and had adopted various roles. Jean described how her sister had the job of doing the nice things and that Jean was the level-headed one for when things got bad.

"My sister was a practical one, she did all the taking to the spas and getting nails and hair done and things done and I was the logical one going, well if she's going to start choking, what's it going to look like, how scary is it going to be."

This contradicts the description of the light-hearted approach mentioned earlier and instead suggests a very real fear of HD and a need for hope. It became clear that witnessing her mother's experience of HD underpinned how she saw her own position and how she viewed the future for both herself and her children. Jean often used comparison as a mechanism to make sense of her own situation and how she could use this to plan for the future.

"Yes, yeah, the amount of help you can get (now) is unbelievable, cos last time when my mother had it, we used to have to go to the DV, DLA every 3 years and get her thing renewed or you know, we'd be going, yes, but, it's neurodegenerative."

The exasperated tone of voice heard here towards the end of the sentence suggests a sense of frustration at the lack of understanding surrounding HD in the past. This is reinforced by the enthusiasm with which Jean described current and future healthcare provision noted at the beginning of the statement.

This contrast was particularly of note when Jean discussed interactions with healthcare professionals. Jean indicated that with regard to her HD, the relationships with her HD professionals are beneficial and that this allowed her to feel supported. When describing the situation of somebody else, unrelated, Jean described how others were not as fortunate as she was.

"...she was saying, because she grew up in Merthyr, she didn't know medical genetics, they didn't have any of the support, any of the extra help or anything at all and it shows what a difference that early contact makes."

By stating "what a difference that early contact makes", Jean suggested that she has seen others with HD struggle in the past, but her contemporary experience is one of support and mutual understanding.

"I've known (name of doctor) for 20 odd years and (name of nurse), God, since she's been there, about 15 years. So, it's good because I can just phone up either of them, I'll email them and go, right okay, this is going on, I need this..."

Both the informal tone and the use of first names as opposed to professional titles suggest a movement away from a formal relationship and instead towards one more like a friend or family. This might be due to the longevity of having known each other but later descriptions of interactions using words like "chatting" suggest a deeper and more meaningful relationship.

"Yes-uhm, when I saw (name of doctor) about 2 years ago we were chatting about it (NCT) then and we were chatting about it and how important it was and everything else. So yeah, it is something that has been talked about."

Jean appeared to describe an intensely important relationship with her doctor, the personal value that this type of connection had for her, and how it helped her plan for the future, especially with regard to her children. Jean indicated that she wanted her sons to experience the same open and friendly relationships that she has with her HD team.

"Yeah, so that's why I started taking my boys there. Because, uhm, I want them to get to know them so that, when you're going there, you're not going to see somebody I don't know and just to say, I'm fine, I'm fine".

"Getting to know them" implies that Jean does not just want her children to understand professional roles but to get to know the healthcare professionals as people. It could be implied that Jean was suggesting that she wanted her sons to build trusting and meaningful therapeutic relationships with healthcare professionals.

A further subordinate theme which emerged was that Jean had begun to restrict the number of people who she informed about her HD over time. Jean, again comparing the past and present, described how she originally had no boundaries in who she told about her HD but that had changed.

"I used to be very open about and tell everyone when I was younger, but it was all about me back then and oh, cos you are when you're at that age, but these days… (pauses changes direction of conversation towards her children)".

Jean suggested that when she was younger, she had been very self-focused. She indicated that she had had no strong desire to consider others but this has changed as she has grown older. The change of direction indicated that her children were at the forefront of her mind when contemplating her HD, however, she did not state a specific and growing need for non-disclosure.

What was clear, however, was that Jean saw NCT as a potential source of hope. As with the move away from the previously self-focused perspective, Jean emphasised that she needed hope, not for herself but for her children and wider family.

"Uhm I hope it's okay and it does really well for my boys' sake. Yeah, for all of us because, I'm the youngest of 4 and there's 3 of us who have tested positive, and I've currently got my mum's 2 sisters who are 60 and 50".

It is notable that Jean mentioned her children first before moving onto herself and wider family. This appeared to signify that she was more concerned about the potential impact of NCT for her family, rather than herself. This hope was, however, tempered by the realisation that the clinical trial process can take time.

"But there has been so many studies in the past that just haven't done anything. They've gone, oh yeah, this is brilliant, it's brilliant and then as it's done and it starts in human trials it's just, yeah, that's not quite what we need."

Table 13 demonstrates the emergent themes with illustrative quotes.

Table 13: Jeans Themes

Super-ordinate themes	***Subordinate themes***	***Illustrative quotes***
Pervasive HD	Intrusion on Life Events	***"Uhm, I got tested when I was 23 just after I got married".*** ***"We were going to go to London to do the IVF, where you have the kids with testing positive with them, but because I've got polycystic ovaries uhm, it took years and years and years for me to get pregnant anyway and I kept having miscarriages. So, by the time I was pregnant with (XXXX), it was just like, shall we get him tested and then we thought, no we've waited this long. Because I didn't want to be an older mum, I didn't want be a mum".***
Pervasive HD	The Impact on Family	***"So, they started asking questions about family and he was the only one who thought it was Huntington's with my mum."*** ***"I was the one who sorted out, all the stuff she needed in the house. My sister was a practical one, she did all the taking to the spas and getting nails and hair done and things done and I was the logical one going, well if she's going to start choking, what's it going to look like, how scary is it going to be."***
Pervasive HD	Past and Future	***"When we first did the study, we made sure that we did the tests, and made sure that we did living wills and things like that. Because my mother, when she was tested, although she stated her wishes, all the rules changed…"*** ***"Years ago, when my mother, every time she had a psychotic episode she'd end up in (name of psychiatric hospital) for 6 to 8 weeks."*** ***"Yeah so that's why I started taking my boys there because uhm, I want them to get to know them…"***
My Selective HD Circle	Interactions with Healthcare Professionals	***"I didn't want to be a mum this age, so then when I found out I was pregnant with (second child) six years later, that was a bit of a shock so I had to kick up a fuss and get my tubes tied…"*** ***"But after sort of 5 years, well before she died, she was allocated a really good nurse, from Glamorgan and she was absolutely amazing, did so much for my mum, umm, but it is a lot better, you've got so much help."***

My selective HD Circle	Selective Declaration	***"A lot of people don't know about it, the only people who know about it is my family, uhm and some of my friends."*** ***"In work nobody knows, it's only my boss."***
Hope	Hope for Us	***"…it takes such a long time for it all, all the animal testing and then you've got all the human trials and then you've got all this and it's got to be passed, this that and the other and it sometimes it seems like it takes too long. Uhm, so I'm hoping that it's all okay but hopefully we'll all get it…".*** ***"Uhm I hope it's okay and it does really well for my boys' sake. Yeah, for all of us…".***

7.3: Tabitha

My second interview was with Tabitha. Tabitha is in her early thirties. She lives in a small town in the West of England where she is a business owner working in health education.

She lives with her husband, who was not present, and she does not have any children. Tabitha was initially approached at the clinic and handed the recruitment materials, however, following review, she requested that the interview be undertaken via videoconference due to travelling distances. I did offer to travel to her house, but she stated that she would prefer an electronic meeting.

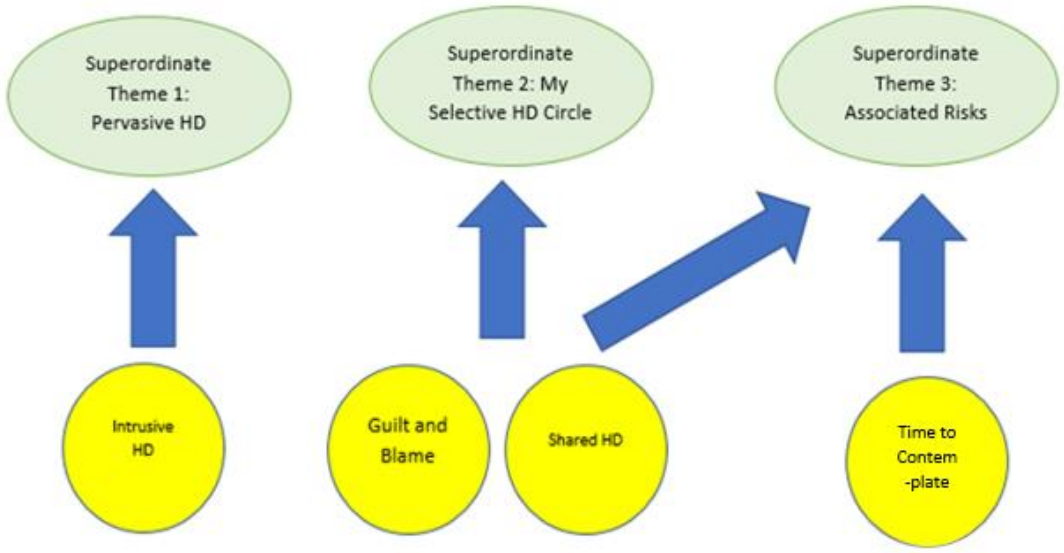
All consent documentation was forwarded securely and electronically.

Some of the benefits of this method were that body language and facial expressions could still be noted, which would have been impossible via phone. However, the video meeting process felt less personal than if the interview had been conducted face to face. There were occasions when the screen froze but her voice could still be heard. Occasionally, this impacted the flow of the conversation.

Throughout the interview Tabitha was very considered, pausing to contemplate frequently. The resultant effect was seemingly well-considered answers which were articulated clearly. Tabitha displayed confidence in her understanding of science and frequently used scientifically appropriate terminology.

Throughout the interview, Tabitha came across as warm and friendly, yet the expression of her emotions appeared tightly controlled. Her answers, although hinting at emotional and psychological difficulties, often focused on the facts. She provided a candid and frank account of her experiences of the HD and her understanding and feelings about NCT.

Figure 2: Tabitha's themes



The first subordinate theme identified was that HD had pervaded into multiple aspects of Tabitha's life and it had punctuated many important memories and life events.

"My mum told me that I had, well she didn't tell me that I had HD she told me that there was Huntington's Disease in the family when I was 18. So, I'm 33 now and I had actually just finished my A-levels."

The use of specific ages at specific time points suggests that the disorder had vividly punctuated her life. It was interesting to note what was not said, in that Tabitha used a friendly but "matter-of-fact" tone and wording to describe these events. There was no explicit mention or suggestion surrounding the emotional or psychological impact that HD had had on these episodes in her life. This dissipated somewhat as the interview progressed, indicating the importance of early rapport building.

When recollecting past events and people, Tabitha described how even her memories of loved ones were enveloped by HD.

"My grandfather, he is the one who had the disease and he had died when I was about 7, I think. So, I have memories of him, and the fact he was ill and that he was in a home and that he was looked after but I don't have a lot of memories about him".

The fact that her memories of her grandfather do not exist outside of the illness further underpinned the pervasiveness of the disorder. Tabitha's descriptive account focused on the infirmity of her grandfather rather than him as a person potentially suggesting that, for her, he could not be separated from HD.

Tabitha's story of her discovery of her own genetic status again indicated that HD is a constant presence and that it often intrudes into her thoughts. She described how she had had symptoms that she knew were consistent with stress, but the fact HD was in the background led to her incorrectly thinking that it must be HD. This was a significant motivation for her to get tested.

"So, I went to see the genetic counsellor and said, look I have these symptoms, the GP thinks it's all in my head but I'm sure it's not all in my head".

This suggestion, that HD is a constant and fearful presence, even prior to manifestation, was emphasised when recounting the memories of her mother, again suggesting that HD envelops and pervades people and their lives.

"My mum knew that she was at risk and having the disease at that time. She didn't know that she had HD and so she's always lived her life in fear really, the fact that she could develop this disease at any time."

This fear appeared to be a reflection of what her mother perceived that she might have caused for Tabitha and her sister. Tabitha described an immense sense of guilt that her mother had felt.

"...she always felt very guilty because you've been obviously told that it's a dominant gene at some point, by a doctor. But when she had my sister and myself, she didn't know that there was this disease in the family, because at that point they thought my Grandad had Parkinson's Disease."

The emphasis on her mother not knowing suggests that Tabitha did not blame her mother and that she felt that this sense of guilt was unnecessary. The excusing language and tone used appeared to suggest a degree of empathy and understanding of how and why her mother felt this way.

This is further emphasised by the described attempts, by Tabitha and her sister, to normalise their situation in front of their mother thereby attempting to comfort her and absolve her of any ill feeling.

Tabitha also described a sense of community, shared experiences, and communal goals amongst people with HD. She often used collective pronouns to describe the fight against the disorder even specifically identifying people with HD as a group.

"I think, from talking to other people with HD there is definitely a sense of live for today and I think as a group we are very much, yeah everyday counts".

Tabitha implied that, due to the familial nature of HD, many would have had a shared witnessing of how it can impact individuals. She suggested that these experiences allow individuals to predict their own future, and this forms the drive to want to combat the disease.

"People who, who either are preclinical or at the very beginning stages, as they know what's to come because they've seen it in their families, so they know what's coming in most cases".

Tabitha did not specifically describe the latter effects of HD, instead opting to use phrases like "what's coming". This might suggest an attempt at avoiding a description of symptoms or might have simply been an assumption of shared understanding between us.

A further subordinate theme was that of time to contemplate. Whilst Tabitha acknowledged a need for hope amongst both herself and her HD community, this was tempered by a "do not rush in", attitude. Throughout the interview, Tabitha suggested an understanding of the complexities of NCT clinical trials and often thought out loud prior to answering a question or drawing a conclusion. An example here is the consideration of the sources of stem cells.

"I don't know, I suppose it's because I suppose maybe because it's (foetal cells) more alive, that sounds awful. The animals aren't alive, I don't mean it in that way, but I mean I am, I am pro-choice so not anti-abortion in the fact that I don't think that a foetus should be used aborted whatever….".

It could be suggested that Tabitha was looking for wider reassurance surrounding her thoughts, however, the lack of punctuation or gaps for a reply indicated that these were her genuine considerations. She outlined that, for interventions like NCT, she would need an extended period to contemplate the moral and ethical aspects of the therapy. An interesting note was that, throughout these thoughts, Tabitha did not discuss how she might be viewed by others surrounding her decision-making, indicating further that this would need a very personal self-deliberation. This is further suggested by the repeated use of "I". The table below demonstrates the emergent themes with illustrative quotes.

Table 14: Tabitha's themes

Super-ordinate themes	***Subordinate themes***	***Illustrative quotes***
Pervasive HD	Intrusive HD	***"My mum told me that I had, well she didn't tell me that I had HD she told me that there was Huntington's disease in the family when I was 18, so I'm 33 now and I had actually just finished my A-levels".*** ***"It's not so much that it was in my head, I mean probably some of it might well have, been but because people with HD if they do get really, really stressed it brings out symptoms that they wouldn't normally have and I think that what was happening".***
My Selective HD Circle	Guilt and Blame	***"Two and a half years ago and she couldn't really accept it she wasn't able to accept it, so, so we tried to get rid of the stigma".*** ***"We tried to bring it into natural conversation".***
My Selective HD Circle	Shared HD	***"I don't think you'll find anybody in the HD community that cares about the fact that it's a new thing because we've been waiting for trials since HD was initially described, which is about 120 years ago".*** ***"I think the whole HD patient world is waiting".*** ***"Well that's a big thing in the HD community, is to be able to be useful".***
Associated Risks	Time to Contemplate	***"It's going to take you a day to have whatever it is done to you and there's bound to be a recovery time and there will be side effects as well so you that account for that".***

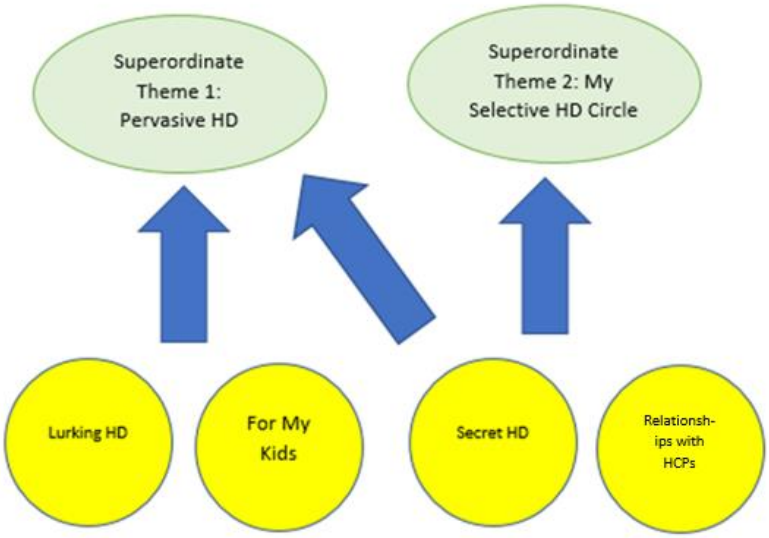
7.4: Eirian and Maggie

Eirian is in his fifties and lives at home with his wife Maggie. They live in a rural community in mid-Wales. This was my third interview and first as a dyad. Eirian and Maggie have been married for several decades. They have grown-up children and grandchildren who live locally.

Eirian has worked in agriculture his entire adult life in a manual and supervisory capacity. He obviously took pride in his work and frequently used stories and farming analogies to express himself. Throughout the interview, Eirian portrayed a constant cheery persona, even when discussing topics which might elicit negative emotions. Upon meeting and throughout the interview, Eirian acted in a very traditional manner, shaking hands, keeping hold of his emotions, and portraying himself in a stoic way. He often spoke in metaphors and spoke with a strong dialect, which is consistent with the local agricultural community.

Maggie was present throughout the interview. She is of a similar age to Eirian and has worked in healthcare for several years. Although to some extent, they shared experiences of HD, it became clear that they sometimes differed in their opinions, concerns, and priorities. However, throughout the interview, they appeared to be very respectful of each other's perspectives, rarely speaking over each other but not afraid to disagree over things. Another notable feature of the interview was that, as well as trying to help them uncover their thoughts and feelings myself, Eirian and Maggie often helped each other by clarifying and questioning each other. This relationship appeared to make the conversation more natural and appeared to uncover things which might have otherwise remained hidden.

Figure 3: Eirian and Maggie's themes



The first subordinate theme identified was that of HD being a lurking presence. Eirian immediately referenced that it is ever-present, but he described a dynamic relationship with the disease.

"Huntington's, it affects you every day depending on what you're doing. If you have been busy enough you can go past it and keep going some days, it is, it's alright to have a bit of fun with it".

In this statement, there appears to be an interesting contradiction. Eirian suggested that HD can be a source of amusement, but at the same time, he tries to avoid it. It could have been that Eirian was suggesting that he tries to avoid thinking about HD, but when he cannot, humour allows him to cope with it. However, I was also aware that, Eirian might have wanted to portray an image of masculinity, especially when interviewed by another man.

Both he and Maggie went on to describe an almost superstitious active avoidance of thinking about HD. Essentially, if you contemplate HD too much, it will accelerate the decline in health. Using metaphor and comparison with family members who do not act in the same way, Eirian implied that, by not thinking about HD, you can potentially protect yourself from it.

"It goes way too fast once you let the handbrake off. It's gone and gathers speed. Sometimes just sit there hold it quietly".

Seemingly referring to the unstoppable nature of HD once it has started, both Eirian and Maggie prefer keeping it lurking rather look for signs and symptoms. This avoidance appeared to be limited to talking about the disease, however, it appeared at odds with their active approach to research. This juxtaposition did not appear obvious to them, either that, or it was inconsequential for them.

Rather than completely avoiding HD in their lives, Eirian and Maggie instead described how they were proactive in HD research. When I questioned why, the response was very much focused on their children.

"It's for the kids. Because that's all it is, just need to leave something for them. They haven't got a chance at the moment".

Eirian spoke of research in terms of inheritance. That he wanted to leave them something. When asked about what benefits he might get from research into NCT, he stoically stated that he did not care about any personal benefit and that it was just for future generations. What was also notable was the notion that he felt that he had a personal responsibility to do so. Continued use of "I", rather than "we", when discussing this could have been a reference to his role as a provider and possibly reflected, again, his sense of traditional masculinity. Alternatively, this might have meant that he was the one with the gene, so he had a responsibility to act. Using metaphors from his agricultural

background Eirian described how, to achieve future benefits for his children, a great deal of work and sacrifice needs to be undertaken now.

"But you want to grow grass, if you grow grass, grow it to its best".

"...if you do the field today you can pass it on".

The relationships with healthcare professionals was also a subordinate theme, however, this appeared to be more of a primary concern for Maggie. Maggie appeared to recognise the importance of HD-specific care provision, however, she often described a dissatisfaction with services. The centralisation of services to locations away from their home had meant more travel to appointments and reduced the personalised experience.

"When we first knew about the Huntington's where the local nurse, which was only in (name of local town), which we could go to discuss and do some research with her, and she was taken away and we've ended up back in (name of centralised clinic) again".

"Taken away" further emphasised the dissatisfaction in that it implies a decision enforced upon them rather than one of consent. Maggie's tone of voice also reflected a sense of dissatisfaction.

Even though Eirian carried the gene, it seemed that Maggie was just as reliant on the services of the healthcare professionals. When Maggie was talking about this, Eirian did not interrupt. Instead, his gentle nodding suggested agreement with his wife. When Maggie discussed service changes it appeared to correspond with a reduction in trust in health professionals.

"I would trust her more than doctor (name) because she sat and talked to us. She didn't sit there and look at a piece of paper and ask you the questions off the piece of paper".

Looking at the paper appeared to be a metaphor for adopting a more personalised approach. Maggie suggested that a trusting relationship with HCPs was essential, rather than a formalised relationship, which lacked intimacy and trust. Maggie outlined how, for them to consider potentially dangerous therapies like NCT, personalised and trusting relationships would need to be built between themselves and HCPs.

The discussion around relationships then proceeded to extend beyond that with professionals. It became apparent that both Eirian and Maggie maintained a degree of secrecy about his HD status and only told select individuals.

"We don't discuss his Huntington's out of this house, because we never have".

The word "house", in this instance could again be interpreted as a metaphor for a select circle of people. They would further describe how HD was very much a secret.

Eirian elaborated on this. At work, he has kept his HD secret from everyone except his boss. He did, however, say that he has told a few people that he has a gene for Parkinson's disease (PD). Eirian's explanation for this is that there is an absence of awareness surrounding HD in society, but people are aware of PD. Maggie initially agreed with this but suggested that this explanation is not as simplistic as first seems. When describing the story of another family, Maggie hinted that there is a more deep-seated reason for non-disclosure.

"...he's got Juvenile Huntington's and they keep saying that it is Parkinson's. It's not what you know, it's not we know, it's Juvenile Huntington's because well, I have spoken to his wife and they understand it but the wider public think that he has got Parkinson's. Because they put two and two together and she doesn't want to advertise it and she doesn't want them knowing exactly what he has got".

The use of the phrase "putting two and two together" implies a suggestion that the public might understand that he is ill but what remains unclear is why the couple felt PD is acceptable but HD is not. Both were clear, however, in that HD is something for individual families to deal with and not for public knowledge.

The themes identified are summarised in table 15.

Table 15: Eirian and Margaret's themes

Super-ordinate Themes	***Subordinate themes***	***Illustrative Quotes***
Pervasive HD	Lurking HD	***"...we don't go on about it 24 hours a day we know it's there we know it may appear someday ".*** ***"...we don't actually discuss it every day it doesn't come up very often the only time that really comes back is when we get the call asking us to go to clinic".*** ***"But that's a problem with one of our sisters-in-law, who is too dwelling on this Huntington's. Twenty-four hours a day which is making his brother a shell of what he was".***
Pervasive HD	For My Kids	***"I can do a little bit more down there; I would have been happier at the end of the day."*** ***"...it's a disease that we know will affect future generations isn't it".*** ***"What it is, that I'm just thinking of him and then her, there's two kids".***
My Selective HD Circle	Relationships with HCPs	***"He was a young GP coming in and of course you just thought about the bigger picture and I'll hang on but I think I don't like, and I know this sounds horrible but I don't like doctor (new doctor)".*** ***"...she just looks at you ticks the box on the papers and said thank you very much".***
My Selective HD Circle	Secret HD	***"...he's got the gene obviously but as he's got no symptoms there's no point".*** ***"...other than one on shift that I will talk to you and all the other understands is that I've got a gene for Parkinson's".***

7.5: Claire and Dan

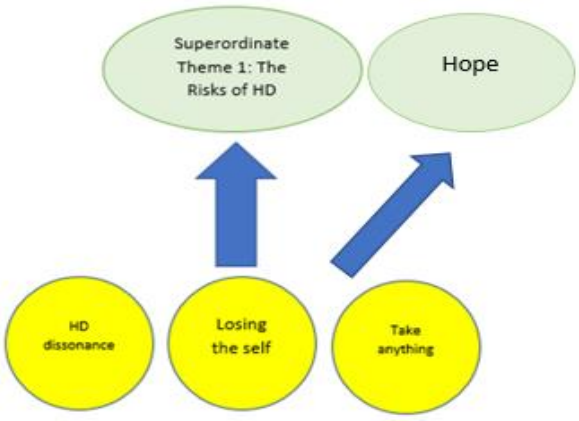
My fourth interview was with Claire and her husband Dan. Claire is gene-positive and in her early fifties.

Claire works in a clerical role within a local business and together they have teenage children. The interview was undertaken within her city centre home.

Dan is of a similar age to Claire. He did not declare his occupation. Dan appeared relaxed from the start of and throughout the interview process. Dan frequently used humour. In contrast, Claire appeared nervous initially, but this appeared to dissipate as the interview progressed. Claire frequently looked to Dan for support and it appeared that his presence was a source of reassurance for her. At the beginning of the interview, Claire spoke in short monologues with little elaboration, suggesting an uncertainty or discomfort in disclosing information. However, it did appear that the presence of Dan and his input into the interview facilitated Claire to explore more as the interview progressed.

The interview was also undertaken with their pet dog present which seemed to contribute towards a more relaxed atmosphere. The relationships between themes are summarised in Figure 4.

Figure 4 Claire and Dan's themes



Claire began by talking about the of difficulty living with HD. She started by talking about the death of her father and followed this by discussing the potential impact on her own children.

"It's very hard to live with. I was tested because I've got three daughters and I wanted to know so that they would then have the knowledge but but would never been tested if I didn't have children already".

Claire continued that her rationale for initially avoiding testing was that there had been an absence of hope surrounding HD. In essence, why find out if you cannot control it? This was reinforced by statements suggesting that knowing about her gene status was more difficult than ignorance as there was no cure. However, it was the driver of the potential impact on her children which ultimately guided her decision to undergo genetic testing.

Initially, Claire even avoided using direct terms describing HD and instead referred to the disease as "it". This suggested a discomfort in even using direct terms associated with HD due to awareness of the negative outcomes of having the gene. A dichotomy would, however, appear as the interview progressed in that, despite avoiding thinking about HD, Claire often took actions including research participation where the disease would be brought to the forefront of her thoughts. Throughout the interview, it appeared that Dan adopted a different stance. His thoughts and actions appeared more consistent. He wanted to know more and more about HD and to participate in the research which could be used to combat it. However, aware of Claire's feelings, Dan said that he would often do this when she was not around. Claire appeared to appreciate Dan's covertness as acts of beneficence and non-maleficence. When Dan described his secrecy, Claire acknowledged with gentle nodding, smiling and occasional touching of his hand, suggesting gratitude.

What was consistent between the couple was the need for hope. They both had an awareness of what would happen. For Claire, this was grounded in the memories of seeing her father in the late stages of the disease. This need for hope was linked to an awareness of what she would lose as an individual and what they would lose as a couple when the disease progressed. Both Claire and Dan described HD would not just lead to a shortening of life in terms of years but, more importantly, the loss of quality and loss of Claire's self.

"Sitting here now physical problems bit of a wobble a bit jerky movement I could cope with perhaps, but the whole, you know the whole changing of the personality, personality changes they're scary. I suppose I don't want to become a different person if that makes sense?".

Despite the suggestions that she could cope with physical issues, Claire described how she feared the personality changes associated with HD. Repetitive use of the words "personality" and "person" suggested that she was less concerned about the physical manifestations of HD but she had a real fear of the loss of self. Claire described how eating and drinking wine with Dan were key personal activities which characterised her and that she hoped that NCT would be a mechanism for maintaining these. Claire appeared to be using her enjoyment of dining as a simple example which reflected the much wider context of experiencing pleasure in life.

Reflecting on the decline of her father, she appeared to suggest that HD robs people of the characteristics which make them unique. Again, referencing eating, the phrase “things like that” indicated that Claire was thinking much wider than this single activity of living.

“And yeah, and that was very hard watching my Dad when he was in the nursing home, sitting at a Christmas party. Whenever I was eating and he couldn't, that's tough isn't it because he had a great appetite until he started until his swallow, went then yeah things like that”.

A further subordinate theme was that of being open to anything to preserve Claire’s sense of self. Both Claire and Dan stated that they were aware that NCT would involve potentially risky neurosurgery and that the source of cells would be from foetuses. This sense of risk acceptance did not, however, appear to be a barrier.

“I'm sure I'll be terrified, but you know it's that hope thing again isn't it it's about giving us back some time down the line and together and all I dream”.

Again, Claire recognised her own fears but appeared to suggest that these would have to be overcome. She appeared to recognise an acute sense of risk in being recruited to clinical trials of NCT or potentially receiving it as therapy in the future. This was supported by Dan, who stated that he would go to extreme lengths to ensure more quality time with Claire.

“...you can test my dog, and I love my dog, you can take anything out of her if that's going to solve the problem”.

Dan, although expressing a sense of jest, appeared to be indicating that sacrifices would have to be made to get the outcome that they both desired. Again, he acknowledged the need for risk acceptance. Dan knew that Claire would have to make the primary risk sacrifice but indicated, that he also had the potential of a great deal to lose.

The final theme identified in this interview was that of NCT being the first good news. As stated previously, there appeared to be a dissonance between Claire’s lack of desire for knowledge and active participation in research. NCT did, however, appear to be the exception she appeared to want to know as she finally had hope.

“...we honestly didn't think we’d got a long retirement to look forward to. Now unfortunately, we're going to be skint but happy, as long as everything goes to plan”.

Whilst the language suggests a confidence that NCT will be successful, the latter part of the statement seems to be an attempt at reigning in of over expectations. Claire outlined how, despite having hope, outcomes cannot be certain.

The themes identified are summarised in Table 16.

Table 16: Claire and Dan's themes

Super-ordinate themes	***Subordinate themes***	***Illustrative quotes***
Avoiding HD	HD Dissonance	***"...it's been very hard it's been very hard all these years especially up until now when there's been no real hope, no treatments".*** ***"I know a lot of the research has been about finding what causes the onset or what starts the onset, so we've done all sorts of things probably about a good 10 years".***
Associated Risks	Losing the Self	***"I think people underestimate the impact it had since we knew about it it's changed everything I, outlook and everything even financial decisions because I don't want to be sitting on money when my wife can't do anything."*** ***"...maybe longer retirement together and grandkids so you know you just have to do it you just have to get on with it be brave".*** ***"And the preference would it be for her never to experience a real symptom and if they said tomorrow if you have it now then the likelihood is you'll never have any sort of symptoms, or it would have been slow it down for an extra few years then we would probably walk in the surgery tomorrow and get it done".***
Associated Risks	Take Anything	***"Personally, I don't have a problem. You know, having watch my dad died from it I would be prepared for anything really yeah".*** ***"...I'm sort of watching something, I shouldn't go on the Internet when she goes to bed, I'm doing that sort of research ".*** ***"...when you're in that situation, that's your only hope".***
Hope	First Good News Ever	***"it's so close".*** ***"...so, this has been amazing news for us really, because it's very hard".*** ***"...two years from now they will be able to start you know treating everybody so, so that's been a massive boost obviously".*** ***"...you know it's that hope thing again isn't it it's about giving us back some time down the line and together and all I dream, maybe longer retirement together and grandkids. So, you know you just have to do it, you just have to get on with it, be brave".***

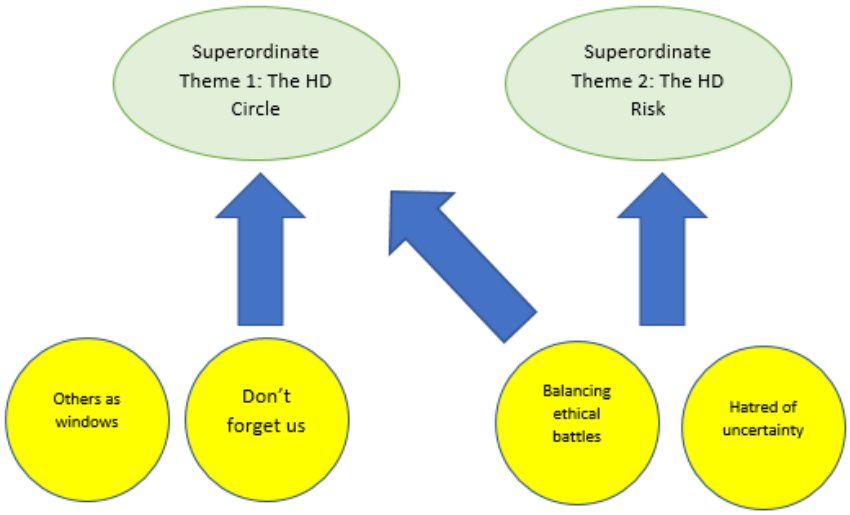
7.6: Angharad and Robert

The fifth interview was with Angharad and Robert. Angharad is a professional woman in her mid-thirties and was interviewed in her rural home in a relatively isolated geographical area. Her husband, Robert, was present and prior to the interview, indicated a very strong desire to be involved with this research. They have no children, and the interview took place in the dining room with their dog present.

Angharad, although quietly spoken, provided a candid account of her life with HD. Robert spoke passionately and was far more animated in both his voice and body language. He used interesting linguistic techniques not noted in previous interviews, particularly the use of memes.

The themes are summarised in the diagram below:

Figure 5: Angharad and Robert's themes



The interview began with Angharad recollecting her discovery of her HD status. She described how she is a person who hates uncertainty so, very soon after she was aware of her mother's status, she also got tested.

"So, we decided straight away to get tested, because I just wanted to know. I'm the kind of person who hates and, uncertainty, so the thought of living with the 50/50 was worse than having the test".

The unequivocal tone of her sentences appeared to complement the short sharp statements and ultimately emphasised a notion of certainty in her actions. Angharad suggested that there was little need to consider the benefits and pitfalls of testing as knowing allows for planning. Angharad indicated

that this attitude towards genetic testing was grounded in the memories of both her mother and grandmother having the disease. Robert agreed with this and suggested that the witnessing of other family members gave them a window into what would happen to Angharad.

"…you went off every 6 weeks to visit for the weekend and you saw your mum deteriorating and the occasion when I would come over, I could see the difference in her. Tragically, but I never knew her when she was normal".

The statement from Robert implies that the effects of the disease are so profound that he, who had spent little time with Angharad's mother before, could understand the devastating nature of HD. The use of the word "normal" in this context appeared to set a clear divide between a life with HD and one without. It emphasised that HD results in characteristics so profoundly atypical and adverse that life becomes deviant compared to others in society.

Robert also used others as windows in that he empathised with others who he had seen in a similar position. He knew that in the future, he would face similar challenges. In witnessing his father-in-law's experience, it appeared that Robert was suggesting that he would face an indirect but personal burden.

"I'll look at it from the other point of view and I see how my father-in-law was coping when it was getting really bad towards the end and you see that with other people. There was intensity when they were heavily involved, and it can make you quite depressed about it".

What was notable in this instance was the use of the singular pronoun. Despite Angharad having the expanded *HTT* gene, there was a recognition that Robert too would have a very negative yet distinct experience of the disease. This recognition that Robert would have a negative future led to the couple suggesting that clinical trials, including NCT, should consider the partners of participants. In stating this, there was the suggestion that the gene carrier is not the only one who suffers adversely from a diagnosis of HD. This was followed by Robert indicating that an increased focus on partners might encourage research participation.

"I think that would be better, you feel the love, you feel more sense of being included".

Robert repeatedly used the idiom or meme "feel the love" in a light-hearted way, however, its repetition suggested that he felt would be left behind in conversations which would ultimately impact him.

An important topic for Angharad and Robert was that of ethical consideration. During the interview, they spoke about both their internal morality and ethics alongside the pressure received from others in society.

"…because it isn't just about us and what's right for us, it's what's right for the world as well".

Both made numerous references to the consideration of others, ethics, and their faith. There was a suggestion that the actions they took in life had impacts on wider society, both within the HD community and outside. Therefore, both Angharad and Robert described how the thoughts and feelings of others should be considered.

"But it is hard when your sister tells you you're a murderer for even considering it".

The graphic and visceral language used, however, suggested to me that they felt that their actions would be subject to the judgements of others.

That there was a genuine suggestion of fear of ostracisation and the breakdown of relationships with family, friends, and their community. Angharad was suggesting a genuine ethical battle between preserving her status within her family and community and potentially preserving her own life.

The themes identified are summarised in Table 17:

Table 17: Angharad and Robert's themes

Super-ordinate themes	***Subordinate themes***	***Illustrative quotes***
My Selective HD Circle	Others as Mirrors	***"I don't know for me it was a choice between the future that I saw my mum had and almost seeing myself in her position."*** ***"…one doctor thought my grandmother had it and then another doctor said, I don't know what she's got but it's definitely not Parkinson's and that was even just over 20 years ago".***
Associated Risks	Hatred of Uncertainty	***"I found out well I found out that my mum had the gene in 2005 yeah and then I got tested then once we had it confirmed that she had the gene, so I got my results in June 2006."*** ***"…it might be you've got the gene and then you definitely know that you're going to get HD, but for me even if it's bad news, I would rather know so we can plan."***
The Pervasiveness of HD	Balancing Ethical Battles and Relationships	***"It forces you to really think about which side do I come down on? I can't really sit on the fence, I've got a think yes or no but yeah, it's good to look at all the evidence and all the research weigh it up for yourself".*** ***"…people in our faith environment would find it very difficult for us to be involved in that sort of thing."*** ***"…it isn't just about us and what's right for us, it's what's right for the world as well".***
My Selective HD Circle	Don't Forget Us	***"…you feel the love you feel more sense of being included".*** ***"Sometimes it is more about looking after the person who's come with the person".***

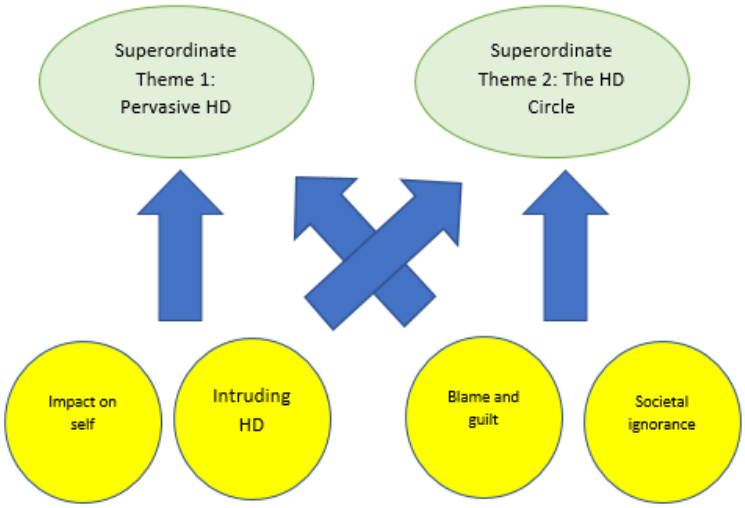
7.7: Dai and Lisa

Dai and his partner Lisa, both in their late forties, live together in a semi-rural setting. The interview took place in the living room of the home that they shared. Both have been in previous relationships and had children with their ex-partners. Their children were unaware of HD as a genetic disease within their family.

Throughout the interview, Dai remained relaxed, light-hearted, and open but Lisa appeared uncomfortable with the discussion. She often displayed a degree of caution throughout the interview and spoke infrequently. Both prior to and during the interview, Lisa referred to and indicated time constraints, stating they had plans later that day.

The interview was characterised by little need to interject. Dai often spoke in long and rich monologues, with the frequent use of humour and anecdotes. Dai spoke in a tone which suggested he was relaxed throughout the interview. On reflection, the interview was very reminiscent of the "rugby club storytelling" characteristic in Welsh culture. The diagrams below illustrate the themes and relationships.

Figure 6: Dai and Lisa's themes



At the outset, Dai was asked what it was like having the HD gene. He launched into an extensive and rich monologue surrounding his experience, frequently using metaphor to describe the impact. He described how HD had impacted him personally and how it had pervaded into his memories and wider life.

"Everything changes a little bit. It's like it's like a spinning top being off, being off the point, just slightly".

Dai used very soft language indicating that the impact so far had not been too severe and that, for the moment, his HD was "trundling" along and yet to have a profound impact on him. Dai never spoke about the consequences that HD would have for him despite an obvious understanding of HD as a disease. This might have been avoidance and instead, he appeared more concerned about the impact that HD had had on others in his past and how it might impact others in future. On reflection, I also feel that this might have been a response to Lisa's apparent anxiety with discussing HD.

Dai frequently indicated the need for compassion for those affected and often turned to his childhood memories of his uncle. Dai described how he and his siblings would mock his uncle but it was a "comical innocence". At the time they were ignorant of HD so could not recognise the significance of his uncle's behaviour and no malice was intended

"…he was a hell of a lovely guy, but Christ he's a bit simple you know. He would make tea and it would be all over the shop."

This statement appeared to capture both the physical and cognitive symptoms associated with manifest HD for Dai. The language used appeared to recognise that HD is beyond anyone's control and Dai maintained an overall sense of compassion, especially towards his father from whom he had inherited the gene.

"…it came about, they had tested me and the results and so on and, I went up to see him and you could see, he was not one for sort of, and I went to see him, and I said Dad, and he was he was gutted and I think he felt at fault".

The frequent punctuation of the sentence with "and" followed by a short pause suggested that Dai found this memory difficult to express and that he was reluctant to display any negative emotions in the interview. Again, this appeared to reflect the common masculine expectations which exist in South Wales. This was particularly noted when compared with other excerpts of the interview where there was less emotional charge and Dai was far more "free flowing" in his speech.

Dai did, however, appear to suggest that with HD, there comes sense of blame and guilt for gene carriers. Dai suggested that his father felt blame for having and passing on the expanded *HTT* gene. Dai also appeared to suggest that he might also become an object of blame when it came time to inform his children of their potential risk.

Dai spoke of the pervasive nature of HD and how he hoped NCT would prevent this.

"If I found out more how this is going to bloody work, if you want to know how much it would have effect on my life besides my health, I'll put a hold on that".

The use of mild swearing, not used in other areas of the interview, indicated frustration. The statement seems to suggest that Dai understood the impact of HD on the physical self but felt angry at the impact on wider life including "bloody insurance and mortgages".

This was not the only frustration that Dai expressed. He described frustration at the wider societal ignorance of HD, particularly amongst healthcare professionals. When telling the story of one admission his father had to hospital, Dai described a doctor "Googling" HD in front of him. This appeared at odds with his earlier suggestions that people cannot be blamed for their ignorance.

"…that's in the medical profession. You just seem to think they know everything, and we take it for granted and you do think that as soon as you mention something you shouldn't have to Google it. Could come with some random some 16th century bloody thing".

He suggested that very few people in society have an awareness of HD and that knowledge of the disorder is limited to those who live with HD and with HD healthcare professionals.

The themes identified are summarised in the table below with illustrative quotes.

Table 18: Dai and Lisa's themes

Pervasive HD	Impact on Self	***"And it's one of them. It's one of those you can see it sort of happening stretched out and you can see it coming along it's on the road and that car is just trundling along".***
My Selective HD Circle	Need for Compassion	***(Diagnosis) Lisa "you were 39 because our daughter would have been 9".*** ***Dai "Well obviously my mothers' had 39 years of freedom from it like…"*** ***"…of course, the children with me, from my first marriage. And it got all that sort of fragmented bits and bobs and there's these conversations that can go off in all sorts of directions. So, it's kind of like you're letting your ex-missus know etc, sort of for the kid's sake".*** ***"…if you look at the symptoms, the behaviour side of things, at the reflexes you know, he was like a textbook. You know, you got his jumper, it would be on inside out. You know, he was desperate for a haircut and he was always he was always very prim and proper".***
My Selective HD Circle	Blame and Guilt	***"I went to see him, and I said Dad, and he was he was gutted, and I think he felt at fault himself. He would never speak like that he was very kind of, oh there we are crack on, but I know he definitely felt gutted and guilty".***
Pervasive HD	Intruding HD	***"…all the side issues which you wouldn't even think that bloody insurance, mortgages".*** ***"…think about it all right ok think about something you wouldn't have to consider and there's loads of different bits and bobs".***
My Selective HD Circle	Societal Ignorance	***"…if you going to talk to your GP about it, you wouldn't be bothered. There's no point in making them understand, trying to explain it because he probably doesn't need to know and they haven't got the time to, to look".*** ***"I brought the subject up then and said, by the way he suffers from Huntington's Disease and one thing and another and he stopped in his tracks. I can't believe it, the first thing then, he had a laptop then and, was Googling it".*** ***"I've only ever seen Huntington's mentioned on TV perhaps twice ever".***

7.8: Connections between Themes

As stated previously, IPA research involves a detailed examination of particulars, firstly providing an in-depth account of each case before moving to look for patterns where themes and concepts might converge or diverge across each individual experience (Eatough and Smith 2008). Whilst I did not want to lose sight of the particularities of individual lived experiences, noting this convergence and divergence across the interviews was compelling and achieved by the following.

Firstly, I reviewed the tables of themes from each interview, and I then began exploring the overlaps between each table, looking for similarities and differences in personal experience. I also re-listened to the interviews to listen to the way in which each theme was being described, for example, differences in tone and emotion.

I recognised that the idiographic and inductive approach taken towards each individual case had resulted in individualised structure and wording, however, I was able to identify the concepts which, in some cases, were worded differently between each participant. This process requires analysis at a more conceptual level due to the recognition of the idiosyncratic differences occurring with each interviewee (Smith and Nizza 2022). The process was not a linear one and required an iterative approach; I repeatedly moved back and forth and across cases.

It can be suggested that IPA should maintain focus on individual experiences and that identifying patterns across themes is at odds with this, however, the cross-case patterns remain grounded in each individual story (Shaw 2010). The process also led to revisiting and, in some instances, relabelling or reconfiguring them as strong similarities were noted.

Table 19 below demonstrates each superordinate theme in the context of each interview. These themes were present in more than one interview. Where a theme was present in only one interview, it has been left out. The table also demonstrates the convergence and divergence of themes between identified in each interview with ✓ indicating it was present and X indicating absence.

Table 19: Table of cross-case themes

	The Pervasiveness of HD	My Selective HD Circle	Associated Risks	Hope	Avoiding HD
Jean	✓	✓	X	✓	✓
Tabitha	✓	✓	✓	✓	✓
Eirian and Maggie	✓	✓	✓	✓	X
Claire and Dan	✓	X	✓	✓	✓
Angharad and Robert	X	✓	✓	X	✓
Dai and Lisa	✓	✓	X	X	X

Table 19 highlights the definitions of each theme accompanied by illustrative quotes.

7.8.1: Convergence

This process exposed "The Pervasiveness of HD" as an extra superordinate theme with all of the other themes underpinning it. It appeared in five of the interviews with the interviewees describing how multiple aspects of their lives are impacted by the disease. This includes memories, life events, life decisions, and relationships. It is ever present for many, not always at the forefront of thoughts but constantly influencing the course of their lives. It was interesting to note that there were significant similarities in the way each interviewee described this pervasiveness in that they spoke about how HD had punctuated their lives. All of the interviewees described their lives with HD chronologically, from early life, through to their lives now. For example, Dai spoke about HD in terms of his childhood experience with his uncle and the "comical innocence", and Jean described the impact that it had on her becoming a mother. As stated, "The Pervasiveness of HD" was a dominant theme across the interviews in that all the interviewees described key moments, life events, and memories in which HD was always present.

In five of the interviews, "The Selective HD Circle" appeared. The interviewees described how they kept knowledge of their HD status within this circle. The circle was dominated by family members but occasionally friends and healthcare professionals would be permitted in. There was often a sense of shared goals in terms of mutual support as well as collectively helping find treatments and a cure for HD. The relationships were beyond a professional transaction and instead had deeper meaning to the

participants. The impact on who the participants disclosed their HD status to and who was in their circle appeared very consistent across the cases. The circles tended to incorporate close family members, including partners, parents, and siblings but not always children.

The recognition of risk emerged in four of the interviews. This included understanding that NCT involved the potential risk of morbidity and mortality which would not be experienced if they refused involvement in NCT activities. There appeared to be recognition that it was not an established therapy and that it might not necessarily result in a cure. What was apparent, however, was the understanding that unless NCT was trialled with willing participants, there would be a certainty that both the interviewees and their families would go on to experience the full impacts of HD.

Consideration of risk was also a factor in other areas of the participants' lives. There was risk in terms of relationships with others and the impact that HD may have on relationships. Where the interviewees had children, there was a very acute recognition of the risk of morbidity and mortality associated. This included weighing up risk when having children and the likelihood of transmission to any children, and the risk of informing children about HD and the potential of an adverse reaction were acknowledged. Finally, there was some concern expressed about what other people might think of them for having children in the first place and the decision to have children given the high risk of transmission to their offspring. The participants were concerned that they might be perceived as being irresponsible or as risk-takers.

Hope also appeared in four of the interviews in that without therapies such as NCT, there is an absence of a healthy future. As stated, HD pervades significantly into all aspects of life. Hope was not just for the interviewees but also for future generations. NCT offers a chance of avoiding HD thereby limiting the pervasiveness of the disease.

Tabitha captured much of this in the statement:

"…understanding risk does mean something different to somebody who's going to develop a disease that has no treatment or cure. So, I think if you look at people in this group then they're not going to make a decision like a normal person…" (Tabitha)

It was interesting to note that the hope was not always simply about the potential for a cure for themselves. The participants saw HD as impacting their families and even the wider "HD community". It was expressed that HD could be viewed as a transgenerational disease where many of the participants knew people who had had HD, but they also knew those at risk of the disease going forward.

Without NCT and clinical trials, there is an absence of hope, and NCT, although not certain, has the potential to break the cycle of the HD-associated hardships which will continue in future generations.

7.8.2: Divergence

There was a congruence between participants surrounding several points but, it was notable that their descriptions of experiences were markedly different. Examples of this include the way in which female interviewees rarely, if at all, talked about their occupations and instead tended to focus on their roles within the family. The male participants notably describe their roles in society in terms of occupation. When the participants were talking about the pervasiveness of HD, the men focused heavily on their role as a provider and indicated their concern that the disease would prevent them from fulfilling their roles in the workplace. When viewed using the life-world model, for the male interviewees, project was centred around their job and role as a provider, whereas project for the female interviewees was more diverse and involved roles within the family.

Avoiding HD was also described in different ways by the different interviewees. For example, Claire desperately wanted to avoid the impact that HD would have on her as a person. She did not want to lose her personality, the aspects of her life which made her unique, and ultimately, her sense of self. However, when Tabitha spoke about avoiding HD it appeared to centre more on avoiding disability and mortality.

Although multiple participants spoke about the associated risks of undergoing NCT, there was a divergence of what those risks actually were. For the majority of participants, who addressed risk, it was more associated with surgery and also the understanding that NCT, as a procedure, might not work. For Angharad and Robert, however, the risk was more societal. It was clear in their interviews that religion was important to them and that their faith community had strong thoughts and feelings about the use of foetal tissue. For Angharad and Robert, the major risk was one of ostracisation from friends and family due to the therapy being associated with abortion.

Finally, a very notable divergence appeared around the use of humour as a coping mechanism. For interviewees, including Eirian, Jean, and Dai, the use of humour allowed them to better process the impact that HD had on their lives, however, for Tabitha and Claire this was not the case.

Eirian specifically stated that there are times you can *"have a laugh with it",* and Jean described how her whole family uses dark humour as a means of coping as stated however, as stated, this was not ubiquitous.

7.8.3: The Absence of NCT as a Theme

Whilst there was convergence and divergence noted in terms of what was included in the interviews, a surprising aspect was the avoidance or reluctance perhaps of the participants to specifically speak about what NCT was. Instead of discussing the process, the surgery, and the exact details of NCT, the participants spoke about it in vague terms. There was a convergence in that the interviewees instead spoke about the impact that NCT might or might not have. This could potentially mean that they did not know much about the process, however, as Jean pointed out, NCT could just be another new and "magic" treatment which might fail.

It was interesting to note that the participants focused instead on how NCT might impact the various fractions of their lifeworld. Examples include Claire and how NCT could potentially help her maintain her self-hood, Dai and how it could help him maintain project in terms of his occupation, and Eirian describing how NCT had the potential for him to maintain his embodiment.

Figure 7: Layers of themes

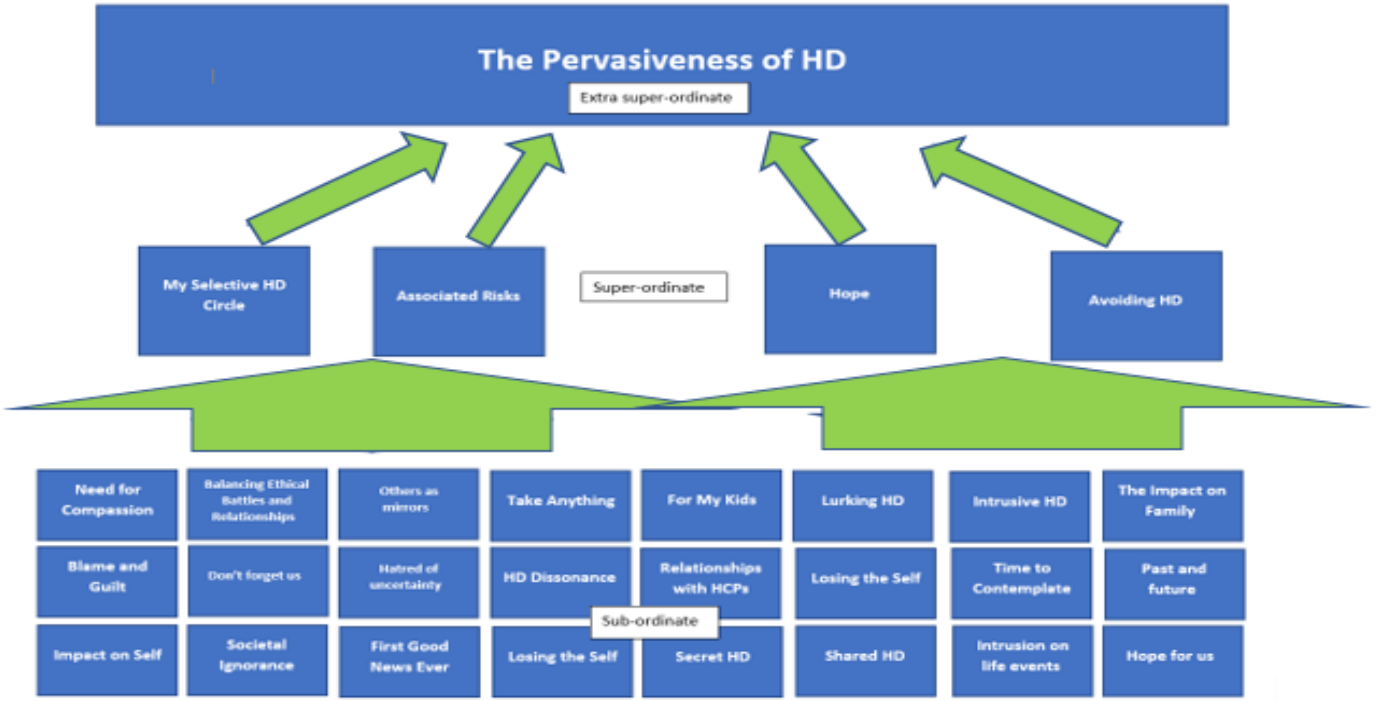


Table 20: Themes, definitions and illustrative quotes

Theme	***Definition***	***Illustrative quote***
Pervasive HD (Expressed in 5 Interviews) ***Extra Super Ordinate***	HD has pervaded into all or multiple aspects of my life. These include life events, memories, everyday activities. Whilst not all-encompassing, HD has a presence.	***"… it's different to what it used to be. You just kind of come across that, but it's something that just ushers in, it's like somebody's open the door on a draught comes in".*** (Dai) ***"…because it's never just one person in the family, it affects all of them even the ones who are positive, uhm I mean aren't positive. Like my brother, I mean was gutted because he was the only one who wasn't married, no kids, absolutely gutted you know, really, really gutted and he went through a phase of setting fire to his skin and things like that."*** (Jean)
My Selective HD Circle (Expressed in 5 Interviews)	Knowledge of HD is guarded. There are selective people who are aware of my HD and I am selective about who I talk to. This includes some family, some friends, some people on a professional level. The majority of people are excluded.	***"He was a young GP coming in and of course you just thought about the bigger picture and I'll hang on but I think I don't like, and I know this sounds horrible but I don't like doctor (new doctor)".*** (Maggie)
Associated Risks (Expressed in 4 Interviews)	I know the risks associated with HD and have seen the consequences. I also have an awareness of the risks of NCT. They are not always physical and can be psychosocial.	***"It's a very serious thing, it's not like a drug trial where you can just take a bag of you know coloured pills and you don't know if you're in the treatment, it's not something you can easily do".*** (Tabitha)
Hope (Expressed in 2 Interviews)	I am aware that there are no treatment options. NCT might offer this. The hope is not just for me but also for others.	***"...you know it's that hope thing again isn't it it's about giving us back some time down the line and together and all I dream, maybe longer retirement together and grandkids. So, you know you just have to do it, you just have to get on with it, be brave".*** (Claire)

Avoiding HD (Expressed in 1 Interview)	I know it's there, but I can't think about it all of the time.	***"She sort of shuts herself away from it because her way of dealing if it was not to have any hope".*** (Dan)

7.9: Conclusion

This chapter has explored the idiographic experiences of each participant. Themes were identified for each individual and grouped into subordinate and super-ordinate. Cross-case analysis was undertaken and patterns between participants identified, the aim being to develop shared themes based on their experiences. A deeper interpretation is then presented in the discussion section. This cross-case analysis led to the addition of a third layer of themes labelled “The Pervasiveness of HD”. This suggests that HD impacts multiple aspects of an individual’s life, influencing their thoughts, choices, and actions. These findings will now be discussed using a theoretical framework and within the context of the literature presented earlier.

Part Four

8.0: Discussion

The last chapter explored the individual, unique experiences of each of the participants and identified themes. Cross-case patterns were also noted (see Table 22). The aim of this chapter is to discuss these shared themes in relation to a theoretical framework and the literature presented in the literature review. I did not want to form generalisations but instead to help provide a structure with which to consider the stories previously presented (Smith and Osborn 2015).

8.1: Identifying a Theoretical Framework

I understood that theoretical frameworks are often introduced earlier in some theses. However, my thought process was that, prior to data collection and the presentation of the findings, I was unsure which theoretical framework would best act as the lens through which to understand the findings.

Multiple theoretical frameworks were considered which might be used to make sense of the data collected in relation to the interviewees' experiences, including the transactional model of stress and coping (Lazarus and Folkman 1984) and empowerment theory (Perkins and Zimmerman 1995; Rappaport 1981).

However, following deep consideration, I thought that Ashworth's (2016) lifeworld framework was most useful for considering the pervasive nature of HD within the interviewees' lives and how NCT might influence this. Consideration of the "fractions" of existence allows for an enriching of the description of the data (Ashworth 2016). It is worth noting that Ashworth (2016) used the term "fractions" because they should not be considered to be independent categories, instead, they are interwoven with overlapping meanings. This complements IPA's double hermeneutic stance in looking at the parts in the context of the whole. Ashworth (2016) suggested that each fraction might hold more weight than others for individuals. This once again complements IPA through the notion of the idiographic rather than the general. There might be commonalities across cases but the personal importance of each fraction can differ between the interviewees.

8.2: HD and NCT within the Lifeworld

Table 23 offers my understanding of the fractions alongside a brief explanation. The table also states how the lifeworlds of the participants can be impacted by HD and NCT. Each fraction will now be explored within the context of the interviewees' idiographic and shared experiences.

Table 21: Fractions and the lifeworld

Fraction and definition	Summary of relationship HD and NCT
Selfhood-Me being an individual. My interests, concerns, priorities etc.	HD influences how I live my life. It will ultimately alter me.
Sociality-My relationships with others.	HD has resulted in both a tightening of some relationships and tension in others.
Embodiment-My body's impact on the life-world.	My HD is hidden in my genetics for now. This will change. NCT could keep it there.
Temporality-Time and my life-world.	An awareness that HD is time limiting and that NCT has the potential to change things.
Spatiality-How I physically navigate geography and its associated norms	HD will be progressively limiting and the ability to adhere to norms will be challenged. NCT might offer a remedy.
Project-How my situation relates to activities to which I am committed.	I am in an undesirable situation with regards to my HD but also a valuable one in order to change things
Discourse-How language impacts on my life-world	The language surrounding NCT is one of hope.
Moodedness-Mood as atmosphere. My feelings within a given situation.	NCT gives hope when we are otherwise hopeless.

Based on Ashworth's (2016) lifeworld model.

8.2.1: Selfhood

For the interviewees, their perception of self was influenced by the presence of the expanded *HTT* gene and the unpredictability of when their symptoms might manifest. Ashworth (2015) suggested that the self, as a fraction of the lifeworld, differs from that of ego and that there is no access to an inner self. Instead, self-hood is the way in which the lifeworld is an expression of activities and preferences as well as the things which are avoided. Within phenomenological research, experiences are explored in terms of meaning such as how lifeworld reflects individuality, identity, and agency, as well as the way an individual senses their own presence and voice within a given situation.

Throughout the interviews, there were examples of HD nestled in the background and its presence increased the complexity of life decision-making. Jean discussed how, in having the HD gene, this led her to initially decide to undergo prenatal testing prior to having children but she eventually decided to forgo it. Predictive testing or prenatal diagnosis (PND) has been used for testing genetic neurodegenerative disorders in the UK since 1988, with direct variant testing becoming available in 1993. People can utilise this technology to avoid having offspring who will develop HD. Whilst Jean ultimately avoided this step and went on to have children without using (PND) it could be argued that HD, as a presence, complicated the activity of becoming a mother, adding complexity and stymieing her ability to live her life as she wished to.

What was clear was that whilst Jean wanted to be a mother, HD prevented her in being a mother in the way that she wished. HD had, therefore, imposed itself on her role, lurked in the background and, by the emotion shown and words demonstrated, had left her in a juxtaposition. The mothering role is synonymous with protection but, in Jean's eyes, by having children, she had put them at risk.

Jean was not unique in making this decision as people who carry the HD gene can convince themselves that it would be safe to have children as exemplified in Quaid et al. (2010). This is because they believe that research is progressing rapidly and a cure, or at least a treatment, would be found in the near future. Consistently with this, Jean appealed to this hope that science could "fix" HD in the future for everybody, including her own children. Arguably, this helped her sense of selfhood and the decisions that she has made regarding having children.

The presence of HD within the family can impact an individual's ability to express themselves within the world thereby impacting the self. Claire also identified that self-hood would, in the future, be severely impacted by HD. This is consistent with Wieringa et al. (2021) who identified that people who carry the expanded *HTT* gene can feel limited by time, wish to stall time, and feel the need to make the most of time.

Having witnessed her father's symptoms, she expressed how her own ability to undertake activity, express preferences, and, ultimately, maintain her sense of self within the lifeworld that would be impinged by HD. She used the frame of eating Christmas dinner as a way of describing her understanding about what would happen to her. She recounted how her father had once had a good appetite but now his ability to eat had gone. Arguably, her memory of her past was being used as a window into her future.

When considering Claire's disclosure in relation to Lazarus and Folkman's (1984) transactional model of stress and coping, it seemed that Claire had undertaken primary appraisals surrounding perceived susceptibility, perception of severity, and personal relevance. Both for Claire and other participants, witnessing family members' inevitable decline seemed to facilitate this appraisal. The methods of coping with this varied from avoidance to active participation in research, and it appeared for many that NCT and the hope it gives offered a measure of coping with HD. This was supported by Etchegary (2009), who suggested that having faith in science was a common strategy used by people when situations are beyond their control.

Some of the interviewees saw NCT as a means of maintaining self-hood or at least slowing the loss of self. Dan often referred to the development of symptoms which he hoped that Claire would avoid. It appeared that Dan and Claire felt that there would be an inverse relationship between symptom development and selfhood. With each symptom that developed, Claire would lose a part of what she

was. If NCT could prevent the development of symptoms, it would, therefore, reduce the loss of self. Arran et al. (2012) argued that interventions that change illness perspective can reduce psychological stress. Therefore, if NCT can change the perception of HD for people, this could potentially have a positive impact for people. This was also noted heavily in Angharad and Roberts' interview.

When experiencing the world, people see their own projects, cares, and concerns. In essence, the lifeworld is composed of the objects and events that matter to the individual. Throughout the interviews, it was seen that HD bleeds into the relationships, aspirations, objects, and events which matter to individuals. HD, undesirably, pervaded all aspects of self-hood and many saw NCT as a means of alleviating the impact. Arguably the removal of HD, potentially by NCT, would result in a change of self-hood for the interviewees.

8.2.2: Sociality

Ashworth (2015) outlined how other people are a central part to the lifeworld primarily due to their impact on our self-hood. Sociality is essentially about relationships with others. This was particularly noted in the "My Secret HD Circle" theme.

Self-identity is dependent on others and is maintained by interactions. Referring to Husserl's Cartesian meditations, Ashworth (2015) described how people understand the essential characteristics of another person as being conscious or minded like themselves. Also, that they know the world is intersubjective but that reciprocity can take place and perspectives can be shared.

In many of the interviews, it was acknowledged that shared perspectives exist. The interviewees spoke about shared perceptions, goals, and projects amongst others in close-knit, almost exclusive, circles. For example, Tabitha spoke about the fact that the entire HD world is waiting and desperate for something which will help. There was not just a sense of an individual longing for therapy development but a shared HD community, eager for the disease burden to be lifted.

In many of the interviews, this appeared to give validation to their own individual perspectives and resulted in relationships with shared goals and views. Much of the research surrounding sociality in HD has focused on negative impacts amongst families and groups (Forrest Keenan et al. 2007; Aubeeluck 2012), however, this research has identified that tight-knit circles are often implemented as a means of supporting each other. This is supported by Downing et al. (2012), who suggested that emotional support and planning for the future together were common mechanisms used for coping with HD. Exuzides et al. (2020) even identified that discovering that closer relationships can form following the identification that a loved one carries the expanded *HTT* gene.

Jean also discussed the shared goals of caring for her mother and alleviating the impact of HD in her family, even amongst those who were not genetically positive for the disease. Jean spoke about the self-harm that her brother had experienced, including burning his own skin, as a means of him sharing the suffering. It appeared that there was a tremendous amount of guilt felt by Jean's brother and that, even though he was genetically negative for HD, he felt a great degree of vicarious suffering. As per the title of this thesis, Jean did not just want NCT to be a means of treating her and those with the gene, she felt that NCT could offer alleviation from suffering for everyone within her circle.

Overall, there appeared to be a sense of protective collectivism. She described the inclusion of HCPs into this circle and it was echoed in other interviews that this inclusion was dependent on trust. Pilgrim et al. (2011) argued that trust in healthcare is complex because it is both a personal and social matter. Trust, however, can be contradictory because it involves risk to autonomy when vulnerable, whilst also having the possibility to increase autonomy. This was reflected in multiple interviews with the interviewees both describing the need to develop trusting relationships with mutual goals as well as the process of how trust can be obtained by HCPs.

Maggie appeared to be suggesting that there needs to be a reciprocity of perspectives between both HCPs and patients and vice-versa. Røthing et al. (2016) also described the need for family/people impacted by HD to establish trustful relationships with HCPs. This notion was echoed in many of the other interviews, including Angharad and Robert, who suggested that professional relationships were a key factor in research participation and that there must be a sense of shared goals.

Throughout the interviews, there was discussion of shared ideas and goals, but it was Angharad and Robert who indicated a concern about societal risk. They acknowledged that they had shared perspectives between them but that others might not share their perspectives. They referred to a potential for familial and social exclusion based on differing opinions, particularly surrounding the use of foetal tissue. It was suggested that this might even impede disclosing their actions to others.

Etchegary (2007) stated that illness can also lead to predicted social rejection and fear responses from others within a social group. This stigma can be real or perceived, with the former referring to actual social rejection and the latter meaning fear of future discrimination. Angharad and Robert described experiencing actual social rejection related to decision-making around the decision to undergo embryo selection and invitro fertilisation. They described how their family had questioned their morality and how, moving forward, having NCT using foetal tissue might lead to ostracisation from their religious community. Stem cell research has been debated globally from the perspective that the development of innovative therapies for the treatment of disorders is of upmost importance, but on the other hand, there is the moral argument against the use of embryos. Angharad and Robert are

from the Christian faith and Charitos et al. (2021) state that, according to most Christian doctrines, from the moment of conception, humans are psychosomatic units which then become free due to the will of God. Therefore, from the moment of conception, a foetus, is, therefore, a potential person. Therefore, despite the fact that Angharad and Robert had no real ethical issues with NCT, navigation and socialisation within their religious community could be problematic in future. Again, for this additional reason, secrecy might need to be maintained within a close-knit circle.

Others, including Dai, spoke of perceived and anticipated social stigma but many of the interviewees either spoke directly about or alluded to the need for a secret circle, and it was repeated throughout that HD was not disclosed to certain groups. Although not fully revealed, it could be suggested that these circles are created not only for support but through a fear of social stigma surrounding carrying HD.

As stated, however, a clear description or explanation of the necessity for these circles was not identified and this is an area which would warrant further exploration.

8.2.3: Embodiment

Embodiment relates to the body within the lifeworld which for all the interviewees would become compromised. The interviewees considered how their physical bodies would be expressed and perceived by others within the lifeworld.

In multiple interviews, embodiment was either spoken about directly or it could be interpreted as being spoken about. Tabitha spoke about how her own perceptions of her body, with knowledge of HD in her family, led to her being initially tested.

Hagberg et al. (2010) suggested that knowledge of genetic status can be negative for some but positive for others, with Hamilton et al. (2005) identifying that knowledge for some is dependent on an individual's perceived need to plan for the future. Leotoni (2006) described how discovering genetic status can lead to the formation of new sense-making. People anticipate their illness, might experience their own bodies in new ways, and look for symptoms in everyday life via being in a state of "neither health nor disease" (Hagen 2018). This pervasiveness of HD through people's own sense of their body was present in many of the interviews.

Leder (1990) suggested that as individuals, we have parts of our bodies that we have no sensory experience of as they are hidden in corporeal depths and are, therefore, phenomenologically null points. However, this stance can be interpreted as doing to a disservice to people with HD in that, although the abnormal gene itself is corporeal, the experience of having a pre-manifest, genetic disease is not. The expanded *HTT* gene itself is not visible in everyday life but the implications of the

disease, be they social, psychological or emotional, are present – even prior to testing or the physical manifestation of the disease. Arguably, even the awareness that the expanded *HTT* gene "might be present" is an experience in its own right; it is not hidden and is certainly experienced.

Leder's (1990) position contradicts with the data in this thesis in that throughout the interviews there was a very real understanding of the presence within their bodies and the adaptations that have had to be made. Examples include Jean's discussion of motherhood, Claire's vision of eating and drinking in the future, and Dai's concerns about others judging his physical ability to work. Instead, in agreement with Hagen (2018), it would appear that for the people in this study, the HD gene is very visible and its abstract qualities are reconfigured by people and pervade their lived experience.

The spinning top metaphor stated by Dai exemplifies this point. Even awareness of the HD gene can lead to a sense of infirmity. Dai's metaphor appeared to create a response beyond descriptive language and attempted to elicit a sensation of instability and dizziness in me, the listener. It emphasised the notion that experience and sensation are felt way before the disease manifests.

The impact of having the gene on how people's physical bodies are expressed and perceived by others within the lifeworld was addressed in that knowledge of the gene impacts the participants' subjective perception of their own bodies. Frustration was identified surrounding the physical problems which HD would bring. It was highlighted when Maggie was discussing a challenge to the embodiment of Eirian. She described how the HD clinician had questioned Eirian's suitability to be driving and how it should be Eirian and Maggie who judge his physical capabilities, as it was they who knew best. Again, this alluded to close-knit circles of people who knew their situation and outsiders who did not.

Preservation of the physical body, potentially by NCT, was not directly addressed but alluded to. As with Lundin et al. (2018) it appeared that the clinical trial of NCT provided a means of counteracting the involuntary passivity of the disease and provided hope that physical embodiment can be maintained. Whilst participants, including Claire and Dan and Angharad and Robert, saw NCT as a means of preserving embodiment, it was interesting to note that Eirian did not. Eirian stated that he did not care whether there was a physical or cognitive benefit. The opportunity to participate in a trial of NCT went beyond that as was instead one of legacy, that it was not to preserve his own embodiment but potentially the lives of his children and grandchildren. This echoes Gog et al.'s (2013) findings that personal meaning can be found through active participation in research. It also resonates with Cleret de Langavant et al.'s (2013) suggestions that the priority is not hope for a personal cure. Instead, some people with HD take part in research "for scientific progress", "for my children", and "helping others".

However, the need to preserve the self and add more quality time to life suggests that, for some interviewees, NCT might allow them to pursue aims and projects that might have been lost to HD.

8.2.4: Temporality

Temporality in the context of this study is the passage of time with HD. It suggests that any experience is grounded in history and past experiences, which the person both consciously and unconsciously view as being relevant (Ashworth 2016).

Jean expressed this when describing how HD had pervaded multiple timepoints within her life. She described a changing attitude surrounding HD, which has developed and evolved with time and contemplation.

This conflicts somewhat with Ho et al. (2011), who suggested that, across all stages of the disease, there were no significant emotional and social changes. Concerns about cognition rarely featured at all pre-manifestation stages in Ho et al.'s (2011) findings but primary data from this study and others suggested changes do occur throughout the timeline of the disease.

The literature review explored the process surrounding "Finding Out" about HD. Forrest Keenan et al. (2009) described how it can alter life expectations. Life with HD will be abnormal and take a standardly perceived pathway. Jean, however, expressed changing emotions over time. In expressing that she was aware of what was to come, it appeared that growing exposure to the disease within her family circle had resulted in a concurrent growth in the fear of the disease. A direct relationship between exposure and worry might, therefore, exist in some people.

Dai, however, appeared to offer an alternative view of an unchanging and slow pathway towards the inevitable. His use of a metaphor of a car "trundling" along, slowly moving down a road, suggests inevitability. Dai appeared to be describing a linear and bumpy route over time with no option, currently, to divert.

Downing et al. (2012) explored people's coping strategies with HD and these included planning for the future and emotional support. Emotional support was key for many participants, however, as recognised by Downing et al. (2012), denial and behavioural disengagement were also a means of coping and adaption to having the gene.

The latter was noted in the interview with Claire. Initially, she described an attitude of avoidance and denial of HD, however, it appeared that the emergence of NCT had changed this and that her view of her present and future had been altered. NCT had given her hope for a future which had once seemed lost.

The interviews suggest that HD does impact both past and future life events. It can manipulate life events and it influences the ability to plan. Although NCT has no ability to alter past life events, interviewees felt it could impact their ensuing lives.

8.2.5: Spatiality

Spatiality is an individual's understanding of the geography they need to traverse and the ways in which to act within a given context (Ashworth 2015). Geography in this context is not necessarily physical and attends to the social norms and meanings associated with places; it is also about the spaces that people occupy and how they move within them. The participants described how difficult life might become for interviewees and that NCT might provide a means of helping them navigate their lifeworld.

This was particularly noted amongst the male interviewees in that they particularly expressed senses of normality and abnormality. Dai, in reference to his uncle, identified that his uncle was different and that this was even noticeable as a child. Dai described his uncle's "clumsiness" in performing everyday activities such as getting dressed and making a cup of tea. Dai described that, even as a child, he viewed his uncle's movements as being different but he appeared to be stating something beyond the words spoke. Dai was describing how even children could see difference and abnormality in his navigating of spatiality. It was interesting to note that the movements were viewed as not something to be concerned about or pitied but instead they were more associated with comedy. There was a suggestion Dai felt that, in the future, he might also be a source of amusement for others.

Seemingly aware of the physical impacts of HD, both Eirian and Dai appeared to want to avoid the physical symptoms and even discussion of HD, particularly in the world of work. They both kept HD secret and within a specific circle of people. Dai indicated that he felt people might judge him and that it might impact his image as a professional. He described an occasion where he nearly and unintentionally told a client about his HD. This echoes Januario et al. (2010), who suggested that both the mental and physical dimensions of health amongst people with HD and patients' perceptions of their QoL are decreased, particularly by functional ability.

Claire also highlighted the fraction of spatiality by describing an ever-shrinking world in which people occupy. When Claire talked about when her father was in the late stages of the disease, she described him as being stuck in a chair. The implication is that not only does HD initially make navigating the world difficult but it slowly reduces the spaces one can occupy and the activities one can undertake. Claire and Dan hoped that NCT would result in no new symptoms, therefore, Claire's ability to navigate the world would remain smooth and unimpeded across her life.

The interviewees understood that HD will impact their ability to navigate their physical and social worlds. For many of them, having witnessed others experience physical difficulties and break social norms gave them a window into their own futures if a cure cannot be found.

8.2.6: Project

Project is a person's ability to carry out the central activities to which they are committed. Ashworth (2016) described how everything in the lifeworld can be linked to this. Ashworth (2016) described how humans have fundamental project in terms of which actions can be understood. This was, however, felt to be far too encompassing and instead we should focus on how a situation can relate to an individual's ability to undertake and complete activities to which they are committed and which are regarded as central. Throughout the interviews, participants expressed concerns about the loss of project, from seemingly minor tasks like making a cup of tea to the loss of occupation and even intimate relationships.

HD appears to have permeated into many of the participants' life goals and ambitions. In two interviews, the impact on becoming, or thinking about becoming a parent, was identified. Although in Jean's case, she had gone onto have children, Angharad and Robert were unsuccessful. In having HD, they had opted for pre-plantation genetic diagnosis (PGD), which had failed. The project of having a family was, therefore, shrouded by the presence of HD. Even though Jean went on to have children, HD appeared to cast a shadow of the genetic risk potentially being passed on.

Both Dai and Eirian expressed concerns surrounding the impact the HD might have on their occupations. Eirian had told only his boss, fearing that co-workers would not view him in the same way and Dai attempted to hide the fact that he had the gene for HD. For Eirian and Dai, the experience of HD, even pre-manifest, seems to elicit concern that others will not view them as capable of fulfilling roles and tasks.

Dai and Claire also described the desire to grow old together, joking that they want to spend their children's inheritance. Again, this could be viewed as project. Their long-term goal was to have a long and fulfilling relationship with each other but HD was the major obstacle in preventing this. Claire suggested that NCT could help achieve this goal and, although she understood the risks concerned, the chance of fulfilment could justify this.

That HD could impede a significant goal in their lives appeared to suggest a sense of unfulfillment, however, research and clinical trial surrounding HD appeared to conversely provide project for some of the interviewees. For some, participation in research provided meaning and a goal, the aim of which was to cure or at least manage HD. There was a suggestion that this was almost globally felt amongst people with HD and particularly linked to the theme of hope.

As stated, project can be linked to all fractions, and it is suggested that participation in research offers hope of maintaining the self, embodiment, temporality, and spatiality. The emergence of NCT appears to have altered the discourse surrounding HD as well as the mood.

This was also noted with Jean, who suggested a familial approach towards combatting HD, especially amongst those who are not affected genetically. Once again, this linked to the theme of "My Selective HD Circle".

8.2.7: Discourse

Ashworth (2016) described how there are substantial arguments in favour of exploring discourse and essentially that our experiences are shaped by discursive constructions. Discourse is also concerned with linguistic patterns and how they can transform in a variety of situations.

The discourse surrounding NCT appears to have shifted the interviewees' perceptions of HD over time. This is particularly related, again, to the theme of "Hope". Jean's interview was characterised initially by a description of past negative experiences but the emergence of NCT had resulted in the emergence of a sense of hope. Jean described the emergence of previous experimental therapies as being magic, implying the absence of certainty. However, regarding NCT, Jean felt that the tone and language used by professionals had changed to therapy, which was more grounded in reality. This appeared to give Jean a greater sense of hope surrounding NCT compared to past therapies.

It appears that the emergence of experimental therapies like NCT alter THE discourse and that HD could evolve from being viewed as fatalistic and that it offers options within the lifeworld which might have previously been absent.

When describing HD, Dai in particular seemed to demonstrate a change in discourse surrounding the disease as more knowledge had been gained about HD over time. From the description of his uncle's "comical" behaviour decades ago, Dai spoke in more contemporary and formal terms when discussing HD. Dai was particularly skilled in projecting his experiences and emotions through the use of metaphor. Dai's metaphors moved beyond linguistic description and allowed me to touch upon the sensations he felt. Whether they were that of a dizziness, feeling unsteady, or that of confusion, Dai's discourse stood out as opening a window into the essence of his experience.

Another important linguistic tool was used by Robert in his multiple incorporations of "feel the love". The use of this meme, a unit of cultural information which is spread by imitation, conveyed an instant message for the need for the inclusion of spouses. Although there is recognition that partners and spouses have adverse experiences when their partner has HD, Robert conveyed a sense that people in relationships often come in units. Robert suggested that participation in clinical trials moves beyond that of the person receiving the transplant and that, he as a husband, would also vicariously be participating in any research trial. This was echoed by Dan and Maggie who indicated that, as partners, they would want to know about the process, be told about expectations, outcomes, and recovery as trial activity would impact their lives. These partners suggested that a change in discourse is required

surrounding clinical trial participation and that consideration of family and partners should be considered when devising protocols.

The technical language surrounding NCT used was understandably restricted amongst participants, with the partial exception of Tabitha. This seemed in partial opposition to Wittgenstein's (1921) claim that "the limits of my language are the limits of my world". Despite the limited use of direct terminology related to NCT, there was a sense that there was awareness of the risk associated with it and that, despite the hope, there was pragmatism. There appeared to be an understanding that the therapy was experimental and that success was not guaranteed. This sense was also reflected in Lundin et al.'s (2016) study of attitudes surrounding gene therapy which also identified a pragmatic attitude amongst participants. In this study, participants suggested that even if a cure was not found, useful information would be gathered.

Discourse surrounding HD appears to have moved on with time, from descriptive terms about a person's behaviour towards a more scientific language. With NCT, there appears to be further opportunity for discourse surrounding HD, moving from fatalistic to optimism and hope.

8.2.8: Moodedness

Heidegger described "being-there as a state of mind" and that the lifeworld is punctuated by many fluctuating moods. Rather than simply an emotional state, mood considered as atmosphere (Ashworth 2015).

In many of the interviews, it appeared that the atmosphere surrounding HD had shifted. As stated previously, there appeared to be an emergence of hope, whereas in the past there had been none. It appeared to suggest, however, that, as well as change in atmosphere, the potential of NCT had had an impact on individual mood and switched people from a sense of pessimism to cautious optimism underpinned by "hope".

Jean described in detail the experiences of her mother and how it had created a mood of fear and worry surrounding HD, however, NCT had created an atmosphere of hope amongst her and her family. The shift from a "magical" hope to one grounded in science indicated a more positive atmosphere surrounding NCT when compared to past clinical trials within HD.

Claire and Dan also described a shift in mood from bleakness to one of optimism and hope. They described the movement from an expected decline in their lived experience to a new era of optimism. However, it was notable that the participants often shifted from hope to realism. They recognised that this is a trial therapy and that success is far from guaranteed. The participants acknowledged that

there would be extensive risks, however, many felt that due to the emergence of NCT, there is the potential for a shift in attitudes and mood around HD.

It appeared to be understood, however, that the development of successful treatments for HD was dependent on the partnership between affected individuals and the healthcare and science community. This finding was repeated by Lundin et al. (2016).

8.3: Summary

The aim of this section was to discuss the individual and shared lived experiences of the interviewees using Ashworth's (2015) lifeworld model whilst relating the findings to the available literature. The narration of the experiences and opinions were that of the interviewees, however, IPA recognises the double hermeneutic and the role that I had in interpreting their experiences. The interviews allowed for exploration, however, it is recognised that they are limited by what was declared.

Theoretical frameworks can be used to explain and understand phenomena as well as challenge and extend knowledge. The theoretical framework has structured the findings of this thesis whilst connecting it to the literature. Collins and Stockton (2018) suggested that the use of a theoretical framework allows for the intellectual transition from mere description to describing the complexity of phenomena observed. It specifies which key variables influence a phenomenon of interest and highlights the need to examine how those key variables might differ and under what circumstances.

The framing of the findings within the lifeworld context meant that the interviewees' experiences could be set against the available literature to find both concurrence and dissimilarities and explore the themes identified. Agreement and disagreement were identified both across cases and across the literature. Whilst every lifeworld was unique, there appeared to be shared perceptions, understanding, and sentiments felt by many.

Examples of similarities include that of project in that research participation provides project. It gives a shared sense that, by active participation, treatments may be found to combat HD. Preservation of selfhood differed, however. For people like Lisa, NCT offered hope that her self-hood would be maintained, whilst for Eirian, the preservation of self was less important and participation in NCT research was more about his role as a provider.

HD pervades multiple aspects of the lifeworld, influencing the sense of self, embodiment, temporality, and sociality. The interviewees described how developing knowledge of their genetic status, as well as witnessing other's experiences of HD, has impacted their perceptions of self, familial roles, ambitions and projects, and views of the future. Some of this is consistent within the literature presented in the literature review.

NCT appears to provide a sense of hope that this pervasiveness of the lifeworld can be alleviated. This has potentially led to a changing view of their HD.

The conclusions of the thesis are presented in the next chapter.

9.0: Conclusion

9.1: Introduction

The previous section explored how the voices of the people recruited are located within theoretical frameworks. The thesis will now conclude with a description of how this original contribution can impact healthcare practices. Prior to this, however, the impact of the researcher on the data will be declared, alongside limitations to the research.

9.2: Reflexivity

Reflexivity can be seen to be an integral part to experiential qualitative research (Shaw 2010). I understand that my ambitions and feelings will have impacted the topic of investigation, methods used, findings, and how they were framed and communicated. It is understood that other qualitative researchers might have come to different conclusions due to their own individual stances, however, IPA emphasises that there is an active role for the researcher within the research process (Smith and Osborn 2002). It is, therefore, important that an examination of the researcher and their perspectives are laid bare. To capture my thoughts and feelings throughout the process, I maintained a diary.

My interest in the topic has emerged from both professional and personal experiences. Being a registered nurse and having worked with people with neurodegenerative illnesses and in clinical trials, this undoubtedly fuelled my interest in the topic. Whilst trying to finalise the thesis topic, I was fortunate enough to be approached to explore the perceptions and understanding of people with HD surrounding NCT as the TRIAL study was in planning. Despite this, I was mindful that the motivation for the research should always be about the participants in this study and not be subject to external time constraints. This ensured that justice was given to the voices of those kind enough to participate within the study.

At times, I had difficulty expressing my thoughts in a communicable manner, mainly over complicating language, resulting in multiple revisits to the text. I also initially found it difficult not to immediately try to interpret the data and to act on it as I would in clinical practice. Instead, I needed to revisit the interviews and allow the interviewees' voices to be heard rather than my own.

The interviews were held at mutually convenient times and (apart from the one over Skype) they were undertaken in the interviewees' homes. I was nervous; however, I felt a sense of excitement to be

undertaking data collection. As the interviews proceeded, I grew in confidence, but this was impacted when I inadvertently mentioned that one of Jean's children looked just like her. This led to an instant sense that I was inadvertently implying a strong genetic likeness whilst discussing HD. This resulted in a slight loss in confidence. On reflection and with advice, I was reassured that this was a "normal" phrase.

Whilst the interview on Skype with Tabitha resulted in a great deal of rich data, the mechanism was quite restrictive. The sense of atmosphere, body language, and facial expressions were more difficult to read, and I felt that the interviewer/interviewee relationship was harder to establish. In future, I would treat this means of interviewing with caution.

The interview schedule was formed to elicit data on understanding NCT, however, I sometimes became very aware that the interviewees would often appear to discuss abstract topics away from the question. This led to a sense of personal tension in both wanting to hear their voices but also wanting to them to address the topic. It is with hindsight and by reviewing the transcripts, however, that I realised that they were kindly supplying me with important data which did relate to the topic and, as a novice researcher, I was attempting, again, to analyse rather than just listen to their voice. I have now developed a more pragmatic attitude.

I also sometimes found tension between my role as a researcher and as an RN and became concerned at times that I was being viewed by the interviewees as a clinician rather than a researcher. I also felt, and in some respects still do feel, a strong desire to "check up" on the interviewees to explore their circumstances and welfare. I realise that this is consistent with my role as an RN, however, it is not consistent with research practice. Nevertheless, I hope that this research will be of benefit to them.

I did, however, note comparisons between IPA, as a methodological approach, and aspects of nursing. These included the nursing process being analogous to hermeneutics and idiography as having crossover aspects with patient centeredness. This was helpful in easing the transition from nursing practice and theory to researcher.

9.3: Validity

Despite the popularity of qualitative research methods, there remains debate surrounding how quality can be assessed. As established in a previous chapter, quantitative and qualitative research are based on very different paradigmatic viewpoints, and it is the positivist stance which often dominates, leading qualitative research to be, incorrectly, evaluated by the same criteria (Yardley 2007).

LeCompte and Goetz (1982) suggested that external reliability is difficult to achieve due to the impossibility of freezing social settings and circumstances. As a result, replication will then not achieve

the same results as the original research. Internal reliability is said to increase when there is more than one observer, and it could be argued that this was achieved via supervision. Also, rather than bracket, IPA embraces the interviewer, arguing that objectivity is never the aim. Internal validity is a strength of qualitative research due to the prolonged participation with the group (LeCompte and Goetz 1982). The iterative nature of IPA in reading and re-reading the data and immersing myself within the transcripts and voice of the interviewees allowed for the development of congruence between observations and theoretical concepts. External validity is also an invalid term, as the aim of qualitative research is not to generalise; instead, Geertz (1973) stated that "thick description" should occur whereby rich accounts are provide by researchers, which allow others to make judgements about the possible transferability to other areas.

Instead, Yardley (2007) suggests that different criteria are required. Sensitivity to context was ensured by ensuring transparency. By declaring the socio-cultural and linguistic context of the research and my interpretations, this allowed sensitivity towards the data. This transparency, hopefully, demonstrated a lack of imposing my own preconceptions on the data and allowed for the emergence of meaning from the voices of the interviewees. Commitment and rigour were demonstrated via in-depth engagement throughout data collection, a rationale for methods, and a demonstration of how the interpretations were undertaken. In addition, a degree of triangulation was achieved via supervision and auditing was demonstrated by the clear laying bare of each stage of the research.

Nizza, Farr, and Smith (2021) clearly and concisely outlined these quality markers and summarised the criteria which are the hallmarks of high-quality IPA research. These start with the construction of a compelling and unfolding narrative whereby the analysis demonstrates a clear and coherent story. This is supported by selectively identifying and interpreting extracts from the participants. Careful consideration was given to conveying the interviewees' voices and stories, both within and across the themes, and quotes were presented which captured their perspectives. The themes presented are also representative of the meaningful and important experiences described by the interviewees and, throughout this study, close analytic reading of the participants' words was undertaken. The quotes presented were analysed to explore their significance prior to presenting them in this thesis. I carefully considered their meaning within the context of the entire interviews. Finally, as outlined by Nizza, Farr, and Smith (2021), I carefully attended to convergence and divergence, systematically comparing and contrasting the experience of the interviewees. As demonstrated in this thesis, patterns of similarity were noted across the interviews as well as clear identification of idiosyncratic characteristics and experiences.

The strengths of the research have been discussed; the limitations will now be described.

9.4: Limitations of this Research

The limitations of this study can be identified as being in two categories; the researcher and the methodology.

As a novice researcher, this was a learning experience. There were times when I became impatient with the process and sought to leap ahead, resulting in a missing out on detail and meaning. This resulted in extensive re-reviewing and re-writing; however, this lesson has been valuable.

It is acknowledged that personal and professional experience will have influenced the observations and conclusions presented, however, IPA embraces this. What is conceded is that others with different backgrounds might have had different interpretations. However, to remove suggestions of bias, the findings are presented in a way which demonstrates their grounding in the data. The data is also presented as an honest account, detailing my thoughts as they presented. Again this, hopefully, allows the reader to gain insight into the interpretative process undertaken.

Methodologically, this was a small study. It was never intended to result in generalisable findings, although themes and patterns emerged which potentially have relevance to practitioners.

The sampling was purposeful and the interviewees' motivations for participating in this study were not explored, therefore, there is potential for an unidentified bias.

It is also a potential that in asking people to participate, I had exposed them to the concept of NCT and this had led them to undertake research prior to the interview. However, none of the participants expressed this and it appeared that their sources of information were not the PIS. Despite this, it is difficult to envisage how they could be asked their opinions on a topic which I had not presented to them as part of the consenting process.

As stated, my inexperience might have resulted in a protracted study length, an initial misunderstanding of data and approaches, and methodological imperfections. However, the professional doctorate has been an "apprenticeship" which will hopefully be built upon in subsequent studies.

9.5: Original Contribution

The aims of this research were to:

- To critically explore the thoughts, feelings, and understanding of NCT amongst people with pre-manifest HD within the context of their own lives.

- To explicitly give voice to people with pre-manifest HD who might be approached to participate in clinical trials of NCT, in order that associated research and healthcare can be patient-focused.

It was identified that, although the thoughts, feelings, and understanding of NCT and HD differed, there were shared themes among interviewees. These included:

- A point that does not appear in the literature base but has been identified in this project is that people form selective and tight-knit circles surrounding their HD. People choose carefully who they allow into this circle and even who they declare their HD to. Previous research has pointed to care within the family and fear of stigma, but this study indicates something beyond this. Erwin et al. (2010) and Boileau et al. (2020) said that people with HD experience stigma, therefore, it makes sense that people are reluctant to declare their genetic status. This study indicates that to protect themselves from stigma, the participants form informal groups and people outside of this circle are not informed of HD status. The participants suggested that this circle centres around the partner and family grouping but that healthcare professionals can "become members" once trust has been established. For them to want to actively participate in healthcare services and research, and in particular clinical trials where risk is a factor, it is important that people with HD are approached, recruited, and looked after by healthcare professionals who are in their circle.

  The UK Policy for Health and Social Research Framework (2020) sets out the principles of good practice in the management and conduct of health and social care research in the UK. This framework is designed to promote the interests of patients and protect their safety by outlining ethical conduct to support and facilitate high-quality research in which research participants and the public can have confidence.

  What appears to be absent from frameworks governing research, however, is the importance of the partners of research participants. Clinical trial participants are essential to conducting research and without them we would be unable to advance knowledge and improve clinical care (Terry and Terry 2011).

  This thesis described a feeling amongst people with HD and their partners that the importance of wives, husbands, and partners is forgotten in the design and conduct of clinical trials. Trials, which include surgery, ongoing risk such as immunotherapy, and involve risk of death or disability undoubtedly impact the close family members of trial participants. Partners will inevitably be involved with support and rehabilitation so there is a sense that they should not be forgotten during trial development. This research indicates that, should

the participants wish, the involvement of partners is fundamental and should be considered the gold standard.

- The UK Medicines for Human Use (Clinical Trials) Regulations (2004) are intended to protect the rights, safety, and wellbeing of research participants. As wellbeing and long-term safety, in many cases, involves family and loved ones, this should be reflected in recommendations for good practice. I recommend that clinical trials and research guidelines be reviewed to include the, often essential, role that partners and family have in the research process.

  The importance of co-production and coproduced research has grown steadily in the last two decades, particularly in light of the "Nothing about us without us" declaration (Charlton 2000).

  Work has been done establishing principles and co-production has been demonstrated to have worked well in qualitative research where there is methodological flexibility (Hickey et al. 2018). However, clinical trial activity is often characterised by strict methodological guidelines, which can make co-production challenging in this area of research.

  Examples of where clinical trials have been research have traditionally fallen short surrounding co-production are ascribing low status to people's lived experiences, thereby minimising or ignoring power imbalances which minimise service users' voices (Greenhalgh et al. 2015). As evidenced in this research, there is often a failure to recognise the significance of the patient-clinician/researcher relationship as well as a failure to realise the value of trial participants' support networks.

  To combat these deficits, Goldsmith et al. (2019) suggested the creation of lived experience panels which meet to review trial design and activity, as well as clinicians and researchers writing reflective journals.

  This research has demonstrated an absence of a lived experience input into HD-related clinical trial activity and implementation of these panels could potentially facilitate a greater focus on the personal and familial needs of trial participants. It would then need to be measured as to whether greater appreciation of patients' voices leads to trial design adaptation and subsequent impacts on recruitment and retention of clinical trial participants.

  Goldsmith et al.'s (2019) suggestion of a reflective diary or journal writing done by clinicians and researchers undertaking trials is also an interesting suggestion. However, based on the findings of this research, it could be suggested that a structured reflective tool be used which asks the writer to consider the thoughts, voices, and familial and social needs of clinical trial

participants. This would allow for further appreciation of the lives of the clinical trial participants and also addresses the feelings expressed by the interviewees that trust needs to be developed and that they would like the researchers to know and understand their needs. If this can be achieved, it might facilitate entry into the "Secret Circle".

- Reflecting on relatives who have passed away is a window into to the future. Many people who have the HD gene have witnessed and/or cared for relatives who have developed symptoms and gone on to need extensive care. The participants appeared to use their memories of impacted relatives as a way of predicting their own disease pathway.
- NCT, although not clearly understood by all participants, has brought with it a sense of hope and might even have impacted the atmosphere surrounding the disorder. Historically, there has been a sense of the inevitable and that HD will lead to disability and death. NCT has the potential to transform the way that people view HD and their views on the trajectory of the disorder, potentially avoiding the disease. Hope, however, is not blind optimism. There is a sense that hope in NCT should be treated with caution. There is an awareness that it involves risks, is experimental, and ultimately might not have a significant benefit. The mere fact that potential therapies and cures are now being discussed, however, is having a transformative attitude on the discourse surrounding HD.

9.6: Further Research and Potential Implications for Practice

The research has several considerations for research, education, and practice. These include:

- The interviewees maintained a close circle of people. They kept discussion and knowledge of their HD within these circles. The rationale for this strategy can be presumed, however, the specific reasons for this were not captured. Further research needs to be undertaken on why they do this.
- For HCPs to be included in an individual's circle, relationships of trust need to be built. People often feel more confident with those with whom they already have an established relationship. The nature of this trust, alongside factors which encourage or discourage trusting relationships, needs further investigation. Clinicians should, however, manage expectations surrounding clinical trials in HD. The absence of effective treatments currently fuels hope in therapies like NCT.
- HD does not just impact the individual – focus needs to be given to partners, families, and unaffected family members. The experiences of partners of people undergoing novel therapies needs to be considered by clinicians, and research needs to be undertaken to

explore their experiences. It appears a change in research practice might be required when devising protocols, and that researchers might want to consider a tripartite approach beyond the researcher and participant. Families, particularly partners, might also have a greater input into discussions.

- HD impacts all areas of the lived experience and extends beyond the physical and cognitive. It influences memories, goals, and relationships. Consideration of the impact of HD on individuals needs to be truly holistic. Clinicians should explore this and encourage potential participants to reflect on their own reasons for clinical trial participation.
- Can novel therapies, such as NCT, alleviate feelings of stigma amongst people with HD?

9.7: Dissemination

Finally, these findings are in the process of being shared in order that healthcare education, clinical practice, clinical trial practice, and research practice are informed.

Presentations will be made and synopses presented to inform HD interest groups and networks. This research has relied heavily on the time and input of people impacted by HD and it is, therefore, only right that they should have access to the findings.

HD clinical trial teams will be briefed both in person and via the production of research summaries. The initial motivation in developing this research emerged from an interest in why people take part in clinical trials, therefore, the voices of potential participants deserve to be heard by the healthcare profession. Therefore, applications will be made to present the findings at both HD-specific and more general neurology and clinical trials conferences.

It is also intended that the results be published in targeted journals so that a wider audience can be reached.

It is hoped that these findings will stimulate further research activity both personally and amongst others.

Epilogue

Undertaking a professional doctorate, part-time, whilst being a father to three young children, being employed full-time, switching jobs, undertaking a concurrent Post Graduate Certificate in Higher Education, all whilst being carer to elderly relatives has led this to be the most challenging seven years of my life. In working with the interviewees, however, it has allowed be to gain perspective and led to a greater appreciation of the far greater challenges that others face.

The process, although difficult, has been transformative. In undertaking this course, I have learned to question my own ontological and epistemological assumptions. Undertaking this research has led to an ever-increasing appreciation of ways to see things and the various lenses that people view the world through, alongside the meaning that they attribute to phenomena. It has allowed me to develop new ways of working, including creating a podcast series, which has been incorporated into undergraduate programmes and been listened to in 56 countries. Using IPA has allowed me to develop new ways of questioning, explore lived experiences, and allow the voices of health service users and professionals to be heard in novel ways.

Having started the doctorate when working in clinical trials, I also felt very embedded in the positivist perspective and believed that valuable healthcare research could only, truly, be undertaken within the quantitative paradigm. In undertaking the programme, I have re-evaluated this stance and recognised the depth of meaningful information which is uncovered using qualitative approaches. My view now is that some clinical trials have, in the past, lacked pragmatism. There has been a failure to capture meaning and recognise the people themselves within trial designs. On reflection, I look back with some embarrassment at my own lack of divergent thinking but I do recognise that growth is continuous. I also realised that there was a juxtaposition between my views on knowledge generation and my role as a nurse where the patient is treated as an individual.

In contemplating the various qualitative methods available, I found resonance with IPA. As a nurse, the underpinning philosophy and methods which give “voice” to those who choose to participate is particularly attractive, as professionally we see patients as equal partners. We also see patients as individuals with their own unique lifeworld. IPA also adopts these stances.

IPA research involves a detailed exploration and analysis of individuals’ cases so that we can understand what it is like for a person when they experience a phenomenon (Smith et al. 2009). It allows us to see previously unseen perspectives and produce new insights into how people attribute meaning as well as how these impact interactions in their lifeworld (Larkin et al. 2006). This has huge value in clinical practice.

Although the work had been extensive, I am left feeling a need to do more. I still feel that there are areas to be uncovered, phenomena to explore, and improvements to be made. I have identified areas for further exploration and intend to disseminate the findings of this thesis via publication, conference presentation, and within my role as an educator. As well as the findings, the act of undertaking the doctorate has allowed me insight into processes, techniques, and different ways of thinking – all of which I am keen to pass on.

Although at times arduous, the process has been valuable and rewarding. I sincerely feel that it has allowed me to establish key skills and knowledge which will help continue my development as a researcher, educator, and as a nurse.

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Appendix I-CASP TOOL

CASP
Critical Appraisal
Skills Programme

CASP Checklist: 10 questions to help you make sense of a **Qualitative** research

How to use this appraisal tool: Three broad issues need to be considered when appraising a qualitative study:

- Are the results of the study valid? (Section A)
- What are the results? (Section B)
- Will the results help locally? (Section C)

The 10 questions on the following pages are designed to help you think about these issues systematically. The first two questions are screening questions and can be answered quickly. If the answer to both is "yes", it is worth proceeding with the remaining questions. There is some degree of overlap between the questions, you are asked to record a "yes", "no" or "can't tell" to most of the questions. A number of italicised prompts are given after each question. These are designed to remind you why the question is important. Record your reasons for your answers in the spaces provided.

About: These checklists were designed to be used as educational pedagogic tools, as part of a workshop setting, therefore we do not suggest a scoring system. The core CASP checklists (randomised controlled trial & systematic review) were based on JAMA 'Users' guides to the medical literature 1994 (adapted from Guyatt GH, Sackett DL, and Cook DJ), and piloted with health care practitioners.

For each new checklist, a group of experts were assembled to develop and pilot the checklist and the workshop format with which it would be used. Over the years overall adjustments have been made to the format, but a recent survey of checklist users reiterated that the basic format continues to be useful and appropriate.

Referencing: we recommend using the Harvard style citation, i.e.: *Critical Appraisal Skills Programme (2018). CASP (insert name of checklist i.e. Qualitative) Checklist. [online] Available at: URL. Accessed: Date Accessed.*

CASP
Critical Appraisal Skills Programme

Paper for appraisal and reference:

Section A: Are the results valid?

1. Was there a clear statement of the aims of the research?

Yes ☐ Can't Tell ☐ No ☐

HINT: Consider
- what was the goal of the research
- why it was thought important
- its relevance

Comments:

2. Is a qualitative methodology appropriate?

Yes ☐ Can't Tell ☐ No ☐

HINT: Consider
- If the research seeks to interpret or illuminate the actions and/or subjective experiences of research participants
- Is qualitative research the right methodology for addressing the research goal

Comments:

Is it worth continuing?

3. Was the research design appropriate to address the aims of the research?

Yes ☐ Can't Tell ☐ No ☐

HINT: Consider
- if the researcher has justified the research design (e.g. have they discussed how they decided which method to use)

Comments:

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4. Was the recruitment strategy appropriate to the aims of the research?

Yes ☐
Can't Tell ☐
No ☐

HINT: Consider
- If the researcher has explained how the participants were selected
- If they explained why the participants they selected were the most appropriate to provide access to the type of knowledge sought by the study
- If there are any discussions around recruitment (e.g. why some people chose not to take part)

Comments:

5. Was the data collected in a way that addressed the research issue?

Yes ☐
Can't Tell ☐
No ☐

HINT: Consider
- If the setting for the data collection was justified
- If it is clear how data were collected (e.g. focus group, semi-structured interview etc.)
- If the researcher has justified the methods chosen
- If the researcher has made the methods explicit (e.g. for interview method, is there an indication of how interviews are conducted, or did they use a topic guide)
- If methods were modified during the study. If so, has the researcher explained how and why
- If the form of data is clear (e.g. tape recordings, video material, notes etc.)
- If the researcher has discussed saturation of data

Comments:

CASP
Critical Appraisal Skills Programme

6. Has the relationship between researcher and participants been adequately considered?

Yes ☐
Can't Tell ☐
No ☐

HINT: Consider
- If the researcher critically examined their own role, potential bias and influence during (a) formulation of the research questions (b) data collection, including sample recruitment and choice of location
- How the researcher responded to events during the study and whether they considered the implications of any changes in the research design

Comments:

Section B: What are the results?

7. Have ethical issues been taken into consideration?

Yes ☐
Can't Tell ☐
No ☐

HINT: Consider
- If there are sufficient details of how the research was explained to participants for the reader to assess whether ethical standards were maintained
- If the researcher has discussed issues raised by the study (e.g. issues around informed consent or confidentiality or how they have handled the effects of the study on the participants during and after the study)
- If approval has been sought from the ethics committee

Comments:

CASP
Critical Appraisal Skills Programme

8. Was the data analysis sufficiently rigorous?

Yes ☐
Can't Tell ☐
No ☐

HINT: Consider
- If there is an in-depth description of the analysis process
- If thematic analysis is used. If so, is it clear how the categories/themes were derived from the data
- Whether the researcher explains how the data presented were selected from the original sample to demonstrate the analysis process
- If sufficient data are presented to support the findings
- To what extent contradictory data are taken into account
- Whether the researcher critically examined their own role, potential bias and influence during analysis and selection of data for presentation

Comments:

9. Is there a clear statement of findings?

Yes ☐
Can't Tell ☐
No ☐

HINT: Consider whether
- If the findings are explicit
- If there is adequate discussion of the evidence both for and against the researcher's arguments
- If the researcher has discussed the credibility of their findings (e.g. triangulation, respondent validation, more than one analyst)
- If the findings are discussed in relation to the original research question

Comments:

CASP
Critical Appraisal Skills Programme

Section C: Will the results help locally?	
10. How valuable is the research?	HINT: Consider • If the researcher discusses the contribution the study makes to existing knowledge or understanding (e.g. do they consider the findings in relation to current practice or policy, or relevant research-based literature • If they identify new areas where research is necessary • If the researchers have discussed whether or how the findings can be transferred to other populations or considered other ways the research may be used
Comments:	

Appendix II-Professional's Approach Letter

[redacted]

Date:

Study Title: Exploring understanding of Neural Stem Cell Transplantation (NSCT) as an intervention for Huntington's disease (HD).

([redacted])

Dear Professor,

My name is Ricky Hellyar and I am a lecturer and doctoral student at the School of Healthcare Sciences at Cardiff University.

I am exploring what patients with gene-positive, pre-manifest HD understand about NSCT. The aim is then to utilise this information in order to underpin support for patients undergoing the procedure.

In order to do this, I would first like to speak with consultants who have experience with NSCT to discuss their recollections of the participant experience/understanding and the questions, queries and concerns posed by individuals approached with regard to NSCT. This information will then be used to inform a number of semi-structured interviews which will be undertaken with the above population.

The interview would take place within working hours and it will take approximately 45 minutes.

If you are willing to participate please could you reply via email and I will forward you a participant information sheet and consent form.

I thank you for taking time to read this and look forward to hearing from you.

With kind regards,

Please indicate your preferred method of contact

and provide details:

Email

Telephone

Personal letter

Other

Many thanks for your consideration

Ricky Hellyar

Appendix III-Professional Consent Form

Consent form: **Exploring understanding of Neural Stem Cell Transplantation (NSCT) as an intervention for Huntington's disease (HD).**

1.	I have read and understood the information about the project, as provided in the Information Sheet dated _____.	
2.	I have been given the opportunity to ask questions about the project and my participation.	
3.	I voluntarily agree to participate in the project.	
4.	I understand I can withdraw at any time without giving reasons and that I will not be penalised for withdrawing nor will I be questioned on why I have withdrawn.	
5.	The procedures regarding confidentiality have been clearly explained (e.g. use of names, pseudonyms, anonymisation of data, etc.) to me.	
6.	The use of the data in research, publications, sharing and archiving has been explained to me.	
7.	I understand that only anonymised research data will be accessed by other researchers.	
8.	I agree to the findings of this study being used for educational purposes.	

Participant:

_____	_____	_____
Name of Participant	Signature	Date

Researcher:

_____	_____	_____
Name of Researcher	Signature	Date

Appendix IV-Professional's Questions

Question
Can you tell me about your professional background please? (Standard opening question intended to relax)
What is the feeling amongst the scientific community surrounding stem cell transplantation? Could I ask, what are your thoughts about stem cell transplantation and potential recipients? *(Bachoud-Levi writes about the desperation for a "tool kit", within neuroscience. It is interesting and I'd like to explore it but don't want to be too leading: How to word/construct?)*
How do people with neurological conditions view novel neurological procedures/neuroscience?

Prompts: What is your experience of questions/queries/concerns posed?
How do people with neurological conditions view stem cell therapy? Prompts: If positive/negative, why?
How do you approach a potential recipient of intervention? What are your thoughts as you do so? Prompt: Do you take a standardised approach or not? (This is too closed/leading, I think I need to reword)
How do you think participants view researchers/neurosurgeons/neuroscientists? Prompts: Why do they feel like this?
In terms of the relationship between potential recipients and practitioners, what is important? Prompts: What strategies have helped in the past?

Appendix V-Letter of Ethical Approval

Ymchwil Iechyd a Gofal Cymru
Health and Care Research Wales

Gwasanaeth Moeseg Ymchwil
Research Ethics Service

Ariennir gan Lywodraeth Cymru
Funded by Welsh Government

Wales Research Ethics Committee 1

[redacted]

Please note: This is the favourable opinion of the REC only and does not allow you to start your study at NHS sites in England until you receive HRA Approval

26 September 2016

[redacted]

Study title:	**Exploring understanding of Neural Stem Cell Transplantation (NSCT) as an intervention for Huntington's disease (HD).**
REC reference:	**16/WA/0232**
Protocol number:	**SPON 1531-16**
IRAS project ID:	**211225**

Thank you for your letter received on 26th September 2016 responding to the Committee's request for further information on the above research and submitting revised documentation.

The further information has been considered on behalf of the Committee (as delegated) by the Chair.

We plan to publish your research summary wording for the above study on the HRA website, together with your contact details. Publication will be no earlier than three months from the date of this opinion letter. Should you wish to provide a substitute contact point, require further information, or wish to make a request to postpone publication, please contact the REC Manager, Mrs Jagjit Sidhu, jagjit.sidhu@wales.nhs.uk.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation [as revised], subject to the conditions specified below.

Conditions of the favourable opinion

The REC favourable opinion is subject to the following conditions being met prior to the start of the study.

Management permission must be obtained from each host organisation prior to the start of the study at the site concerned.

Management permission should be sought from all NHS organisations involved in the study in accordance with NHS research governance arrangements. Each NHS organisation must confirm through the signing of agreements and/or other documents that it has given permission for the research to proceed (except where explicitly specified otherwise).
Guidance on applying for NHS permission for research is available in the Integrated Research Application System, www.hra.nhs.uk or at http://www.rdforum.nhs.uk.

Where a NHS organisation's role in the study is limited to identifying and referring potential participants to research sites ("participant identification centre"), guidance should be sought from the R&D office on the information it requires to give permission for this activity.

For non-NHS sites, site management permission should be obtained in accordance with the procedures of the relevant host organisation.

Sponsors are not required to notify the Committee of management permissions from host organisations

Registration of Clinical Trials

All clinical trials (defined as the first four categories on the IRAS filter page) must be registered on a publically accessible database within 6 weeks of recruitment of the first participant (for medical device studies, within the timeline determined by the current registration and publication trees).

There is no requirement to separately notify the REC but you should do so at the earliest opportunity e.g. when submitting an amendment. We will audit the registration details as part of the annual progress reporting process.

To ensure transparency in research, we strongly recommend that all research is registered but for non-clinical trials this is not currently mandatory.

If a sponsor wishes to contest the need for registration they should contact Catherine Blewett (catherineblewett@nhs.net), the HRA does not, however, expect exceptions to be made. Guidance on where to register is provided within IRAS.

It is the responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).

Ethical review of research sites

NHS sites

The favourable opinion applies to all NHS sites taking part in the study, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion" below).

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

Document	*Version*	*Date*
IRAS Checklist XML [Checklist_19072016]		19 July 2016
IRAS Checklist XML [Checklist_26092016]		26 September 2016
IRAS Checklist XML [Checklist_26092016]		26 September 2016
Letter from sponsor [Sponsorship letter]		18 July 2016
Letters of invitation to participant [Revised HD participant letter]	1.1	19 September 2016

Letters of invitation to participant [Revised Professional letter]	1.1	19 September 2016
Other [CV Dr Anstey]		July 2016
Other [CV Dr Sydor]		
Other [Revised professional PIS]	1.3	26 September 2016
Other [PIS family/carer]	1.2	26 September 2016
Other [Response letter]		26 September 2016
Participant consent form [Consent form participants]	1.3	19 September 2016
Participant consent form [Support consent-family/carers]	1.0	19 September 2016
Participant information sheet (PIS) [Revised HD participant PIS]	1.5	26 September 2016
REC Application Form [REC_Form_19072016]		19 July 2016
REC Application Form [REC_Form_26092016]		26 September 2016
Referee's report or other scientific critique report [School research ethics]	NA	16 June 2016
Research protocol or project proposal [Protocol]	V1.0	19 May 2016
Summary CV for Chief Investigator (CI) [CV RHellyar]	1.0	12 July 2016
Summary CV for student [CV RHellyar]	V1.0	12 July 2016
Summary CV for supervisor (student research) [CV Prof Busse]		
Summary, synopsis or diagram (flowchart) of protocol in non technical language [Project Summary]	1.0	13 May 2016

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

After ethical review

Reporting requirements

The attached document *"After ethical review – guidance for researchers"* gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Adding new sites and investigators
- Notification of serious breaches of the protocol
- Progress and safety reports
- Notifying the end of the study

The HRA website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

User Feedback

The Health Research Authority is continually striving to provide a high quality service to all applicants and sponsors. You are invited to give your view of the service you have received and the application procedure. If you wish to make your views known please use the feedback form available on the HRA website: http://www.hra.nhs.uk/about-the-hra/governance/quality-assurance/

HRA Training

We are pleased to welcome researchers and R&D staff at our training days – see details at http://www.hra.nhs.uk/hra-training/

16/WA/0232	**Please quote this number on all correspondence**

With the Committee's best wishes for the success of this project.

Yours sincerely

Appendix VI-Original Questions

Interview Schedule-HD participants

1) Can you tell me what it is like being gene-positive for HD please? Prompts-holistic impact

2) You have read the information leaflet, tell me what you understand about the potential treatment. Prompts-surgery/stem cells/sources of information (internet/professionals/family/community)

3) How do you feel about it? Prompts-hopes/fears/anxieties/impacts/motivators/barriers

4) What would you think if was offered to you? Prompts- What would be important?/People/Family/Care providers

5) If it were offered to you what do you think that the uncertainties or risks would be? Prompts-surgical/ethical/family/social/experimental

6) Can the fact that it runs in families' effect how you think about things such as this? Prompts children/wider family/Huntington's Community/Relationships with professionals

The questions are intended to reflect the four themes identified from Phase 1 interviews which are:

Making sense via contrast-people making sense of their illness, circumstances and the procedure by comparing with others. For example, illness trajectory might be compared to that of their parent/sibling, NSCT might be understood via the work done in Parkinson's, stem cell might be understood via organ transplant.

Chronological Risk-attitude towards risk is influenced by chronology/trajectory of the disease. For example, asking people "to take a hit", (quote from interview) now for symptoms which might occur five years down the line might differ from undergoing an intervention where deterioration is imminent.

Ethical Dissonance-this might be displayed in multiple ways. The balance of cultural/religious etc views compared with the drive to stay alive/benefit the Huntington's population. Also are ethics driven by the scientific/societal ethical community when the individual ethics of participants/potential recipients might be vastly different.

Familial/Community drivers and brakes- the desire to undergo the intervention might/might not be driven by the familial context of Huntington's.

Appendix VII-Participant Approach Letter

Date:

Study Title: Exploring understanding of Neural Stem Cell Transplantation (NSCT) as an intervention for Huntington's disease (HD).

Dear Sir/Madam,

My name is Ricky Hellyar and I am a lecturer and doctoral student at the School of Healthcare Sciences at Cardiff University.

I am conducting a study into what people understand about an experimental treatment for Huntington's disease. The treatment involves injections of stem cells into the part of people's brains damaged by Huntington's disease.

This will involve interviews which will be approximately 1 hour long. If you are interested in taking part, further and more detailed information will be sent to you. I will also be happy to answer any questions you have about the study.

Thank you for considering participating. If you are willing to participate please complete the details below and return them to me in the enclosed SAE.

With kind regards,

Richard Hellyar

Reply Slip.

Agreement to contact in the research study

I agree to being contacted in relation to the above study.

Name Date Signature

Please indicate (circle) your preferred method of contact

and provide details:

Email

Telephone

Personal letter

Other

Thank you

Ricky

Appendix VIII-Participant Patient Information Sheet and Consent Form

Title: Exploring understanding of Neural Stem Cell Transplantation (NSCT) as an intervention for Huntington's disease (HD).

Participant Information Sheet (PIS) for people accompanying research participants

I would like to invite individuals with the HD gene to explore what they understand about a potential, new treatment.

This will be done via a 1 hour interview which they have consented to.

As you have been requested, by the participant, to be present during the interview and might comment, I would like you to consider providing consent for your comments to be used in the research.

Providing your consent is entirely up to you but before you decide it is important to understand why the project is taking place.

Please take time to read the following information carefully. I (Richard Hellyar) will be more than happy to go through this information sheet with you, to help you decide whether or not you would like to consent. I will also be happy to answer any questions you may have. Please feel free to talk to others about the study if you wish?

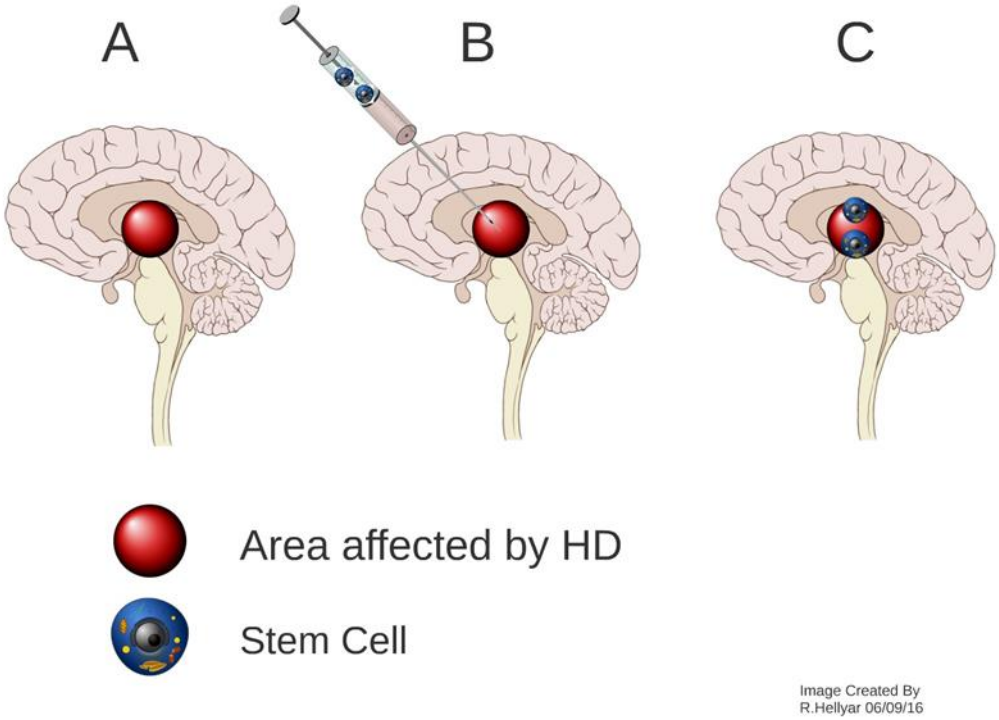
Part 1 of this information sheet tells you the purpose of this project and what will happen if you consent. Part 2 provides more detailed information about the conduct of the project.

Part 1

Summary

This project is part of a Doctoral Degree and the main aim is to explore what people with Huntington's disease understand about a potential new treatment. This research wants to explore what people think about the therapy and find new ways to support patients during this process.

The treatment involves having cells injected into the part of the brain which damaged by Huntington's disease. These cells (stem cells) are intended to repair the parts of the brain which are damaged and lead to altered movement and thought processes.



If you consent to your comments being used take part in this study, you will attend an interview with your family member/client/friend. They will not receive any treatment as part of this study and there is no intended clinical benefit for them with regard to participation in this research.

What is the purpose of the project?

Ongoing research has led to hope for a new treatment to repair brains of people who have Huntington's disease. The procedure is very early in development, however, further research trials are due to take place in Cardiff over the next few years.

As such, I would like to investigate what people, with Huntington's think about the treatment and what they understand by it before these trials take place.

I would then like to use this information to create new ways to support people who choose to have this intervention.

Why have I been asked to consent to my comments being used?

As you have a family member/client/friend with experience with Huntington's disease, this means that they might be able to offer valuable insight into how people would like to be treated and what information patients would like before making any decisions about stem cell transplantation in the future.

As you will be in the room, any comments that you make could affect the interview. To include these comments in the research, it is a requirement that your written permission be sought.

Do I have to consent to my comments being used?

It is entirely up to you to decide, you are under no obligation to do so. If you wish, I will describe the project and go through this information sheet, which you can keep.

If you do want to consent to your comments being used, I will ask you to sign a consent form to show you have agreed to their use and that you understand what is involved.

You are free to withdraw from the project at any time, without giving a reason.

What is involved?

The person you are accompanying will have a one to one interview with myself, lasting approximately 1 hour. It will be conducted in a private place of their choosing. This could be the Cardiff University Clinic or their own home. It is their choice to request support from a carer, partner, spouse or family member, and they have asked that you be present.

If you agree to be part of the project, I will ask you to sign a consent form before the meetings starts.

All conversations will be recorded using a Dictaphone and I will also take notes

The recordings from the meetings and the written summaries will be stored on password protected computers and I will not use your real name but a pseudonym (false name) of your choosing. This will ensure that anything you say will be treated confidentially.

I would like to tell other researchers and health care workers about our project and we will only use the pseudonyms when we do this.

What are the possible benefits of taking part in the project?

Neither yourself or the person that you are accompanying will receive any direct benefit. They will not receive any treatment as part of this study and there is no intended personal clinical benefit with regard to participation in this research.

However, by sharing their thoughts and their experiences they will have the potential to help influence future care for patients who might be offered this treatment.

To reiterate, there will be no direct benefits to them if they choose to take part in the study.

What are the possible disadvantages and risks of taking part in the project?

A disadvantage of being part of the project is that it will take up some of your time, approximately 1 hour. It is also possible that both you and the person you are accompanying might become distressed or upset by the topics which come up in the interview. If this occurs, the interview will be stopped immediately and support offered. This might include reporting back to the HD doctor or nurse, with your permission.

I will ensure that all of the information gathered will be stored safely as the law requires.

Details of people on the project team are at the end of this sheet. This information will not be shared with any other healthcare workers and being part of this project will not influence your clinical care.

If you have any things that you want to discuss because of being part of the project, I can meet with you to chat.

What happens when the project ends?

After the interview you are still free to contact me with any question or queries you may have regarding the project.

If you are interested in the information collected during your participation, I would be happy to send you a report.

Reports of the project will be published in scientific journals and be presented at scientific meetings. You will not be identified in any report, publication or presentation.

The findings will also be shared with research teams undertaking the procedure.

Confidentiality- Will my taking part in this study be kept confidential?

Yes. I will follow ethical and legal practice and all information about you will be handled in strict confidence. The details are included in Part 2 of this information sheet

What if I would like extra information or advice about taking part in this research?

You are free to contact me at the contact details provided at the end of this letter if you would like more information.

If the information in Part 1 has interested you and you are considering participation, please read the additional information in Part 2 before making any decision.

Part 2

What will happen if I don't want to carry on with the project once I have given my consent?

You can tell me that you wish to withdraw from the project at any time, without giving a reason. This project is not linked with your clinical care and, therefore, any decision you make will not influence the care of the person you are accompanying. If you do decide to withdraw from the project, we will use the information collected up to that point but no other information.

What if there is a problem?

If you have a concern about any part of this project, you can contact me and I will do my best to answer your questions (contact details on the last page). If you remain unhappy and wish to complain formally, you can do this through the School of Healthcare Sciences, Cardiff University, as follows:

In the unlikely event that something goes wrong with the project and you are harmed during the research as a direct result of taking part and this is due to someone's negligence, then you may have grounds for a legal action for compensation against Cardiff University but you may have to pay your legal costs.

Will my taking part in this study be kept confidential?

I will follow ethical and legal practice and all information about you will be handled in strict confidence. Information and data collected during the project (including any audio records) will be stored at the University in locked cabinets and will be kept separate from personal data (e.g. names and addresses). Only the project team will have access to your identifiable

personal data. No personally identifying details will appear in our published results or in any direct quotations. In some instances, official people from regulatory authorities may need to access data for checking the research quality. All research team members and regulatory bodies are trained in data protection issues and bound by the terms of the Data Protection Act 1998. After study completion and it is no longer necessary to keep identifiable information or contact details, we will destroy our records of any personal information. Other information (including any audio or video recordings and transcripts) will be kept securely for up to 15 years, after which time they will be securely destroyed in line with University policy.

What will happen to the results of the research study?

The results of this study will be used as part of professional doctorate thesis and the project may be presented at conferences and published in medical or scientific journals.

If you would like, I can inform you of where you can obtain a copy of the published results. You would not be identified in any of the reports.

Who is organising and funding the research?

The study is part of a Doctoral Degree and supported by the School of Healthcare Sciences, Cardiff University.

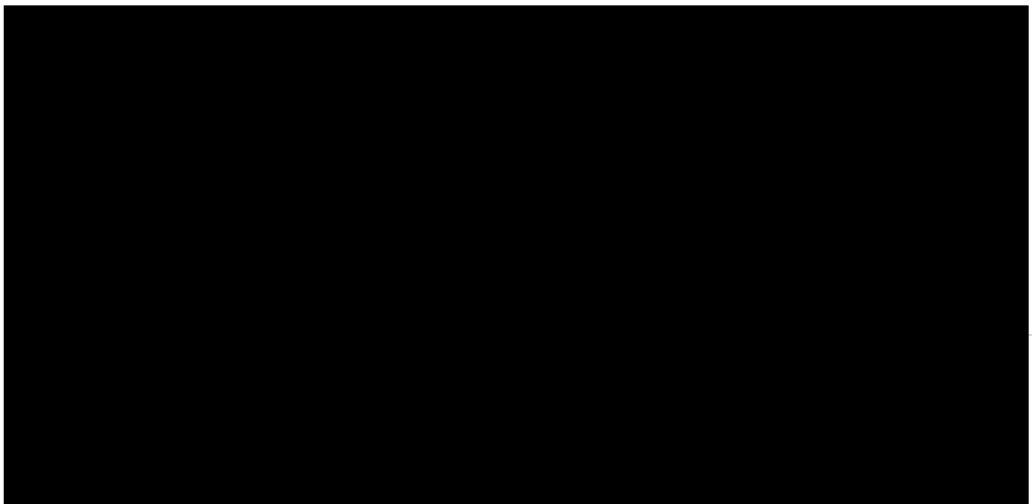
Who has reviewed the study?

All projects are looked at by an independent group of people, called a Research Ethics Committee (REC), to protect your safety, rights, wellbeing and dignity. This study has been reviewed and given favourable opinion by the School of Healthcare Sciences, Cardiff University, Research Ethics Committee.

The study has also been reviewed by a National Health Service-Wales REC 1.

Contact and project team information

Here are my details:



[redacted]

Consent form: **Exploring understanding of Neural Stem Cell Transplantation (NSCT) as an intervention for Huntington's disease (HD).**

1.	I have read and understood the information about the project, as provided in the Information Sheet dated _____.	
2.	I have been given the opportunity to ask questions about the project and my participation.	
3.	I voluntarily agree to participate in the project.	
4.	I understand I can withdraw at any time without giving reasons and that I will not be penalised for withdrawing nor will I be questioned on why I have withdrawn.	
5.	The procedures regarding confidentiality have been clearly explained (e.g. use of names, pseudonyms, anonymisation of data, etc.) to me.	
6.	The use of the data in research, publications, sharing and archiving has been explained to me.	
7.	I understand that only anonymised research data will be accessed by other researchers.	
8.	I agree to the findings of this study being used for educational purposes.	

Participant:

_____	_____	_____
Name of Participant	Signature	Date

Researcher:

_____	_____	_____
Name of Researcher	Signature	Date

Appendix XI-Line by Line Example with Initial Comments

	Transcript	What are they saying?	My interpretations
P	Uhm, I got tested when I was 23 just after I got married, uhm, my mum had it when I was 16, she found out, they found out when she [I] was 16, so it I was all still quite new. But at the time we were just like, oh well, its okay fine and we were just taking the mick out of it, the entire time. All this, well its only in the last 5 years that we've really started to worry about things and uhm, you know, what's going to happen. When we first did the study we made sure that we did the tests, and made sure that we did living wills and things like that. Because my mother, when she was tested, although she stated her wishes, all the rules changed so we couldn't do a lot of what she wanted to do so uhm so we made sure that everything was covered. It's only been recently that it's starting to really upset me. We were going to go to London to do the IVF, where you have the kids with testing positive with them, but because I've got polycystic ovaries uhm, it took years and years and years for me to get pregnant anyway and I kept having miscarriages. So by the time I was pregnant with (XXXX), it was just like, shall we get him tested and then we thought, no we've waited this long. Because I didn't want to be	Life moments/chronology-Impact at timepoint Blasé-coped with it.-coping Chronology- as gets older, life changes, more scared. Aware that terminal early on/sees on others Mother prepared. Reality hitting. Knew that there was risk. Conflict with other conditions? Justifying why risk is taken.	Seems that uses general life experience but reverts to specific ages. Maybe blasé but underneath pinpoint. Humour Blasé but must have been concerning. Is this that the more a case of increased understanding of consequences of HD or change in outlook? Why prepared? Guilt, not wanting to burden more? Increased awareness of consequences. Guilty maybe? Sense of responsibility towards kids. HD does not exist in isolation, there are other disorders which can be concurrent. Undermining own rationalisation. Guilt and responsibility again, justifying to help. Self-reproach. Realisation of mortality or is late motherhood as a acceptable norm.