An Exploratory Study of Mobility-Related Outcome Measures and an Exercise Intervention in People with Huntington's Disease (HD)

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Abstract

An exploratory study of mobility-related outcome measures and an exercise intervention in people with Huntington's Disease (HD)

Objective: There is emerging evidence that exercise may modify disease progression and improve function in a number of neurodegenerative diseases, but this has not been systematically studied in Huntington's disease (HD). The purpose of this study was to evaluate feasibility, acceptability and benefits of an exercise programme in people with HD.

Methods: Using a randomised controlled trial design, 25 participants with manifest HD were allocated to either intervention (home-based exercise; n=13) or control (usual care; n=12) groups. Participants were assessed at baseline and eight weeks later. Eleven participants from the exercise and 10 from the control group completed the intervention study. The primary outcome was gait variability (stride time coefficient of variation (CV)). Secondary outcomes included other measures of gait, disease-specific motor scale and measures of balance, muscle strength, mobility and community walking, functional performance in ADL and quality of life. These measures were included to reflect a range of physical impairments and activity limitations seen in people with HD. Analysis of covariance was used to compare follow-up scores across groups after adjustment for differences at baseline. Effect sizes were calculated for outcome measures based on differences in change scores between groups. Process interviews were conducted at the end of the study to determine acceptability of the intervention to participants.

Cross sectional investigation of outcome measures was undertaken initially to investigate discriminant and concurrent validity as well as test re-test reliability and minimal detectable change (MDC_{95}) along the broad spectrum of the disease. Baseline data from 25 participants with manifest HD (who went on to participate in the intervention), in addition to data from 17 individuals with pre-manifest HD and 25 healthy controls were analysed. This data was of use in interpreting the results from the interventional study. In particular, the MDC_{95} data helped in determining of whether any statistical significant changes due to the intervention are clinically meaningful.

Results: Measures of gait variability, some measures of balance, community walking and measures of functional performance in ADL were able to distinguish between people with manifest HD and pre-manifest HD as well as between people with pre-

manifest HD and healthy controls suggesting good discriminant validity. All these outcomes had also good concurrent validity with a disease specific motor score. The test re-tests reliability scores for the majority of the outcomes were high and the MDC_{95} scores were low, suggesting that the individual variability on these outcomes were low.
Adherence rates to the exercise programme were high (78.8% of participants reported completion of at least 78% of the prescribed sessions). Participants in the intervention group demonstrated significant improvement in stride time CV (95% CI (-11.5, -0.6)) based on complete case analysis. Significant differences between groups were also observed in the disease-specific motor scale and in measures of balance, mobility, community walking and functional performance in ADL, but not muscle strength and health-related quality of life. Effect sizes were large (>0.8) for the majority of the outcomes. The magnitude of the change as a result of the exercise intervention exceeded the calculated MDC_{95} values for some of the outcomes, which suggest that most of the observed changes are clinically meaningful. Qualitative feedback from the participants who completed the exercise programme suggested high levels of acceptability with positive impact on general health and mobility. Participants identified barriers and facilitators that affected performing the exercises at home and described management strategies that helped adherence to the exercise programme.

Conclusions: This study was the first systematic trial to demonstrate that a short-term structured exercise programme is acceptable and can be safely delivered in a home environment; achieve good adherence; and positively affect body function and activity in people with HD. The sensitivity of the outcomes as determined in the cross-sectional study, to mobility deficits the in pre-manifest HD group is important. These outcomes has the potential to be used in future studies of exercise interventions in the pre-manifest stage which aim to target such deficits early in the disease life cycle, before they begin to impact on a person's ability to participate in the community. Overall the data presented from this study provides a platform for further investigations to extend these findings about the role of exercise and physical activity in people with HD. Larger and more detailed studies are needed to replicate findings from this study in other contexts and variations in dose.

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List of publications

Published papers

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Selected conference abstracts

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Khalil H, van Deursen R, Quinn L, Rosser A, and Busse M. Clinical measurement of sit to stand performance in people with Huntington's disease: reliability and validity for 30 seconds chair sit to stand test, in European Huntington's Disease Plenary Meeting. Prague, 2010, Journal of Neurology, Neurosurgery & Psychiatry. p. 81 (Supp. 1)

Khalil H, Dalton A, van Deursen R, Rosser A, Ó Laighin G, Busse M. The Use of an Accelerometer to Evaluate the Performance of Timed Up and Go Test in Pre-symptomatic and Symptomatic Huntington's Disease in European Huntington's Disease Plenary Meeting. Prague, 2010, Journal of Neurology, Neurosurgery & Psychiatry. p. 81 (Supp. 1).

Busse M, Quinn L, **Khalil H**, Rosser A. Move To Exercise: Developing an Exercise DVD for People with Huntington's disease. World Congress on Huntingtons Disease Vancouver: Clinical Genetics 2009. p. 76 (Suppl. 1) 86.

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Chapter One

Introduction

1 Introduction

1.1 Overview

This introductory chapter will describe the general aspects of Huntington's disease (HD). The genetic and neuropathological characteristics of HD will be explained. This will be followed by a description of the major clinical features and the stages of the disease. The currently available management approaches will also be considered with a specific focus on the potential role of exercise interventions in the management of HD. This will then lead to an explanation of the aims of the thesis at the end of the chapter.

1.2 Huntington's disease: General overview

Huntington's chorea was first described by George Huntington in 1872. He provided a clear and concise account of the commonly seen clinical features seen in HD [1]. Huntington's chorea denotes emphasis on the most obvious clinical sign (namely choreic movements); however, not all people affected with HD have chorea, so focusing on this symptom may detract from other important aspects. The term 'Huntington's disease' seems more appropriate and is now widely accepted [1].

Huntington's Disease is a neurodegenerative condition; the major features of the disease may be considered as a triad of motor dysfunction, cognitive deficits and behavioural changes [2]. The disease is genetic, with an autosomal dominant inheritance; each child of an affected person has a 50% chance of developing the disease. Although the recent identification of the mutant gene has allowed for the early detection of gene carriers, the disease has to date no treatment that prevents, delays or slows the progressive neurodegeneration. Current treatments are supportive and symptomatic, provided by a range of healthcare professionals, at different stages of the disease [3].

1.3 Genetics

The gene that causes HD was identified in 1993 after a major collaborative international research effort. The gene has been called IT15 and is located on the short arm of the chromosome 4 at 4p16.3 [4]. This gene directs the cell to make the Huntington's protein that contains a sequence of amino acid glutamines. These glutamines are encoded in the gene by the DNA trinucleotide- cytosine-adenine-guanine (CAG) that is repeated a number of times. In a normal gene, the CAG repeat lengths range from 6 to 39. In a mutant gene, this length varies from 36 to 121 [1]. The number of CAG repeat lengths can be easily determined from a sample of venous blood, making confirmation of the diagnosis reliable in the vast majority of cases [1]. It is possible for people at risk of HD to take a predictive test to determine whether or not they have inherited the mutant gene. An individual who has an unfavourable genetic test for the HD mutation, but has not yet developed any clinical signs of HD (such as chorea), is considered to be pre-manifest.

Studies have shown an inverse relationship between the average age at onset and the CAG repeat length; the more CAG repeats included in the mutant gene, the earlier the onset of symptoms occurs and the quicker they typically progress [5]. However, there is such a wide variation that it is not always possible to predict the age of onset from knowing only the CAG repeat length; the CAG repeats have been demonstrated to account only for about 60% of the age at onset and it is believed that other factors such as the influence of the environment and the other genes may also have an effect [6]. Very broad categorization is possible; CAG repeats between 36 and 39 may cause a late onset or even not at all; CAG repeats between 40 and 60 usually cause an adult onset; and CAG repeats over 60 may cause juvenile onset [5].

CAG repeats at the upper end of the normal range (28-35 repeats) show instability on replications which leads to expansion into the pathological range in future generations [7]. Instability is also greater in spermatogenesis than oogenesis, in that large expansions of CAG repeats on replication happen exclusively in males [8, 9]. This explains the likelihood of paternal inheritance in children with juvenile onset symptoms.

1.4 Prevalence and aspects of life history

Most studies from the UK, US, Australia and Europe quote a prevalence of about 4–10 affected individuals per 100 000. Low prevalence has been documented in Japan where prevalence of the disorder is 0.5 per 100 000, about 10% of that recorded elsewhere. The rate is even lower in most of Asia and Africa [7, 10]. Disease prevalence appears to be slightly higher in women than in men [11]. The average number of new cases per year has been estimated at 4.7 per million per year [11].

Whilst HD may be considered a rare disorder, the burden is great for patients, immediate carers and offspring [1], in which half of them, on average, will inherit the mutant HD gene and develop the disease later in life. People with Huntington's disease can develop the symptoms of the disease at any time in their life. Symptoms typically start to appear between the ages of 35 and 45 years. In very rare cases, symptoms appear before the age of 20 years. This accounts for about 7% of the HD carriers. In this case, symptoms differ slightly and the disease is classified as Juvenile or Westphal variant HD [1, 2]. Life expectancy for all people with HD ranges from 15 to 25 years following the onset of symptoms. Death usually does not occur as a direct result of HD, but rather as a result of complications that occur as a consequence of the disease's symptoms, which include pneumonia and physical injuries from a fall [12].

1.5 Pathology

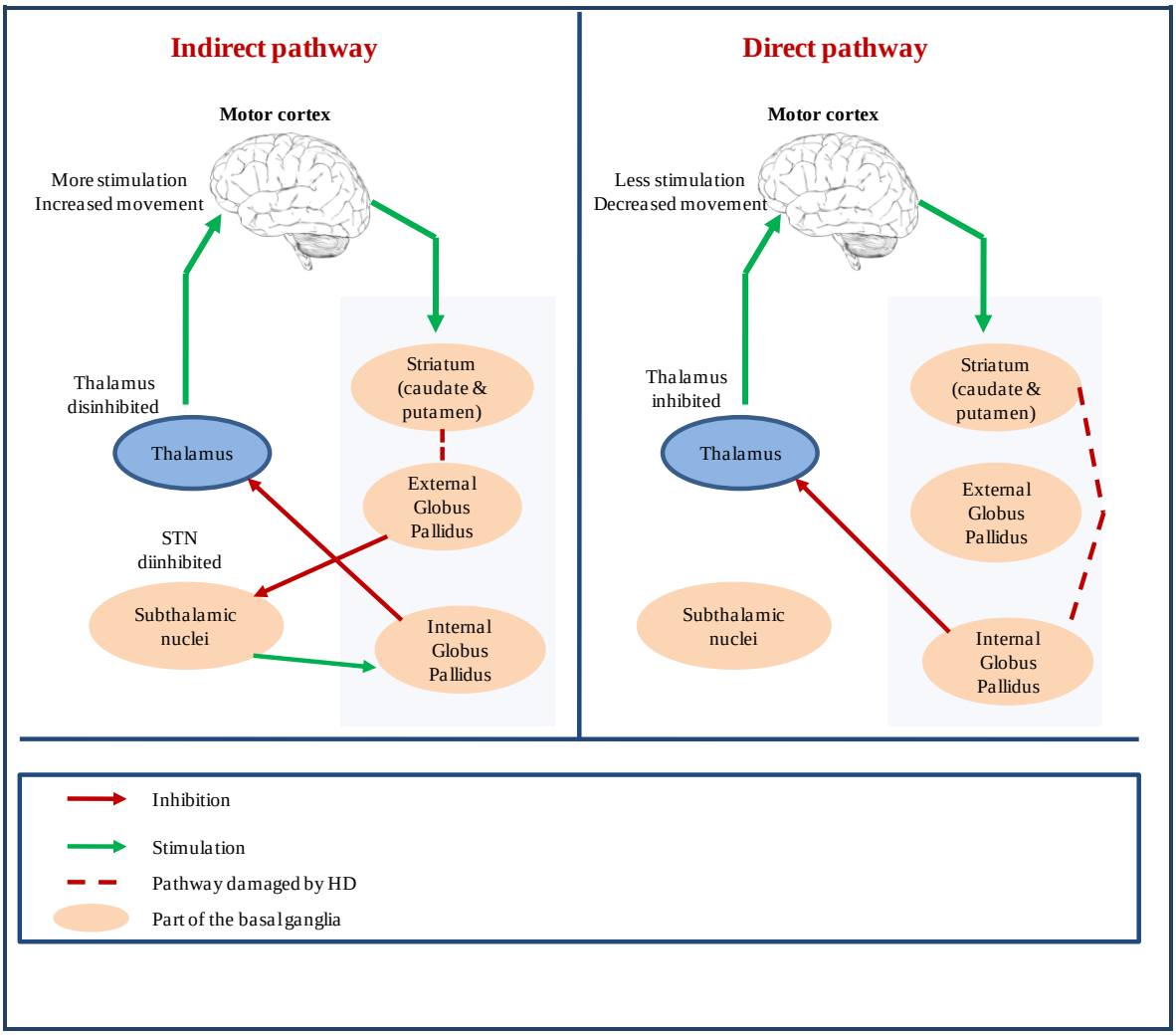
1.5.1 Macroscopic changes

Although the mutant HD gene is expressed in a wide variety of neurons, the pathological changes in Huntington's disease are strikingly selective with prominent cell loss and atrophy occurring in the striatum (substructures of the basal ganglia, namely caudate nuclei and putamen) and deeper layers of the cortex in the early stages. In particular the medium spiny neurons' loss is the most prominent within the striatum. In the advanced stages, other regions of the brain such as the hypothalamus, cerebellum, amygdala and thalamic nuclei also become affected [12, 13].

The striatum receives excitatory neurons from the cortex and has efferent medium spiny neurons. These neurons are rich in gamma-aminobutyric acid (GABA) and project to the internal globus pallidus via the direct pathway and to the external globus pallidus

through the indirect pathway. In part, motor signs seen in people with HD depend on the degree of degeneration between these two pathways (Figure 1.1). Loss of neurons from the indirect pathway leads to loss of inhibition of the external globus pallidus, which produces more inhibition of the subthalamus, less stimulation of the internal globus pallidus, less inhibition of the thalamus and overstimulation of the thalamo-cortical circuit, and therefore to chorea. In contrast, loss of neurons from the direct pathway leads to increased inhibition of the thalamus and less activity of the thalamo-cortical feedback, consequently resulting in bradykinesia and rigidity. Although both pathways degenerate, evidence suggests that the balance between them is disturbed, with the neurons projecting to the external globus pallidus being more involved than the neurons projecting to the internal globus pallidus [14]. Chorea is suggested to dominate early in the course of HD because of preferential involvement of the indirect pathway of the basal ganglia-thalamocortical circuitry [12].

Figure 1.1: Connections of the basal ganglia, demonstrating pathways damaged in HD [14].



1.5.2 Cellular changes

Since the identification of the HD gene, a number of different approaches have been utilised in order to provide a better understanding of how the mutant HD gene can cause selective neuronal loss and neurodegeneration. Work has been conducted on HD animal models, in particular the R6 mice models, suggesting that the mutant HD gene exerts its effect by gaining a new function within the cell. Inserting the mutant HD gene into mice causes proteins to aggregate into the cells and move to the neuclei of neurons to form insoluble inclusions [4, 15]. Aggregate formations are believed to be a key factor in the pathological process of the disease; an abundance of evidence suggests that these aggregates can affect several nuclear and cytoplasmic proteins within the neurons that regulate transcription, apoptosis, mitochondrial function, neurotransmitter release, and axonal transport, leading eventually to neurons' death [13, 16]. Although it is not clear

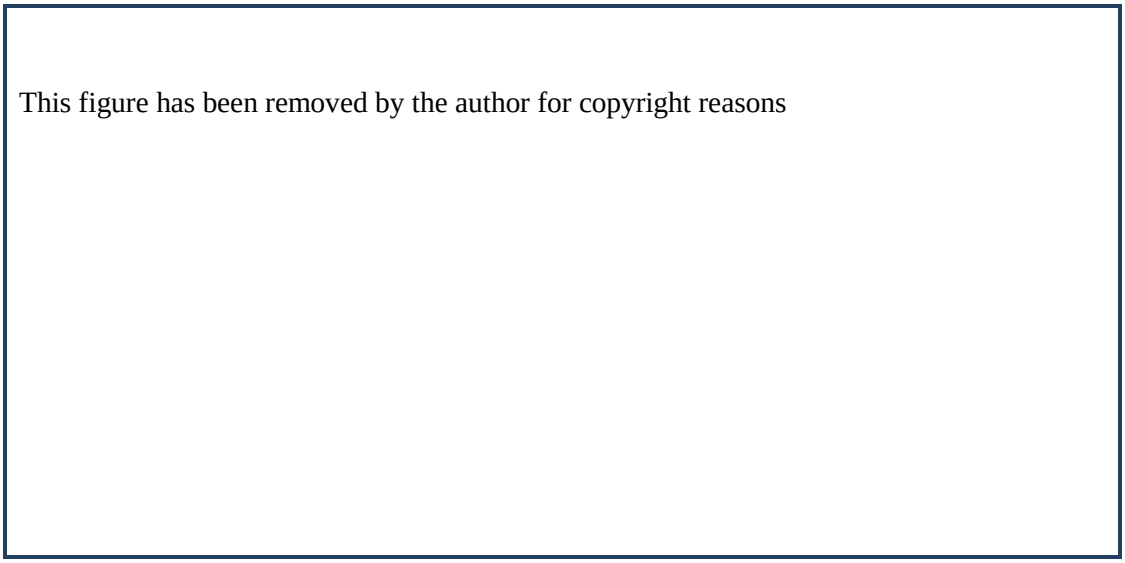
whether these aggregates are directly related to the cellular pathology or represent a defence mechanism within the neurons, it is apparent that neuronal cells are dysfunctional ('sick') before they die, which gives the promise for developing interventions that would modify the natural history of the disease [12, 13]. The natural history of HD is discussed in detail in the following sections.

1.6 Signs and Symptoms of Huntington's disease

1.6.1 Natural course of the disease

When people inherit the HD gene, there will be a period of time when they are healthy and have no clinically detectable abnormalities. In time, the neurons become dysfunctional and this healthy period merges with a pre-diagnostic phase in which subtle changes in mood, personality and cognition may develop [12, 17]. This pre-diagnostic phase (when an early non specific symptom indicates the start of the disease before specific symptoms occur) is often called the prodromal stage (Figure 1.2). The healthy and prodromal phases are together called the pre-manifest stage. A clinical diagnosis is usually not made at this stage until the onset of obvious motor disorders occur [13].

Figure 1.2: The pre-manifest stage in HD [13, 18]



As depicted in Figure 1.2, the pre-manifest stage merges eventually with a manifest stage which is characterised by the appearance of a triad of progressive motor deficits, cognitive disorders and behavioural changes that over time affect a person's ability to participate in activities of daily living, community and work. This triad of symptoms affects people at different rates and at different levels of severity, although most people with HD display components of these symptoms at some point in the disease progression.

1.6.2 Cognitive disorders

Cognitive deficits in HD often do not involve short term memory but are more related to executive functions such as planning, sequencing, organisation and prioritization [19]. This is consistent with the fronto-striatal pathway disruption seen in this population [20]. These impairments may start from very early in the disease, even before the onset of the motor symptoms, and clearly progress over time [21-23]. A vast number of studies have described the deficits in executive functioning in people with HD. For example, Lawrence et al [24] investigated the ability of people with early-stage HD to organise and plan during performing a task. Participants were asked to rearrange balls as seen in a display model, in an attempt to solve the problem in a minimum number of moves. Participants were advised against making a move until they felt confident that they could execute the entire sequence; this required them to figure out the sequence first. Results showed that the proportion of correct solutions decreased as the problem difficulty increased. There was also an increase in the mean number of excess moves and an increment in initial thinking times with increasing problem difficulty levels. Participants showed deficits in all 3 endpoints: perfect solutions, initial thinking times, and subsequent thinking times. Authors suggest these findings to be due to deficits in spatial working memory.

At a clinical level, the cognitive impairments described above can affect the ability to maintain employment and manage daily routine. Activities such as keeping a daily planner or completing a list of household tasks can become overwhelming in early stage HD. The initiation or starting of an activity, conversation or behaviour is also often compromised [3]. As the disease progresses, perseveration, or being fixed on a specific thought, becomes noticeable [19]. In addition sustained or complex types of attention become impaired; individuals therefore may have difficulty doing more than one task at

a time [23]. Deficits in spatial perception are also noticeable [25] and can cause people with HD to bump into walls or a table, resulting in injuries [18]. These symptoms can lead to loss of independence, and the ability to complete daily living tasks such as dressing, shopping and managing finances can be greatly affected [2], which in turn may have great impact on family members and caregivers by increasing the burden of care. At present, interventions aimed at the cognitive component of the disease are primarily based on assisting individuals to develop effective compensatory strategies. Some people with HD may find it useful to rely on a routine to initiate or continue an activity without guidance, or make lists which help to organize tasks needed to do an activity. Others may rely on family members or carers to assist with cognitive tasks such as managing finances [3].

1.6.3 Behavioural changes

Unlike cognitive deficits, most of the behavioural symptoms arise with some frequency but do not show progression with increasing severity of the disease [12]. Depression is typical; in a number of studies the prevalence of depression was high, ranging from 39% to 53% [26, 27]. Suicidal ideation is also frequent in people with HD. In a cross sectional study [28], about 22% of people with pre-manifest HD contemplated suicide occasionally, perhaps as a result of being aware of the natural history of the disease. Other studies have reported behavioural disorders; including anxiety, irritability, aggression, obsessive compulsive behaviour and apathy [19, 29]. Apathy in particular is common in people with HD. In a cross sectional study examining the prevalence of neuropsychiatric symptoms in a sample of people with HD who ranged from pre-manifest to mid stage, apathy was present in 55.8% of the participants [30]. Apathy can be defined as "disengagement, with passivity and loss of enthusiasm, interest, empathy and interpersonal involvement" [19]. Unlike all the other behavioural symptoms, apathy becomes more severe as the disease progresses [12].

The combination of each of these behavioural symptoms would significantly affect the patient's functional abilities and quality of life. However, some of these symptoms can still be managed effectively with drug therapies. Tricyclic antidepressants are used to address the depression-related problems and atypical neuroleptics are used to address aggressive and irritable behaviours [3, 31].

1.6.4 Motor deficits

Motor deficits in HD are typically characterized by the presence of both voluntary and involuntary movements. The most common involuntary movements are chorea and dystonia. Chorea is the most noticeable feature from a motor perspective and can be defined as "a state of excessive, spontaneous movement, irregularly timed, randomly distributed and abrupt" [3]. All body parts can be affected and severity can range from restlessness with mild intermittent exaggeration of gesture to continuous flow of disabling, violent movements. At the early stages, chorea can be barely perceptible but with the progression of the disease it becomes more obvious until it reaches a plateau. Although chorea is the symptom most often associated with HD, it may be one of the least disabling characteristics of the disease. Drug trials aimed at reducing chorea did not demonstrate an increase in functional abilities, including walking [32]. A number of cohort studies also demonstrated that with worsening functional capacity, chorea decreases and dystonia increases [33, 34].

Dystonia can be described as "a slow sustained muscle contraction that causes a twisting movement of the trunk and abnormal posture of the limbs" [3]. Dystonia is a very prominent feature of HD. The prevalence of dystonia of any severity in a cohort study of 42 participants was found to be 95%. In this study, 75% of the participants had a dystonia of moderate severity on at least one body part and approximately 17% had severe and constant dystonia [35]. The most prevalent dystonic postures that were noted in this study included shoulder internal rotation, sustained fist clenching, excessive knee flexion and foot inversion during walking. Age of onset can affect the severity of dystonia. In adult onset HD, dystonia is less severe and more obvious in the late stage, while in juvenile onset it is very prominent from early stages [36]. Unlike chorea, dystonia usually increases with disease severity and is correlated with a decline in functional capacity [36]. It also has secondary effects such as decreased flexibility and range of motion [35] and possibly altered postural control, which can increase the risk of falls.

Disorders of voluntary movements in HD include oculomotor dysfunctions, dysarthria, impaired balance and gait deficits [37]. Gait and balance disturbances are considered highly correlated to activity limitations in this population [38]. Gait disturbances are the most prominent of the voluntary movement disorders in HD and include a combination

of hypokinesia, akinesia and disordered regulation of rhythmic stepping reflected by increased variability of speed, step length and time across the spectrum of the disease [39-42].

Mobility deficits in gait are likely to be linked to the occurrence of falls in this population. Incidence of falls in HD patients is particularly important in determining the ability to live independently and is a major factor implicated in admission to a nursing home [43]. Evidence suggests that a high proportion of people with HD fall frequently [38, 44, 45]. Aetiology of falls in this population is likely to be multi-factorial [2], but observed deficits in gait and balance are considered the main contributing factors [38, 45]. In particular gait deficits, which are well documented in HD, are likely to contribute to progressive functional loss and may also detract from health-related quality of life. A full review of the literature investigating mobility deficits in HD is provided in Chapter 2.

1.6.5 Stages of the disease

The Unified Huntington's Disease Rating Scale (UHDRS) is routinely used to quantify the severity of the symptoms in HD. This scale provides uniform assessment of the clinical features and course of HD over the 4 domains of the disease (motor, cognitive, function and behaviour). The scale is highly reliable and valid which means that it can be used for tracking symptoms in this population [46]. The motor section of the UHDRS includes 15 items rated on a 0-4 scale, with 4 indicating the most severe impairment. This scale contains measures of saccade initiation and velocity, alternating hand movement, finger tapping, chorea, rigidity, dystonia, bradykinesia, gait, tandem walking and retropulsion test. The 5 items of the cognitive component consist of a verbal fluency test, the symbol digit modalities test, and the 3 items Stroop test. The behavioural section of the test includes 28 items assessing the severity and frequency of a number of behavioural abnormalities. The functional component consists of a Functional Assessment Scale (FAS), which is a checklist of 25 yes/no questions, the Independence scale, which ranges from 0 to 100, and a Total Functional Capacity Scale (TFC).

Stages of the disease in HD are usually documented using the TFC score. Scores derived from the TFC scale range from 0 to 13 and provide an assessment of a person's

capacity in relevant functional domains; including employability, financial tasks, domestic responsibilities and self care skills. The average rate of TFC decline ranges from 0.63 to 0.72 points per year [33, 34]. According to the TFC score, people with HD, once they have become symptomatic, can be differentiated into 5 stages of the disease progression as follows; stage I (TFC 11-13); stage II (TFC 7-10); stage III (TFC 3-6); stage IV (TFC 1-2); stage V (TFC 0) [47]. Stage 1 corresponds to early stage HD, stage II-III middle stage HD, and stages IV-V late stage HD. This classification can serve as an organizational tool for planning interventions; however, considering the variability of the disease, these stages are not definitive categories. Table 1.1 provides an overview of the general features for each stage as first described by Shoulson and Fahn [47].

Table1.1: General features of HD according to the stage of condition [47]

Stage of the disease	General features	TFC score
Pre-manifest	No clinically detectable symptoms: the patient has had a positive gene test confirming that they will develop the disease, but is still fully functional and independent at home and work.	13
Stage I	Mild impairments: the patients maintain their independence in performing activities of daily living (ADL), domestic chores and managing finances. They may still be employed.	11-13
Stage II	The patients maintain their independence in performing ADL and domestic chores. They may need slight assistance in managing finances. Capacity for normal job is reduced.	7-10
Stage III	Patients need minimal assistance in performing ADL and domestic chores. They need major assistance in managing finances and capacity for normal job is obviously reduced.	3-6
Stage IV	Patients need major assistance in performing ADL, domestic chores and managing finances.	1-2
Stage V	Patients needs complete assistance with ADL, domestic chores and managing finances. Twenty four hour supervision at home or facility placement might also be required.	0

1.7 Management approaches and experimental treatments in HD

Despite research advances in the past 20 years, medical treatment in HD has made little progress. The 2009 Cochrane review of therapies for modifying disease progression [48] concludes that there is no evidence that any pharmacological therapy modifies the

progression of HD. The 2009 Cochrane review of adequate symptomatic treatment of HD [49] concludes that conclusive evidence is available only for tetrabenazine that it can treat the symptoms of chorea. Although tetrabenazine seems to offer HD patients with severe chorea a respite from their constant involuntary movement, it has serious side effects as it can cause bradykinesia, rigidity, and depression or sedation [31].

Currently, several approaches for HD are being investigated with the aim of developing therapies that would slow or modify the course of the disease. A few of these approaches have shown potential in work done in animal models. One of these approaches suggests reducing the toxicity produced by the mutant Huntington protein by silencing the expression of the mutant allele. Within this context, early studies tested the effects of allele- specific knockdown (i.e. silencing), in which an inhibitory Ribonucleic acid (iRNA) was directed against the mutant Huntington fragment in a transgenic model of HD [50]. Knocking down the mutant allele demonstrated positive effects in reducing the disease progression and improving the disease-related symptoms in the HD mice model [50]. This approach, however, has disadvantages; silencing both the normal and the mutant alleles can have serious side effects. The complete loss of expression of the mouse HD gene was found to cause an embryonic lethal phenotype [51]. To overcome this, research has been focusing on investigating alternatives to silencing HD gene expression by instead examining approaches that would reduce the amount of mutant Huntington protein. This involves examining mechanisms to reduce its production or enhancing its clearance (i.e. degradation) [13, 51]. Recently, considerable research has been advocated to develop tools to quantify and characterize Huntington protein and aggregates [51]. These efforts, although slow moving, are producing a better understanding of the underlying mechanisms of the disease which may lead to the identification of the specific toxic species and this in turn may help to select a lead compound that reduces mutant Huntington protein and in turn the symptoms of HD [51].

Additional lines of research that are designed to yield therapies for HD are focused on how mutant Huntington causes its toxicity [12, 13, 51]. Prominent among the mechanisms identified so far are increased oxidative stress, reduction in the synthesis and secretion of protective growth, changes in pre- and post synaptic neurotransmitter induced activities and reductions in mitochondrial function [13, 51]. Development of

compounds that are designed to prevent or reduce these toxicities is currently under investigation in cell based and model organisms and this may yield useful therapeutic leads in the future.

Whilst the approaches cited above are still investigated in cell-based and model organisms, other approaches which are reconstructive (i.e. surgical) have been tried in people with HD. In response to successes with deep brain stimulation in Parkinson's disease (PD) [52], trials of this surgical method have been conducted in HD. The published papers comprise individual case reports that suggest chorea and dystonia are reduced in the short-term [53, 54]; however, there is not enough evidence of the long-term benefits of this approach. Other therapies such as primary-foetal neural-transplantation, have reported success in reducing the neuronal degeneration associated with HD and stopping symptomatic progression for some time in subjects with HD [55, 56]. These observations, however, were seen in only a few subjects with HD; thus larger clinical trials are needed to establish the safety and efficacy of this approach.

It is clear that there has been striking progress made in terms of understanding the pathogenesis of HD and possible therapeutic approaches. However, it should be noted that new treatments may take many years until they become generally available, taking into account the process of pre-clinical assessment and then clinical assessment once a treatment has been identified in the laboratory. For this reason, there is a need to improve all modes of management approaches, including the conventional therapies. Within this context, there has been growing attention in terms of research towards understanding the environmental factors that may affect the disease. The concept is that, although HD is an inherited disease, environmental factors may play a role in the mechanisms of gene expression and subsequently may alter the symptoms of the disease. It is known that significant variability exists in symptoms and age of onset, even among people sharing the identical CAG repeat length in their HD gene and most surprisingly among monozygotic twins [6, 57-60]. This lends support to the idea that the mutant HD gene expression can be altered by environmental factors and further exploration into such factors is required.

Recently there is also increasing understanding of the role that exercise and physical activity may play as an environmental modifier in a variety of animal models, including

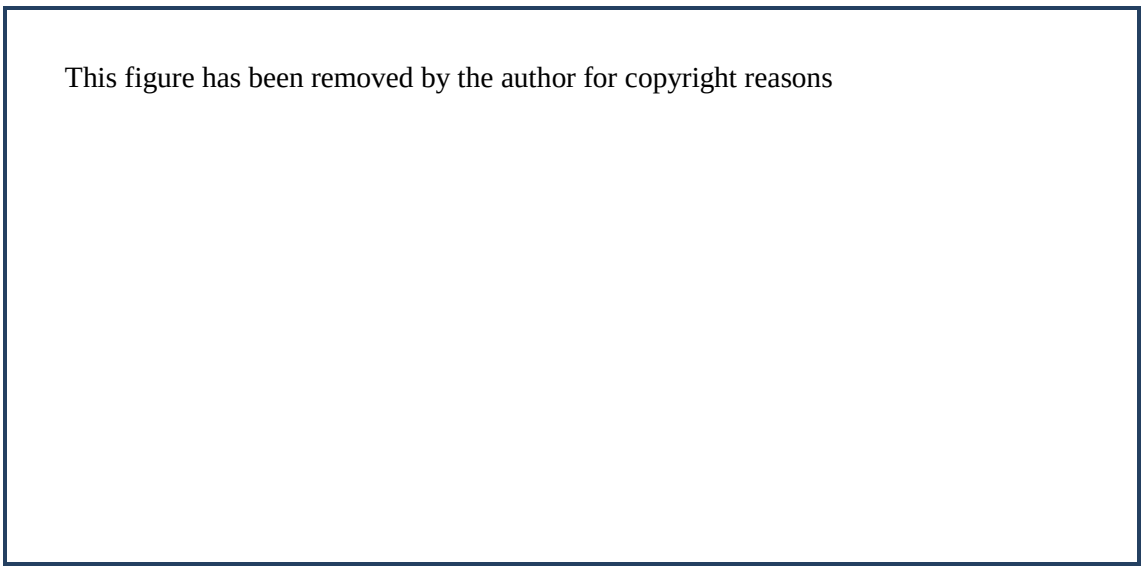
the HD animal models. Laboratory studies have demonstrated improved function in normal rodents in response to exercise, and have indicated some of the underlying resulting physiological changes, such as gene expression changes in the brain [61]. Recent evidence has revealed that similar benefit can be achieved in animal models of neurodegeneration, such as the R6/1 and R6/2 mice models of HD. Housing such mice in enriched environments, in which there are increased opportunities for physical activity, results in better performance of motor tasks compared to mice in standard housing [62-65]. Even minimal amounts of enrichment produced phenotypic slowing and, perhaps more remarkably, was associated with delayed loss of peristriatal cerebral volume [62, 65]. The extent to which the physical intervention has its effect through a general increase in activity or through activation of specific neural circuits is currently not known. However, a study of task-specific training following transplantation of developing striatal neurons into the striatum of an adult rodent model of HD suggests that activation of specific circuits may be useful, at least in some circumstances, and was important for "learning to use the graft" [66]. These observations, along with reports that a passive lifestyle may potentially influence symptom onset in patients with HD [67], have direct implications for developing therapeutic exercise interventions in this population and provide theoretical support for implementing strategies to encourage more active lifestyles in people with HD.

1.8 Exercise interventions in HD and the MRC framework

Exercise interventions for people with HD are likely to be complex. They are likely to involve many components that need to be considered such as; providing information, advice, prescribing different types of exercise and giving demonstrations. A further complexity is that at the same time individuals may be undergoing investigations and taking medication. Exercise interventions can also be modified by a number of factors such as severity of the disease and individual personal factors. It is therefore essential that the main "active ingredients" within the intervention are defined and benefits evaluated [68]. The Medical Research Council (MRC) Framework for design and evaluating complex interventions provides a methodology for evaluation of complex interventions [69, 70]. **Four** phases have been identified in this framework to be assured that an intervention is fully defined, developed and evaluated before long term implementation; these phases are demonstrated in Figure 1.3. The pre-clinical phase deals with exploring the underlying theory and developing hypotheses. This is followed

by a modelling phase to identify components of the intervention and potential outcomes and then an exploratory trial to evaluate feasibility and pilot methods.

Figure 1.3: Phases of developing randomised controlled trials of complex interventions. The figure shows the different stages of the MRC for developing and evaluating complex interventions [69].



As discussed earlier, mobility deficits are an important component of HD symptomology which may impact on safe, independent ambulation and detrimentally affect quality of life. As currently there is no disease-modifying treatment available for this condition and very little in the way of symptomatic treatment, it is important to improve all modes of possible management approaches, including conventional therapies [71]. Within this context, exercise interventions to improve mobility may offer a means to enrich the lives of people with HD and their carers by improving health, helping to maintain independence, and subsequently reducing health and care costs. This suggestion, along with available evidence that exercise may alter symptoms and disease progression in animal models of HD, provides theoretical support for the need to consider exercise interventions as a management approach in people with HD.

Whilst exercise has been shown to be of benefit in improving the mobility status of people with other neurodegenerative disease such as Parkinson's disease and Alzheimer's disease [72-75], it is not known if or how exercise affects people with HD. Two recent reviews [37, 71] highlighted the scarcity of available literature in which

only 5 papers addressed exercise type interventions for people with HD. To date, only 5 additional studies have been identified [2, 76-79]. External cueing techniques and balance training, as well as a combination of muscle strengthening, stretching and cardiovascular exercise, were used as strategies for helping people with HD to enhance their walking ability and functional status in these studies. However, the vast majority of these studies were either observational or non experimental in design and were limited by the lack of randomisation, lack of blinding, the lack of the use of objective outcome measures and poorly-defined intervention content. It is clear that there has been little recent progress in the field of exercise interventions for people with HD.

Efficacy of exercise interventions should be confirmed with controlled clinical trials; however, the implementation of such trials is still limited by the lack of knowledge about specific components of appropriate interventions. A series of interviews and surveys with physiotherapists working in the field [80, 81] has given some insight into potential exercise intervention and evaluation strategies. This work indicated that although exercise interventions are crucial in managing mobility deficits in this population, sustained interventions may not be the most feasible for life-long disease management and it is therefore critical for physical therapists to find ways to facilitate early engagement and participation in independent exercise programmes. People with HD involved in this preliminary work were interested in exercise programmes, but found it difficult to engage in independent exercise programmes in the community mainly because of their limited ability to travel to a formal exercise setting such as the gym. A home-based exercise may therefore be an appropriate tool for many people with HD to engage independently in an exercise programme.

Although an independent home-based exercise programme may be optimal for people with HD, there are a number of factors that may influence the ability of people with HD to engage in such programmes, which include cognitive and motivational issues [80]. Exercise adherence is suggested to decrease after professional supervision stops in this population, when patients no longer receive external support or feedback about their progress [80, 81]. There is clearly a need to develop methods that facilitate patients' engagement and adherence to an independent exercise programme. The technology capabilities of DVD/ videotape (such as the use of sub-titles, music and rhythm, demonstration and structuring of content) make it a useful format to facilitate

engagement in such programmes, particularly for people who have motivational and cognitive problems, as is common in people with HD. Such audiovisual methods have been used in different clinical settings and disciplines with a positive outcome [82-84] and better adherence [85, 86].

An exercise videotape has also been used to successfully support a person with mid-stage HD to follow a home exercise programme [2]. This single case study is the first to use a videotape to support an independent exercise programme in the HD population. Using this case study as a basis, the Cardiff physiotherapy group developed an exercise DVD for people as part of the modelling work of the MRC framework to develop exercise interventions for people with HD. The DVD was developed for use as a home-based exercise resource. Consultation in the form of focus groups with physiotherapists (n=8) working in the field, and interviews with people with HD (n=5) was undertaken in order to determine the content and structural requirements of the DVD. The final DVD included exercises specifically designed to target the specific physical problems seen in this population. The DVD had subsections, which means that it can be individualized. Feedback from people with HD involved in the development stage suggested that people would use the DVD as a support mechanism to develop their home-based exercise routines. Although the developed DVD seemed to have the potential to provide sustainable training in this population with ultimate contribution to an integrated physiotherapy service for people with HD, further evaluation was required.

In line with the MRC framework, an exploratory trial was needed for evaluating the use of the exercise DVD before undertaking a definitive phase III randomized controlled trial (Figure 1.3). An exploratory study would provide an opportunity to determine the safety of an intervention as well as feasibility of recruitment, method of randomisation, content of the comparative arm (the control group) and factors that may impact on delivering the intervention and how these factors can be managed in future studies. An exploratory study would also provide an opportunity to determine the acceptability of the intervention to the users and their carers.

1.9 Aims of the thesis

This thesis focuses on the exploratory phase (phase II) of evaluating a home-based exercise programme for people with HD (using the aforementioned exercise DVD as a

basis for the exercise intervention). The primary aim was to evaluate feasibility, acceptability and benefits of a home-based exercise programme that was designed to specifically target physical factors which are typically impaired and are potentially modifiable in people with early to mid stage HD. Potential benefits were evaluated in: a) deficits in gait, muscle strength balance; b) functional mobility and c) health-related quality of life.

As this was a stage II (exploratory) study, piloting of the battery of outcome measures that could be used to evaluate benefits in future definitive phase III randomized controlled trials was also necessary. Choosing appropriate outcome measures that are valid and reliable is crucial in developing clinical trials. The battery of clinical outcome measures that were used in this study (see Chapter 3) has been shown to have utility in people with HD and other neurological diseases. However, to date, the reliability of the vast majority of these outcome measures has not been evaluated in people with HD.

Although this study aimed primarily to evaluate the feasibility, acceptability and benefits of an exercise programme in people with manifest HD, the ultimate goal is to develop exercise interventions that may potentially modify the disease process. The optimum point at which to introduce such interventions is likely to be the pre-manifest stage, before the onset of rapid neuronal degeneration and the emergence of clinical symptoms. Exercise in general is known to promote synaptic plasticity, stimulate brain perfusion and improve neurovascular integrity, promoting the development of new neural architecture [61, 87]. These potential changes may have a neuroprotective effect in the pre-manifest stage by keeping the neuronal cells fit for longer; thus delaying the onset of the disease. Overall, to test potential interventions, outcome measures that are sensitive to motor changes and reliable in individuals with pre-manifest HD must be identified. Therefore, validity and reliability of the outcome measures was also examined in a group with pre-manifest HD.

In developing the research presented here, a review of the available literature was conducted to determine criteria for delivering the intervention and to highlight potential outcome measures that could be used to evaluate potential benefits (Chapter 2). Details of methods that were applied to this study are provided in Chapter 3. Validity and reliability of the outcome measures across the continuum of the disease were examined

(Chapter 4). A repeated measure design was used to evaluate benefits of the home-based exercise programme. The benefits to: a) deficits in gait, balance and strength; b) functional mobility and c) health-related quality of life were examined (Chapter 5). Acceptability of this exercise programme to user and carers was also determined using a process evaluation (Chapter 6). Outcomes of this study are required to provide a sound basis for determining methodological designs for Phase III randomised controlled trials.

Chapter Two

Literature Review

2 Literature Review

2.1 Overview

In developing the research presented here, a review of the available literature was conducted to review the evidence for physical interventions in the management of mobility deficits in people with HD; determine criteria for delivering the intervention and to highlight potential outcome measures that could be used to evaluate potential benefits. In terms of outcomes, it was relevant to examine literature related to outcome measures used in the assessment of factors related to deficits in gait, balance, muscle strength and health-related quality of life in this population.

Because of the very limited evidence available that is specific to exercise in HD, it was necessary to make inferences from evidence in other neurodegenerative diseases; searches therefore also included evidence related to exercise in Parkinson's disease (PD) and Alzheimer disease (AD). The main aim of this expanded search of literature was to develop the protocol of the delivered exercise programme in terms of determining key elements that needed to be incorporated into the intervention to ensure its acceptability and benefits.

This Chapter is divided into 5 sections. The first section will focus on methods of the search strategy; the other 4 sections will address the results and the discussion of the literature reviewed and the fifth section will address the study specific objectives and hypothesis.

2.2 Search strategy

2.2.1 Introduction

In total, 4 main literature searches were conducted:
Search 1 aimed to review evidence for physical factors related to mobility deficits in people with HD.

Search 2 aimed to review evidence in the exercise type interventions in managing mobility deficits in people with HD.
Search 3 aimed to review evidence in the home-based exercise interventions in managing mobility deficits in PD and AD.
Search 4 aimed to review evidence in the home use of exercise DVDs or videos in influencing adherence rate and physical outcomes in different populations.

The literature search for all the 4 searches was limited to English language journals. Comprehensive searches were conducted using the following electronic databases; PubMed (1966- February 2012), Medline (1969- February 2012), EMBASE (1980- February 2012), AMED (1985- February 2012). Bibliographies of all relevant studies and systematic reviews were searched by hand. The results were managed using End Note Version X3.

Key words for all 4 searches were structured using a population, intervention, comparison and outcome (PICO) approach [88]. Table 2.1 shows the search strategy used in Medline, AMED and EMBASE databases.

2.2.2 Search strategy for search 1

Population key words for search 1 included 'Huntington's disease', 'Huntington's' and 'chorea'. Because only observational studies were searched, intervention key words were not specified for this search. Outcome key words included, 'dystonia', 'daily living', 'mobility', 'posture', 'balance', 'postural control', 'falls', 'functional status', 'gait', 'muscle strength', 'quality of life'. Both prospective and retrospective observational studies were included if the paper identified factors in a sample of people with pre-manifest or manifest HD related to the following key words: physical activity, physical mobility, range of motion, posture, balance, postural control, muscle strength, gait and quality of life. The paper was excluded if all members of the population were aged <18 years and if the diagnosis of HD was not evident by a positive genetic test or a family history of HD.

2.2.3 Search strategy for search 2

Population key words for search 2 included 'Huntington' and 'chorea'. Intervention keywords included 'physical therapy', 'physiotherapy', 'rehabilitation', 'exercise therapy', 'exercise', 'stretching', 'strengthening'. Outcomes were searched using the following key terms: 'daily living', 'mobility', 'postural control', 'balance', 'posture', 'falls', 'functional status', 'gait', 'muscle strength', 'quality of life'. Studies were included if they investigated changes in mobility status following an exercise based intervention. Due to the limited amount of published papers, all publication types were considered; including review papers, conference proceedings, experimental trials, quasi experimental trials, observational trials and experts' opinion. Studies were excluded if all members of the population were aged <18 years and diagnosis of HD was not confirmed by a positive genetic test or a family history of HD with signs of chorea or if the intervention did not influence mobility status or function.

2.2.4 Search strategy for search 3

Population key words for search 3 included 'Parkinson's disease', 'multiple sclerosis' and 'Alzheimer disease'. Intervention keywords included 'physiotherapy', 'physical therapy', 'exercise', 'home exercise' and outcome keywords included 'balance', 'postural control', 'falls', 'functional status', 'mobility', 'gait', 'muscle strength', 'quality of life'. Full text randomised controlled trials and experimental studies which investigated changes in mobility status and function following a home based exercise programme in PD or AD were included. Exclusion criteria were if all members of the population were aged <18 years, the intervention was not fully or partly home-based, the intervention did not influence mobility status or function, or only one subject was studied.

2.2.5 Search strategy for search 4

There were no limits placed on the types of patient population. Keywords for intervention included: 'video', 'recording', 'DVD', 'home exercise'. Outcomes key words were 'compliance', 'adherence', 'physical'. Full text randomised controlled trials and experimental studies which investigated the influence of a home use of an exercise DVD or videotape on adherence rate and health outcomes were included. The study was excluded if the use of a DVD or videotape was not considered as part of the home-based

exercise programme and if compliance or adherence was not recorded or considered as an outcome measure.

Table 2.1: Summary of search strategy and records of findings

	Search 1	Search 2	Search 3	Search 4
Search strategy	1= Huntington* 2= Chorea 3= 1 OR 2 4= Dystonia 5= Daily living 6= Posture 7= Balance 8= Mobility 9= Postural control 10=Muscle strength 11= Gait 12= Functional 13= Falls 14= quality of life 15= 4 OR 5 OR 6 OR 7 OR 8 OR 9 OR 10 OR11 OR 12 OR 13 OR 14 16= 3 AND 15	1= Huntington* 2= Chorea 3= 1 OR 2 4= Physical therapy 5= Physiotherapy 6= Rehabilitation 7= Exercise therapy 8= Exercise 9= Stretching 10= Strengthening 11= 4 OR 5 OR 6 OR 7 OR 8 OR 9 OR 10 12= Daily living 13= Posture 14= Balance 15= Postural control 16= Muscle strength 17= Gait 18= Function 19= Falls 20= quality of life 21=12 OR 13 OR 14 OR 15 OR 16 OR 17 OR 18 OR 19 OR 20 22= 3 AND 11 AND 21	1= Parkinson* 3= Alzheimer* 4= 1 OR 2 OR 3 5= Physiotherapy 6=Physical Therapy 7= Exercise 8= Home 9= 5 OR 6 OR 7 OR 8 10= Daily living 11= Posture 12= Balance 13=Postural control 14=Muscle strength 15= Gait 16= Function 17= Falls 18= quality of life 19= 10 OR 11 OR 12 OR 13 OR 14 OR 15 OR 16 OR 17 OR 18 20= 4 AND 9 AND 19	1= Video* 2= Recording 3= DVD* 4= Exercise 5= Adherence 6=Compliance 7= 1 OR 2 OR 3 8= 5 OR 6 9= 4 AND 7 AND 8
Records retrieved	9,974	557	2,994	1,357
Records excluded by title or abstract	9,948	542	2,982	1,346
Records excluded by full text	5	4	6	4
Records included	21	11	6	7
Records identified by hand search	7	3	3	2
Total included	28	14	9	9

2.2.6 Search outcome

One reviewer (the PhD student) identified and reviewed all titles and abstracts followed by the full text of each paper. In total 14,882 papers were retrieved from the 4 conducted searches; 14,818 studies were excluded by the title, abstract or method and 19 studies were excluded by full text. Fifteen papers were identified by hand searching. Twenty eight of the included papers were related to mobility deficits in HD. Research conducted to investigate the benefits of exercise interventions in HD was very limited with only 10 studies identified. Two qualitative studies and 2 reviews were also included. Exercise interventions in PD appeared to be much more widely researched in areas relating to mobility deficits and therefore this search focused mainly on the studies related to home-based exercise interventions in which 7 papers were reviewed. An additional 2 papers related to home-based exercise interventions in AD were also included. Nine papers related to impact of the home use of an exercise videotape on adherence and health outcomes in different populations were included.

Details of study design, sample size, methods of assessment and/or intervention and the key findings were extracted and summarized in tables. Using the Critical Appraisal Skills Programme (CASP) appraisal tool [89], each of the included papers from search 1 and search 2 were critically appraised by one reviewer (the PhD student). The CASP tool is comprised of 3 appraisal sections: an assessment of study validity, an evaluation of methodological quality and presentation of results, and an assessment of external validity. The level of evidence from each paper included in the review for search 2 was classified according to Sackett's rules [90]. According to Sackett, there are 5 main levels of evidence for clinical interventions. At the highest level (Level 1) are interventions that have been validated with RCTs with low false-positive (alpha) rates and high power. Level 2 is where the intervention is supported by RCTs with high false-positive rates and low power. Level 3 applies when nonrandomized comparisons between concurrent, matched groups have been used. Alternatively, a group may be compared with their own performance at another point in time. Level 4 applies to nonrandomized group comparisons which includes experimentally controlled single-case time-series designs. Level 5 refers to case series without controls, where information is provided only on the outcome of patients without evidence of experimental design. Single case studies can be classified under this heading. Due to heterogeneity of populations, interventions and outcome measures, on each search, it

was not possible to carry out a meta-analysis. A narrative review of all included studies was therefore undertaken.

2.3 Mobility-related deficits in HD

2.3.1 Mobility-related deficits in HD and the International Classification of Functioning, Disability and Health (ICF) model

To allow for the integration of several perspectives regarding mobility deficits in this population, the International Classification of Functioning, Disability and Health (ICF) model of the World Health organisation (WHO) [91], which is commonly used in assessing mobility in neurological conditions, was applied in this review. The advantage of using the ICF is that it provides specific terminology that can be used to refer to a specific health condition which can be used by all health care professionals. Thus it provides a common international language for communication and research.

The ICF framework describes aspects of a person's health and health-related wellbeing at 3 levels; the individual body parts and functions, the individual as a whole (activity) and the individual in a social context (participation) [91]. Within the ICF framework, each of these 3 levels encompasses different domains. The ICF provides specific descriptions that can be used to refer to a specific domain. These descriptions provided by the ICF framework were used in this review to guide categorization of the mobility-related deficits in HD according to their relevant domains (Figure 2.1). Detailed discussion regarding the categorization of mobility-related deficits in HD in line with the ICF model is provided in the sections below.

In the context of the ICF, body structures can be defined as the anatomical parts of the body, whereas body functions are defined as the physiologic functions of body systems. A problem in body function or structure such as a significant deviation or loss is interpreted as impairment. As per the ICF, muscle strength can be seen as a function of the musculoskeletal system, whilst balance is an integrated function of the vestibular, visual, somatosensory as well as the musculoskeletal systems. In the health condition of HD, deficits in balance and muscle strength which are reported in the literature in HD [38, 44, 45, 92-98] represent main impairments in body functions in this population. Both muscle strength and balance are linked with the ability to move independently.

Balance and muscle strength form the foundation to undertake a wide range of mobility activities that constitute normal daily life, including walking, and therefore impairments in muscle strength and balance are known to have negative effects on mobility activities [99]. In people with HD, there is growing evidence to suggest that impairments in balance and muscle strength may restrict mobility [38, 45, 96]. Impairments in balance, predominantly, may place individuals with HD at increased risk of falls [38, 45]. Therefore this review focused on muscle strength and balance as two categories of physical impairments in people with HD.

Activity forms the intermediate level of the ICF model. As per the ICF, activity is the component of function which involves execution of a task or action by an individual [91]. Among the most important and common day-to-day activities are tasks that involve mobility components. WHO defines mobility as the "individual's ability to move about effectively in his/her surroundings" [100]. This definition however, informs only aspects of ambulant mobility. In a more general and comprehensive sense mobility can be defined as the process of moving oneself and of changing body position or location [101].

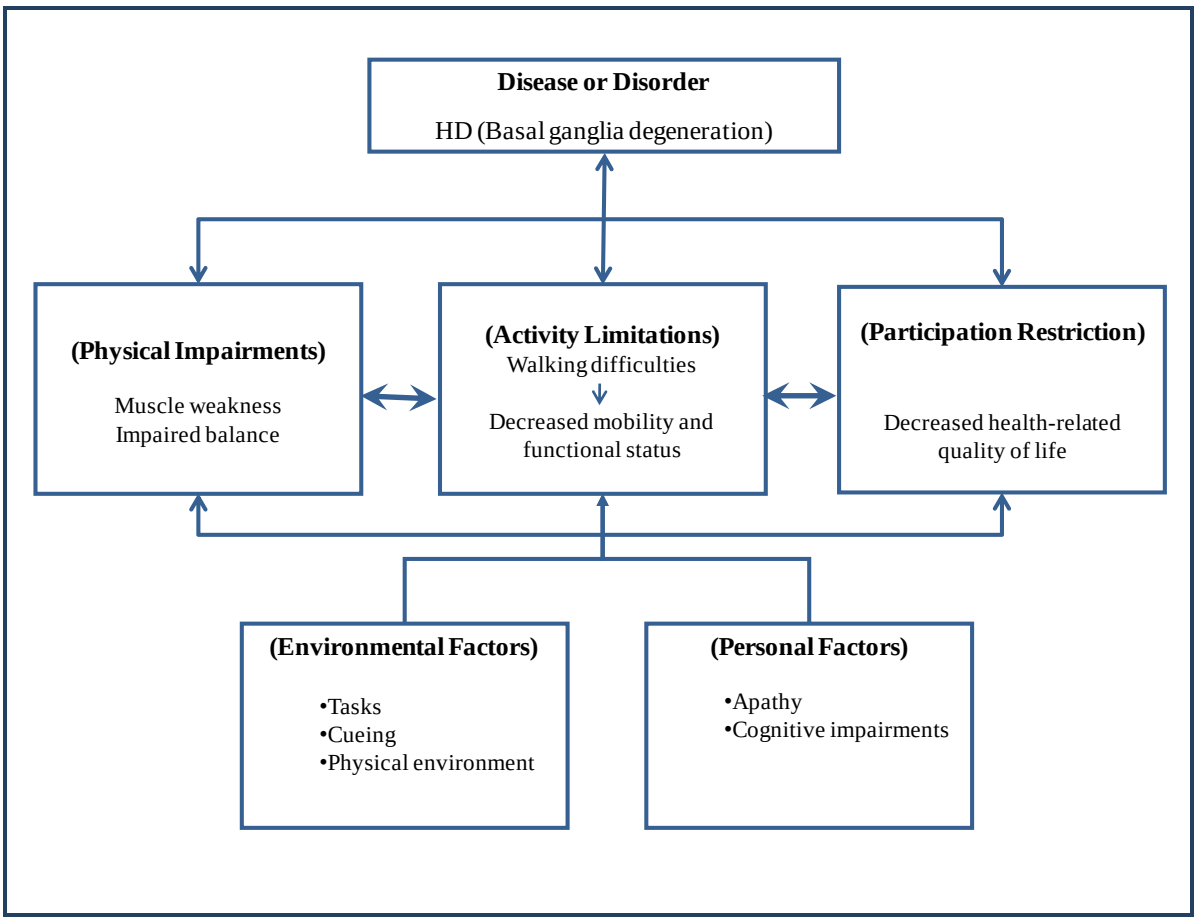
According to the ICF, a number of activities can be listed under the mobility domain and this review focused on evaluating the aspects of mobility that are believed to be limited in people with HD. This included aspects of mobility that incorporates walking, sit to stand, turning and stepping [91]. Walking in particular represents a common and an integral activity of daily life. It serves as an individual's basic need to move from one place to another. In people with HD, accurate data regarding limitations in walking are important, because loss of independence in ambulation is the greatest predictor of nursing home placement in this population [43]. For these reasons, aspects of limitations in walking and other forms of mobility activities in HD were addressed in this review.

Participation forms the third and the last level of the ICF. As per the ICF, participation can be viewed as the involvement in a life situation and participation restrictions as problems individuals may experience in involvement in life situations [91]. Participation may be best presented by health-related quality of life measures [102]. Quality of life can be defined as the physical, social and psychological functioning of an

individual as being influenced by a disease or therapy [103]. It refers to the subject's appraisals of their current level of health and functioning as well as satisfaction compared to what they perceive to be ideal. In people with HD, the progressive loss of mobility may put people at risk of falls and lead to functional dependence; the aspects that may detract from health-related quality of life [104]. For this reason aspects of quality of life related to mobility deficits in this population were also addressed in this review.

The ICF takes into account both the personal and environmental contexts that may impact on the functional performance of an activity. In people with HD, personal factors such as cognitive impairments and behavioural disturbances such as apathy [2, 38] as well as environmental factors such as the physical environment including the level of the supervision [80] and cueing strategies [105, 106] may have an impact on the mobility tasks that are performed. Figure 2.1 below shows how the different domains of the ICF in people with HD can be influenced by both individuals and environmental factors. The following sections will provide a detailed review of papers related to mobility deficits in HD across the 3 domains of the ICF model through the spectrum of the disease. Both personal and environmental factors and their influential impact on activity performance in HD will be discussed in detail in later sections in the context of exercise interventions in this population.

Figure 2.1: Physical impairments, activity limitations and participation restrictions related to mobility deficits in HD, structured according to the International Classification of Functioning, Disability and Health (ICF) model



2.3.2 Review of available studies related to mobility deficits in people with HD in line with the ICF model

In total 28 papers related to mobility deficits in HD were reviewed; of these, 7 studies were related to balance, 3 studies to muscle strength, 13 studies to gait deficits and 6 studies to deficits in other mobility activities such as sit to stand, stepping and turning. Furthermore, 4 papers related to health-related quality of life in people with HD were also reviewed. The vast majority of these studies were conducted with good methodological quality (according to the CASP critical appraisal tool). Summaries of these studies are provided in Tables 2.2; 2.3; 2.4 and a summary of their critical appraisal is provided in Table 2.5 below.

Table 2.2: Summary of papers included for body function, ICF categories: balance and muscle strength

	Authors/time	Subjects	Mean age (SD)	Main methods/outcome measures	Key findings
Papers related to balance impairments in HD	Kloos et al, 2011 [44]	MHD=94	MHD=50.8 (10.7)	Fall history in the previous 6 months / Tenitti mobility test (TMT) of balance	The TMT scores significantly predicted the risk of fall in HD
	Salomonczyk et al, 2010 [92]	MHD=11 PHD=22 HC=17	MHD=46.3 (3.2) PHD=42.4 (10.5) HC=39.2 (2.8)	Force platform/ 6 conditions of standing in which visual information was degraded	MHD had significantly greater postural sway on all conditions compared to PHD and HC PHD close to onset had significantly greater postural sway on conditions when visual information was degraded compared to PHD far to predict years of onset and HC
	Rao et al, 2009a [93]	MHD=30	MHD=53.2 (11.2)	Functional reach test (FRT)	FRT scores were worse in stage II compared to stage I and had worsened further worse in stage III compared to stage II FRT scores correlates with TFC, gait speed, CV step length
	Rao et al, 2009b [94]	PHD=15 HC= 15	PHD=38.9 (10.5) HC=39.5 (9.1)	Functional reach test (FRT)	No significant differences between PHD and HC in the FRT
	Busse et al, 2009 [45]	MHD=24	MHD=56.6 (11.7)	Fall history in the previous 12 months / Berg balance scale (BBS)	The BBS scores significantly predicted the risk of fall in HD
	Grimbergen et al, 2008 [38]	MHD=45 HC=27	MHD=51.1 (10.1) HC=52.2 (8.5)	Fall history in the previous 6 months and prospective falls monitoring for 3 months / BBS	BBS scores are significantly higher in fallers compared to non-fallers
	Tian et al, 1992 [95]	MHD=20 HC=20	MHD=53.1 (10.4) HC=51.2 (9.5)	Force platform / 6 conditions of standing in which visual, proprioceptive and vestibular cues were attenuated	Sway: for all tests the AP sway was significantly higher in MHD compared to HC Response to external protrusion: the latency to the initiation of the corrective response to sudden translation of the force platform, was prolonged in MHD compared to HC
Papers related to muscle weakness in HD	Busse et al, 2008 [96]	MHD=20 HC=20	MHD=51.7 (7.6) HC=48.9 (7.3)	Hand held dynamometer /6 muscle groups of hip, knee and ankle	MHD had on average about half the strength of HC Muscle strength indices in MHD correlated with TFC, the UHDRS motor score, functional assessment scale and independence scale
	Kosinski et al, 2007 [97]	PHD=1	PHD=37	Muscle biopsies/analysis of fibroblast culture	Deficits in mitochondrial function including deficiency in the complex IV cytochrome oxidase enzyme activity
	Saft et al, 2005 [98]	MHD=15 PHD=15 HC=37	MHD=43.7 (8.8) PHD=37.1 (9.6) HC=39.8 (8.1)	P magnetic resonance spectroscopy	Mitochondrial ATP synthesis and oxidative function were significantly lower in MHD and PHD compared to HC

MHD, manifest HD; PHD, pre-manifest HD; HC, healthy controls; CV, coefficient of variation; TFC, Total Functional Capacity scale; UHDRS, Unified Huntington's Disease Rating scale

Table 2.3: Summary of papers included for activity, ICF categories: gait, stepping, turning and sit to stand transitions

	Authors/time	Subjects	Mean age (SD)	Main methods/outcome measures	Key findings
Papers related to gait deficits in HD	Rao et al, 2011 [39]	PHD=10	PHD=38.6 (7.9)	Automated walkway / spatiotemporal gait parameters/ assessment at baseline, 1 year and 5 years later	Gait velocity significantly decreased and variability of stride length and swing time significantly increased over five years
	Delval et al, 2011 [107]	PHD=17 HC=25	PHD=36.5 (6.4) HC=36.0 (7.3)	Force platform and 3D camera system / gait parameters of the first 4 to 5 steps under self triggered condition	1st and 2nd step speed and length significantly decreased in PHD compared to HC
	Tabrizi et al, 2009 [108]	MHD=123 PHD=120 HC=123	MHD=48.8 (9.9) PHD=40.8 (8.9) HC=46.1 (10.2)	Automated walkway/spatiotemporal gait parameters at self selected speed	CV% stride length was significantly higher in both MHD and PHD when compared with HC
	Busse et al, 2009 [45]	MHD=24	MHD=56.6 (11.7)	Fall history in the previous 12 months / walking speed (10 m walk test)	Gait speed was significantly lower in fallers compared to non-fallers
	Rao et al, 2008 [40]	MHD=30 PHD=15 HC=20	MHD=50.2 (9.2) PHD=36.9 (2.1) HC=44.3 (9.1)	Automated walkway / spatiotemporal gait parameters at self selected speed	Gait speed, stride length, double support time, % of stance time, CV stride length, CV step time decreased in MHD and PHD when compared with HC
	Delavl et al, 2008 [109]	MHD=15 HC=15	MHD=43.9 (9.8) HC=40.5 (10.5)	Video motion system/spatiotemporal gait parameters/ walking under 3 conditions; free gait, walking with dual motor task, walking with dual cognitive task	Significant differences between MHD and HC in all conditions in cadence, stride length, gait speed and CV of all these parameters
	Grimbergen et al, 2008 [38]	MHD=45 HC=27	MHD=51.1 (10.1) HC=52.2 (8.5)	Fall history in the previous 6 months and prospective falls monitoring for 3 months / automated walkway (spatiotemporal gait parameters)	MHD people had a decreased gait velocity and decreased stride length and stride length CV compared to HC MHD-fallers had significantly greater stride length CV compared to MHD non-fallers
	Delval et al, 2007 [41]	MHD=15 HC=15	MHD=47.3 (10.2) HC=40.5 (10.5)	Force platform and 3D camera system/ gait parameters of the first 4 to 5 steps under self triggered condition	1st and 2nd step speed and length decreased and step duration increased for MHD compared to HC
	Bilney et al, 2005 [110]	MHD=30 HC=30	MHD=51.2 (10.6) HC=50.9 (11.6)	Clinical stride analyzer / spatiotemporal gait parameters/walking at self selected slow, preferred and fast speeds	Slow, preferred and fast walking: cadence, stride length were significantly lower and CV of stride length was higher in MHD comparing to HC
	Churchyard et al, 2001 [111]	MHD=20 HC=16	MHD= 50.2 (9.2) HC= 52.2 (8.5)	Clinical stride analyzer/ spatiotemporal gait parameters/walking at self selected slow, preferred and fast speeds	Preferred gait speed: (compared to MHD): decreased velocity, stride length, cadence and increased variability. Slow and fast gait speed: (internal cue)(compared to HC): MHD group could modify velocity and stride length but velocity, stride length, and cadence remained less than for HC

Table 2.3: *(continued)* Summary of papers included for activity, ICF categories: gait, stepping, turning and sit to stand transitions

	Authors/time	Subjects	Mean age (SD)	Main methods/outcome measures	Key findings
Papers related to gait deficits in HD	Hausdorff et al, 1998 [112]	MHD=20 PD=15 HC=16	MHD=47 (11.3) PHD=67 (12.8) HC=39 (10.4)	Force sensitive insoles / walking at self selected walking speed/spatiotemporal gait parameters	All measures of gait variability were increased in PD and even more in MHD when compared to HC
	Hausdorff et al, 1997 [113]	MHD=17 HC=10	MHD=46.8 (12.8) HC=34.5 (13.4)	Force sensitive insoles / walking at self selected walking speed/ α; a measure of the degree to which one stride interval is correlated with the previous and subsequent intervals over different time scale was calculated	α was lower in MHD when compared with HC α was significantly correlated with disease severity (TFC)
	Koller and Trimble, 1985 [32]	MHD=13 HC=10	MHD= 57.3 (10.2) HC= 53.2 (11.2)	Clinical stride analyzer / spatiotemporal gait parameters at self selected gait speed	Gait speed, stride length and cadence decreased in MHD and stride time increased compared to HC
Papers related to deficits in stepping, turning and sit to stand transitions	Panzera et al, 2011 [114]	MHD=11 HC=17	MHD=47.1 (11.0) HC=39.2 (2.8)	Force platform/ COG sway and velocity in 3 tests 1) step up and over an obstacle 2) sit to stand 3) step and turn.	MHD developed significantly less rising force during the step up and over test and also during rising up from a chair compared to HC Sway velocity of COG was significantly higher for MHD when performing the sit-to-stand and step and turn tests
	Goldberg et al, 2010 [115]	MHD=14 HC=9	MHD=46.5 (9.1) HC=40.8 (12.1)	Multi- operational Apparatus for Reaction time / stepping response time	Stepping response time was significantly lower in MHD comparing to HC
	Khalil et al, 2010 [116]	MHD=10 PHD=5 HC=6	MHD=57.3 (10.2) PHD= 47.3 (10.4) HC=48.3 (17.1)	Triaccelerometer/ duration, slopes and ranges of sit to stand transitions during the timed Up and Go test	TUG duration, sit to stand duration, slope and range were significantly worse in MHD when compared with HC Sit to stand duration and slope were significantly worse in PHD when compared with HC
	Rao et al, 2009a [93]	MHD=30	MHD=53.2 (11.2)	Timed Up and Go test (TUG)	TUG scores were significantly worse in stage II compared to stage I and further worse in stage III compared to stage II TUG scores correlate with TFC, gait speed, CV step length
	Rao et al, 2009b [94]	PHD=15 HC= 15	PHD=38.9 (10.5) HC=39.5 (9.1)	Timed Up and Go test (TUG)	No significant differences between PHD and HC in the TUG
	Busse et al, 2009 [45]	MHD=24	MHD=56.6 (11.7)	Fall history in the previous 12 months / Timed Up and Go test (TUG)	The TUG scores significantly predicted the risk of fall in HD

MHD, manifest HD; PHD, pre-manifest HD; HC, healthy controls; PD, Parkinson's disease; CV, coefficient of variation; TFC, Total Functional Capacity scale; COG, centre of gravity

Table 2.4: Summary of papers included for participation, ICF category: health-related quality of life

	Authors/time	Subjects	Mean age (SD)	Main methods/outcome measures	Key findings
Papers related to deficits in health-related quality of life in HD	Ho et al, 2009 [117]	MHD=70	MHD=50.1 (11.9)	QoL / SF-36/control data obtained from previous publication	SF-36 scores in MHD decreased comparing to the control data SF-36 scores significantly correlated with UHDRS-motor, TFC and BDI scores
	Ready et al, 2008 [118]	MHD=22	MHD=47.3 (13.2)	QoL / study-specific developed questionnaire	QoL scores significantly correlated with UHDRS-functional and cognitive scores
	Ho et al, 2004 [119]	MHD=79 CG=79	MHD=55.2 (11.9) CG=54.7 (11.4)	QoL / SF-36, SIP	SF-36 and SIP scores is significantly lower in MHD when compared to CG SF-36 and SIP sub-scales correlated significantly with UHDRS-motor and BDI scores
	Hedler et al, 2001[120]	MHD=77 HC=74	MHD=51.4 (11.4) HC=52.3 (8.2)	QoL; SIP	SIP scores were significantly lower in MHD when compared to HC SIP scores significantly correlated with UHDRS-motor scores, disease duration and MMS scores UHDRS-motor was the only disease specific variable to significantly predict SIP score

MHD, manifest HD; HC, Healthy controls; CG, care-giver; QoL, Quality of life; SF-36, Short form 36; SIP, Sickness impact profile; UHDRS, Unified Huntington's disease rating scale; TFC, Total functional capacity scale; BDI, Beck Depression Inventory scale; MMS, Mini Mental status score

Table 2.5: Summary of the critical appraisal of papers related to mobility deficits in HD

Authors/time	Focused question	Appropriate method	Acceptability of cases recruitment	Acceptability of control selection	Appropriate outcome measures	Accounting for confounding factors	Appropriate data analysis	Appropriate results	Can the results be applied to local population	Fitness of results with other available evidence
Rao et al, 2011[39]	Yes	Yes	Yes	NA	Yes	Yes	Yes	Yes	Yes	Yes
Delval et al, 2011[107]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Panzera et al, 2011[114]	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	NC	Yes
Kloos et al, 2011 [44]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Salomonczyk et al, 2010 [92]	Yes	Yes	Yes	Yes	Yes	No	Yes	NC	NC	Yes
Goldberg et al, 2010 [115]	Yes	Yes	Yes	NC	Yes	Yes	Yes	Yes	Yes	Yes
Khalil et al, 2010 [116]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Tabrizi et al, 2009 [108]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Rao et al, 2009a [93]	Yes	Yes	Yes	NA	Yes	Yes	Yes	Yes	Yes	Yes
Rao et al, 2009b [94]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Busse et al, 2009 [45]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Ho et al, 2009 [117]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Rao et al, 2008 [40]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Delavl et al, 2008 [109]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Busse et al, 2008 [96]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Grimbergen et al, 2008 [38]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Ready et al, 2008 [118]	Yes	Yes	Yes	NC	Yes	Yes	Yes	Yes	Yes	Yes
Delval et al, 2007 [41]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Kosinski et al, 2007 [97]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Bilney et al, 2005 [110]	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes
Saft et al, 2005 [98]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Ho et al, 2004 [119]	Yes	Yes	Yes	NC	Yes	Yes	Yes	Yes	Yes	Yes

*Items of critical appraisal are derived from the Critical Appraisal Skills Programme (CASP) appraisal tool [89]; NA, Not applicable; NC, Not clear

Table 2.5: *(continued)* Summary of the critical appraisal of papers related to mobility deficits in HD

Authors/time	Focused question	Appropriate method	Acceptability of cases recruitment	Acceptability of control selection	Appropriate outcome measures	Accounting for confounding factors	Appropriate data analysis	Appropriate results	Can the results be applied to local population	Fitness of results with other available evidence
Churchyard et al, 2001 [111]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Hedler et al, 2001 [120]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Hausdorff et al, 1998 [112]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Hausdorff et al, 1997 [113]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Tian et al, 1992 [95]	Yes	Yes	NC	NC	Yes	No	No	NC	NC	Yes
Koller and Trimble 1985 [32]	Yes	Yes	NC	NC	Yes	No	Yes	Yes	NC	Yes
*Items of critical appraisal are derived from the Critical Appraisal Skills Programme (CASP) appraisal tool [89]; NA, Not applicable; NC, Not clear										

2.3.2.1 Physical impairments in body structure and function

2.3.2.1.1 Balance

In people with HD, impairments in balance are well characterized particularly at the mid stage of the disease [38, 44, 45, 92-95]. Two studies [92, 95] investigated aspects of static balance whilst standing on a stationary platform in people with manifest HD and demonstrated increased antero-posterior sway when compared to controls (Table 2.2). The postural sway increased when visual feedback was not available [92, 95]. On imposing an external perturbation by unexpected movement of the support platform, corrective postural responses were of similar magnitude compared to control groups, but they were significantly delayed in people with HD [95]. Thus it appears that greater postural sway may be related to deficits in using sensory cues rather than being a primary postural impairment.

In addition to static balance, aspects of impairments in dynamic balance and internal protrusion were documented in people with manifest HD using clinical tools. In one study, 2 clinical balance tools (Functional Reach Test (FRT) and the Berg Balance Scale (BBS)), were used to assess balance in a sample of 30 subjects with manifest HD [93]. The FRT evaluates response to internal perturbation and the BBS includes a number of items that test static and dynamic balance as well as response to internal perturbations. The study demonstrated significant differences in balance as scored using these 2 tests between subjects with manifest HD and healthy controls and between subjects with manifest HD at different stages of the disease. The latter finding suggests that balance impairments in this population continue to progress with the progression of the disease. In fact there are some indications that impairments in both static and dynamic balance may start well in the pre-manifest stage, before the onset of clinical symptoms, and continue to worsen in the manifest stage in this population. Individuals with pre-manifest HD who were close to their predicted age of onset ($\leq$ 5 years) demonstrated greater postural sway compared to healthy controls in standing on a stationary force platform, when the visual and proprioceptive information was degraded and only vestibular information was available [92]. Although this study was limited by the small sample size and the failure to report clear information about how the control group was recruited and how factors such as age and height were controlled, it was one of the first to report on balance impairments in the pre-manifest stage. Findings from this study were consistent with data from another study in which participants with pre-

manifest HD demonstrated an increased base of support whilst walking (an indication of impaired dynamic balance) when compared with healthy controls [40].

The findings from the above 2 mentioned studies about the existence of balance impairments in the pre-manifest stage contradicts reports from a single study by Rao et al [94], where the authors report no significant differences in balance between individuals with pre-manifest HD and healthy controls as measured using the Functional Reach Test (FRT) [94]. The small sample size of this study (n=15 pre-manifest HD and 15 healthy controls) may explain the lack of sensitivity of the FRT test to detect balance changes in the individuals with pre-manifest HD. More importantly, there is a possibility that the sample in this study was far to the predicted age of onset; an aspect that was not clearly reported by the authors. The other possibility is that this test may be inappropriate to measure balance in individuals with pre-manifest HD as the other studies that demonstrated impaired balance at this stage were based on biomechanical quantitative measures that can be sensitive to subtle changes. There is a potential that other clinical assessment tools which incorporate more complex patterns of movement may be able to capture subtle changes in balance at this very early stage of the disease. Therefore validation of such measurement tools in future studies is clearly required.

Assessment of balance in this population may be an important component, as there is a growing evidence to suggest that balance impairments may restrict mobility in people with HD. Three of the 4 studies that screened falls in HD demonstrated that impairments in balance predominantly may place people with HD at increased risk of falls. In a study by Grimberg et al [38] that included 45 participants at early to mid stage HD, recurrent fallers (participants who had at least 2 falls in the last 12 months) had significantly lower performance on the Berg Balance Scale (BBS) when compared with non-fallers. Similarly, in a study by Kloos et al [44], recurrent fallers had significantly lower balance scores on the Tinetti Mobility Test. Furthermore, in a study by Busse et al [45] which was conducted in 24 participants at mid stage HD, balance as measured using the BBS was a significant predictor for the risk of falls in this population. Taking into account these observations and the fact that the risk of falls is the number one predictor for loss of functional independence in HD [43], assessment of balance in people with HD is clearly important and needs to be targeted in therapeutic trials in this population.

2.3.2.1.2 Muscle strength

Only one study was identified in this review that assessed the muscle strength of the lower limbs in people with HD (Table 2.2). In this study, Busse et al [96] measured the isometric muscle strength of 6 lower limb muscle groups (hip extension, hip abduction, knee flexion, knee extension, ankle plantarflexion, ankle dorsiflexion) using a hand held dynamometer in 20 subjects with manifest HD and 20 healthy age-matched controls. A maximal muscle strength index was calculated in which contribution from all muscle groups was combined into a single index. People with HD were significantly weaker relative to an age matched healthy control group. This was reflected both in the individual muscle groups as well as by the maximal strength index. Although this study is limited by the use of the hand held dynamometer which is known to have greater error in assessing muscle strength in neurological populations [121, 122], it is the first one to report muscle strength reduction of the lower limbs in people with HD. It should be noted however, that the muscle strength reduction in people with HD has also been implied in other studies that focused on evaluating muscle strength of the upper limbs [123, 124]. This lends support to the existence of muscle strength reduction in this population. For example, grip force reduction and the increase of its variability was reported in people with early to mid stage HD [123]. Furthermore, the effects of creatine supplementation in people with HD were studied over a period of 1 year [124]. In this study, a 5 - 10% reduction in muscle strength of elbow flexors over time was recorded in people with HD.

The assessment of muscle strength of the lower limbs in HD may be important as it is known that muscle strength reduction in other populations is inter-linked with a decline in functional performance [125]. In fact, the study by Busse et al [96] reported significant correlations between functional and motor scores (TFC, the UHDRS-motor, functional assessment and independence scales) ($r>0.45$, $p<0.05$) and strength indices, suggesting that muscle weakness may contribute to functional decline in people with HD. Further in-depth analysis is still required to interpret the influence of the muscle strength reductions on functional performance of mobility activities of daily living in people with HD. However, it should be noted that some insights can be drawn from available literature on other neurodegenerative disease such as PD. In people with PD, reduction of muscle strength of the lower limbs correlates well with reduced ability to perform mobility activities such as navigating stairs, rising from a chair and walking

[125, 126]. In the realm of walking, strength of the ankle, knee and trunk was found to be positively correlated with gait speed in individuals with PD, and knee strength explained about 15% of the variance in the gait speed while individuals with PD were on medication [126]. These relations between muscle strength and the functional performance of mobility activities, such as walking in people with PD, are important and provide insights into exercise interventions. Exercise interventions that aim to improve muscle strength may also have a positive impact on mobility activities such as walking.

The origin of muscle strength reduction in the HD population is unknown; however it can be as a result of multiple components. For example, the alteration of muscle tone seen in HD secondary to dystonia [35] may impair the ability to produce a maximum voluntary muscle contraction effectively, leading to a reduction in the muscle strength. Furthermore, biological changes in skeletal muscle tissue such as mitochondrial dysfunction and morphological changes of neuromuscular junctions which have been observed in individuals with HD [97, 98] may potentially impact on muscle strength in this population. Deficits in mitochondrial function have even been identified in individuals with pre- manifest HD [97], which suggests that skeletal muscle changes may start to develop years before the onset of clinical diagnosis, although this has not been empirically studied.

In addition to the above mentioned factors, loss of muscle strength in HD can be secondary to physical inactivity. Although an in-depth activity monitoring has not been carried out yet in people with HD, there are some reports to suggest that people in this population tend to be physically less active with the progression of the disease [127]. This is in agreement with the evidence available from other neurological diseases of a relationship between decreased physical activity and worsening of the voluntary motor symptoms [128, 129]. Physical inactivity induces further plastic changes to the muscular tissues such as fibre-type transformations and protein loss [130]. In such cases, the reduction of muscle strength would be generalised to all the inactive muscle groups. The findings reported by Busse et al [96] of a non-specific pattern of muscle strength reduction (muscle weakness was not restricted to a particular muscle group of the lower limbs) lends the support of physical inactivity as one contributing factor of muscle weakness in this population. Taking into account that muscle weakness in HD

may be secondary to physical inactivity along with the other factors provides further support for the need to consider exercise interventions in this population. Muscle strength reductions as a result of physical inactivity have the potential to be ameliorated by exercise interventions [125]. Improvements of muscle strength in other neurodegenerative disease and in the elderly with sedentary life styles, as a result of exercise interventions are well documented [125].

In conclusion, reduction in muscle strength, although it is an under reported clinical feature across the spectrum of the disease in HD, may be an important component. The suggestion that impairments in muscle strength can contribute to mobility deficits in this population and that these impairments can be amenable to exercise interventions, emphasizes the need for assessing muscle strength in future exercise trials in HD.

2.3.2.2 Activity

2.3.2.2.1 Walking

Walking represents a common and an integral activity of daily life. It serves as an individual's basic need to move from one place to another. In people with HD, deficits in walking are the most prominent of mobility limitations. Accurate data regarding limitations in walking are important, because loss of independence in ambulation is the greatest predictor of nursing home placement in this population [43]. In particular, knowledge about specific deficits in gait in this population may be crucial as gait deficits such as decreased walking speed and increased stride to stride variability were associated with a higher risk of falls in people with HD [38, 44, 45].

Thirteen studies have examined the characteristics of gait in this population [32, 38, 40, 41, 45, 106-113]. The vast majority of these studies have focused on the spatiotemporal aspects (time and distance) of the foot pattern. Most of these studies have been carried out in gait laboratories or hospital ward settings. Most studies have demonstrated that bradykinesia, hypometria, akinesia, and greater variability of movement are the main features of gait in HD (Table 2.3). In terms of temporal measures, a number of studies have shown that people with manifest HD walk more slowly than usual, typically in the range 0.76-1.09 m/s, rather than 1.02-1.4 m/s which is typical for age-matched controlled subjects [32, 40, 41, 110-112]. These studies also demonstrated that people

with HD had lower cadence, stride time, and higher double support time than control subjects. With respect to spatial measures of gait, subjects with HD showed shorter stride length at fast, slow and preferred walking speeds compared to control subjects. The stride length at the preferred walking speed in manifest HD ranged from 0.74-1.2 m rather than 1.3-1.5 m as would be expected from age matched controls in these studies. Reduced step length, step time and gait speed in manifest HD tend to become more accentuated while performing a secondary cognitive or motor task such as counting backwards [109, 111] or carrying a tray [109], suggesting that the automaticity of executing motor tasks in HD is primarily impaired. Thus performing dual motor or cognitive tasks may place greater attentional demands on people with manifest HD than they do in healthy controls. Other abnormalities of walking in HD have been observed during gait initiation, in which people with HD demonstrated lower first step speed and length compared to controls [41] suggesting that akinesia is an important component of locomotion disorders in HD.

One of the prominent features of gait deficits in this population that has been reported in a number of studies and has been demonstrated even at a very early stage of the disease is increasing variability of gait. Individuals with manifest HD have been found to have greater variability in gait speed from trial to trial [111]. Greater variability in HD has also been noted in stride time, stride length, swing time and double support time compared to controls [40, 110-112]. Quantitative evaluation indicates that variability in stride intervals in manifest HD tends to be more random when compared to age matched healthy controls [113]. This means that the correlation of one stride with nearby strides is reduced; suggesting that individuals with HD may have difficulty in using sensory feedback to alter their walking in an ongoing manner, which may influence the quality and adaptability of their walking.

Gait deficits present throughout the course of the disease and there is a growing evidence to suggest that these deficits may start from the pre-manifest stage [40, 107, 108]. People with pre-manifest HD have been found to have decreased gait speed and stride length, increased step time, double support time and percentage of time in stance [40] and increased stride length [40, 107, 108] and step time variability [40, 107] when walking along a computerized walkway that recorded the spatiotemporal parameters of gait and their variability. Furthermore, individuals with pre-manifest HD have been

found to have deficits in gait initiation under self triggered and externally triggered conditions in which the first step speed, duration and length was reduced and variability of stride length and time increased compared to gene negative, age matched controls, as measured using a video motion system connected to two force platforms [107]. Longitudinal analysis demonstrated that these deficits in gait worsen over time in the pre-manifest stage. A study that examined gait in ten subjects with pre-manifest HD over a period of five years demonstrated significant decrease in gait speed and increase in gait variability as measured using the stride length and swing time coefficient of variations [39].

The origin of increased gait deficits in HD is still not clearly understood. In people with neurodegenerative disease such as HD, deficits in the central nervous system's ability to regulate motor output could be a contributing factor, but many physical associated changes that have been reported in HD can also contribute to this process, including muscle weakness and impaired balance. As mentioned earlier, gait deficits are likely to place people with HD at increased risk of falls [38]. These deficits may also contribute to self-imposed mobility restrictions and detract from quality of life [104]. It is not surprising that many people with HD may report that physical activities in general and levels of mobility in the community in particular are significantly affected, although monitoring of mobility activities has not yet been empirically studied in this population. It can be suggested that because of the walking difficulties observed in this population, people with HD find it difficult maintaining their balance over uneven surfaces and successfully monitoring changes in the surrounding environment, which may affect their levels of mobility in the community. Overall, it must be noted that gait deficits may be an important component of activity limitations in HD and as such may be amenable to exercise interventions [104] and therefore they need to be considered in future trials.

2.3.2.2.2 Other mobility activities

In addition to walking; sit to stand, turning and stepping are other activities that are limited in people with HD [114, 116]. In general, these activities are essential to change body position, negotiate obstacles and monitor changes in the surrounding environment. In particular in the realm of sit to stand, rising from a seated to a standing position is one of the most common activities of daily living, it is a prerequisite for walking, and is

particularly important to maintain physical independence [131], which makes this an important activity to be evaluated in people with mobility deficits such as people with HD.

Six studies were identified in this review that examined aspects related to these mobility activities (sit to stand, turning and stepping) in people with HD [45, 93, 94, 114-116] (Table 2.3). In one study, deficits, particularly in stepping in manifest HD, were examined [115]. The study demonstrated that people with HD had a significantly and markedly reduced stepping response time when compared to healthy controls. In a more recent study [114], the performance of 3 mobility activities (step up and over an obstacle, sit to stand transition and step up and turn) in individuals with manifest HD was examined using kinetic and kinematic data. The study demonstrated that the HD group were significantly slower when moving from a seated to standing position, when stepping and turning and when stepping onto and over an obstacle, confirming clinical observations that bradykinesia is a marker of HD when completing mobility activities. In addition, the HD group in this study developed less rising force during the sit to stand test and experienced greater velocity in centre of gravity (COG) sway during the sit to stand as well as step and turn tests. This gives further insights into how postural deficits in this population may affect the performance of functional activities. The production of less rising force during the sit to stand test, which indicates that the performance of such activity is challenging for individuals with HD, is consistent with the previous reports of reduced muscle strength of the lower limbs of individuals with HD [96]. Furthermore, the greater COG sway velocity indicates that control of posture, which may be related to the balance impairments seen in this population, significantly challenged the performance of such activities, even though the individuals with HD tend to move with slower movement time than the controls.

The combination of sit to stand and turning was further assessed in another study [94] using a clinical assessment tool (the Timed UP and Go (TUG) test). The performance of the TUG test times a task that requires walking, turning and transfer from sit to stand. The study demonstrated that people with HD were slower in completing this test when compared with healthy controls. In a study by Busse et al [45] which was conducted in participants at mid stage HD, mobility status as measured using the TUG was a significant predictor for the risk of falls in this population. In a follow-up study [116],

the performance of the TUG test was assessed along the spectrum of the disease using a kinetic sensor. The total TUG duration as well as slopes, range and durations of sit to stand transitions were extracted from the sensor. Results obtained from this study demonstrated that the sensor derived measures detected decreased TUG duration, decreased slopes, range and duration of sit to stand transitions of the test in the individuals with manifest HD when compared with healthy controls. More importantly, findings from this study demonstrated that the sensor derived measures detected decreased slopes and durations of the sit to stand transitions of the test in individuals with pre-manifest HD when compared to healthy controls. The findings from this study are important and suggest that subtle changes in the performance of such mobility activities may start to develop from the pre-manifest stage.

Although data of sit to stand, turning and stepping activities are limited in the HD literature, particularly along the broad spectrum of the disease, assessing HD in the context of these tasks is important. The inability to successfully complete these "every day" activities can negatively impact life style and affect health-related quality of life [132]. As exercise interventions that target impairments such as muscle strength and balance have the potential to simultaneously improve performance in such activities [125, 132], assessing these activities in future exercise interventions in HD is required.

2.3.2.3 Participation

As indicated earlier, participation may be best presented by health-related quality of life. In medical care, health-related quality of life has become firmly established as an important endpoint [133]. This is especially true of chronic disease for which a cure is unlikely [134] and HD is a classical example of such a long-term condition. Therefore, the evaluation of health- related quality of life in this population is important.

Four studies were identified in this review that evaluated health-related quality of life in people with HD [117-120] (Table 2.4). In all of these studies, findings suggest that HD has an effect on individuals' health-related quality of life. Using generic health-related quality of life measures such as the Short Form- 36 (SF-36) and the Sickness Impact profile (SIP), individuals with mild to moderate HD reported a lower quality of life than population norms.

In individuals with HD, factors such as the depressive mood, cognitive and motor impairments, as well as functional dependence, may contribute to a reduced quality of life [117-120]. Of these factors, motor impairments and functional independence appear to have the most detrimental effect on health-related quality of life in this population. In 3 studies motor impairments, as measured using the UHDRS-motor scale, were found to significantly correlate with the measures of health-related quality of life [117, 119, 120]. In one of these studies which examined the effects of cognitive and motor impairments as well as disease duration on health-related quality of life, motor impairments were the only disease-specific factor which significantly predicted health-related quality of life [120]. In 2 other studies, functional abilities as measured by the Unified Huntington's Disease Rating Scale (UHDRS)-functional score [118] and the Total Functional Capacity (TFC) scale [117] were also found to significantly correlate with measures of health-related quality of life. These data are consistent with findings that motor impairments and a decline in functional performance tend to be robust predictors of quality of life in other populations with mobility disorders [135]. In HD, motor impairments are common and very obvious. As described earlier, these impairments may contribute to the mobility deficits seen in this population such as difficulties in walking. The suggestion that motor impairments and decline in functional performance are related to quality of life in this population is important and has clear implications for clinical trials of exercise interventions. Exercise interventions that target motor impairments and functional limitations in people with HD show promise in simultaneously improving health-related quality of life [136]. For these reasons, assessing health-related quality of life in clinical trials of exercise interventions is clearly required.

2.3.3 Summary of literature review of mobility-related deficits in HD and the need to validate outcome measures in line with ICF model

In developing appropriate trials of exercise interventions to improve mobility in HD, it is important to consider ways in which clinical improvements can be measured. The UHDRS is a disease specific scale that is routinely used to quantify the severity of the disease in HD. Although the scale is highly reliable in people with HD, it may not be specific to measure changes in the functional abilities as a result of exercise interventions in this population. For example, such a scale may lack the sensitivity to identify clinically related changes at the early stages of the disease due to ceiling

effects. In a multisite, observational study of 786 research participants at the pre-manifest and early stages of HD, over 88% of the participants were scored at ceiling as having the maximum score on both the Total Functional Capacity (TFC) scale and the Functional Assessment Scale (FAS) [137]. Similarly in two studies, 95% to 100% of the individuals at pre-manifest stage scored at the ceiling on gait, tandem walk and retropulsion items of the motor section of the UHDRS. The fact that the UHDRS is an ordinal type of measure may have influenced its sensitivity to detect early changes in this population. Ratio or interval measures based on timing certain tasks instead, as suggested based on observations from other neurological populations, can to be more sensitive to a wide spectrum of severity of impairments and functional losses [138]. Such measures need to be considered when evaluating mobility deficits in people with HD and in response to exercise interventions.

Taking into account the wide range of physical impairments, activity limitations and participation restrictions seen in this population (Figure 2.1), the choice of outcomes to evaluate mobility deficits in HD may be best considered in the light of the ICF model. As depicted in Figure 2.1, at the impairments level, physical factors that are believed to be impaired in this population and are potentially modifiable by exercise interventions need to be considered. This includes balance and muscle strength. At the participation level, aspects that are believed to be restricted by mobility deficits such as health-related quality of life which can be positively influenced by exercise interventions need to be taken into account. At the activity levels, although tasks such as sit to stand and stepping and turning need to be considered, activity limitations may be best presented by walking difficulties in this population. In particular, deficits in gait parameters need to be taken into account. As described earlier, deficits in gait are well characterized in HD. Increased gait variability in particular is known to exist early in the life cycle of HD and progress over time [39, 40, 107, 108]. Furthermore, increased gait variability relates to functional status in this population [38], and the amelioration of this component of gait has the potential to translate into functional improvement [104]. This makes gait variability one potential primary outcome measure in exercise interventions in this population.

In the realm of walking, it must be noted that the ICF framework results in an increased emphasis on the need to consider both the performance and capacity measures of an

activity in assessing people with mobility deficits [91] as is the case in people with HD. Capacity can be defined as the highest probable level of functioning that a person may reach in a given domain at a given moment, whilst performance represents what an individual does in his/her environment. Gait parameters such as gait variability that can be derived from directly observed tests administered in standardized laboratory settings are thus more likely to evaluate capacity of walking. The assessment of an individual's walking performance (what they actually do) may include measures of the number of paces over a representative time period in the community. These measures that provide indications of individuals' performance need to be taken into account along with those measures that provide indications of capacity in assessing walking of people with HD in therapeutic trials.

In clinical trials, the used outcome measures need to be valid and reliable. As described earlier, measures of gait have been extensively validated using quantitative laboratory assessment tools in this population. However, to date only a few studies have examined the validity of a range of measures of balance [38, 45, 94], muscle strength [96], health-related quality of life [117, 119, 120] and measures of other mobility activities [45, 93] with no validation for any measures of levels of mobility carried out in the community. There is clearly a need to further validate clinical measures of the range of physical impairments, activity limitations and participation restrictions which are related to mobility deficits seen in this population. The validation of these outcomes may be best considered in the context of the proposed model of the ICF of the mobility deficits in HD (Figure 2.1). As indicated earlier, gait variability at the activity level is a primary component of gait deficits in HD that can be linked with measures at the impairments level (muscle strength and balance) and it may have an impact on measures at the same level (functional performance of ADL and community mobility) as well as measures at the participation level (health-related quality of life). Validation of mobility outcomes in HD, therefore, may require primarily exploring these inter-relations between measures of balance, muscle strength, health-related quality of life as well as levels of mobility carried out in the community with the primary component of gait deficits (gait variability).

As noted before, valid outcome measures in neurological diseases need to be sensitive to the spectrum of impairments and functional losses seen in a population [138]. In

people with HD, there is clearly a need for outcome measures that are sensitive to the very early changes seen in the pre-manifest stage. The ultimate goal of therapeutic trials in HD is to develop treatments that prevent, slow down or modify the disease process [139] which are targeted to be applied at the pre-manifest stage, before the onset of rapid neuronal degeneration and the emergence of clinical symptoms. Thus clinical tools that are sensitive to change in pre-manifest HD are needed for such trials. To date, and apart from the gait measures, there are very limited data on validation measures of balance, muscle strength, other tasks of mobility and community walking as well as health-related quality of life in individuals with pre-manifest stage. Only 2 studies investigated the sensitivity of balance outcomes in pre-manifest HD [92, 94], 1 study investigated the sensitivity of measures of the sit to stand activities [116], with no report of evaluation of clinical measures of muscle strength, community mobility and health-related quality of life. As future interventions may be best applied in the pre-manifest stage, there is clearly a need for further evaluations of outcome measures that are sensitive to early changes in the pre-manifest stage.

In addition to the need for further validation of outcomes along the spectrum of the disease, the reliability of mobility outcomes in HD has yet to be established. The mobility outcome measures cited above in this review have been shown to have utility in people with HD. However, to date and apart from gait measures evaluated using an automated walkway [140], there has been no evaluation of the reliability of any of these outcomes in people with HD. Choosing appropriate outcome measures that are reliable is crucial in clinical trials. Documentation of any change of mobility as a result of an intervention should incorporate knowledge of reliability of the included measures and take associated variability into account [141]. Any measured difference may include some variability that could be due to the normal biological variability of the participants or to error in the measurement system or both. Therefore, knowledge of the reliability and associated variability of the used measures is important to be able to judge whether true change exists as a result of an intervention. This knowledge is also important to optimize our choices of outcomes that can be used to measure change in clinical trials.

2.4 Exercise interventions directed towards improving mobility in people with HD

2.4.1 General overview

As discussed in the previous section, gait deficits are an important component of HD symptomology, which may decrease independence in activities of daily living. Exercise may potentially play a role in reducing gait deficits and therefore in enhancing walking ability and functional status in HD. Despite this potential, the evidence base in support of exercise interventions in HD is still lacking. To date, only 10 papers [2, 76-79, 142-147] that have addressed the role of exercise interventions for people with HD have been identified. The vast majority of these papers were either an observational or non experimental design. None of these papers was of sufficient methodological quality (according to the CASP critical appraisal tool). The presentation and evaluation of the available evidence on exercise studies directed toward improving mobility for people with HD is provided in the later sections of this chapter. Summaries of these studies are provided in Table 2.6 and a summary of their critical appraisal is provided in Table 2.7 below. Full review of these papers is provided in the later sections.

Table 2.6: Summary of studies related to exercise interventions directed towards improved mobility in HD

Authors/ time	Study design	Exp/control (n)	Stage of HD	Mean age (SD)	Type of intervention for Exp (setting; wks/freq/min or hr)	Type of intervention for control (wks/freq/min)	Measures/Results
Kegelmeyer et al, 2010 [abstract] [77]	Randomised controlled trial	Exp= 12 Control= 8	Not reported	NR	Video game (Dance Dance Revolution) (home; 6/2/45 min)	A handheld video game (home; 6/2/45 min)	Balance; Tinetti Mobility Test-balance section, Four Square Step test [a]
Ekwall et al, 2010 [abstract] [76]	Individual-case control study	Exp= 12	Early to mid stage	NR	Transitions and balance training (clinic; 6/2/1 hr)	NA	Disease specific motor score; UHDRS-motor Balance; the Berg Balance Scale [a], a one leg stance test, a figure of eight test Mobility; the Timed Up and Go test and the falls efficacy scale
Zinzi, 2009 [79]	Postal survey	Exp= 40	Early to mid stage	Exp= 49.4 (11.0)	Patient's and caregiver's perceptions of an intensive rehabilitation programme on survey	NA	Perceived improvements in mobility status by all of the respondents after discharge
Zinzi, 2007 [78]	Individual-case control study	Exp=40	Early to mid stage	Exp=52.0 (3.3)	Combination of occupational therapy, speech therapy and physiotherapy exercises (inpatient; 3/6/8 hr)	NA	Mobility and functional status; Tinetti Mobility Test-gait score [a], Physical Performance Test [a]
Quinn et al, 2002 [2]	Single case study	Exp=1	Mid stage	Exp= 49	Exercise video; balance and muscle strength (home; 14/5/35 min)	NA	Disease specific motor score; UHDRS-motor [b] Balance; the Berg Balance Scale [b] Mobility; gait speed [b] and falls efficacy scale [b] Quality of life; SF-36 [b]
Imbriglio and Peacock, 1992 [143]	Expert opinion	NA	NA	NA	NA	NA	Exercise interventions are essential to maintain independence and quality of life
Sheaf, 1990 [146]	Single case study	Exp=1	Late stage	NR	Hydrotherapy (NR)	NA	No objective outcome measures were reported. Chorea subjectively noted to be reduced
Peacock, 1987 [145]	Case series	Exp=10	NR	NR	Balance and muscle strength exercises (clinic & home; 12/1/45 min)	NA	No objective outcome measures were reported
Lavers, 1981 [144]	Case series	Exp=6	NR	NR	Balance and muscle strength exercises (inpatient; 8/1/NR)	NA	No objective outcome measures were reported
Binswanger, 1980 [142]	Case series	Exp=5	NR	NR	Content is not defined (home; 4/2/1hr)	NA	No objective outcome measures were reported

Wks, weeks; freq, frequency; Exp, experimental group; NR, Not Reported; NA, Not Applicable; [a] statistically significant differences; [b] improvements in descriptive statistics when statistical analysis is not applicable

Table 2.7: Summary of the critical appraisal of papers related to exercise interventions directed toward improve mobility in HD

Authors/ date	Study design	Level of evidence	Focused question	Population defined	Inclusion criteria defined	Sample size calculation	Allocation defined	Intervention reproducible	Outcome measure defined	Assessor blinded	Data analysis defined	Inferential analysis employed	Generalisability
Kegelmeyer et al, 2010 [abstract] [77]	Randomised controlled trial	Level 2	Yes	Yes	NR	NR	NR	No	Yes	NR	Yes	Yes	No
Ekwall et al, 2010 [abstract] [76]	Individual-case control study	Level 4	Yes	Yes	NR	NR	NA	No	Yes	NR	Yes	Yes	No
Zinzi, 2009 [79]	Postal survey	Level 4	Yes	Yes	Yes	NA	NA	NA	NA	NA	Yes	NA	No
Zinzi, 2007 [78]	Individual-case control study	Level 4	Yes	Yes	Yes	No	NA	No	Yes	NA	Yes	Yes	No
Quinn et al, 2002 [2]	Single case study	Level 5	Yes	Yes	NA	NA	NA	Yes	Yes	NA	Yes	No	No
Imbriglio and Peacock, 1992 [143]	Expert opinion	Level 5	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	No
Sheaf, 1990 [146]	Single case study	Level 5	No	No	NA	NA	NA	No	No	NA	No	No	No
Peacock, 1987 [145]	Case series	Level 5	No	No	No	No	NA	No	No	NA	No	No	No
Lavers, 1981[144]	Case series	Level 5	No	No	No	No	NA	No	No	NA	No	No	No
Binswanger, 1980 [142]	Case series	Level 5	No	No	No	No	NA	No	No	NA	No	No	No

NR, Not Reported; NA: Not Applied; * items of critical appraisal are derived from the Critical Appraisal Skills Programme (CASP) appraisal tool [148].

2.4.2 Review of available exercise studies directed towards improving mobility in people with HD

Binswanger [142] evaluated the benefits of an individualized home-based exercise programme in 5 people with HD. The author indicated that people were included if they had a good mental status and were motivated to perform the exercise programme, although it was not clear how this was determined. Demographic data of participants such as their age, gender and data about cognitive scores, functional ability, disease severity and medication status were not provided. The exercise programme consisted of one hour of exercises performed twice a week for 4 weeks in the home, with the help of a physiotherapist. The components of the exercise programme were not specified but thought to include a combination of stretching, strengthening exercises and gait training. Outcome measures that were used to evaluate benefits were not clearly defined; the author stated "standard physiotherapy tests of physical and functional capacity were used". Participant's alertness and ability/ willingness to participate in activities were subjectively observed. The author noted an improvement in alertness and balance that appeared to result in safer ambulation. The methodological quality of this study was low, especially considering the failure to report the use of objective outcome measures. The intervention, although directed towards specific areas of deficits such as balance and muscle weakness, was not described sufficiently to allow replication. There was no follow up period to assess carry over effect, which makes it difficult to draw any conclusion regarding the potential long term effect of the utilized exercise programme in this study.

In a similar study, the effects of a group therapy exercise programme for 6 participants in a long term care psychiatric ward was described by Lavers [144]. The exercise programme was conducted weekly over a 12 month period and included balance, strengthening and coordination exercises. The exercises took the form of mat and chair exercises. Mat exercises focused on performing bridging, kneeling, crawling, long sitting and standing which are all important exercises to enhance balance and muscle strength. Chair exercises focused on training with weighted cuffs for upper limb strengthening. Despite the author stating that the aims of the exercise programme were to maintain mobility, balance, increase social interactions and decrease passive behaviours, no objective outcome measures were reported which limits the ability to draw firm conclusions about the effectiveness of the exercise programme in this study.

In another case series study, Peacock [145] evaluated the effects of an outpatient exercise programme for 10 participants at an early stage of HD. A 5-level disease severity rating scale, which was not clearly defined, was used to screen for people who were not severely affected by HD. Details of the study participants were not provided. The exercise programme included participation in a 12- week exercise class, in which participants met once a week. Subjects attended 3 additional booster sessions held monthly. The programme included 45 minutes of exercises that focused on improving overall flexibility as warm up exercises which were followed by a set of balance and muscle strengthening exercises. As indicated by the author, although exercises were delivered in a group setting, they were individualized for each subject. Subjects were given a list of exercises and were encouraged to continue their exercises at home independently or with the support of a family member. The benefits of the exercise programme were evaluated using outcome measures which were not clearly defined and included tests of flexibility, standing balance and balance in kneeling. The author reported that all participants on the completion of the 6 month exercise programme showed improvement on the tests of flexibility. Furthermore, most of the participants also improved on the tests of standing balance and muscle strength. Data to support these claims were not provided. Although this study indicated that exercise interventions may be beneficial for people at early stage HD with minimal impairments, the study was limited by low methodological quality for a number of reasons. The data of pre-and post intervention were not provided and no inferential statistical analyses were conducted. The details of exercises completed during the group session and at home were not sufficiently reported to enable replication; the content of the exercises, frequency, intensity and duration was not reported. Adherence to any home-based exercises was not monitored thus limiting conclusions about the frequency of exercise needed to attain therapeutic effects.

Similarly, the potential benefit from hydrotherapy in minimizing the effects of the impairments and improving function for a patient in the late stage of HD has been reported in a single case study by Sheaff [146]. The included subject, as described by the author, who had very prominent chorea and experienced difficulties in walking. No other details about this subject were provided. The exercise programme was composed of gentle exercises conducted in water once a week. The duration of the programme was not stated. Outcomes of the exercise programme were not objectively quantified;

however, effects on chorea and ability to exercise in water were subjectively described. Adherence to the exercise programme in addition to the subject's view on the intervention was reported. The author indicated that the subject demonstrated good adherence to the exercise programme as only one session was missed due to illness and that the subject appeared to enjoy the sessions. Although benefits of the exercise programme were subjectively reported by the author, the failure to use any objective outcome measures precludes conclusions being drawn regarding the usefulness of the exercise programme utilized in this study.

The potential benefits of a physiotherapy programme which included components of exercise interventions for people with HD at the mid stage was addressed in a paper by Imbriglio and Peacock [143] based on their extensive experience with people with HD. The authors suggested that the main aim of evaluation and intervention at the mid stage is to achieve the maximum independence with minimal risk. The importance of routine exercises that included flexibility, strengthening, balance and endurance training was addressed by the authors. However, the details of the specific content and aspects on how to deliver such training as well as the use of objective measurement tools to evaluate the effectiveness were not provided.

A major shortcoming in all the studies described above is the lack of use of recognised outcome measures for the assessment of benefits of interventions. In contrast to the above studies, a few more recent publications considered the use of standardized measurement tools to evaluate the benefits of the proposed interventions, thus giving more support to the potential role of physiotherapy exercise programmes in the management of people with HD. In a single case study presented by Quinn and Rao [2], a 14 week home exercise programme was provided for a patient with mid stage HD. The basis of the intervention in this study was an exercise video that was designed to address elements of flexibility and balance aiming to decrease disease specific impairments and improve the patient's functional abilities and quality of life. A detailed description of the exercises included in the exercise video was provided by the authors. Outcome measures included the short form 36 (SF-36), Berg Balance Scale, number of falls, the Modified Efficacy Falls scale, gait speed and Unified Huntington Disease Rating Scale (UHDRS). Improvements as a result of the intervention after the 14 weeks were reported in all of the outcome measures that were used in this study. Although the

results from this study could not be generalized, this case study was the first to report improvement in the routinely used outcome measures as a result of a home exercise programme for a person with HD. Improvement in balance, walking speed, reduction in the number of falls and improvement in the overall quality of life upon completion of the programme were reported. The results from this case study are important as this study was the first to report improvements as a result of an exercise intervention in people with HD based on the use of objective measures.

Recently 2 studies using within subject design provided results that gave further insight into how exercise interventions may benefit mobility in people with HD. Zinzi et al [78] investigated the benefits with respect to participation of people with early to mid stage HD in an inpatient rehabilitation programme. Forty participants with a confirmed diagnosis of HD were recruited to this study. The rehabilitation programme consisted of respiratory exercises, speech therapy, occupational therapy and a physical therapy exercise programme; however details of the specific content of each component of the rehabilitation programme was not provided. Participants were admitted for 3 week-long periods of intensive treatment that were repeated 3 times a year for 2 years. Data from the first year indicated that only 20 patients completed the 3 admissions in that year. Data from the second year showed that only 11 patients of the initial 40 who were involved in the baseline measurements completed all 6 admissions over two years. A standard clinical assessment was performed at the beginning and end of each admission using the Physical Performance Test (PPT). The PPT test is a 9 item measure of motor function and balance. The findings revealed that each 3-week period of treatment resulted in highly significant ($P<0.001$) improvements of motor performance. No carry over effects were recorded from 1 admission to the following on the PPT, however, no motor decline was detected over 2 years (n=11). This suggests that a multidisciplinary rehabilitation programme including physiotherapy positively influences the motor and functional performance of subjects affected with HD and results in an overall stable condition for at least 2 years. The lack of a control group and the high drop-out rate in this study, however, limits the drawing of definite conclusions from the obtained results. Subjects who had completed at least 1 course of the inpatient rehabilitation protocol in this study completed a questionnaire in a follow up study [79] that aimed to evaluate their perspectives on their involvement in the rehabilitation programme. All the respondents (n=37/40) perceived improvements after discharge. Improvements were

reported on gait, balance and fall reduction. The duration of benefit was estimated to last between 1 and 3 months by 71% of the respondents. The majority of the respondents (n=30/37, 81%) reported their intention to continue with the rehabilitation programme in the future; confirming the acceptability of the programme to subjects with HD and their carers.

In another study, Ekwall et al [76] evaluated the benefits of an outpatient physiotherapy exercise programme in 12 subjects with early to mid stage HD. The exercise programme focused on training of transitions and balance and was conducted twice weekly for a period of 6 weeks. Benefits resulting from the intervention were evaluated using a battery of outcome measures that included the UHDRS motor score assessment, the Berg Balance Scale, the Timed Up and Go test, a 1 leg stance test, a figure of 8 test and the falls efficacy scale. Significant improvement was observed in balance only, as measured by the Berg Balance Scale. The study was limited mainly by the small sample size and the lack of a control group.

An observed improvement in balance on completion of an exercise programme was also reported by Kegelmeyer et al [77] in the first controlled trial of an exercise programme to date. In this study the efficacy of an exercise programme using a video game to improve dynamic balance and mobility in individuals with HD was examined in which 20 subjects with early to mid stage HD were randomly allocated to either the experimental group (n=12) or the intervention group (n=8). As the reported study is currently in abstract format only, methods of recruitment, randomisation and data about characteristics of participants on each arm of the study are not available and therefore a full appraisal of evidence obtained from this study is not possible. The experimental group performed a video game of Dance Dance Revolution (DDR) for 45 minutes twice weekly for 6 weeks. The control group performed a handheld video game. The study demonstrated that participation in the DDR programme resulted in significant improvement in the 4 square step test (FSST) but not in the Tinetti Mobility Test (TMT) balance scores. The contradictory results obtained may be explained by the fact that the 2 tests of balance (the FSST and the TMT) are based on 2 different scales of measurements. The FSST is a timed test of dynamic balance which is based on interval data, while the TMT is based on an ordinal scale of measuring balance. As indicated

earlier, ordinal scales may lack the sensitivity to capture functional related changes as a result of exercise interventions [138].

2.4.3 Summary of review of available exercise studies directed towards improving mobility in people with HD

To summarize, the evidence base in support of exercise interventions directed to improve mobility in people with HD is very limited. Five of the reported papers [2, 142, 144-146] were conducted at an observational level; they were papers of either a single case or case series designs. In addition, methodological quality for the vast majority of the reported papers is poor. In most of the papers (n=6) [76, 77, 142, 144-146], participants' characteristics were not described in sufficient detail and factors that may have an impact on the effectiveness of the intervention; such as severity of the disease, functional ability, cognitive status and medication use were not reported or taken into consideration. Apart from two studies [78, 79], all studies did not clearly report inclusion criteria, although all included a diagnosis of HD. None of the studies reported power and sample size calculations. One study [77] reported the use of randomised controlled design, but the study as it is currently only as an abstract of conference proceeding, the randomization procedure is unknown and therefore selection bias cannot be discounted. In this study, it was also not clear if the assessor was blinded or if the authors took any measures to protect against assessor bias. Almost half of the studies (n=4) [142, 144-146] failed to report the use of valid and reliable outcome measures. Across all of the studies, the interventions were not described in sufficient detail that allows replication, and in addition they were clinically heterogeneous with regards to the type of exercise and to the frequency and duration of exercise being undertaken which makes it difficult to combine evidence for analysis.

2.5 Determining criteria for conducting studies of exercise interventions in people with HD

The evidence from animal studies and other neurological diseases, as well as limited support in studies of people with HD, suggests that exercise interventions may potentially play a role in facilitating independence in activities of daily living in people with HD by addressing impairments and limitations to functional activities. The review above, however, indicates that there is a critical need to establish a stronger evidence

base that can support the use of physical activity/exercise in clinical and community practice for people with HD. More rigorously designed studies are needed to examine the potential benefits of such interventions on key mobility outcomes in the HD population. Rimmer et al [138] suggested that in conducting exercise trials, researchers must consider developing structured exercise programmes that build on previous research regarding the targeted group. The type and severity of activity limitations and associated impairments and participation restrictions in the targeted group within the context of the ICF model need to be taken into account. In addition, exercise exposure in terms of intensity, frequency, type, mode and settings needs to be considered and specified. Providing such specifications will support a stronger evidence base and may potentially facilitate that the intervention can be replicated or translated into clinical practice. The following sections provide key findings from the literature that helped to determine specifications of the protocol of the exercise programme that was used in this project.

2.5.1 Content of exercise programme

The specific content of the intervention should be determined to support the conduct of well conducted trials of exercise interventions in HD. As indicated earlier, deficits in balance and muscle strength are the main impairments in HD that may relate to activity limitations in this population (Figure 2.1). Thus, targeting these impairments should be considered in exercise interventions in HD. The small amount of evidence in support of exercise intervention in HD (Table 2.6) suggests that exercise programmes that include a combination of muscle strengthening and balance exercises should be beneficial in managing the motor symptoms seen in this population. The beneficial role of these types of exercise interventions has been previously illustrated in other neurodegenerative diseases. For example, 2 recent systematic reviews in Parkinson's disease (PD) [72, 73] reported that exercise programmes focusing on balance and muscle strength can improve multiple factors, including gait and health-related quality of life. In a questionnaire survey and a series of interviews conducted with physiotherapists working routinely with HD, there was an emphasis that balance and strengthening exercises directed to improve mobility in HD, should be functional and task-specific [81]. Task-specific activities involve the practice within the context of functional tasks of everyday living such as walking, standing up from sitting position, turning and stepping [149]; aspects of activities that seem to be limited in HD [45, 93,

114-116]. Task-specific exercises involve using repetitions, alterations of the environment, and modification of the conditions of the task as a means of progressing task difficulty [149, 150]. For example, for balance training, task-specific exercises involving the progression from a wide to a narrow base of support, from static to dynamic activities and from a low to high centre of gravity could be included. A task-based model for the exercise intervention is designed to enhance skill learning [151] and may be particularly important for people with HD. The benefits of a task-specific exercise as a means to improve functional abilities and task performance have not been empirically studied in HD but have been documented in other neurodegenerative diseases with basal ganglia disorders such as PD. In one study [152], a 4 week period of training on sit to stand performance in 19 participants with PD resulted in a reduction of the time taken to complete the sit to stand transition by 25% and increased both the horizontal and vertical velocities by 18% and 51% respectively compared to the conventional exercise programme. In another study by Lehman et al [153] improvement in gait velocity and step length in individuals with PD was demonstrated after 10 days of walking and specific orientations for a longer step length. Similar results were obtained by Morris et al [154] who conducted a similar study with a similar training protocol in people with PD. These results along with data from a review paper [132] indicate that skills in people with PD can be learned most effectively when they are practiced repeatedly in relation to meaningful goals. Task-specific exercises may therefore be equally important in people with HD and need to be considered in exercise interventions in this population.

2.5.2 Considering influential factors

A notable shortcoming of most of the literature investigating the benefits of exercise interventions in people with HD is the failure to quantify disease severity and functional and cognitive status. These disease specific factors may influence response to exercise interventions and therefore should be considered when planning exercise interventions. This is particularly crucial as there is an increased emphasis within the ICF model to consider such individual factors in assessing people with mobility deficits as it is in people with HD [91] (Figure 2.1).

Cognitive impairments in particular can act as a barrier in delivering exercise interventions as they are likely to impact on the ability to learn new motor skills,

including the performance of new exercises [80, 81]. Studies that investigated the mechanisms of motor learning in HD have demonstrated that people with manifest HD had poor acquisition of information and use more of an explicit learning strategy, rather than implicit, when compared with controls [155]. Implicit learning refers to "reinforcement or habit learning, involving no verbalisation or meta-cognitive processing of the learned material" [156]. The basal ganglia are suggested to be highly implicated in implicit sequence learning [157]. Explicit learning, on the contrary, refers to "using a high degree of awareness and ability to verbalise the learning process" [156]. A comparative study by Pillon et al [155] showed that HD patients performed as poorly as patients with Alzheimer's disease on free recall of items in a list-learning task (implicit learning), but significantly better with cued recall (explicit learning). Another study [19] used a paired associated learning task, involving unrelated word pairs (for example, gold-sugar; friend-train). Whereas recall improved over successive trials in controls, neither the HD nor the Alzheimer group demonstrated improvement. However, when participants were actively encouraged to form an associative link between words (for example, imagine a gold bar in a bowl of sugar); recall improved dramatically in HD but showed no change in Alzheimer Disease. The data suggest that HD patients do not spontaneously adopt active strategies for learning, but when external cues are provided, performance can improve. This specificity of learning in HD has apparent clinical implications on the delivery of exercise interventions in this population; external cues can be used to improve the performance of the delivered exercises. Cueing applied in clinical settings provides a reference or external trigger for movement generation, which usually involves the use of augmented sensory information in the form of external visual or auditory cueing [156]. A major aim of using the cues in therapeutic interventions in HD can be to teach people with HD how to effectively bypass the damaged basal ganglia structures, and use frontal lobe pathways to control movement by responding to auditory or visual input [135]. This bypassing theory is based on suggestions which indicate the existence of a distinctive medial and lateral system for movement generation [156, 158, 159]. The medial system, including the basal ganglia, supports the generation of movements based on self initiation. The lateral system, including the pre-motor cortex (frontal pathways), dominates during externally-generated movements.

Despite the suggestion that cueing can be useful as a motor learning tool only a few studies have investigated its benefits in people with HD, with contrasting results. Thaut et al [105] demonstrated the modulation of gait speed in people with HD as a result of their ability to synchronize their gait to rhythmic cues from a metronome. However, Delval et al [106] demonstrated that under dual task conditions metronome cues were not helpful. The use of different designs in these 2 studies may explain these contrasting results; the potential benefits of using the sensory cues in HD may be potentially masked on performing tasks that require more attentional demands, which explains the results obtained by Delval et al [106].

Whilst data are limited in HD, there is abundant evidence that cueing improves motor performance in PD. A number of studies [151-153, 160] have examined the effects of cueing on walking performance and other mobility activities such as sit to stand in un-cued conditions after the intervention. The results from these studies demonstrated the positive effects of cueing on acquiring and retaining motor performance. For example, the effect of a 3-week period of cued gait training was examined immediately after the intervention period and after 6 weeks [151]. Significant changes in gait performance were demonstrated after the intervention, and retention at the 6-week follow up was maintained. In another study, the effect of cued sit to stand training versus non-cued was examined [152]. Results from this study demonstrated that the cued sit to stand-training had a greater effect than non-cued training and that this effect was maintained for 2 weeks after the intervention. Overall, these findings along with data from a review paper [156] suggest that the acquisition and retaining of motor learning in basal ganglia disorders can be improved when associated with external stimuli. As such, cue-augmented modes need to be incorporated into the delivery of exercise interventions in HD.

2.5.3 Intervention settings and the home-based exercise programmes

Environmental factors, including the physical environment of exercise settings, need consideration in planning exercise interventions. This is in line with the ICF model which emphasizes that environmental factors along with the individuals' needs should be taken into account when delivering therapeutic interventions for people with mobility deficits [91].

In terms of exercise settings, clinic, hospital or gym based exercise programmes involve travel to a health facility or specific exercise settings. These programmes may be inaccessible and exclude some individuals with HD [80] from being able to participate in exercise therapies. Home-based exercise programmes have the advantage of the convenience of doing the exercises when one is able and not having to travel to an exercise facility, potentially reducing direct cost to the patient [161]. There is additional support for this approach in that delivering exercise programmes in the homes of people with neurodegenerative disease has been shown to promote efficient transferability of skill acquisition [160, 162]. In one study using a within-subject controlled design, functional activities including walking and carrying out transfers were measured in 33 participants with PD, at home and in the hospital before and after a 6-week baseline period and after 6 weeks home-based exercise programme [162]. The study revealed that participants had significantly higher scores on a functional activity scale after treatment in the home setting compared to the hospital. The results support application of the treatment concept and highlight that exercise interventions aimed at improving function in neurodegenerative disease may be best provided in the home situation. Whilst conclusive trials of exercise interventions in HD are lacking, there is accumulating evidence to suggest that home-based exercise programmes in other neurodegenerative diseases such as PD and AD are feasible and have a positive impact on various aspects of mobility measures. This review identified 7 clinical trials in PD [160-166] and 2 others in AD [74, 167] that has investigated the feasibility and benefits of home-based exercise programmes. Methods of monitoring and delivery of the exercise programmes in these studies varied with supervision ranging from being maximal (fully supervised by a therapist on each session) to very minimal (self supervised exercise programme) (Table 2.8 & 2.9). A summary of these papers is provided in the sections below.

2.5.3.1 Home-based exercise programmes in PD

Recently, Nieuwboer et al [160] demonstrated that 3 weeks of an external cueing training programme conducted in people's own homes improved walking speed, step length and balance and reduced severity of freezing gait in freezers at 6-week follow up. Each individual in this study was trained in a variety of situations and daily activities by a physiotherapist who was present at each training session. In another study [164], a personalised 6 week, supervised home-based exercise which focused on

balance and muscle strength training was compared with usual care, with participants being tested at baseline, and at 8-week and 6-month follow-up assessment. The study demonstrated a consistent but non-significant trend towards lower fall rates in the exercise group at both 8 weeks and 6 months. However, significantly lower rates of repeat near falling were evident for the exercise group at 8 weeks and 6 months.

Although the above mentioned studies demonstrated feasibility of home-based exercise programmes that were fully supervised by a health care professional, findings from other studies demonstrated that people with PD can exercise safely at home using a pragmatic, minimally supervised exercise programme. In a recent study conducted by Allen et al [163], the feasibility and benefits of a 6 month exercise programme aimed at reducing the risk of falls in people with PD was evaluated. Participants attended a monthly exercise class conducted by a therapist, and were instructed to complete exercises between sessions at home 3 times a week for the intervention period. No adverse events were documented and the reported adherence to the exercise programme was high with an average of 2.2 out of 3 of the weekly home sessions completed. Findings from the study demonstrated a greater improvement, although not statistically significant, in the falls risk score in the exercise group compared to the control. Significant improvements were observed on the freezing of gait questionnaire and timed sit to stand test. Furthermore, there were statistically non-significant trends toward greater improvements in the exercise group in the measures of walking speed and fear of falling.

In addition to the above cited study by Allen et al, 2 other studies conducted by Nocera et al [166] and Caglar et al [165] used a similar protocol and demonstrated similar findings. In both of these studies, participants attended a practice session and were instructed on the proper method and mechanics for each exercise at the beginning of the home exercise programme. Participants were then provided with an exercise booklet outlining the movements for each of the exercises and instructed to perform the exercises at home for the intervention period. In the study by Nocera et al [166], participants were also contacted by weekly phone calls to monitor their progress. In both of these studies, no adverse effects were reported and participation in the home exercise programme resulted in improvements in gait speed, step length [165] and in measures of static as well as dynamic balance [165, 166]. Results from these studies

suggest that if people with PD are taught individualized and detailed home exercises by a therapist, there is potentially a significant clinical improvement in their motor performance.

Lun et al [161] in a controlled trial, examined whether benefits seen in self supervised home-based exercise programmes would be similar to a therapist supervised exercise programme. Participants in this study who were in the self-supervised home based group received the same set of exercises as the therapist-supervised group. They were familiarized with the exercise programme over 2 1-hour sessions with the same therapist who supervised the other group and then were instructed to continue their exercises at home twice a week for 8 weeks. The adherence rates were similar between the groups (87 and 91% for the self supervised and therapist supervised groups, respectively). Both programmes were found to result in statistically significant improvements in motor symptoms, as measured by the Unified Parkinson's Disease Rating Scale (UPDRS)-motor subsection score (the primary outcome in the study). These results are important and imply that people with neurodegenerative disease who still live in their own homes may potentially best receive exercise intervention in the home.

Table 2.8: Summary of papers related to home-based exercise interventions in PD

Authors/ time	Study design	Exp/ control (n)	Mean age (SD)	Type of intervention for Exp (wks/freq/min or hr)	Type of intervention for control (wks/freq/min or hr)	Measures/Results
Allen et al, 2010 [163]	RCT	Exp= 24 Control= 24	Exp= 66 (10) Control= 68 (7)	Minimally supervised programme; Progressive balance and muscle strength exercises (24/3/40-60 min)	Only falls prevention advice at the start of the study	Mean of adherence; 70% of prescribed sessions Freezing of gait (FOG); FOG questionnaire [a] Mobility; sit to stand time [a], gait speed, falls efficacy scale QoL; PDQ39
Nocera et al, 2009 [166]	Individual-case control study	Exp= 10 Control= NA	Exp= 73.4 (8.5)	Minimally supervised programme; Exercise booklet focused on balance training with task-specific exercises to target limitations on the subjects daily function (10/NR/NR)	NA	Mean of adherence; NR Balance; posturography measures on composite score of sensory organization test (SOT) [a]
Nieuwboer et al, 2007 [160]	Randomised cross over trial	Exp 1= 76 Exp 2= 77	Exp 1=67.5 (7.0) Exp =69 (5.3)	Supervised programme; Cueing training at variety of tasks using a prototype cueing device supervised by therapist (3/3/ 30 min)	NA	Disease-specific motor score; UPDRS- gait and balance items [a] FOG; FOG questionnaire [a] Balance; functional reach test, timed single leg [a], timed tandem stance [a] Mobility; gait speed [a] and step length [a], falls efficacy scale [a] QoL; PDQ39
Ashburn et al, 2007 [164]	RCT	Exp = 70 Control =72	Exp= 72.7 (12.3) Control=71.6 (8.0)	Supervised programme; Individualized exercises; ROM, balance, and muscle strength training (6/2/1 hr)	Usual care	Balance; Berg balance scale (8 wk, 6 months), Functional reach test (8 wk, 6 months [a]) Mobility; rate of falls (8 wk, 6 months), rate of repeat fall (8 wlk [a], 6 months [a]) QoL; Euro Quol (8 wk, 6 months [a])
Caglar et al, 2005 [165]	RCT	Exp =15 Control =15	Exp=64.3 (9.6) Control=67.4 (5.1)	Minimally supervised programme; Exercise booklet focused on ROM, balance, gait and functional activity training (8/7/1hr)	Usual care	Mean of adherence; 90% Mobility; gait speed [a], first step length [a], cadence, time to walk around a chair [a].
Lun et al, 2005 [161]	Parallel group-controlled trial	Exp 1= 8 Exp 2= 11	Exp 1=66 (8.0) Exp 2=67 (11.1)	Exp1; home based unsupervised exercise programme Exp2; group supervised exercise programme For both groups; balance and strength training (8/2/1 hr).	NA	Mean of adherence; Exp1 (87%), Exp2 (91%) Disease specific scale[*]; UPDRS motor score [a] Balance; Berg balance scale, ABC confidence scale Mobility; Timed up and go test [*]Significant and equal decrease in the UPDRS-motor in both groups from baseline to 8wlk
Nieuwboer et al, 2001 [162]	Within subject controlled trial	Exp= 33 Control=NA	Exp=66.2 (7.0)	Supervised programme; Cueing and mobility training with task-specific exercises (6/3/30 min)	NA	Disease specific scale; UPDRS total score [a] Mobility; activity scale [a], gait speed [a], stride length [a], cadence (measured at home & hospital)[*]. [*]Scores obtained at home setting were better than those obtained at hospital settings

Wk, week; freq, frequency; Exp; Experimental group; RCT, Randomised Controlled Trial; NA, Not Applicable; NR, Not Reported; QoL, quality of life; [a] statistically significant differences

2.5.3.2 Home-based exercise programmes in AD

The home-based exercise interventions that have been investigated to date in AD focus mainly on involving the carer in delivery of the home-based exercise programmes. Considering that cognitive impairments and depression are 2 impacting factors in people with AD, the carers are needed for structuring patients' day- to- day activities and providing ongoing care. Therefore they can be trained to supervise home-based exercise programmes [74, 167]. In a randomised controlled trial (Reducing Disability in Alzheimer Disease (RDAD study) [74] that involved 153 participants with AD and their family carers, participants were randomly allocated to either a home- based exercise intervention or to routine medical care. During a 12-week treatment period, carers in the intervention group were taught to guide the participant with AD on performance of an individualized exercise programme. The exercise programme included endurance activities (primarily walking), strength training, balance, and flexibility exercises at home. In addition, carers in this group were taught a problem-solving approach and behavioural management strategies with the aim of encouraging subjects with AD to exercise, and at the same time to decrease undesirable agitated or depressed behaviours that may affect their engagement in the exercise programme. Participants were evaluated at baseline, post-treatment, and 6, 12, 18, and 24-month follow-up. Patient health status was measured with the Short Form 36 (SF-36), the Sickness Impact Profile (SIP), and carers' reports of patients' restricted activity days, bed disability days, and falls. Study findings indicated that carers were able to direct subjects with AD to follow scheduled exercise activities. Significant differences between intervention and control groups were obtained at follow up post intervention with those in the intervention group having fewer restricted activity days and improved SF-36 scores. Over 24 months of follow-up, changes in SF-36 were maintained and improvements in SIP mobility were noted. These findings were consistent with the findings from Steinberg et al [167] that used a similar protocol of a home-based exercise intervention mediated by the carer that demonstrated good adherence to the exercise intervention, significant improvement in ADL performances and a trend in improvement in the chair sit to stand test and walking speed, as well as health-related quality of life. These findings are important and suggest that in neurodegenerative diseases where cognitive aspects are a potential issue, carers can be trained successfully to use effective strategies in order to encourage and facilitate participation in home-based exercise programmes.

Table 2.9: Summary of papers related to home-based exercise programmes in AD

Authors/ time	Study design	Exp/control (n)	Mean age (SD)	Type of intervention for Exp (setting; wks/freq/min or hr)	Type of intervention for control (wks/freq/min)	Measures/Results
Steinberg et al, 2009 [167]	RCT	Exp= 14 Control= 13	Exp= 74 (8.1) Control= 76.5 (3.9)	Home based exercise programme delivered by the carer; 2 home visits by PT to ensure correct performance of exercises; exercises focused on aerobic, muscle strength and balance training (12/6/NR)	Home safety assessment and recommendation on interventions (2/1/ 1hr)	Mean of adherence; 75% of the targeted goals Mobility; gait speed*, time for 5 repetitions sit to stand*, performance of ADL test [a] QoL; Alzheimer Disease quality of life Scale* Trends that were not statistically significantly toward improvements
Teri et al, 2003 [74]	RCT	Exp= 76 Control= 77	Exp= 78 (6) Control= 78 (8)	Home based exercise programme delivered by the carer; training for the carers on behavioural management of participant to enhance adherence to the programme; weekly visits of therapist to effectively train carers; exercises focused on balance, flexibility, muscle strength and endurance activities (12/2/ 1hr)	Usual care	Balance; functional reach test, standing balance Mobility; gait speed, number of days of restricted activity (3 months [a], 24 months) QoL; SF-36 (3 months [a], 24 months [a]), Sickness impact profile (3 months, 24 months [a])
Wk, week; freq, frequency; Exp; Experimental group; RCT, Randomised Controlled Trial; NR, Not Reported; QoL, quality of life; [a] statistically significant differences						

2.5.4 Mode of exercise delivery and the use of DVD/videotape approach

2.5.4.1 Considering motivational aspects

Considering the neurodegenerative nature of HD, individualised exercise instruction on a regular basis may be desirable in this population [80, 81]. Sustained interventions, however, may not be feasible or cost effective for life-long disease management. It is therefore critical for therapists to find ways to facilitate engagement in independent exercise programmes. Given that home-based exercise programmes are feasible in other neurodegenerative diseases, encouraging people with HD to engage and participate in regular physical activity, outside of scheduled therapist-supervised clinic appointments at their homes, may promote achievement of therapy goals in this population [80]. There are a number of factors, however, that may influence the ability of people with HD to engage in unsupervised exercise programmes which include motivational issues [80, 81]. Lack of motivation (apathy) is a core feature of the disease that could impact on the initiation of a new life routine, including an exercise programme. Considering that motivation is vital to adherence [168], finding strategies to improve motivation is a key to the success of any provided therapy programme. A number of strategies that have been used in other neurodegenerative disease such as PD and AD have potential for application in HD. The ParkFit study [169] suggests that behavioural motivation techniques can be used successfully in subjects with PD to encourage them to engage in a regular physical activity. Within this strategy, counselling is used to promote behavioural change through working closely with subjects. The strategy includes education about the benefits of physical activity, advice about suitable activities, setting goals, and recruiting social support. Similarly the RDAD (Reducing Disability in Alzheimer Disease) study [74] found that using a behaviour management approach is a key component to encourage subjects with AD to engage in an independent home-based exercise programme. Within this approach it was essential to involve the carer and to provide a personalised rationale for the programme (specific to the specific individual) in order to maximize motivation and enhance adherence to the programme. Such strategies are important and can be incorporated into the design of exercise intervention trials in people with HD.

2.5.4.2 The use of DVD/videotape approach

Taking into account the cognitive and motivational aspects associated with HD, there is clearly a need to develop methods that facilitate a person's engagement and adherence to an independent exercise programme. The technological capabilities of DVD/ videotape (such as the use of sub-titles, rhythm, augmented visual and auditory cues provided through real life demonstration of exercises) make it a useful format to facilitate engagement in such programmes, particularly for people who have motivational and cognitive problems as is common in people with HD.

Such audiovisual methods have been used to support the delivery of home-based exercise programmes in different clinical settings (Table 2.10). Nine randomised clinical trials [83, 85, 86, 170-175] that investigated the home use of an exercise DVD/videotape in different clinical conditions were identified in this review. Clinical conditions included Chronic Obstructive Pulmonary Disease (COPD), shoulder and back pain, knee and hip osteoarthritis, orthopaedic surgery for upper and lower limbs and balance training for elderly who were at risk of fall. Findings from these papers suggested positive outcomes of the home use of an exercise DVD/videotape that were classified into 3 main categories 1) exercise performance 2) exercise adherence 3) physical outcomes. A summary of these findings is provided in the sections below.

2.5.4.2.1 DVD/videotape impact on exercise performance

The effect of the mode of delivery of exercises on the quality of exercise performance was investigated in 4 studies [83, 85, 86, 175] with mixed results. However, the balance of evidence suggests that the use of a videotape approach has a better impact on the quality of exercise performance over the other modes of exercise delivery. Three studies reported positive impact of the use of the videotape approach on the quality of exercise performance over other modes of exercise delivery [83, 85, 86], whilst only 1 study reported no difference [175]. Schoo et al [175] reported that providing additional videotapes to facilitate correctness of exercise performance in older adults with lower limb osteoarthritis resulted in no further benefits than when exercise booklets were given together with verbal instructions. As discussed by the authors, the level of exercise simplicity required in this study may have influenced these findings. In another study by Weeks et al [86], videotape instruction was compared with still-photograph instruction in a group of healthy subjects on the quality of performing common simple

and complex exercises. Subjects were scheduled for an acquisition session and retention test 24 hours apart after demonstration of exercises using either videotape or still photograph instructions. Exercise acquisition was easier and knowledge retention was significantly higher in the videotape group and subjects in this group reported greater motivation and confidence about performing the exercises correctly. Additionally, all subjects in this group, when viewing the still photograph approach, indicated a preference for using a videotape over illustrations to learn the exercises. Similar conclusions were reported by 2 other studies. In one of these studies [85], a group of subjects following total knee replacement who viewed a videotape to reinforce learning had significantly higher knowledge of total knee surgery precautions and performed their exercises with less errors than those in the control group. Similarly, a group of subjects with shoulder or back pain who received home-based exercise videotapes to help them manage their condition were more skilled in performing exercises as evaluated using a standardized procedure and more motivated to continue self treatment based on data from qualitative interviews with subjects on completion of the study [83].

2.5.4.2.2 DVD/videotape impact on exercise adherence

There is evidence to suggest that using a DVD or videotape to support delivery of home exercise programmes may lead to better adherence, although some of the reported findings show mixed results. Four of the included studies [85, 170, 172, 175] assessed whether the use of an exercise videotape would enhance the rate of adherence. Only 2 of these studies reported a better impact of the videotape strategy over other modes on adherence rates [85, 172]. The fact that the findings regarding adherence are varied can be attributed to a number of reasons, including the heterogeneity of the clinical settings, the populations included and the structural and content aspects of videotapes being used in these studies. Whilst Lysack et al [170] and Schoo et al [175] concluded that there was no statistically significant difference in adherence or satisfaction with the use of video instruction, compared with the use of written materials or audiotapes, Lin et al [85] found that subjects who received an exercise videotape, were significantly more compliant in prescribed exercises, when compared to a group who received written information about exercises. Similarly, Petty et al [172] found a customised videotape to be more effective in helping people with COPD to initiate and adhere to the exercise programme.

2.5.4.2.3 DVD/videotape impact on physical outcomes

Six studies [83, 85, 171-174] of the included papers assessed whether the adherence to the home use of an exercise videotape had any effect on physical outcomes such as knee symptoms, shoulder and back pain, disease severity, range of motion, muscle strength and health related quality of life. The vast majority of these papers (n=5/6) [83, 85, 171, 172, 174] highlighted positive effects on outcomes in using a home-based exercise videotape in their respective fields. For example, in one study, the effects of using a home exercise videotape along with educational booklet in people with COPD were compared with the use of the educational booklet alone. The use of the exercise videotape in this study was demonstrated to significantly improve symptoms related to exercise tolerance and to breathlessness [171]. Findings from this study were consistent with findings from another study [172] in which the effects of using home-based exercise videotape were found to improve fatigue and aspects of health-related quality of life in people with COPD. Similarly, in one study of elderly people with balance disorders, the use of a home-based exercise videotape resulted in improvements in muscle strength, flexibility and balance [174]. Furthermore, in 2 studies of orthopaedic conditions (knee surgery and shoulder and low back pain) [83, 85], the use of a home-based exercise videotape was found to improve range of motion, reduce pain [85] and increase physical functioning [83].

Table 2.10: Summary of papers related to the home use of an exercise DVD/videotape

Authors/ time	Study design	Population	Exp/ control (n)	Mean age (SD)	Type of intervention for Exp (wks/freq/min or hr)	Type of intervention for control (wks/freq/min or hr)	Measures/Results
Moore et al, 2009 [171]	RCT	COPD	Exp= 10 Control= 10	Exp= 70.5 (5) Control= 70 (13)	Educational booklet about COPD and exercise and home exercise videotape (6/4/30 min)	Educational booklet only about COPD and exercise	Exercise tolerance; Incremental Shuttle Walk Test [a] Breathlessness; Chronic Respiratory Questionnaire [a]
Petty et al, 2006 [172]	RCT	COPD	Exp1= 72 Exp2= 69 Control= 73	Exp1= 68.8 (9.2) Exp2= 68.4 (9.0) Control= 66.8 (9.9)	Exp1; home-based customized exercise videotape (8/3/NR) Exp2; standard exercise videotape (8/3/NR)	Usual care	Adherence, conversion to and retaining exercise habits were significantly better in both videotape groups relative to control Impact of lung disease; Fatigue Impact Scale [a*] , Seattle Obstructive Lung Disease [a*] Questionnaire QoL; SF-36 [a*] [*]significantly improved in customised video tape group compared to the other groups
Lysack et al, 2005 [170]	RCT	Total knee or hip replacement	Exp= 18 Control= 22	Exp= 64.8 (11.6) Control= 61.8 (11)	Home-based customized exercise videotape (4/6/30)	Written and verbal instructions of exercises to perform at home (4/6/30)	Adherence; study specific questionnaire Satisfaction; study specific questionnaire
Miller et al, 2005 [83]	RCT	Shoulder pain or low back pain	Exp1= 134 Exp2= 194 Control= 222	Exp1= 55.1 (13.9) Exp2=52.4 (16.2) Control= 52.7 (15.3)	Exp1= home exercise video (the treating PT) (4/NR/NR) Exp2= home exercise video (anonymous PT) (4/NR/NR)	Verbal face to face instructions of exercises to be performed at home (4/NR/NR)	Progress of the condition; Shoulder disability index or Roland and Morris disability scale Perceptions of exercise instructions; qualitative interviews [b] Patient's self treatment skills; Measure of patient self treatment skills scale [a*] QoL; SF-36 [a*] [a*]Both video groups were significantly different comparing to controls [b] videotape motivated patients to continue self treatment
Schoo et al, 2005 [175]	RCT	OA of hip or knee	Exp1= 30 Exp2= 30 Control= 30	Exp1= 69.2 (6.4) Exp2= 70.9 (7.2) Control=71.1 (6.8)	Exp1= a home exercise brochure with audiotape of instructions (8/6/NR) Exp2= a home exercise brochure with videotape of exercises (8/6/NR)	Home exercise brochure (8/6/NR)	Adherence rate; exercise diary Correctness of exercise performance; correctness of exercise performance scale

Table 2.10: *Continued for* summary of papers related to the home use of an exercise DVD/videotape

Authors/ time	Study design	Population	Exp/ control (n)	Mean age (SD)	Type of intervention for Exp (wks/freq/min or hr)	Type of intervention for control (wks/freq/min or hr)	Measures/Results
Sohng et al, 2003 [174]	RCT	Elderly who are at risk of fall	Exp= 22 Control= 23	Exp= 75 (7.6) Control= 76.4 (6.5)	Instructions from PT and videotaped instructions of exercises to be performed at home (8/4/45 min)	Usual care	Muscle strength; isometric muscle strength of knee and ankle [a] Balance; sharpened Romberg test [a] Ankle ROM [a] Instrumental activities of daily living (IADL)
Weeks et al 2002 [86]	RCT	Healthy subjects	Exp= 10 Control= 10	Exp= 23.1 (7.4) Control= 23.6 (8.1)	Videotape instructions of exercises (1/2/30 min)	Instructions of exercises via still photograph illustrations (1/2/30 min)	Acquisition of exercise performance [a] Retention test of exercise performance in 24 hours of acquisition [a] Motivation toward performing the exercises [a]
Roddy et al, 2002 [173]	RCT	Repair of rotator cuff tear	Exp= 54 Control= 54	Exp= 58.7 (10.6) Control= 57.2 (9.1)	Videotape instructions of exercises (24/4/NR)	Personal instructions of exercises from a physiotherapist (24/4/NR)	Exercise adherence; exercise diary Shoulder pain and disability index; The University of Pennsylvania Shoulder Scale scores
Lin et al, 1997 [85]	RCT	Knee arthroplasty	Exp= 31 Control= 29	Exp= 63.7 (11.6) Control= 62.4 (11)	Instructions of an exercise booklet and exercise videotape (6/5/30 min)	Instructions of an exercise booklet but no video (6/5/30 min)	Adherence rate [a] Quality of performance of exercises [a] Pain and ROM of knee flexion and extension [a]

Wk, week; freq, frequency; Exp; Experimental group; RCT, Randomised Controlled Trial; NA, Not Applicable; NR, Not Reported; QoL, quality of life; [a] statistically significant differences; OA, osteoarthritis; COPD, Chronic Obstructive Pulmonary Disease; ROM, Range of Motion.

2.5.5 Summary of review related to determining criteria for conducting studies of exercise interventions in people with HD

Figure 2.1 shows a model of the key elements that emerged from this literature review and may potentially impact on the acceptability and benefits of an exercise programme delivered for people with HD. This model indicates that a well defined exercise programme specifically tailored to target the physical impairments and activity limitations seen in this population and focusing mainly on balance and muscle strength and incorporating task-specific activities, may be able to improve functional abilities and health-related quality of life in people with HD. As transferability of functional improvement is most noticeable in the setting in which training is delivered, a person still living in his/her own home would be better receiving an exercise intervention in their own home. Considering the cognitive and motivational issues associated with the disease, home-based exercise interventions may potentially be best delivered with an exercise resource that augments the information provided by the provision of attention-focusing verbal and visual cues such as an exercise DVD or videotape. In such settings, it may be important to train the carer how to guide and supervise the person's exercise programme. The success of the programme may depend largely on the carer's ability to continue to support the programme outside the actual training sessions. The success of the exercise programme may also depend on using motivational behavioural strategies that entail providing an introduction and rationale about the delivered programme and potential short term and long term benefits to maximize motivation and enhance adherence.

2.6 Thesis aims, objectives and hypothesis

2.6.1 Aims of the study

Based on the literature reviewed here, there is evidence to suggest that exercise interventions can be beneficial in preserving or improving physical performance of people with HD. It is evident, however, that exercise interventions for people with HD have not been subject to rigorous research. Furthermore, it is clear that further investigations are required to examine reliability and validity of outcome measures that can be used to evaluate potential benefits of exercise interventions in this population.

Exercise interventions in this population are likely to be complex. The Medical Research Council (MRC) Framework for design and evaluation of complex interventions provides a methodology for evaluating complex interventions [69, 70]. It incorporates an exploratory phase which should be undertaken prior to the initiation of definitive phase III randomized controlled trials in order to determine feasibility and acceptability of the intervention and pilot the use of outcome measures. This research therefore focused on a phase II exploratory study of a home-based exercise programme and was conducted with 2 aims in mind. The first aim was to determine reliability and validity of the outcome measures that were used in the main part of the study and the second aim was to investigate feasibility, acceptability and the potential benefits of a home-based exercise programme. The study therefore, consisted of 2 main parts: the first part was a preliminary investigation of the reliability and validity of potential outcome measures across the spectrum of the disease and the second part was an evaluation of feasibility, acceptability and potential benefits of a home-based exercise programme that was designed to specifically target physical factors which are believed to be impaired and are potentially modifiable in people with early to mid stage HD (using an exercise DVD that was previously developed as the basis of the intervention and the criteria determined in this review). Benefits on measures of mobility and health-related quality of life were evaluated.

2.6.2 Objectives and hypothesis

2.6.2.1 Objectives and hypothesis for part 1

The specific objectives for the first part of the study include the following:

1. To determine test re-test reliability of a battery of outcome measures representative of spatiotemporal gait, balance, muscle strength, functional status and health- related quality of life in people with pre-manifest HD.
2. To determine test re-test reliability of a battery of outcome measures representative of spatiotemporal gait, balance, muscle strength, functional mobility and health- related quality of life in people with manifest HD at early to mid stage.
3. To examine the validity of the above battery of outcome measures by examining their sensitivity to detect deficits in gait, muscle strength, balance, functional mobility and health-related quality of life in both pre-manifest and manifest HD.

4. To examine the validity of the measures in muscle strength, balance, functional status and health-related quality of life by understanding their relations with measures of gait variability.

The specific hypotheses for the first part of the study include the following:

H_1 There are significant differences in measures of gait, muscle strength, balance, functional status and health-related quality of life in people with pre-manifest HD compared to healthy controls.

H_2 There are significant differences in measures of gait, muscle strength, balance, functional mobility and health-related quality of life in people with manifest HD compared to healthy controls.

H_3 Measures of gait in HD are significantly related to measures of: a) muscle strength; b) balance; c) functional mobility; and d) health-related quality of life.

2.6.2.2 Objectives and hypothesis for part 2

The specific objectives for the second part of the study include the following:

1. To evaluate potential benefits of a home-based exercise programme on: a) impairments in gait, b) balance and muscle strength; c) functional mobility and d) health-related quality of life in people with early to mid stage HD.
2. To evaluate if people with early to mid stage HD adhere to a home-based exercise programme and what factors would impact on their adherence.
3. To evaluate the acceptability of a home-based exercise programme to the people with early to mid stage HD and to their carers.

The specific hypotheses for the second part of the study include the following:

H_1 Individuals with early- to mid-stage HD who participate in a home-based exercise programme will demonstrate significantly decreased gait deficits upon completion of the exercise programme compared to the control group.

H_2 In relation to decreased gait deficits, individuals with early- to mid-stage HD who participate in a home-based exercise programme will demonstrate significantly: a) improved balance; b) improved muscle strength; c) improved functional mobility; and d) improved health-related quality of life, upon completion of the exercise programme compared to the control group.

Chapter Three

Methods

3 Methods

3.1 Outline of overall study design

This exploratory research study consisted of two parts. Part 1: An observational study that aimed to investigate reliability and validity of a set of mobility related outcome measures across the continuum of the disease. Measures were chosen to reflect a range of physical impairments, activity limitations and participation restrictions which may relate to mobility deficits seen in people with HD [176] and were potentially modifiable with exercise interventions. This included biomechanical measures of gait and clinical measures of balance, muscle strength, physical functioning in ADL and health-related quality of life that have been shown previously to have utility in people with HD and other neurological conditions (details of the outcome measures are provided in section 3.3.4). Evaluating the validity and reliability of the outcome measures used in this part of the study was helpful in interpreting the results from the exercise intervention study (Part 2).

Part 2: Potential benefits, feasibility and acceptability of the exercise programme were evaluated in this part of the study. A repeated measures randomised design was used. Twenty five participants with early to mid-stage HD were asked to complete the home-based exercise programme at a certain time point during the study (see study flow chart: Figure 3.1). Participants who completed the study were assessed 3 times by the researcher (the PhD student) over the study duration (at baseline; at 8 weeks and at 16 weeks) using a battery of outcome measures whose psychometric properties were evaluated in the first part of the study. User opinion of the process and benefits of involvement in the programme were obtained after completion of the study. Details of inclusion and exclusion criteria and recruitment strategy are provided in section 3.2. Details about Part 1 are provided in section 3.3 and about Part 2 are presented in section 3.4.

Figure 3.1: Flow chart of the study

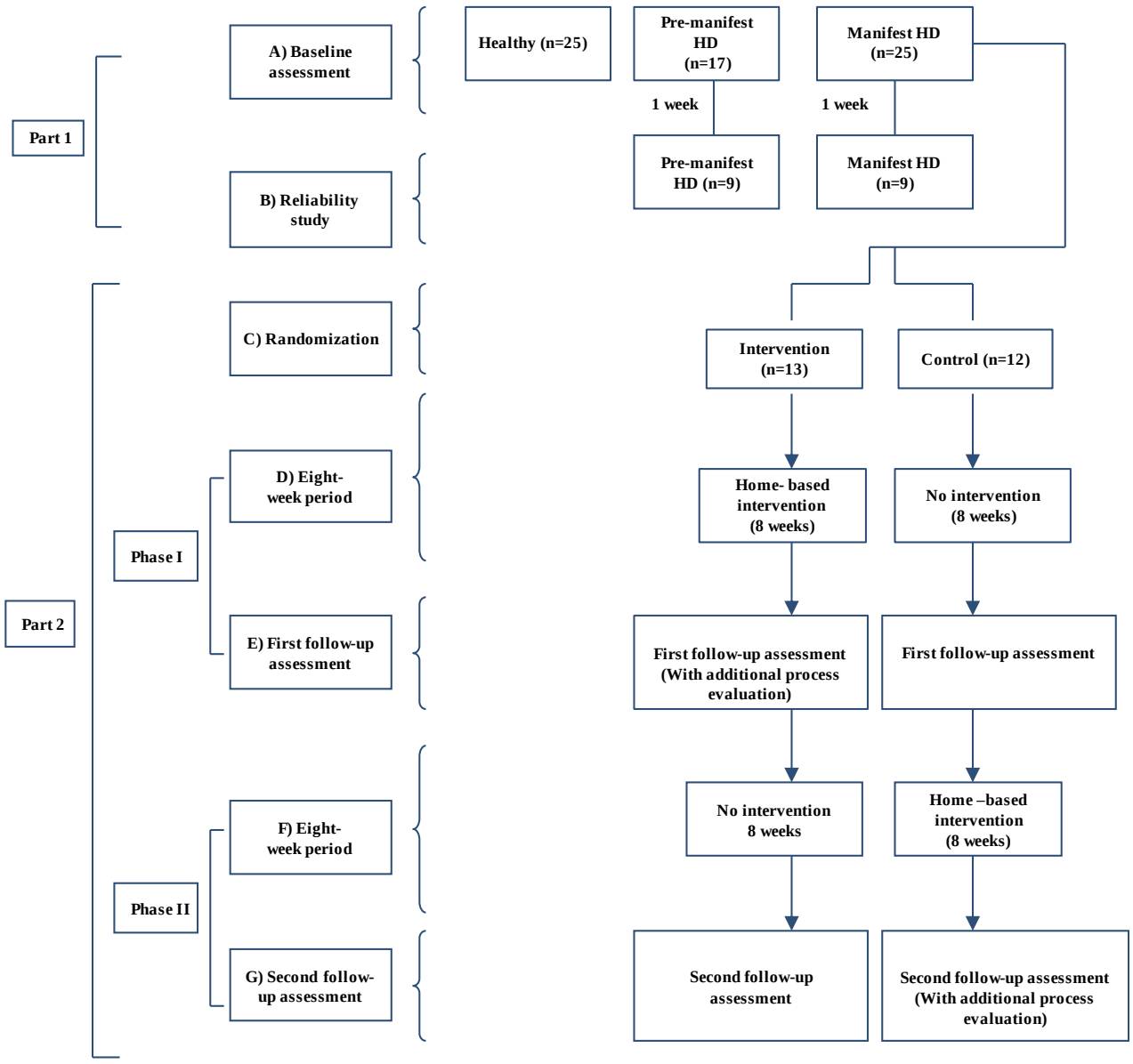


Figure 1: Study design. This figure shows the flow chart of the study. **A)** Evaluation of discriminative validity of the outcome measures was undertaken in a sample of 67 participants. The sample (n=67) included 17 participants at the pre-manifest stage, 25 participants at the early to mid stage of the disease and 25 healthy controls. **B)** Eighteen participants ((n=9 pre-manifest) and (n=9 manifest)) were tested twice with a 1 week gap between the 2 assessments to evaluate the reliability of the battery of outcome measures. **C, D, E, F&G)** The existing 25 manifest HD participated in evaluating a home-based exercise programme. Participants who completed the study were assessed 3 times (at baseline (point A), at 8 weeks (first follow-up assessment; point E) and at 16 weeks (second follow-up assessment; point G)). Participants were asked to complete the home-based exercise programme for 8 weeks at a specific time point during the study duration (either between baseline and first follow-up (i.e. early intervention) or between the first and second follow-up assessment (i.e. delayed intervention)). Participants who received the intervention after the first follow-up assessment provided control data for those receiving the intervention following the baseline assessment. Second follow-up assessment was on the main outcome measure (gait variability) only and additionally focuses on collecting data about adherence of early intervention group to any kind of programme after cessation of formal exercise input.

3.2 Participants

3.2.1 Inclusion and exclusion criteria

3.2.1.1 Inclusion and exclusion criteria for HD participants (Part 1 & 2)

The aim was to recruit participants who were gene positive for HD. This included people who were pre-manifest and those who were in the early and mid stages of the disease. Potential participants were screened for the following inclusion criteria:

1. A positive genetic test for HD.
2. Total Functional Capacity (TFC) score 13 with a diagnostic confidence score of either 0 or 1 of the UHDRS-motor as rated by neurologist, indicating the presence of none-specific motor signs of HD for pre manifest participants.
3. Presentations of motor signs and a score of 4 on the motor diagnostic confidence scale of the UHDRS-motor as rated by neurologist providing confirmation of HD diagnosis for participants with manifest HD.
4. Ability to walk independently with or without an assistive device but without the aid of another person.
5. Self-reported or physician-reported difficulties with walking and/or balance for participants with manifest HD.
6. Maintaining a stable medical regime for 4 weeks prior to initiation of study.
7. Aged above 18 years.
8. Capacity to give informed consent.

Participants were excluded if they had a history of coexisting neurological conditions such as stroke, or other causes of balance disorders and severe visual problems, or if they have any other medical condition which would prevent them from engaging in regular physical activity; or if they had cognitive or behavioural symptoms that would prevent them cooperating with the intervention.

3.2.1.2 Inclusion and exclusion criteria for healthy controls (Part 1 only)

A group of healthy controls was recruited to match the age range of the recruited pre-manifest and manifest participants. Healthy participants were excluded if they had any peripheral injury or other medical condition that made them unable to walk without assistive device or prevented them from completing the battery of outcome measures.

3.2.2 Recruitment

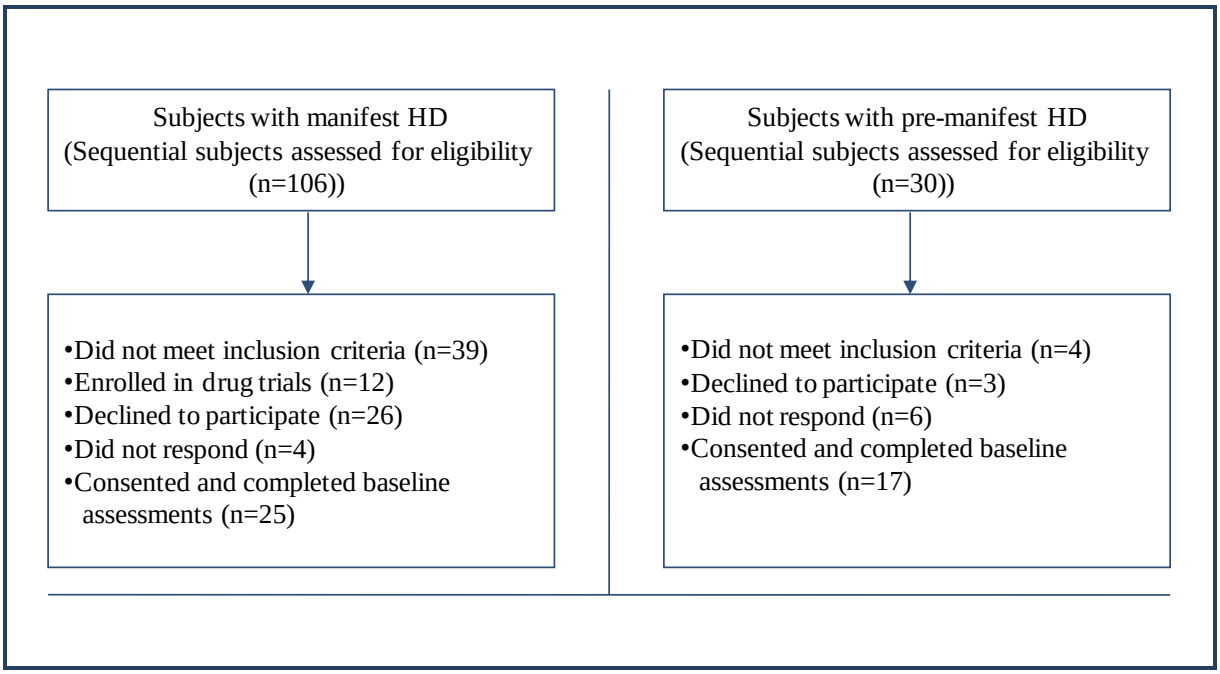
3.2.2.1 Recruitment of participants with HD (Part 1 & 2)

Potential participants attending their routine neurology clinic appointment at University Hospital of Wales, Cardiff were first screened by the clinic neurologist for the inclusion and exclusion criteria mentioned above. If suitable, they were invited to participate in this study alongside the 'Registry' study. Many subjects attending the HD clinic were already enrolled in the Registry study (04//WSE05/89). The registry study is a full clinical dataset, including the full medical and medication history. One of the optional components within the Registry project includes permission to be contacted between visits. Subjects who have consented to this component were contacted by letter and informed of the study.

Once approached, potential participants were given an information sheet (Appendix1), reply slip and stamped addressed envelope. Potential participants who were given the information sheet had sufficient time, at least one week, to consider the information provided before being contacted to discuss their involvement, unless they indicated a positive response by post prior to this time. All participants gave their written informed consent before participation, in accordance with Local Research Ethics Committee approval (09/WSE02/24).

Recruitment began in June 2009 and ended in November 2010. One hundred and six sequential subjects with manifest HD were screened for eligibility for this study. Fifty five were eligible and given information sheets. Only 25 consented and completed baseline assessments. In addition, 30 potential participants with pre-manifest HD were invited to participate in Part 1 of the study. Seventeen of them agreed to participate, consented and completed baseline assessments. Details of flow of recruitment for the study are provided in Figure 3.2.

Figure 3.2: Flow of recruitment of participants with HD for the study



3.2.2.2 Recruitment of healthy controls (Part 1 only)

Twenty five healthy controls were recruited. These people were either carers or relatives of people with HD who were mutation negative and introduced to us by the participant with HD (n=15) or were students and staff (n=10) at Cardiff University who did not have a family history of HD. All potential participants received an information sheet (Appendix 1) and were given at least 1 week to consider the information, before being contacted to discuss their involvement. All participants gave their written informed consent before participation in accordance with the Local Research Ethics Committee approval mentioned above.

3.3 Part 1: Evaluating validity and reliability of the outcome measures across the continuum of HD symptoms

3.3.1 Rationale

Discriminant and convergent validity are both considered subcategories of construct validity [177] which was evaluated in this study. In terms of discriminant validity, tests that are required to detect differences on the same construct should discriminate in known groups; this is often called the known group method [178]. For example people

with HD are expected to demonstrate differences in balance relative to a healthy matched control group as they are known to be clinically different.

Gait variability is a well validated measure in HD that is known to correlate with functional status in this population [38]. Tests that measure similar constructs should converge [178] which means that in the presence of higher gait variability (indicator of poorer functional performance), one may expect a poorer performance on measures of balance for example. Knowledge of the relationship between measures of gait variability and clinical measures of balance, muscle strength, functional performance in mobility activities and other activities of daily living as well as community walking and health-related quality of life is important and may potentially provide insight into outcome measures that can be used in therapeutic interventions.

Validity of a test relies on its accuracy and reliability. If an outcome measure is to be used in interventional research, it is crucial to evaluate its test re-test reliability, to evaluate the ability of the test to be replicated in the same subject [141]. An instrument that has an adequate test re-test reliability gives consistent results if a subject is re-tested whilst under stable conditions. Test re-test reliability has been described as relative or absolute [179]. Both of these forms of reliability were examined in this study. Relative reliability examines the relationship between 2 or more measurements and the consistency of an individual's position within the group. Absolute reliability examines variability in scores in repeated measurements. Although intra-class correlation coefficients (ICCs) are generally considered to be more appropriate indicators of relative reliability than simple correlation coefficients (i.e. Pearson's r and Spearman's rho), their use is limited by the fact that ICC values are not related to the actual scale of measurement and are dependent on the range of the individuals' performances. In situations where there is a large range of scores in the sample, a high ICC may be obtained, despite there being large within-subject differences in the actual scores between repeated measurements and vice versa [141]. To overcome this, the complementary use of an absolute reliability, as opposed to relative reliability, is recommended [179]. Statistically, absolute reliability is determined by the standard error of measurement (SEM), or the standard deviation of the measurement errors, and a clinically useful mechanism for looking at absolute reliability is the minimal detectable change (MDC) score [141]. The MDC is defined as the minimal amount of change that

is not due to natural variation in measurement or due to error. Scores at or above the MDC are due to real change on the test rather than measurement error. Thus the MDC score is useful in determining whether an improvement in interventional research is truly a change in subjects' status or due to an error in measurement [178].

3.3.2 Evaluating validity of outcome measures in HD

An evaluation of the validity of a battery of outcome measures to assess mobility in HD, considering the disease stage, was undertaken (Figure 3.1). The sample (n=42) included pre-manifest mutation carriers (n=17) and manifest HD at early to mid stage of the disease (n=25). In addition, healthy controls (n=25) were recruited for this part of the study.

Discriminant validity of the outcome measures was investigated by evaluating their responsiveness to detect differences between the 3 study groups. In particular, the sensitivity of the battery of outcome measures to differentiate between people with manifest and pre-manifest HD and between people with pre-manifest HD and healthy controls was examined. On the other hand, convergent validity was investigated by examining the relationship between measures of balance, muscle strength, functional performance in mobility activities and other activities of ADL, community walking and health-related quality of life with a measure of gait variability.

3.3.3 Evaluating reliability of outcome measures in HD

As part of this study, an evaluation of the test re-test reliability and the minimal detectable change of the used battery of outcome measures along the broad spectrum of the disease was conducted. Eighteen of the existing participants who were assessed at the baseline (9 pre-manifest (gene mutation carrier) and 9 manifest HD) completed a second assessment session, with a 1-week gap between, on the used battery of outcome measures. The order of assessments for each participant was randomized (between participants). This randomized order remained the same for repeated testing (within participants).

3.3.4 Outcome measures

Outcome measures included here were chosen to reflect a range of physical impairments, activity limitations and participation restrictions related to the mobility deficits seen in people with HD. These outcomes were structured according to the International Classification of Functioning, Disability and Health (ICF) framework. As depicted in Table 3.1, physical impairments in body functions were represented by a disease-specific motor scale (the modified motor score of the UHDRS (mMS)) [180] as well as measures of balance and muscle strength. Balance was assessed using the Berg Balance Scale (BBS) [181], the Romberg (RT) and Sharpened Romberg (SRT) tests [182] and measures of postural sway [148]. Muscle strength was assessed using the Maximal Voluntary Isometric Muscle Contraction (MVIC) scores of knee flexors and extensors which were obtained using the Kin-com isokinetic testing chair dynamometer unit [183].

In the realm of mMS and BBS, both tests involve the evaluation of physical impairments in the contexts of assessing the performance in some tasks such as walking (for both mMS and BBS), stepping and turning (for the BBS) (see section 3.3.4.1 for more details about these tests). As these tasks are principally listed under the activity level within the ICF [184] (see Chapter 2 for more details about what is considered as an activity), categorization of the mMS and BBS as measures of body function can overlap with the activity level. These 2 tests seem to be multi-dimensional; however their constructs are predominantly based on evaluating motor impairments as a body function [46, 185]. Therefore it is more appropriate for these 2 tests to be listed under the level of body structure and function within the ICF model rather than being listed under the activity level.

Activity was represented by a number of mobility measures as well as a measure of functional performance of activity of daily living (ADL). The main component of mobility which was assessed was walking. Walking measures included gait speed, stride time and gait variability as reflected by the stride time coefficient of variation. All these measures were quantified using the GAITRite system [140]. Measures of community walking over an extended period of time provided indications of performance and were recorded using a mobility monitor (StepWatch Activity monitor) [186]. Other components of mobility activities that are believed to be limited in HD such as sit to

stand, stepping and turning [114, 116] were assessed using other measures of mobility which included the Four Square Step test (FSST) [187], the Timed Up and Go (TUG) test [93] and the 30 seconds Chair Sit to Stand test (CSST) [188]. Functional performance of ADL activities that involve upper motor function was assessed using the Physical Performance Test (PPT) [189]. Levels of participation were represented by a health-related quality of life measure; the Short Form (SF-36) [119] was used to provide a measure of health-related quality of life in this study.

Table 3.1: Summary of the outcome measures evaluated (structured according to the International Classification of Functioning (ICF) model)

Domain	Category	Method of assessment	Main variables
Body structure and function	Disease-specific motor score	Modified motor score of the UHDRS section (mMS)	Total score of the mMS
	Balance	Berg Balance Scale (BBS)	Total score of the BBS
		Romberg and Sharpened Romberg tests (RT & SRT)	Total timed score to complete RT & SRT
		Force platform	COP sway; rms-AP, rms-ML, excursion-AP and exertion-ML
	Muscle strength	Isokinetic dynamometry (Kin-com)	MVIC of knee flexors and extensors
Activity	Walking- gait	Automated walk-way (GAITRite)	Gait speed, stride time, stride time CV
	Community walking	Activity monitor (SAM)	Average of daily step count, percentage of time spent at low, med and high physical activity and peak activity index
	Other measures of mobility activities	Four Square Step Test (FSST)	Time to complete the FSST
		Timed-Up and Go (TUG) test	Time score to complete the TUG test
		30 sec Chair-Sit to Stand Test (CSST)	Number of sit to stand transitions completed in 30 seconds
	Functional performance in ADL	Physical Performance Test (PPT)	Total score of the PPT
Participation	Health-related quality of life	SF-36	SF-36 **subscales**

UHDRS, Unified Huntington's disease rating scale; COP, Centre of pressure; rms, root mean square; AP, anterior-posterior; ML-medio-lateral; MVIC, maximal voluntary isometric contraction; CV, coefficient of variation

3.3.4.1 Measures of physical impairments in body structures and functions

3.3.4.1.1 A measure of disease-specific motor score

The modified motor score of the UHDRS (mMS) [180] was recorded at baseline for all HD participants. The mMS includes 10 items rated on a 0 to 4 scale with 4 indicating the most severe impairment. This modified scale rates dysarthria, tongue protrusion, alternating hand movement, finger tapping, luria, rigidity, bradykinesia, gait, tandem walking and reactive balance.

3.3.4.1.2 Measures of balance

3.3.4.1.2.1 Berg Balance scale

The Berg Balance Scale (BBS), a 14 item comprehensive test of static and dynamic balance, was used to assess balance [181]. Validity and reliability of this test has been established in the elderly and in people with stroke, traumatic brain injury and Parkinson's disease (PD) [181, 182, 185, 190, 191]. The scale has also been previously used in HD [38, 45] and validated to predict the risk of falls in this population [45].

For rating using the BBS, 14 observable tasks common to everyday life measured on a 5 point scale were completed by participants. Participants were asked to perform the following tasks; 1) sit unsupported 2) change position from sitting to standing 3) change position from standing to sitting 4) transfer 5) stand unsupported 6) stand with feet together 7) tandem standing 8) standing on one leg 9) standing with eyes closed 10) turning trunk 11) turning 360 degrees 12) retrieving object from the floor 13) stool stepping and 14) reaching forward while standing. The total score on all sub-tasks (out of a possible score of 56, with higher scores indicating better performance) was used for data analysis.

3.3.4.1.2.2 Romberg and Sharpened Romberg tests

The Romberg and Sharpened Romberg tests evaluate static balance and measure the ability to maintain steady standing in a variety of foot positions (Table 3.2). Participants were asked to perform 4 tasks of Romberg test; 1) standing feet apart and with eyes open 2) standing feet apart and with eyes closed 3) standing feet together (medial malleoli touching) and with eyes open and 4) standing feet together and with eyes

closed. No hierarchical order was used (i.e. participants who failed to perform the lower level of the test continued to be examined on the higher levels).

To perform the Romberg tests, participants were asked to maintain their position in standing with the arms folded across the chest for a maximum of 30 seconds. In addition to Romberg's test, participants were asked to perform 2 tasks of sharpened Romberg which included 1) standing in tandem (heel-toe position) with eyes open and 2) standing in tandem with eyes closed. To perform the Sharpened Romberg tests, participants were asked to stand in tandem with arms folded across the chest and eyes open and eyes closed for a maximum of 30 seconds. Participants were asked to perform 2 trials of each task of the Romberg and Sharpened Romberg tests. The amount of time the participant remained in the position without moving the arms or the feet or losing balance was recorded for each trial. The average of the 2 trials of each task was calculated. The total of the average times of the 6 tasks (out of 180 seconds) was calculated and used for analysis.

Table 3.2: Tasks of Romberg and Sharpened Romberg tests

Test	Tasks	Maximum score
Romberg tests	Standing with feet apart and with eyes open	30
	Standing with feet apart and with eyes closed	30
	Standing with feet together and with eyes open	30
	Standing with feet together and with eyes closed	30
Sharpened Romberg tests	Tandem stand with eyes open	30
	Tandem stand with eyes closed	30
Total		180

3.3.4.1.2.3 Measures of postural sway

Quantitative static force platform measurements, which are based on body sway assessment through the observation of the centre of pressure (COP) trajectory, were recorded in this study. These measures have demonstrated excellent reliability in healthy elderly people and in other neurological conditions (ICC>0.9) [148, 192].

Participants in this study were asked to stand on a static force platform (Kistler®) for 2 successive trials of performing quiet standing with eyes open. Two minutes of rest were given between trials. Instructions were standardized, as different experimental set ups and protocols are known to affect platform outcomes [193-196]. Participants were instructed to stand on the force platform placing their feet side by side 15 to 25 cm apart, and looking straight ahead with their heads erect while visually fixing a black spot that is placed at a distance of 3 meters on a flat screen and at eye level. Participants were also instructed to cross over their arms with the opened palm of the hand falling on the opposite shoulder. Once stable, instructions were provided to the participants to stand as still as possible for as long as they could up to a maximum of 30 seconds.

The Kistler® force platform was connected to an 8 channel amplifier. Data were acquired for 30 seconds for each task and sampling frequency was 1000 Hz. The signals from the platform were processed on a PC connected to a converter. Data were then analysed using a purpose written computer programme using software (MatLab R2007a), to calculate parameters from the COP data. The programme provided graphics of the mono-directional and planar displacements of the COP and of the diffusion stabilogram. The calculated parameters included the root mean square and excursion of the movement of the centre of pressure (COP) in the anterior posterior (AP) and mediolateral (ML) directions. Root mean square represents the variation of the movement of COP in a certain direction; whilst excursion represents the path taken by the COP over the duration of the test [148].

3.3.4.1.3 Measures of muscle strength

The maximal voluntary isometric contraction (MVIC) is the simplest and most commonly used method of accurately measuring the force-producing capabilities of a muscle group [183]. This is because isometric testing holds constant the variables of velocity of joint motion and muscle length [197]. Furthermore, measurement of MVIC using isokinetic dynamometry has become the standard method of strength measurement in research studies of neurological disorders [183, 197]. For the purposes of this study the MVIC values of quadriceps and hamstring were evaluated using the Kin-com isokinetic testing chair dynamometer unit.

A standardized procedure was used in order to ensure consistency of application of the technique. Participants were seated on the chair. The backrest was adjusted to 110 degrees of posterior incline. Seat belts and pads were used to stabilize the lower leg, thigh and pelvis. The most inferior portion of the transducer pad was adjusted above the lateral malleoli. The axis of the lever arm was aligned to be at the same level of the inferior part of the lateral epicondyle of femur. The knee was flexed at an angle of 90 degrees. The angle of the knee was determined by using a universal goniometer. Participants performed 3 trials of 3 seconds of MIVC for each of the right and left knee flexors and knee extensors. Sixty seconds of rest were given between trials. Subjects were instructed to keep their back against the backrest and to fold their arms against their chest during the test. Participants were given verbal coaching during the 3 seconds of contraction "to push or pull as hard as they can". Three progressive sub-maximal warm up repetitions of both knee flexors and extensors were performed prior to testing in order to familiarize the participants with the testing procedure. Thirty seconds rest interval was given after the warm up and prior to the main testing procedure. In order to ensure consistency between all research assessment sessions, information relating to the chair position, chair height, pad position and lever arm length were documented at the first session to enable them to be reproduced in the following sessions. The average of the 3 trials for the knee flexors and extensors was used for data analysis.

3.3.4.2 Measures of activity

3.3.4.2.1 Measures of mobility

3.3.4.2.1.1 Walking-measures of gait

Gait speed, stride time and stride time coefficient of variation were computed for all participants using the GAITRite system (CIR Systems, Inc.: Havertown, PA) [140]. The system is designed to quantify gait parameters in an automated fashion. It consists of an instrumented walkway with sensors embedded within its surface. As participants walk on the walkway, sensors record pressure applied at each footfall as a function of time. The walkway is connected to a serial port of a laptop computer in which footfall data can be collected, processed, and spatial and temporal gait parameters can be computed. The GAITRite walkway used in this project was 427 cm long and 61 cm wide. This contains an active area of 16,149 sensors arranged in a grid pattern with a spatial resolution of 1.27cm and a sampling frequency of 60 Hz (Figure 3.3). The reliability of

the GAITRite system in quantifying gait parameters has been established with reports of good to excellent test re-test reliability in studies examining the walking of young and older normal adults, and in individuals who have arthritis, Alzheimer disease, Parkinson's disease (ICC range from 0.75 to 0.99) [198-204]. Excellent test re-test reliability (ICC above 0.8 for all parameters) has also been established in a HD population [140].

Figure 3.3: GAITRite walkway (CIR Systems, Inc.: Havertown, PA) which was used to quantify gait parameters in the study

Each participant was asked to perform 10 trials of walking along the walkway at their comfortable pace. Standardized instructions at each assessment session were provided "walk toward the end of the walkway at a pace that is comfortable for you". The participant was allowed to rest at the end of each trial if required. A self determined pace was used so as to minimise walking variability [205]. A 2 meters acceleration and deceleration distance at either end of the walkway was included so that a steady state of gait was captured on the walkway. Two familiarisation trials at the beginning of the testing session were included.

Data from the GAITRite was processed using GAITRite GOLD, version 3.9 software. The setting for light and short footsteps was used for all processing of footsteps. If a participant's first or last footstep did not fall completely within the active area of the walkway, those footsteps were removed from the recorded walk. The number of steps included in computation of gait parameters was standardized to improve the consistency of the measure [206]. An average of 50 steps (5 steps per trial for 10 trials) was therefore used to calculate the gait parameters (gait speed, stride time and stride time coefficient of variation) from each participant at each session. The stride time coefficient of variation was calculated as the (standard deviation/mean×100%). To calculate the stride time and stride time coefficient of variation, the pooled left and right strides were used. The advantage of this approach is that it allows for increased the number of strides to be included in the analysis; thus providing a more precise measure of gait variability [104]. Furthermore, this method was used in this study so as to facilitate comparison of data obtained in this study with data from previous studies on gait deficits in HD in which a similar approach of calculating gait variability was used [41, 42, 107]. It should be noted however, that one of the concerns of using this method (i.e. averaged data from pooled right and left strides) is that the calculation of the coefficient of variation could be confounded by any underlying spatiotemporal asymmetry in the presence of disease [207]. In this study a pilot analysis was conducted on a sub-sample of HD individuals (n=10) which demonstrated no clear underlying spatiotemporal asymmetry. Furthermore previous research demonstrated that an asymmetrical distribution of impairments is not a clear expected feature of gait deficits in Huntington's Disease [112] (in contrast to other neurological diseases such as stroke).

3.3.4.2.1.2 Community walking

Levels of community walking were measured using the Step Watch ^{TM} (Cymatech, Seattle, Washington, USA), step activity monitor SAM, a sealed waterproof 2-dimensional accelerometer. The monitor is reliable and valid for use in a range of neurological conditions [186, 208] and has been used in people with HD [45]. The monitor was attached to the right lower limb immediately above the lateral malleolus of the ankle with an elastic strap and recorded level of activity by counting steps taken per minute continuously over the monitoring period. The SAM was programmed using an infrared docking port (SAM Dock Programme 1.6.La) before the monitoring period with sensitivity settings appropriate to height, cadence and gait speed for each

participant. The settings were verified by visual inspection during a test trial as a light on the monitor is programmed to blink each time a step occurred for the first 30 steps taken by the participant. All participants were asked to wear the monitor for all the waking hours for 7 consecutive days and remove it only for bathing. Participants were asked to report any instances where the monitor had to be removed. Following the monitoring period, data were downloaded into a computer using the infrared docking port and the following activity indices were extracted; the average 24 hour step count over a week, percentage of time spent in inactivity in minutes, low activity, medium activity and high activity and peak activity index (Table 3.3).

Table 3.3: Activity indices extracted from the Step Activity Monitor

Activity index	Parameters	Description
Average of step total	Average of step total	The average 24 hr step count over a week
Percentage of time spent at different levels of activity	Percentage of time spent in inactivity	Percentage of time in which no steps were recorded
	Percentage of time spent in low activity	Percentage of time in which the step count fell between and inclusive of 1 and the limit for low Activity (less than 15 steps per minute)
	Percentage of time spent in medium activity	Percentage of time in which the step count fell between and inclusive of the low activity limit +1 and the limit set in for medium activity (between 15 and 40 steps per minute)
	Percentage of time spent in high activity	Percentage of time in which the step count was greater than the medium activity limits (greater than 40 steps per minute)
Peak activity index	Best 30 minutes	The average step rate of the highest 30 minutes of the included time in a day, regardless of when they occurred

3.3.4.2.1.3 Other measures of mobility

3.3.4.2.1.3.1 Four Square Step Test

The Four Square Step Test (FSST) requires participants to rapidly change direction and step while stepping forward, backward, and sideways, over a low obstacle, while time to complete the test is measured. The test is valid and reliable in measuring balance in the elderly [187] and has been used previously in people with stroke, vestibular disorders and peripheral limb amputations [209-211].

To perform this test, 4 canes resting flat on the floor were used to form 4 squares. Participants were asked to stand in square number 1 facing square number 2 and to step as fast as possible into each square in the following sequence; square number 2, 3, 4, 1, 4, 3, 2, and 1. The time taken to complete the sequence was recorded with a lower time indicating a better performance. Timing of the test started when the first foot contacted the floor in square 2 and finished when the last foot came back to touch the floor in square 1. The following instructions were given to participants, "Try to complete the sequence as fast as possible without touching the sticks, facing forward through the entire sequence. Make sure that both feet make contact with the floor in each square." Following a demonstration, a practice trial was performed to ensure that participants knew the sequence. The average of 3 trials was computed for data analysis. A trial was repeated if the subject failed to complete the sequence successfully, lost balance, or made contact with a cane during the sequence. Participants who were unable to perform the test by being unable to face forward through the sequence and needed to turn to step were given a fixed score of 60 seconds that resembles a higher score relative to the maximum score obtained by participants who were able to complete the test successfully.

3.3.4.2.1.3.2 Timed Up and Go test

The Timed Up and Go (TUG) test measures the time taken to rise from a seated position, walk 3 meters, turn, walk back and sit down again. The test re-test reliability of this test has been previously established in the elderly and in people with Alzheimer's disease (AD) and PD [182, 191, 212]. The scale has also been previously used in HD [45, 93] and validated to predict the risk of falls in this population [45].

To perform this test, participants were instructed to sit with their back against a chair (48cm from floor to seat with armrests), feet behind a tape marker, and arms resting on the armrests of the chair. Participants were instructed to independently rise on the word "go", comfortably walk a clearly marked distance of 3 meters, turn around a cone, walk back to the chair, and sit down with their back against the chair. Time started on the word "go" and ended when the participant's back returned to the chair. One practice trial and 2 timed trials were performed; the 2 timed trials were averaged for data analysis.

3.3.4.2.1.3.3 Chair Sit to Stand Test

The 30 second Chair Sit to Stand Test (CSST) quantifies the maximum number of sit to stand repetitions that can be performed in 30 seconds (higher scores indicate better performance). The test is reliable and valid for use in the elderly and in people with balance disorders [213-215]. The test started with the participant seated in the middle of the chair, back straight, feet firmly planted on the floor approximately hip width apart and the back of lower legs away from the chair. Knees were bent at a 90-degree angle with arms crossed over the chest. At the signal "go," the participant rose to a full stand (body erect and straight) and then returned back to the initial seated position. Participants were encouraged to complete as many full stands as possible within a 30-s time limit. Participants were instructed to be fully seated between each stand. While monitoring the participant's performance to assure proper form, the completion of each correct stand was counted. Following a demonstration, a practice trial of 1 repetition was given to check proper form, followed by the 30-s test trial. Participants completed 3 trials of the test with 2 minutes rest interval. The scores from the 3 trials were averaged for data analysis.

3.3.4.2.1.4 Measures of functional performance in ADL

Functional performance in ADL was assessed using the Physical Performance Test (PPT). The PPT is a direct observational test that assesses multiple dimensions of physical function (basic and complex activities of daily living [ADL]) with different levels of difficulty [189]. The test is valid and reliable for use in the elderly [216] and was previously used in people with PD [217]. Scoring of this test is by timing the completion of a task. This time is then related to a categorical score of 0 to 4, in which 4 represents people in the fastest 20% at completing the task, 1 represents those in the slowest 20%, and 0 represents those who cannot complete the task. The test includes lifting a book and putting it on a shelf, putting on and removing a jacket, picking up a penny from the floor, turning 360 degrees and a 50-foot walk. The total score on the 7-item PPT (out of 28 with higher scores indicating better performance) was used for data analysis.

3.3.4.3 Measures of participation

3.3.4.3.1 Measures of health-related quality of life

The Short Form 36 (SF-36) (version 1) was used to evaluate the perceived health-related quality of life and level of participation [218]. This survey was previously used in HD [117, 119] and has also been validated in numerous populations with neurological disabilities [182]. Participants in this study were asked to complete the SF-36 form on their own and with the help of their carers if required. The scores from the eight subscales of the SF-36 which include 1) physical functioning, 2) role limitations due to physical problems 3) vitality/ energy 4) bodily pain 5) social functioning 6) role limitations due to emotional problems 7) mental health and 8) general health perceptions (out of 100 for each subscale with higher scores reflecting better quality of life) were used for data analysis. In addition the summary of physical components and the summary of mental components (out of 100) were included in the analysis.

3.3.5 Outcome measures and potential confounders

To estimate the effect of the variables such as gender, age, height and weight on the used outcome measures, these variables were recorded at baseline. As an entry to the study, medical history including current medication use and living circumstances was also obtained from all participants at the baseline. Data of CAG repeat lengths for all participants with pre-manifest and manifest HD participants were obtained from medical notes or the Registry study. In addition, the Total Functional Capacity Scale (TFC), the UHDRS- cognitive score and the modified motor score of the UHDRS (mMS) were recorded at baseline for all HD participants.

3.3.6 Statistical considerations for part 1

3.3.6.1 Statistical analysis

Data from all measurements, excluding data from the process evaluation, were analysed using the Statistical Package for the Social Sciences (SPSS) Version 18 (SPSS, Chicago). Data were visually assessed for normality using histograms and Q-Q plots and for variance assumptions using Levene's test for equality of variances to allow for the appropriate choice of statistical test.

To examine the discriminative validity of the clinical outcome measures, differences between groups on the outcome measures used were examined using one way ANOVA, after checking for appropriate matching according to age, height and weight. Between group comparisons were considered significant if $p \leq 0.05$. When significant differences were identified, post-hoc analyses were conducted using Tukey HSD or Dunnet T3 tests (based on whether Levene's test was significant or not). In cases where normality was not shown, the non parametric Kruskal-Wallis test was used to compare between groups (Group comparisons were considered significant if $p \leq 0.05$. If significant differences for main effect were indicated, post hoc analysis was conducted using Mann-Whitney U-tests with appropriate Bonferroni correction for multiple comparisons; an adjusted alpha level of 0.017 as significant was applied in this case.

To test convergent validity of clinical tests of mobility, balance, muscle strength, functional performance in ADL and health-related quality of life, their correlations with measures of gait variability (stride time coefficient of variation) were computed using Pearson's or Spearman correlation coefficients (dependent on the normal distribution of each variable). Data were checked for the presence of outliers using casewise diagnostic procedure [219]; cases where standardized residuals (differences between observed and predicted values divided by an estimate of their standard deviation) were greater than 1.96 or lesser than -1.96 were considered to be outliers (i.e. cases where standardized residuals were outside 2 SD of their distribution). In addition, data were visually inspected with scatter plots. In cases where outliers were identified, data sources were firstly checked for coding errors. Additionally, analyses were run with and without the outlying cases so as to estimate the effects of outliers on the obtained results.

To evaluate test re-test reliability, a paired t-test or Related Samples Wilcoxon Signed Ranks test using the test and re-test scores was used to evaluate if there were any systematic differences between the 2 test scores. Furthermore, Bland and Altman methods were used to assess the magnitude of differences between the 2 test scores (i.e. between-days). Calculations included the mean difference between measures, the 95% confidence interval (CI) for the mean differences and the standard deviations of the differences [220]. Additionally, differences between scores obtained from day 1 and day 2 were plotted against the average of the 2 scores for each individual. These graphs were helpful to illustrate the size of each difference, the range of the differences and

their distributions about zero which represents no difference (i.e. perfect agreement). These graphs were also useful to indicate if there were any outliers and biases in the measurement or if the differences were related to the size of the mean (i.e. if the size **of** differences increases in cases where the mean increases or decreases). It should be noted however, that 95% limits of agreement were not calculated in this study. Rankin and Stocks [220] suggest that the sample size should be large enough, preferably larger than 50 for the limits for agreement to be estimated well. As the sample size in this study was small (i.e. 9 subjects in the manifest HD group and 9 subjects in the pre-manifest HD group), limits of agreement are not reported here.

The intra-class correlation coefficients (ICC) were calculated to assess both systematic and random error that may affect relative test re-test reliability. The ICC (3,k) (the 2 way mixed model of consistency), either a type 3,1 3,2, 3,3 or type 3,10 ICC was used [221]. The ICC (3,1) was used for the BBS, PPT, and SF-36 because final scores on these tests were based on a single trial. The ICC (3,2) was used for the TUG, Romberg tests and measures of postural sway because final scores for these outcomes were based on an average of 2 trials. The ICC (3, 3) was used for the CSST and the FSST because the final scores for these tests were based on the average of 3 trials. The ICC (3, 10) was used for all gait parameters because final scores were based on the average of 10 trials.

Measures of absolute reliability were expressed as the standard error of measurement (SEM) and the minimal detectable change (MDC) [141]. The standard error of measurement (SEM) was estimated from the square root of the mean error term from a repeated measure ANOVA [222, 223]. The MDC at the 95% confidence level (MDC_{95}) was calculated. The MDC_{95} was calculated as $1.96 * \sqrt{2} * SEM$. Thus, the MDC_{95} values provide information about the confidence limits associated with measurement error so that, for example, it can be stated with 95% confidence that an individual's change score that exceeds the MDC represents a true change.

3.3.6.2 Sample size

An a priori sample size calculation was conducted for Part 1 of the study. A main aim of this part of the project is to investigate the ability of the outcome measures to discriminate between participants with pre-manifest HD and healthy controls and between participants with manifest HD and healthy controls. Changes in gait variability

were chosen as the primary outcome measure for the power calculation, since measures in gait variability were found to be the most sensitive and specific gait parameters in distinguishing between healthy controls and people with HD in a previously published study by Rao et al [40]. In this study, authors reported results which suggest a mean difference for stride length coefficient of variation of 4.6 between pre-manifest HD and healthy controls, 4.1 between manifest HD and healthy controls and 2.3 between manifest and pre-manifest HD. This equated to effect size index of 0.7 based on a formula reported by Portney and Watkins [178] for estimating effect sizes when comparing between groups using the one way ANOVA. In the same study by Rao et al [40], the authors reported results which suggest a mean difference for step time coefficient of variation of 3.0 between pre-manifest HD and healthy controls, 5.1 between manifest HD and healthy controls and 2.1 between manifest and pre-manifest HD. This equated to effect size index of 0.4. As this was the first study to report deficits in gait variability along the spectrum of the disease and there is a possibility that effect size of 0.7 for stride length coefficient of variation is overestimated, an effect size of 0.4 was used in this study for sample size calculations. Using an effect size of 0.4, a sample of 20 participants in each group was required, using a power of 0.8 and an alpha of 0.5 (two tailed) [178].

In addition 20 participants were required to detect a Pearson's correlation coefficient of 0.6 with a power of 0.8 and an alpha of 0.05 (two-tailed). A sample of 18 participants (tested twice) was also sufficient to be able identify an intra-class correlation coefficient (ICC) of 0.8 as being significantly greater than an ICC of 0.45 (moderate) which would be the minimally accepted value [224]. This sample size was both feasible for recruitment purposes in this study and sufficient to identify substantial [225] reliability (Appendix 6).

3.4 Part 2: Evaluating feasibility, acceptability and benefits of a home-based exercise programme

3.4.1 Study design

Feasibility, acceptability and benefits of a home-based exercise programme for people with manifest HD at early to mid stage of the condition were evaluated at this part of the study which comprised 2 phases. In the first phase, the existing participants with

manifest HD who completed the baseline assessments (n=25) were randomly assigned to either early intervention group (n=13) or delayed intervention group (i.e. control) (n=12). The delayed intervention group (i.e. control) initially received standard care. This involved no specific exercise interventions. Whilst this was not a perfect control group (standard care can be as complex as the intervention being evaluated and may change with time) [69], it was the best compromise that could have been achieved at this stage of the project. The early intervention group received a home-based exercise programme for 8 weeks. During these 8 weeks, participants in the control group were advised not to change their routine related to performing physical activity and were asked to record their weekly physical activity in a diary (Appendix 2). After 8 weeks, both groups were assessed (first follow-up assessment). At this point, the exercise programme for the early intervention group was completed and the intervention was offered to the delayed intervention group (i.e. control) which compromised of the start of the second phase of this part of the study (see Figure 3.1 for the flow chart of the study). This design facilitated comparison of intervention with no intervention (i.e. control) whilst at the same time assured that each participant in the study was offered the intervention at a specific time point. Following the first follow-up assessment, both groups were reassessed after an additional 8 weeks on the main outcome measure (stride time coefficient of variation) (second follow-up assessment). In addition, a debriefing was undertaken at the second follow-up assessment as to whether the early intervention group continued with any of the programme after cessation of formal exercise input. Second follow-up assessments, therefore, provided information on any carry over (in the main outcome measure; gait variability) as well as adherence with home-based interventions for the early intervention group, who received the intervention following the initial baseline and then had no intervention after the first follow-up assessment. The second follow-up assessments also had the potential to enhance adherence and commitment specifically in those allocated to the delayed intervention group (i.e. control group) [69, 70]. Completion of the intervention was followed by a process evaluation that aimed to ascertain participants' and carers' opinion of the process and benefits of involvement in a home-based exercise programme (see section 3.4.4 for more information about the process evaluation).

3.4.2 Randomization

Participants were randomly allocated to either early or delayed intervention groups using a minimisation procedure [226] which is an accepted alternative method to stratified randomization [227, 228]. With minimisation, allocation of the next participant enrolled in the study to a particular group depends on the characteristics of those participants already enrolled. Minimisation has the advantage, particularly in small trials, that there will be only minor differences between groups in those factors used in the allocation process [227]. Such balance is particularly important where there are strong prognostic factors that would impact on the outcome.

For the purposes of this project the randomization was carried out with the aid of the MINIM software [229] that is designed specifically to perform randomization in clinical trials by the method of minimisation. MINIM assigns the next participant to the study arm that would best minimise the imbalance between groups based on the categories provided. MINIM calculates the balance between the groups, using the weighting of each included variable using a method described by Pocock [228]. This balance is calculated assuming the next participant will be allocated to each of the possible treatment groups in turn (usually 2). It then takes into account the assignment that would result in minimal imbalance. In cases where the 2 groups have the same imbalance, the next participant will be allocated with a probability of 0.5 to each. However if there is a preferred allocation, the next participant will be allocated to the group that would best minimise imbalance with a probability of 0.7.

Using the MINIM software helped to adhere to the randomization protocol as the study progressed. Two prognostic factors were considered to potentially impact on the outcome of this study and needed to be balanced between the 2 study groups at the baseline. These factors were age and severity of the functional impairment as based on Total Functional Capacity (TFC) scores. These 2 factors were treated equally (i.e. both age and disease severity were given the same weighting during the minimisation procedure. Using MINIM software, age was classified into 6 categories as follows: 1) less than 30, 2) between 30 and 39, 3) between 40 and 49, 4) between 50 and 59, 5) between 60 and 69, 6) more than 69. Similarly, the TFC was classified into 4 categories; 1) TFC scores correspond to stage I (11-13), 2) TFC scores correspond to stage II (7-10), 3) TFC scores correspond to stage III (3-6), 4) TFC scores correspond to stage IV

(1-2). Using these categories, MINIM software helped to randomly allocate participants and at the same time ensure balance between the study groups in terms of age and disease severity as determined by the TFC score.

3.4.3 Protocol of the exercise programme

Participants were asked to perform exercises at home 3 times a week using a purpose developed exercise DVD. The exercise DVD was structured based on consultations with therapists working routinely with people with HD as well as findings from the exercise literature on other neurodegenerative disease. The included exercises were chosen to target the physical factors that are believed to be impaired in HD, such as balance, and focused on practicing task-specific activities that are believed to be limited in this population.

Overall, the exercise DVD consisted of 5 sections; the first section focused on warm up and flexibility activities; the second, third and fourth sections focused on strength, and balance exercises specifically tailored for people with HD and the fifth section focused on cooling down and included relaxation, stretching and breathing techniques (Table 3.4). The balance exercises were divided into 2 sections in which the first section focused on practicing narrowed and altered functional base of support exercises. The easiest of these exercises required participants to maintain body position in standing whilst the medial malleoli of the feet are touching each other. To progress in difficulty, these movements were then performed while 1) standing with eyes closed, 2) standing on one leg, 3) standing, placing one foot in front of the other, with eyes open and then closed, 4) forward and side lunges. At the easiest level, these movements could be performed while holding onto a table, chair or countertop. The progression was then to perform these movements without holding and touching the countertop only as needed for balance. The second section of the balance exercises focused on performance of task-specific activities that required alterations of dynamic balance such as standing and sitting, turning and stepping up onto stairs. Each of these exercises was performed for 1 minute and the set of exercises was repeated a number of times on completion of the first circuit. To progress in difficulty the number of repetitions of each of the exercises was increased and the number and length of rest breaks decreased.

Table 3.4: Sections of the exercise DVD

Section 1: Flexibility and warm up	**Section 2: Balance and coordination**
• Neck stretches • Shoulder rolls • Horizontal shoulder flexion • Arm circles • Hand stretches • Ankle circles • Calf muscle stretches • Hamstring stretch • Lying supine twist • Quadriceps stretch • Prone press ups • Kneeling child's pose	• Standing with feet together, eyes open • and then closed • Standing on one leg • Tandem standing • Forward lunges • Side lunges
Section 3: Circuit resistance training	**Section 4: Strengthening**
• Sit to stand repetitions • Shoulder press with weights • Squatting • Shoulder abduction with weights • Trunk rotations & reaching with weights • Step Ups	• Instructions on getting on/off floor • Bridging • Alternate Arm and Leg Raises • Plank
Section 5: Cool down and relaxation	
• Cat/Camel stretch • Trunk Rotations • Breathing exercises	

All participants were provided with the exercise DVD, which was individually prescribed with sub-sections based on the participants' specific abilities; suitable exercises from the DVD (based on what the participant was able to do) were chosen and taught to participants by the researcher (PhD student). Participants were encouraged to progress their exercising by gradually increasing the number of repetitions whilst decreasing the number and length of rest breaks until they were able to perform each exercise in the same manner and frequency as indicated in the DVD. At this point, participants were encouraged to increase the difficulty of the exercise by increasing the level of progression.

In addition to performing the exercises from the DVD, participants were instructed to undertake a 30 minute gradual progressive walking programme. Participants were asked to walk once a week on level ground around their homes and neighbourhoods.

Participants were instructed to walk at their freely chosen pace and to take rest breaks during walking if required. Participants were encouraged to progress their walk by decreasing the number of breaks and increasing the amount of time they could walk until they reached the 30 minutes. Participants were also asked to keep a record of their exercise programme in an exercise diary (Appendix 2).

All participants were supported by a researcher (the PhD student) who conducted an initial home visit to ensure correct execution of the exercises. A pre-planned schedule was used to ensure the comprehensiveness of the topics discussed at the home visit for each participant (Appendix 3). During the home visit, the potential benefits of the exercise programme were discussed with participants. The relevance of doing each of the exercises was communicated. Advice about intensity of the exercises, equipment required, precautions and postural instructions was also provided. In addition, instruction and demonstration on how to use the DVD and to perform the exercises was given by the researcher during this home visit. When introducing the walking as an exercise, the researcher spent time explaining to the participant the desired level of intensity. Participants were instructed to walk at normal pace. Preferably, participants were instructed to walk at a speed that does not cause shortness of breath. Participants were instructed to walk for whatever length of time they were able at first with the goal of increasing the time until they could walk for at least 30 minutes. All participants were advised on recognition of any warning signs, such as severe pain, at which to cease the execution of exercise and they were provided with the telephone contact number of the researcher to ask for any advice. All discussions and instructions during the home visit were performed in the presence of the carer (if applicable) who was asked if he/she would help the participant if needed and in such case, carer's involvement was discussed and agreed with the participant.

All participants were provided with weekly phone calls by the same researcher to monitor their progress, encourage them to continue their exercises and discuss any issues which might arise. A pre-planned schedule (Appendix 3) was also used for the phone calls to ensure the comprehensiveness of the topics discussed with each participant. During the phone calls, participants were asked if they performed the exercises from the previous week, how often they performed the exercises, what exercises they performed, what exercises they would do in the following week, if they

had difficulties in performing any of the exercises and if they had any concerns that they wanted to discuss.

3.4.4 Outcome measures

Outcome measures which were described in Part 1 were evaluated at baseline and 8 weeks post intervention in both groups. The primary outcome measure was gait variability due to the reported sensitivity to disease progression in HD [39, 40, 107, 112] and the potential that it has to serve as a clinically relevant parameter in the evaluation of mobility and in response to therapeutic interventions [104]. The focus in this study was on one parameter of gait variability; the temporal variability in the gait cycle duration (i.e. stride time) which is represented using the stride time coefficient of variation. Variability in stride time reflects the walking rhythm; it has reliance on central and peripheral inputs and can be viewed as the final output of the locomotor system [104, 230]. Stride time may be an important parameter to consider, particularly in HD, as disorders of footstep timing are the most obvious gait deficits in this population. For these reasons variability in stride time was used as the primary outcome. Secondary outcomes included the other measures of gait (gait speed and stride time), measures of balance, muscle strength, community walking, other measures of mobility and functional performance of ADL and health-related quality of life as well as a disease-specific motor measure (the mMS) (detailed description of the used outcome measures is provided in Part 1 in section 3.3.4).

3.4.5 Quality control measures

All assessments of outcome measures were undertaken by the researcher (the PhD student). The researcher was not blinded to group allocation; however standard procedures were used (see Appendix 4 for standard operating procedures of outcome measures) and all tests were based on objective measures or were self-administered (i.e. SF-36). Tests that were potentially affected by examiner bias (i.e. BBS and mMS) were videotaped and rated by a blinded assessor using an established methodology [231]. The blinded assessor had no previous connection with the participants and acted purely as a video assessor. After recording, video clips were edited to remove time and date identifiers. Each clip was given a code in which the order of the pre and post intervention clips was reversed for the odd numbered participants so that the clip after

intervention was shown to the blinded assessor before the relevant pre-intervention clip. The blinded assessor was informed that the 2 clips of each participant were separated in time by about 8 weeks in which the participant may or may not have received the intervention and that the clips did not necessarily appear in chronological order. This was performed to avoid bias based on the order of presentation of the clips.

3.4.6 Specific statistical considerations for part 2

3.4.6.1 Statistical analysis

Data analysis of the interventional study was carried out on complete cases; data from all participants who completed the first follow-up assessments were included in the analysis. Analysis of covariance (ANCOVA) was used to compare between groups in which first follow-up scores were compared across groups after adjustment for any observed chance differences at baseline [147]. To aid data interpretation, scatter plots of individual responses were produced; scores at baseline of each participant were plotted against the change scores, categorized by group allocation for all variables. Effect sizes based on the difference in the change score from baseline to first follow-up between the study groups were calculated for each of the outcome measures. Data at the second follow-up assessment on the primary outcome measure (stride time coefficient of variation) were analysed only descriptively.

3.4.6.2 Sample size

A main aim of this part of the study was to investigate the benefits of a home-based exercise programme in reducing gait variability in people with Huntington's disease. Changes in gait variability were chosen as the main outcome measure for the power calculation since they serve as sensitive and clinically relevant parameters in evaluation of fall risk [104]. Consequently, available data in the literature for changes in gait variability in HD among people who are at risk of fall and people who are not at risk of falls, has been investigated. Grimbergen et al [38] reported results that suggest a mean difference of 2.3 for a measure of gait variability (stride length coefficient of variation) between fallers and non-fallers in HD (mean (SD) in fallers and non-fallers were of 6 (3.5), 3.7 (1.4) respectively). This equated to an effect size of 0.9. Using the effect size of 0.9, the number of subjects required for this part of the study to demonstrate a treatment effect was 40 for 2 groups of 20 subjects. This is derived from a power

calculation for t-tests and is based on requiring a power of 0.8, significance level of 0.05 and a two tailed test.

Although the initial power calculations determined that 20 subjects were needed per group, the study was stopped prior to reaching this target because of the difficulty in finding participants who met the inclusion criteria and were willing to participate. The ratio of subjects screened to subjects enrolled and the reasons for exclusion were documented and provide data for feasibility of recruitment in future randomized trials. More details about recruitment and reasons for exclusion are provided in Chapter 5.

3.4.7 Process evaluation

Quantitative and qualitative data were combined to provide multidimensional information about participants' adherence to the exercise programme and their opinions of the process and benefits of involvement in the study. Self reported adherence was obtained using the exercise diaries and self reported motivation, in terms of involvement in the exercise programme, was evaluated using the Intrinsic Motivation Inventory questionnaire. In addition, perceived benefits and factors that could have impacted on the adherence to the exercise programme were explored using semi structured interviews that were conducted with participants and their carers (if applicable) on completion of the exercise programme.

3.4.7.1 Adherence rate

Average adherence rates across the study period were calculated as the number of exercise sessions reported as a percentage of potentially expected exercise sessions prescribed for the 8 weeks. For the purpose of analysis, a cut-off point for acceptable adherence was defined; participants were considered to have a good adherence if they reported performance of at least 50% of the prescribed sessions.

3.4.7.2 Participants' motivation: Intrinsic Motivation Inventory subscales

Participants' self report about their perceptions of their involvement in the exercise programme was assessed using the Intrinsic Motivation Inventory (IMI) scale [232]. The IMI is a multidimensional measurement tool designed to assess participants' subjective experience related to a target activity. It consists of a multi-item

questionnaire assessing the subject's interest/enjoyment, perceived competence, effort, value/usefulness, felt pressure and tension, and perceived choice while performing a given activity. The interest/enjoyment subscale is considered a self-report measure of intrinsic motivation. The perceived choice and competence concepts are regarded as a positive predictor of intrinsic motivation. The pressure/tension is theorized to be a negative predictor of intrinsic motivation. The full version of the questionnaire includes 45 items and 7 subscales. A shorter version of the questionnaire with only 5 subscales that was found to be valid and reliable in neurological patients was used in this study (Appendix 4) [168]. For each item of the IMI scale, a response on a scale of 7 points indicates how true the statement of the item is (1 indicates not true at all and 7 indicates very true). Lower score of the pressure/tension subscale and higher scores of all the other subscales indicate a positive outcome.

3.4.7.3 Semi structured interviews

Semi-structured interviews were used mainly to explore perceived results and factors that impacted on usability to the exercise DVD and adherence to the exercise programme. A schedule that included both open and closed questions (Appendix 5) was used to serve as a guide to the topics covered during the interview. Each interview focused the discussion on debriefing the rate of adherence during the course of the programme and exploring how people used the exercise DVD at home. The main carer was present at the interview in most cases (n=16); carers were invited to participate in the interviews and to provide clarifications where necessary. All the interviews were audio recorded and lasted between 30 to 45 minutes.

The interviews were transcribed in full into text. This process of full transcription helped to strengthen the trustworthiness of the data by avoiding selective recording of the information [233]. Ensuring the truth value (credibility) [234] of the study, the accuracy of the transcripts was confirmed by an independent researcher and by consultation with participants.

3.4.7.4 Data analysis for process evaluation

3.4.7.4.1 Quantitative analysis

Data from the IMI scale were analysed descriptively in which average and standard deviations of each subscale were calculated. Correlations between adherence rate, IMI subscales, stride time CV and UHDRS-cognitive score were calculated using the Spearman correlation coefficient to determine interrelationship between these factors and in particular to explore if the physical and cognitive impairments as well as the participant's subjective experience on their involvement in the programme would relate to the adherence rate.

3.4.7.4.2 Qualitative analysis

A content analysis approach [235] was used to analyse data from the interviews. Responses from closed questions were analysed using a priori coding, while responses from open questions were analysed using an inductive approach in which codes emerged from the data. The qualitative data analysis package NVivo (version 8.0. 163, QSR International Pty Ltd) was used to aid the analysis process. A procedure of coding and recoding was used [234]; the transcripts were read and re-read to do further coding and refinement. This process was continuous and entailed comparing codes from an interview with the codes from a newer interview, which helped to identify prompt questions. After open coding for the first 8 transcripts, the remaining transcripts were coded using the existing codes and with adding new codes on encountering data that did not fit into existing codes. Following identification of codes from each transcript, the modeller option in NVivo [236] was used to help with ordering the codes, linking them together and clustering them into categories and subcategories. The transcripts with their codes were made available to an independent researcher (the same researcher who checked the accuracy of the transcripts) for review and through discussion we refined and defined the codes and their relationship to each other, and to the main question that was being investigated. Final codes were agreed within the research team and were sent to the participants for member checking in which participants agreed that interpretations of the researcher represented their ideas. Final codes were further cross checked and triangulated with information obtained in relevant available literature, thus confirming content and final conclusions [234].

3.5 Ethical considerations

3.5.1 General ethical considerations

Local Research Ethical approvals were obtained from South East Wales Research Ethics Committee for all aspects of this study. All participants were required to provide informed consent. Participants were free to withdraw at any time without giving any reason.

The researcher (the PhD student) conformed to the University and NHS Trust lone-worker policies during the home visits. A risk assessment of the site visit was carried out for each home visit. The initial contact with the research subject was made to arrange a suitable visit time and to explain the purpose and content of the visit and answer any initial queries participants may have. The means of transport to the home and having adequate information on safe routes to and from the destination were clarified along with a clear itinerary of the visits (including appointment times and the names, addresses and contact numbers of the subjects to be visited). Arrangements were put in place for communicating with the supervisor. In this case the PhD student carried a mobile phone at all times and contacted the supervisor on arrival and on completion of the home visit. The PhD student was also provided with a personal alarm system to be used in case of an emergency.

Carers were asked if they were willing to be involved in the process evaluations. Data were pseudonymised and stored electronically on hard disk (and not placed on a server or network) in a secure location within the School of Healthcare Studies (SOHCS), Cardiff University. A laptop computer was used for the clinical assessment procedures; however data would not be permanently stored on these computers. All computers that were used to store data were password protected. Data were transferred to the main hard drive via USB data transfer device on completion of each specific clinical assessment procedure. Any data that was collected via the laptop computer were pseudo-anonymised. The laptop did not hold any patient's identifiable data. Specifically, a unique code name (pseudonym) was calculated from initial personal data obtained. The link between the pseudo-anonymised codes and patients' personal details was stored separately in a lockable filing cabinet in a secure location as per the HD Registry study code.

All conversations that took place during the process evaluation were audio recorded for the purposes of analysis. Consent for audio recording was obtained beforehand. All the recorded tapes were destroyed once they had been transcribed. To ensure the accuracy of the transcript contents, a copy of the transcript was sent back to the participants requesting their comments to ensure that the transcript represented their ideas. All audio and video records obtained were stored in locked cabinets in the School of Health Care Studies, Cardiff University. Audio and video information and data have not been used for commercial purposes. Data will be retained for a period of 15 years. This retention period complies with Guidelines set out by the Cardiff University Research Governance Framework. Data were stored electronically and in paper form in Cardiff University in the School of Health Care Studies.

3.5.2 Specific ethical considerations

3.5.2.1 Risk during assessment

The clinical assessment that was conducted was considered unlikely to cause undue stress to participants. All participants were fully informed of testing procedures before participation, and made aware that they could withdraw from the study without giving reasons at any time. Individuals were carefully monitored during testing by the researcher (PhD student). The care and comfort of the participants was ensured at all times.

Additionally, potential risks anticipated from wearing the mobility monitors were also considered. The StepWatch Activity Monitor (SAM) is a commercially available, battery operated accelerometer device. It has been used in previous long term activity monitoring studies [128, 208] and the device was considered to pose minimal risk to the research subjects. The device is constructed in a sealed case which is routinely visually inspected for damage.

3.5.2.2 Potential risk of involvement in the exercise programme

3.5.2.2.1 Risk of falls

Potential side effects for those study participants involved in the exercise programme were considered. One of the foremost concerns of physiotherapists working with HD is that the person might fall whilst exercising [80]. Some studies suggest a U-shaped

association, in which the most inactive and the most active people might be at the same risk of falls [237]. A number of strategies were utilised in this study to ensure participant's safety whilst exercising. These included providing clear illustration and instructions of the risk factors, involving the carer (if applicable), providing appropriate prescription of exercises and providing a home visit at the beginning of the treatment programme to make sure of the ability of the participant to correctly perform the exercises and the weekly phone calls to monitor progress.

3.5.2.2.2 Risk of muscle damage

Another side effect which has been considered for those study participants involved in the exercise programme was the risk of muscle damage. In people with HD, there may be a risk of muscle damage due to impaired mitochondrial energy function in muscle cells [238] and high-intensity aerobic exercise in people with HD has been suggested to cause muscle damage [97, 239]. The proposed exercise programme was low intensity and did not involve any heavy load bearing exercise or high intensity cardiovascular intervention and therefore posed minimal risk to participants. All participants were advised on recognition of any warning signs at which to cease the execution of exercise, and provided with a telephone contact number of the researcher (PhD student) to ask for any advice.

3.6 Project management (study steering group)

The study was overseen by a Study Steering Group (SSG) which was independently chaired and included an independent statistician and a representative of service user. The steering group met 3 times during the course of the study either face to face or by audio conference. The SSG acted as data monitoring and ethics committee as the study was very small. The SSG provided overall supervision of the study and ensured that it was being conducted in accordance with the principles of Good Clinical Practice and the relevant regulations. The SSG agreed the study protocol and any protocol amendments and provided advice to the investigators on all aspects of the study. The SSG monitored the progress of the study, including the recruitment, data completeness, data analysis and ensured that there were no major deviations from the study protocol.

Chapter Four

Results and Discussion: Part 1

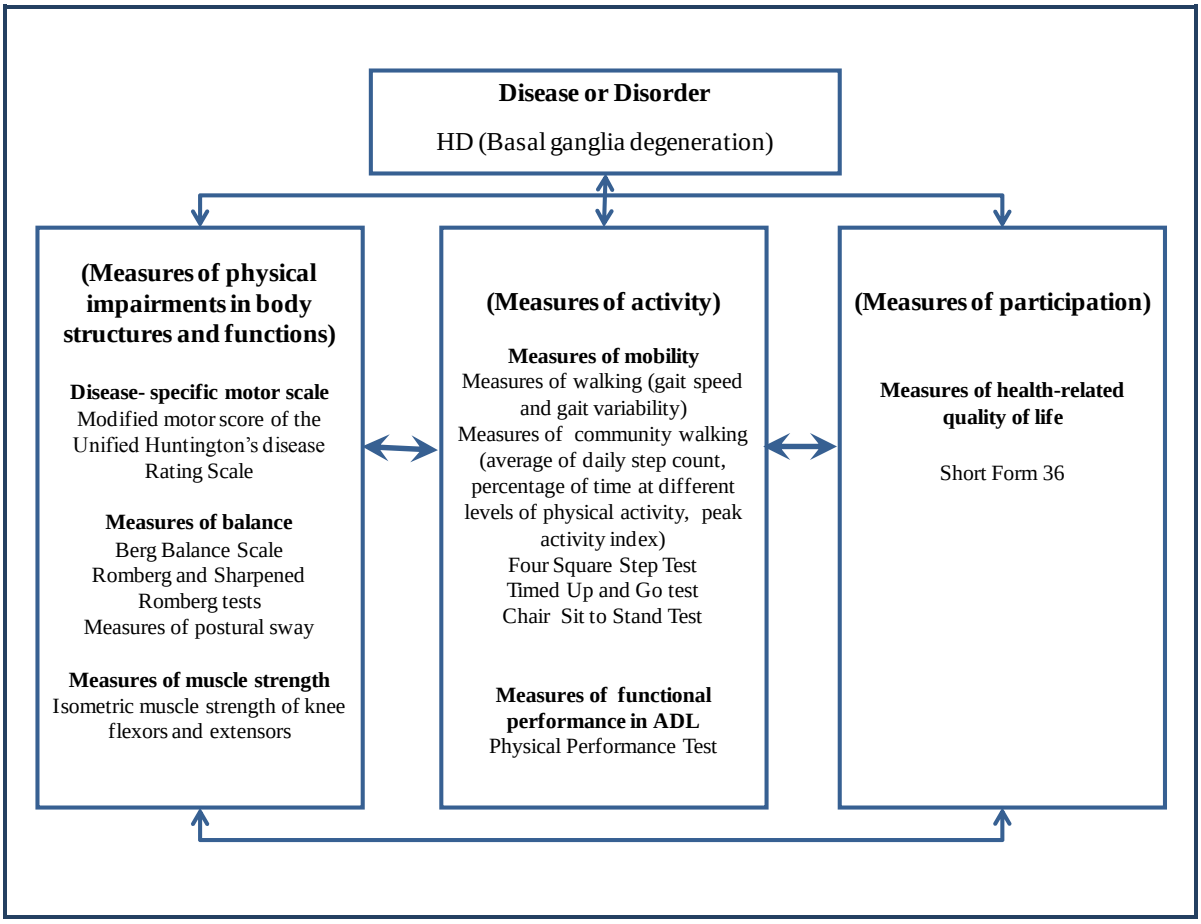
4 Results and discussion: Part 1

4.1 Overview

This chapter presents the results and discussions of Part 1 of the study, which aimed to evaluate validity and reliability of a specific battery of outcome measures in both manifest and pre-manifest HD groups. This psychometric data of the outcomes in the manifest HD group was of use in interpreting the results from the exercise interventional study that was conducted as part of this research (presented in Chapter 5). Furthermore, psychometric data for the outcomes in the pre-manifest HD group were useful to make inferences about the best outcomes that can be used in future trials of exercise intervention at this early stage of the disease.

The measures were chosen to reflect a range of physical impairments, activity limitations and participation restrictions related to mobility deficits seen in people with HD. These outcomes were structured according to the International Classification of Functioning (ICF) [91] (Figure 4.1). Detailed discussion regarding the choice of the measures that were evaluated in this study and their categorization in line with the ICF model is provided in Chapter 2 and Chapter 3.

Figure 4.1: Outcome measures evaluated in this study (structured according to the International Classification of Functioning (ICF) model)



As depicted in Figure 4.1, physical impairments in body functions were represented by a disease-specific motor scale (the modified motor score of the UHDRS (mMS)) as well as measures of balance and muscle strength. Balance was assessed using the Berg Balance Scale (BBS), the Romberg (RT) and Sharpened Romberg (SRT) tests and measures of postural sway. Muscle strength was assessed using the Maximal Voluntary Isometric Muscle Contraction (MVIC) of knee flexors and extensors which was evaluated using the Kin-com isokinetic testing chair dynamometer unit.

Activity was represented by a number of mobility measures as well as a measure of functional performance of activity of daily living (ADL). The main component of mobility which was assessed was walking. Walking measures included gait speed and gait variability, which were quantified using the GAITRite system. Measures of walking carried out in the community by participants over an extended period were recorded

using a mobility monitor (StepWatch Activity monitor). Other components of mobility activities that are believed to be limited in HD such as sit to stand, stepping and turning [114-116] were assessed using other measures of mobility which included the Four Square Step Test (FSST), the Timed Up and Go (TUG) test and the 30 seconds Chair Sit to Stand test (CSST). Functional performance of ADL activities that involve fine upper motor function such as writing as well as "coarse" upper motor function such as dressing was assessed using the Physical Performance Test (PPT). Levels of participation were represented by a health related quality of life measure; the Short Form (SF-36) was used to provide a measure of health-related quality of life in this study.

Validity and reliability data of the above listed outcomes are presented here in 3 sections. In the first section, discriminant (known-groups) validity (i.e. sensitivity) which is examined by the ability of the outcomes to distinguish between the 3 study groups (manifest HD, pre-manifest HD and healthy controls) [177, 178] is illustrated. Individuals with manifest HD, pre-manifest HD and healthy controls are known to be clinically different. Thus outcomes in this study were considered to have good discriminant validity in the manifest HD if they were able to differentiate between individuals with manifest HD and healthy controls. Similarly outcomes were considered to have good discriminant validity in the pre-manifest HD if they were able to differentiate between individuals with pre-manifest HD and healthy controls. Group differences were assessed using either a one-way ANOVA (in the cases of normal distributions) or a Kruskal-Wallis test (where normality could not be assumed) with post-hoc analysis performed whenever differences between groups were identified (see Chapter 3 for more details about methods and the statistical analysis that was applied).

In the second section of the results, concurrent-convergent validity of outcomes of balance, muscle strength, mobility, functional performance in ADL and health-related quality of life is presented. Concurrent-convergent validity of these outcomes was assessed by the strength of their correlations with a measure of gait variability (stride time coefficient of variation). Gait variability was chosen as a criterion measure because it is a well validated measure in HD and is known to predict functional status in this population [38-40, 107, 109]. Associations between the tests were statistically examined using Pearsons or Spearmans correlations (where normality could not be assumed). The

strength of the correlations was classified according to the criteria of Landis and Koch [240] , which are shown in Table 4.1.

Table 4.1: Criteria to evaluate the strength of correlations

Correlation coefficient	Interpretation of strength of agreement
<0.000	Poor
0.00-0.20	Slight
0.21-0.40	Fair
0.41-0.59	Moderate
0.60-0.79	Substantial (high)
0.80-1.00	Almost perfect (very high)

For the interpretation of the results and according to the criteria provided in Table 4.1 above, 2 measures are considered to correlate substantially if the correlation coefficient is of 0.6 or above. For this reason, a correlation coefficient of 0.6 is used as a cut-off point to determine if an outcome measure has a good concurrent-convergent validity. Outcomes of balance, muscle strength, mobility and health-related quality of life were considered to have a good concurrent-convergent validity if they correlated highly or very highly with measures of gait variability (correlation coefficient of 0.6 or above).

In the third section of the results, data about relative and absolute reliability of the outcomes in both individuals with manifest HD and individuals with pre-manifest HD is presented. Relative reliability which is usually used to examine the degree of relationship between 2 or more measurements is illustrated in this chapter by providing the intraclass correlation coefficient (ICC) of each of the outcomes. According to Portney and Watkins [178] an ICC of at least 0.7 is sufficient for group comparisons. Thus an outcome can be considered to have a high relative reliability if the ICC value is larger than 0.7. However, it should be noted that the use of the ICC values is limited by the fact that they are prone to dependency on the heterogeneity of the sample; a high ICC may be obtained when there is a large range of scores in the sample, despite there being large within-subject differences in the actual scores between repeated measurements and vice versa [141]. For this reason, the interpretations of the ICC values obtained for each of the outcomes in the sections below are considered along the

knowledge of their absolute reliability [179]. The absolute reliability is presented using the standard error of measurements (SEM). The SEM provides information about how much within subject variability can be expected on scores on repeated measurements [141, 179]. To be clinically useful, an outcome must have a small SEM to be able to detect real difference from a specific factor [178]. Although no clear criteria are available for acceptable SEM scores of the outcome measures used in this study, it has been suggested that SEM values less than 10% of the total range of measurements in general are acceptable [241, 242]. Thus, for the interpretation of the results from this part of the study, the cut-off point of 10% of the total range of scores was used to determine if the amount of variability of an outcome on repeated assessments as determined by the SEM is acceptable.

In addition to the SEM, the minimal detectable change (MDC) is presented. The MDC represents the minimal amount of change in a subject's status that is not due to natural variation in measurement or due to error [141, 178]. The values of the MDC of each of the outcomes that is presented in this chapter will be used in the following chapter (Chapter 5; results from the interventional study) to determine whether any statistically significant changes on the outcomes in the exercise intervention can be attributed to real changes in the outcomes or are subject to measurement error or natural variations of the tests.

In addition to the above, data from Bland and Altman methods for evaluating test re-test reliability is presented in the reliability section of the results. This method is used to assess the magnitude of the differences between 2 scores (i.e. the agreement between the 2 scores); whether these differences are acceptable and whether there are any directional biases in the measurements. Data that are presented in this section includes the mean of the differences between day 1 and day 2 scores for each of the outcomes as well as the standard deviation and the 95% confidence interval (CI) of the differences. For data interpretations, an outcome measure is considered to have a better agreement if the mean of the differences is close to zero and the standard deviation of the differences is relatively small [220]. The 95% CI of the differences is used to inform if there is a bias in the measurements; if zero does not lie within the interval it can be concluded that a bias exist between the 2 scores [220]. To aid the data interpretation, scatter plots of the difference scores between day 1 and day 2 of each individual plotted against the average

of the 2 scores for each of the outcomes are presented. These graphs are used to illustrate the size of each difference, the range of the differences and their distributions around zero (i.e. perfect agreement). These graphs are also used to visually check if there are outliers, bias in the measurement or if the differences are related to the size of the mean (i.e. if the size of differences increases in cases where the mean increases or decreases).

4.2 Results

For each parameter the assumption of normality was assessed visually by inspection of histograms and Q-Q plots to allow for the appropriate choice of statistical test. Measures of functional performance in ADL and health-related quality of life were normally distributed. All the measures of gait, community walking, postural sway, the CSST and health related quality of life were normally distributed; measures of muscle strength, the BBS and the total score of the RT and SRT tests were right skewed whilst the measures of muscle strength, FSST and the TUG were left skewed, hence non-parametric tests were applied in these cases.

4.2.1 Validity of outcome measures

4.2.1.1 Participants

Twenty five individuals with manifest HD, 17 with pre-manifest HD and 25 healthy controls were recruited for this part of the study (Part 1). Demographic data is presented in Table 4.2 below. Healthy controls were matched with the individuals with manifest and pre-manifest HD for gender, age, height and weight. All participants with pre-manifest HD scored either 0 (n= 11) or 1 (n=6) on the diagnostic confidence score of the Unified Huntington's Disease Rating Scale (UHDRS); confirming no clinically noticeable motor symptoms [46]. The individuals with pre-manifest HD had a mean (SD) score for the modified motor score of the UHDRS (mMS) of 1.5 (1.6) and for the Total Functional Capacity (TFC) of 13 (0) which indicates that clinical examination detected no or minimal specific impairments and no functional limitations in these individuals. The manifest HD subjects had a mean (SD) score for the mMS of 23.9 (7.9). The mean number of years since symptom onset in this group was 5.7 years, ranging from 1 year to 15 years. In addition, the mean TFC was 6.6, ranging from 2 to

11. The mMS and the TFC scales were not administered in healthy controls because they were not at risk of HD.

Table 4.2: Demographic characteristics of participants

Demographic (mean ± SD)	Healthy controls	Pre-manifest HD	Manifest HD
Age in years [a]	49.3 ± 12.1	43.6 ± 12.5	52.1 ± 12.9
Gender (Males/Females)	12/13	9/8	11/14
Weight (kg) [a]	74.7 ± 18.7	82.2 ± 23.5	69.2 ± 11.9
Height (cm) [a]	168.3 ± 11.3	169.7 ± 10.5	167.5 ± 9.1
mMS (unit)	NT	1.5 ± 1.6	23.9 ± 7.9
TFC score (unit)	NT	13 ± 0	6.6 ± 2.4
Years since symptom onset	NA	NA	5.7 ± 3.5

SD, standard deviation; mMS, modified motor score of the Unified Huntington's Disease Rating Scale; TFC, Total Functional Capacity scale; NT, Not Tested; NA, Not Applicable.
[a] An ANOVA test did not demonstrate significant differences in average age (F=2.3; p=0.1), height (F=2.5; p=0.8) and weight (F=0.2; p=0.1) across the 3 groups.

4.2.1.2 Discriminant validity

4.2.1.2.1 Measures of physical impairments in body structures and functions

4.2.1.2.1.1 Measures of balance

Descriptive statistics of all measures of balance are presented in Table 4.3 below. Most healthy controls (16/25; 64%) and participants with pre-manifest HD (8/17; 47%) reached the ceiling score of 56 on the BBS. Furthermore, in the RT and SRT, all healthy controls and pre-manifest HD participants reached the 30 second ceiling on the tasks of standing with feet apart and feet together with either eyes open or closed. The ceiling effect was also observed on the SRT with eyes open for all healthy controls and on the vast majority of the participants with pre-manifest HD (16/17; 94%). A floor effect was seen for the SRT test with eyes closed on the group of participants with manifest HD in which only 4 participants out of the 25 (16%) were able to perform the test. Due to these observed ceiling and floor effects, between group comparisons using the individual Romberg tasks was not useful. The total score of the 6 subtasks of Romberg and Sharpened Romberg tests was therefore calculated and used to compare between group performances.

Both the BBS and the root mean square of the postural sway in healthy controls were significantly different from participants with manifest HD ($p<0.001$) but not from those with pre-manifest HD. These results give indications of the discriminant (known-groups) validity of these outcomes in the manifest HD but not in the pre-manifest HD (i.e. their ability to differentiate between people with manifest HD and healthy controls but not between people with pre-manifest HD and healthy controls).

Out of the 6 balance outcomes used in this analysis, significant group differences were found between each participant category on the total score of the RT and SR tests. The total score of the RT and SRT in healthy controls was significantly different from manifest HD participants and those with pre-manifest HD. This indicates discriminant (known-groups) validity of this measure in both the manifest and pre-manifest stages of HD.

Table 4.3: Measures of balance across groups

Parameter (mean ± SD)	Healthy controls	Pre-manifest HD	Manifest HD
BBS (unit) [b]	55.5 ± 0.9†	55.0 ± 1.5†	42.5 ± 9.7
RFTEO (s)	30 ± 0	30 ± 0	23.2 ± 10.4
RFAEO (s)	30 ± 0	30 ± 0	28.9 ± 3.4
SREO (s)	30 ± 0	29.8 ± 0.8	6.0 ± 10.5
RFTEC (s)	30 ± 0	30 ± 0	20.3 ± 12.1
RFAEC (s)	30 ± 0	30 ± 0	23.3 ± 11.3
SREC (s)	23.3 ± 8.2	14.8 ± 10.9	1.1 ± 3.8
RT and SRT Total score (s) [b]	173.3 ± 8.2*	164 ± 11.1†	102.9 ± 39.9
rms-AP (m) [a]	0.006 ± 0.002†	0.007 ± 0.002†	0.1 ± 0.005
rms-ML (m) [a]	0.005 ± 0.002†	0.005 ± 0.001†	0.1± 0.004
Excursion-AP (m) [a]	12.1 ± 5.5	11.9 ± 5.9	10.6 ± 4.9
Excursion-ML (m) [a]	9.6 ± 5.5	9.8 ± 5.7	10.5 ± 5.2

BBS, Berg Balance Scale; RFTEO, Romberg test with Feet Together and Eyes Open; RFAEO, Romberg with Feet Apart and Eyes Open; SREO, Sharpened Romberg with Eyes Open; RFTEC, Romberg test with Feet Together and Eyes Closed; RFAEC, Romberg with Feet Apart and Eyes Closed; SREC, Sharpened Romberg with Eyes Closed; RT, Romberg test; STR, Sharpened Romberg test; rms, root mean square of postural sway movement; AP, anterior-posterior; ML, medio-lateral.

†Significantly different from Manifest HD ($p<0.05$)

* Significantly different from Pre-manifest HD and Manifest HD ($p<0.05$)

[a] Analysis based on the One way ANOVA test and post hoc tests

[b] Analysis based on the Kruskal-Wallis test and post hoc tests

4.2.1.2.1.2 Measures of muscle strength

Descriptive data of measures of muscle strength are presented in Table 4.4 below. As depicted from Table 4.4 the MVIC measures for both knee flexors and extensors in healthy controls were significantly different from manifest HD participants ($p<0.01$) but not from those with pre-manifest HD. This indicates discriminant (known-groups) validity of the MVIC measures in the manifest HD only.

Table 4.4: Measures of muscle strength across groups

Parameter (mean ± SD)	Healthy controls	Pre-manifest HD	Manifest HD
MVIC of knee extensors (N.m) [b]	352.8 ± 162.9†	373.4 ± 168.5†	212.9 ± 159.8
MVIC of knee flexors (N.m) [b]	195.9 ± 81.6†	220.9 ± 106.3†	111.4 ± 85.7

MVIC, Maximal Voluntary Isometric Contraction
†Significantly different from Manifest HD ($p<0.05$)
[b] Analysis based on the Kruskal-Wallis test and post hoc tests

4.2.1.2.2 Measures of activity

4.2.1.2.2.1 Measures of mobility

4.2.1.2.2.1.1 Walking- measures of gait

Average data for the gait measures are summarized in Table 4.5. The gait speed and stride time in healthy controls were significantly different from manifest HD participants ($p<0.0001$) but not from those with pre-manifest HD. These results therefore, provide indications of the discriminant (known-groups) validity of these measures in the manifest HD only.

Interestingly, significant group differences were found between each participant category for stride time coefficient of variation (CV). Stride time CV in healthy controls was significantly different from pre-manifest participants ($p<0.05$) and those with manifest HD ($p<0.001$). This provides suggestions of the discriminant (known-groups) validity of gait variability measures (stride time CV) in both the manifest and pre-manifest stages of HD.

Table 4.5: Measures of gait across groups

Parameter (mean ± SD)	Healthy controls	Pre-manifest HD	Manifest HD
Gait speed (cm/s) [a]	130.7 ± 11.2†	122.2 ± 12.4†	73.3 ± 32.2
Stride time (s) [a]	1.04 ± 0.08†	1.06 ± 0.08†	1.26 ± 0.41
Stride time CV (%) [a]	2.0 ± 0.5*	2.7 ± 0.9†	14.4 ± 13.5

†Significantly different from Manifest HD ($p<0.05$)
* Significantly different from Pre-manifest HD and Manifest HD ($p<0.05$)
[a] Analysis based on the One way ANOVA test and post hoc tests

4.2.1.2.2.1.2 Walking- measures of community walking

Table 4.6 presents descriptive statistics of measures of levels of walking carried out in the community across each group. Significant differences were identified between healthy controls and participants with manifest HD across the daily step count and the percentages of time spent at no, moderate and high levels of physical activities ($p<0.01$). However, no significant differences were detected on these measures between healthy controls and participants with pre-manifest HD. This indicates discriminant (known-groups) validity of these measures in the manifest HD only.

Interestingly, significant differences were found between each participant category on peak activity index. Peak activity index in healthy controls was significantly different from manifest participants and those with pre-manifest HD ($p<0.001$). This provides indications of the discriminant (known-groups) validity of this measure in both the manifest and pre-manifest stages of HD.

Table 4.6: Measures of community walking across groups

Parameter (mean ± SD)	Healthy controls	Pre-manifest HD	Manifest HD
Daily right step count (step per day) [a]	6928 ± 2423†	5262 ± 1672†	3490 ± 1903
The percentage of daily time spent at no PA [a]	70.4 ± 8.2†	74.5 ± 7.3†	78.6 ± 9.4
The percentage of daily time spent at low PA [a]	17.5 ± 6.2	17.0 ± 4.5	16.1 ± 7.5
The percentage of daily time spent at moderate PA [a]	8.6 ± 4.4†	7.2 ± 4.0†	4.8 ± 3.1
The percentage of daily time spent at high level of PA [a]	3.5 ± 1.9†	1.3 ± 1.4†	0.5 ± 0.7
Peak activity index [a]	49.6 ± 7.4*	42.9 ± 8.5†	29.9 ± 9.1

PA; physical activity
†Significantly different from Manifest HD ($p<0.05$)
*Significantly different from Pre-manifest HD and Manifest HD
[a] Analysis based on the One way ANOVA test and post hoc tests

4.2.1.2.2.1.3 Other measures of mobility

Average data for the other measures of mobility across groups are presented in Table 4.7 below. A floor effect was observed on the FSST in the group of participants with manifest HD; 5 of the participants in this group out of the 25 (20%) could not perform this test.

The scores of TUG in healthy controls' time were significantly different from manifest HD participants ($p<0.001$) but not from those with pre-manifest HD. This indicates discriminant (known-groups) validity of this measure in the manifest HD only. In contrast to the TUG, the scores of the FSST and the CSST in healthy controls were significantly different from manifest HD participants and those with pre-manifest HD ($p<0.01$). This provides indications of the discriminant (known-groups) validity of the FSST and the CSST in both the manifest and pre-manifest stages of HD.

Table 4.7: The other measures of mobility across groups

Parameter (mean ± SD)	Healthy controls	Pre-manifest HD	Manifest HD
FSST (s) [b]	8.5 ± 1.2*	10.4 ± 2.5†	30.4 ± 19.5
TUG (s) [b]	7.8 ± 0.8†	8.7 ± 1.5†	16.2 ± 9.3
CSST (number of repetitions) [a]	13.5 ± 2.8*	11.0 ± 2.5†	7.2 ± 3.5

BBS, Berg Balance Scale; FSST, Four Square Step Test; TUG, Timed Up and Go test; CSST, Chair Sit to Stand Test.

†Significantly different from Manifest HD ($p<0.05$)

↛ Significantly different from Pre-manifest HD and Manifest HD ($p<0.05$)

[a] Analysis based on the One way ANOVA test and post hoc tests

[b] Analysis based on the Kruskal-Wallis test and post hoc tests

4.2.1.2.2.2 Measures of functional performance in ADL

Descriptive data of the measure of functional performance in ADL (PPT) are presented in Table 4.8 below. The PPT in the healthy controls was significantly different from manifest HD participants and those with pre-manifest HD ($p<0.002$). This provides indications of the discriminant (known-group) validity of this measure in both the manifest and pre-manifest HD.

Table 4.8: The measure of functional performance in ADL across groups

Parameter (mean ± SD)	Healthy controls	Pre-manifest HD	Manifest HD
PPT (unit) [a]	25.7 ± 1.4*	23.6 ± 1.9 †	12.3 ± 5.4

PPT, Physical Performance Test.
†Significantly different from Manifest HD ($p<0.05$)
*Significantly different from Pre-manifest HD and Manifest HD ($p<0.05$)
[a] Analysis based on the One way ANOVA test and post hoc tests

4.2.1.2.3 Measures of participation

4.2.1.2.3.1 Measures of health-related quality of life

In the manifest HD, floor and ceiling effects were observed on a number of the SF-36 subscales. In each of the subscales, a floor effect refers to when a participant had a zero score and ceiling effect refers to when a participant had a score of 100. The floor effect in manifest HD was observed on the physical function, the role physical, the social functioning and the role emotional subscales. In addition a ceiling effect was observed on the role physical, bodily pain and social functioning subscales in the manifest HD (Table 4.9). Similarly, a ceiling effect was observed on the physical function, role physical, bodily pain and role emotional in the pre-manifest HD group (Table 4.9).

Descriptive data of all the subscales of the SF-36 are presented in Table 4.10 below. All the subscales of the SF-36 in healthy controls apart from the bodily pain were significantly different from manifest HD participants. However, none of the subscales in the healthy controls were significantly different from the pre-manifest HD group. This suggests discriminant (known-groups) validity of all the subscales of the SF-36 except the bodily pain subscale in the manifest HD only.

Table 4.9: Percentages of floor and ceiling effects on the subscales of health-related quality of life (SF-36-version 1) in manifest and pre-manifest HD groups

Parameter	Pre-manifest HD		Manifest HD	
	Floor effect	Ceiling effect	Floor effect	Ceiling effect
PF (n (%))	none	10 (58.8)	4 (16.0)	none
RP (n (%))	none	14 (82.2)	10 (40.0)	6 (24.0)
BP (n (%))	none	8 (47.1)	none	11
GH (n (%))	none	none	none	none
VT (n (%))	none	none	none	none
SF (n (%))	none	none	2 (8.0)	none
RE (n (%))	none	12 (70.1)	11 (44.0)	9 (36.0)
MH (n (%))	none	none	none	none
PCS (n (%))	none	none	none	none
MCS (n (%))	none	none	none	none

PF; Physical Functioning; RF; Role limited due to physical problems; RE; Role limited due to emotional problems; SF; Social Functioning; MH, Mental Health; VT, Vitality; BP, Bodily Pain; GH, General Health Perception; PCS, Physical Component Summary; MCS, Mental Component Summary.

On each subscale, floor effect refers to when a participant had a score of zero.

On each subscale, ceiling effect refers to when a participant had a score of 100.

Table 4.10: The subscales of health-related quality of life (SF-36-version 1) across groups

Parameter (mean ± SD)	Healthy controls	Pre-manifest HD	Manifest HD
PF (unit) [a]	93.3 ± 10.6†	92.6 ± 17.1†	36.5 ± 28.9
RP (unit) [a]	87.5 ± 25.7†	85.3 ± 39.3†	41.3 ± 47.4
BP (unit) [a]	82.9 ± 18.1	83.0 ± 27.5	77.3 ± 28.9
GH (unit) [a]	79.6 ± 19.1†	76.1 ± 15.1†	46.7 ± 19.9
VT (unit) [a]	73.5 ± 14.4†	70.5 ± 13.4†	48.1±16.5
SF (unit) [a]	81.6 ± 13.7†	73.2 ± 23.2 †	57.9 ± 25.3
RE (unit) [a]	92.3 ± 23.7†	96.1 ± 11.1†	49.3 ± 48.1
MH (unit) [a]	81.5 ± 11.1†	79.1 ± 9.9 †	66.9 ± 15.5
PCS (unit) [a]	84.3 ± 12.5†	82.7 ± 15.7†	46.8 ± 20.3
MCS (unit) [a]	77.9 ± 10.5†	74.8 ± 10.6†	56.9 ± 12.8

† Significantly different from Manifest HD ($p<0.05$)

[a] Analysis based on the One way ANOVA test and post hoc tests

4.2.1.3 Concurrent-convergent validity

Concurrent-convergent validity was assessed in the individuals with manifest HD (n=25) by comparison with measures of balance, muscle strength, mobility, levels of mobility carried out in the community, functional performance in ADL and health-related quality of life with a measure of gait variability (stride time CV).

Associations between the tests were examined using Pearsons or Spearmans correlations (where normality distribution could not be assumed; i.e. MVIC of knee flexors and extensors, BBS, FSST, TUG and RT and SRT). Outliers were identified in a number of variables (Appendix 6). Correlation coefficients including and excluding outliers are reported in Appendix 6. Excluding outliers in all variables apart from the rms-ML of postural sway did not influence conclusions obtained from results based on using the whole sample (Appendix 6). Hence data presented below in Table 4.11 considered the whole set of subjects (n=25) for the calculation of the correlation coefficients between the stride time CV and measures of balance, muscle strength, function, quality of life and level of physical activity.

As depicted in Table 4.11, out of the 6 measures of balance, only the BBS correlated significantly and substantially with the stride time CV (r=0.72). This provides an indication of the good concurrent-convergent validity of this measure.

In term of measures of muscle strength, neither the MVIC of knee flexors nor the MVIC of knee extensors demonstrated concurrent-convergent validity ($r<0.45$). For the measures of community walking, only peak activity index demonstrated good concurrent- convergent validity; peak activity index correlated significantly and substantially with stride time CV (r=0.62). All the measures of mobility which included the FSST, TUG and CSST as well as the measure of functional performance in ADL (PPT) demonstrated good concurrent-convergent validity; all these measures correlated significantly and substantially with stride time CV ($r>0.6$). Out of all the subscales of SF-36 (i.e. measures of health related quality of life) only the physical function subscale and the physical component summary demonstrated good concurrent-convergent validity; only these measures correlated significantly and substantially with stride time CV ($r \geq 0.6$).

Table 4.11: Correlations of measures of balance, muscle strength, mobility, community walking, functional performance in ADL and health-related quality of life with stride time CV

Category	Outcome measure	Correlation with Stride time CV	Category	Outcome measure	Correlation with Stride time CV
Balance	BBS	-0.72**	Community walking	Percentage of time spent at low PA	-0.06
	RT and SRT total score	-0.44*		Percentage of time spent at moderate PA	-0.21
	rms-AP of postural sway	0.50*		Percentage of time spent at high PA	-0.29
	rms-ML of postural sway	0.51*		Peak activity index	-0.62**
	Excursion-AP	0.1	Health-related quality of life	PF	-0.61**
	Excursion-ML	0.19		RP	-0.38
Muscle strength	MVIC of knee extensors	-0.14		BP	-0.11
	MVIC of knee flexors	-0.44		GH	-0.34
Mobility	FSST	0.64**		VT	-0.33
	TUG	0.60**		SF	-0.16
	CSST	-0.71**		RE	0.15
Functional performance of ADL	PPT	-0.66**		MH	-0.15
Community walking	Daily step count	-0.32		PCS	-0.6**
	Percentage time spent at no PA	-0.13		MCS	-0.04
	Percentage of time spent at low PA	-0.06			

BBS, Berg Balance Scale; RT, Romberg test; SRT, Sharpened Romberg test; rms, root mean square of postural sway movement; MVIC, Maximal Voluntary Isometric Contraction; FSST, Four Square Step Test; TUG, Timed Up and Go test; CSST, Chair Sit to Stand Test; PA, Physical Activity; PF; Physical Functioning; RF; Role limited due to physical problems; RE; Role limited due to emotional problems; SF; Social Functioning; MH, Mental Health; VT, Vitality; BP, Bodily Pain; GH, General Health Perception; PCS, Physical Component Summary; MCS, Mental Component Summary.

*$p<0.05$; **$p<0.001$

4.2.2 Reliability of outcome measures

4.2.2.1 Reliability of outcome measures in people with manifest HD

Table 4.12 reports the mean and standard deviations of the demographic and main clinical characteristics of the study participants. Participants who were included in the reliability analysis (n=9) were similar to those who were not exposed to repeated assessments (n=16); no significant differences were found for age, weight, height and disease severity as measured by the TFC score. This suggests that the results of the reliability study could be generalized to the entire study sample**.**

Table 4.12: Characteristics of participants with manifest HD who completed reliability assessments and those who did not

Parameter (mean ± SD)	Participants who completed reliability (n=9)	Participants who did not complete reliability (n=16)	p value
Age in years	48.4 ± 13.3	54.2 ± 12.3	0.31
Weight (kg)	71.5 ± 8.9	68.1 ± 15.1	0.48
Height (cm)	169.2 ± 8.9	165.9 ± 8.1	0.49
TFC	7.0 ± 2.3	6.2 ± 2.7	0.36
TFC; Total Functional Capacity scale			

Table 4.13 shows the means, standard deviations of the scores from the first and second testing days as well as the mean, standard deviation and 95% CI of the differences between the scores obtained from the 2 days. Table 4.14 illustrates the ICCs, the standard error of measurements (SEM) and the minimal detectable change (MDC_{95}). These were calculated for all measures of muscle strength, mobility, and functional performance in ADL and health-related quality of life. In terms of measures of balance, only the BBS, the total score of the RT and SRT and the root mean square of the postural sway were included in the reliability analysis. As the excursion measures of postural sway did not demonstrate any discriminant or concurrent-convergent validity in HD, they were excluded from the reliability analysis in this chapter and also from evaluating the exercise intervention in the next chapter (Chapter 5).

The BBS was the most reliable of the balance measures with ICC value of 0.95. The SEM of the BBS was clearly lower than the predefined acceptable difference of 10% of the total range of measurement (1.4 <10% of 19) which indicates minimal variability within subjects on performing repeated assessments on this test. This was consistent with the data obtained from bland and Altman methods; the mean and the standard deviation of the difference scores were relatively small (Table 4.13 and Figure 4.2a) which indicates good agreement. The total score of the RT and SRT and measures of the root mean square of postural sway had lower ICCs relative to the BBS and their SEM values were higher than the 10% of the corresponding total range of scores. Furthermore, Figure 4.2b indicates a potential bias in the total score of RT and SRT; the difference score (day 2 minus day 1) in had a positive value in 6 cases. This means that 6 out of 9 participants performed better on this test on day 2 comparing to what they did on day 1. Overall the results presented here suggest that out of the balance tests evaluated in this study, the BBS may be the one balance test that has the least amount of variability within subjects on repeated testing in people with manifest HD with no indication of directional bias.

The ICC values for the MIVC of both the quadriceps and hamstring muscle groups were high (ICC 0.94 for each). However, their SEM values were relatively large; the SEM values for MIVC of knee extensors and extensors were much higher than the cut-off point of 10% of the total range of measurements (75.1> 10% of 630 and 35.7> 10% of 299.6). This was also reflected by observing a relatively large mean and standard deviation of the difference scores as well as wide 95% CIs of the differences (Table 4.13 and Figure 4.3). This suggests that these measures are potentially prone to a higher degree of variability on repeated testing in individuals with manifest HD.

All measures of gait including gait speed, stride time and stride time coefficient of variations were highly reliable (ICCs ranged from 0.83 to 0.98). For all of these measures, the SEM scores were lower than the 10% of the corresponding total range of measurements. This provided an indication of the minimal variability within subjects on performing repeated testing on these measures in subjects with manifest HD. These results were consistent with data obtained from Bland and Altman data seen in Table 4.13; means and standard deviations of the difference scores for all these 3 variables (i.e. gait speed, stride time and stride time coefficient of variation) were relatively small

which indicate good agreement. Figure 4.4 shows that the differences were distributed around zero (i.e. there were no indications of directional biases) and in all but one case, the difference was less than 0.03 second in stride time and less than 2.5 unit in stride time coefficient of variation. For gait speed, in all but three cases, the difference was less than 7 cm/s.

The CSST was the most reliable of the mobility measures with ICC values scored above 0.9. The test seemed to be the least variable on repeated testing; the SEM score of the CSST was lower than the 10% of the total range of scores (0.8 <10% 10.0). This was consistent with data obtained from Bland and Altman methods; the mean and standard deviation of the difference scores were relatively very small for this measure (Table 4.13) which indicates good agreement. Figure 4.5c shows that points were distributed around zero (i.e. there was no indication of directional bias) and that in all but one case, the difference was equal or less than 1 repetition.

In both the FSST and the TUG, the SEM scores exceeded the 10% of the corresponding total range of measurements which suggests that these tests relative to the CSST are potentially prone to a higher degree of variability on repeated testing in people with manifest HD. Data obtained from Bland and Altman methods provided further insights into the reliability of the FSST and TUG. In TUG, the differences in eight cases were close to zero; however there was one outlier that may have inflated the degree of variability on this test (Figure 4.5b). Regarding the FSST, Figure 4.5a indicates a potential bias as all but 2 points were below the zero line (i.e. the differences (day 2 minus day1) had a negative value). This means that 7 subjects took less time to complete the FSST on day 2 than the time they took on day 1. This bias was also reflected in the 95% CI for the mean difference (95% CI was 0.9 to 10.2 seconds). Zero did not lie in the interval thus indicating a bias between the 2 testing days. Figure 4.5a also indicates that differences in FSST were potentially related to the size of the mean; the three cases in which the mean score was higher than 30 seconds showed the largest differences.

The test re-test reliability of the PPT was excellent. The calculated ICC value was 0.96 and the SEM score was small (i.e. less than 10% of the total range). This was consistent with data obtained from Bland and Altman methods; the mean and standard deviation of

difference scores were relatively very small (Table 4.13). Figure 4.5d shows that in 4 points the difference was zero and in the 5 other points the difference was 3 units or less.

The ICC values of the subscales of the SF-36 ranged from 0.13 to 0.79. The subscales of bodily pain and vitality had the lowest ICC values (ICC= 0.13 and 0.21 respectively) and the subscales of mental health and physical component summary had the highest ICC values (ICC=0.75 and 0.79 respectively). The SEM was higher than the 10% of the respective range of each of the subscale which suggests that in the absolute term, the subscales of the SF-36 may be subject to a higher degree of variability on repeated assessments in individuals with manifest HD. This was reflected by the wide 95% CI of the mean differences for all the subscales (Table 4.13). As depicted in Figure 4.6 the most variable subscales were the role physical, role limited due to physical problems, bodily pain and role limited due to emotional problems; the ranges of the differences in at least 4 of the cases in these subscales were -20 to 75, -50 to 75, -77 to 33, -33 to 100 respectively. From Figure 4.6, there were indications that in the role physical and the bodily pain subscales, differences may be related to the size of the mean; in the role physical subscale the largest differences were shown in 4 out of 5 of the cases that had a mean that is larger than 40. In the bodily pain subscale the largest differences were seen in cases where the mean is lesser than 88. As depicted from Figure 4.6, there were further indications of directional biases in 4 of the subscales that include general health, vitality, mental health and mental component summary. In each of these subscales, data in 6 out of the 9 participants were below the zero line (i.e. the difference (day 2 minus day 1) had a negative value). This means that in these subscales most participants had a lower score on day 2 relative to their scores on day 1.

Table 4.13: Descriptive data for test re-test reliability for outcome measures in manifest HD

Category	Outcome measure	Day 1	Day 2	Difference between day 1 and day 2	
		mean ± SD	mean ± SD	mean ± SD	95% CI
Balance	BBS (unit)	43.4 ± 6.3	43.2 ± 6.4	-0.2 ± 2.0	-1.7, 1.7
	Romberg test total score (s)	100.4 ± 34.5	109.6 ± 27.1	9.2 ± 20.2	-8.8, 27.4
	rms-AP of postural sway (m)	0.02 ± 0.01	0.02 ± 0.01	0.004 ± 0.003	-0.002, 0.003
	rms-ML of postural sway (m)	0.01 ± 0.002	0.02 ± 0.007	-0.004 ±0.004	-0.004, 0.003
Muscle strength	MVIC of knee extensors (N.m)	250 ± 207.6	280 ± 227.7	29.5 ± 106.2	-53.4, 130.3
	MVIC of knee flexors (N.m)	134 ± 101.4	104.1 ± 104.2	-30.5 ± 50.5	-76.5, 13.5
Mobility-measures of gait	Gait speed (cm/s)	72.4 ± 30.5	74.6 ± 33.1	2.28 ± 11.55	-7.7, 12.9
	Stride time (s)	1.3 ± 0.2	1.2 ± 0.2	-0.04 ± 0.09	-0.13, 0.03
	Stride time CV (%)	12.3 ± 7.9	11.4 ± 7.1	-1.05 ± 1.9	-2.7, 0.6
Other measures of mobility	FSST (s)	25.5 ± 14.8	26.6 ± 19.2	-0.5 ± 11.3	0.9, 10.2
	TUG (s)	15.0 ± 6.0	17.1 ± 12.9	2.1 ± 8.3	-4.6, 9.9
	CSST (number of repetitions)	8.0 ± 3.4	7.4 ± 3.3	-0.5 ± 1.1	-1.3, 0.1
Functional performance in ADL	PPT (unit)	11.6 ± 4.5	12.0 ± 4.6	0.3 ± 1.3	-0.6, 1.6

Table 4.13: *Continued* for descriptive data for test re-test reliability for outcome measures in manifest HD

Category	Outcome measure	Day 1	Day 2	Difference between day 1 and day 2	
		mean ± SD	mean ± SD	mean ± SD	95% CI
Health-related quality of life	PF	41.1 ± 28.1	41.1 ± 28.1	8.9 ± 26.5	-11.5, 29.3
	RP	41.6 ± 41.5	41.7 ± 41.5	-2.8 ± 34.1	-28.9, 23.4
	BP	77.7 ± 28.3	77.8 ± 28.4	-12.3 ± 31.6	-36.7, 11.9
	GH	45.8 ± 24.2	45.8 ± 24.2	-2.1 ± 17.1	-15.3, 11.1
	VT	46.1 ± 18.5	46.1 ± 18.5	-10.6 ± 16.9	-23.5, 2.3
	SF	54.1 ± 22.5	54.3 ± 22.5	-6.2 ± 20.1	-21.6, 9.3
	RE	59.3 ± 46.5	59.3 ± 46.5	0 ± 40.8	-31.4, 31.4
	MH	67.8 ± 16.3	60.4 ± 26.5	-10.2 ± 14.7	-21.5, 1.1
	PCS	48.2 ± 21.2	53.4 ± 20.7	0.2 ± 14.8	-9.8, 10.3
	MCS	53.4 ± 20.7	53.4 ± 20.7	-9.0 ± 14.8	-20.4, 2.4

rms, root mean square of postural sway movement; AP, anterior-posterior; ML, medio-lateral;MVIC, Maximal Voluntary Isometric Contraction; FSST, Four Square Step Test; TUG, Timed Up and Go test; CSST, Chair Sit to Stand Test; PPT, Physical Performance Test; CV, coefficient of variation; PF; Physical Functioning; RF; Role limited due to physical problems; RE, Role limited due to emotional problems; SF; Social Functioning; MH, Mental Health; VT, Vitality; BP, Bodily Pain; GH, General Health Perception; PCS, Physical Component summary; MCS, Mental Component Summary.

Table 4.14: Intra Class Correlation Coefficients (ICCs) for test re-test reliability, standard error of measurements (SEM) and minimal detectable changes (MDC_{95}) for outcome measures in manifest HD

Category	Outcome measure	Day 1		ICC	SEM	MDC_{95}
		range	range (10%)			
Balance	BBS (unit)	19.0	1.9	0.95	1.4	3.9
	Romberg test total score (s)	101.0	10.1	0.88	14.3	39.6
	rms-AP of postural sway (m)	0.02	0.002	0.90	0.003	0.008
	rms-AP of postural sway (m)	0.01	0.001	0.81	0.002	0.005
Muscle strength	MVIC of knee extensors (N.m)	630.0	63.0	0.94	75.1	155.5
	MVIC of knee flexors (N.m)	299.6	29.9	0.94	35.7	98.8
Mobility-measures of gait	Gait speed (cm/s)	85.0	8.5	0.97	8.1	22.5
	Stride time (s)	0.9	0.09	0.83	0.08	0.22
	Stride time CV (%)	20.1	2.0	0.98	1.3	3.6
Other measures of mobility	FSST (s)	42.0	4.2	0.91	7.0	19.3
	TUG (s)	18.2	1.8	0.74	5.9	16.3
	CSST (number of repetitions)	10.0	1.0	0.97	0.8	2.2
Functional performance in ADL	PPT (unit)	13.0	1.3	0.96	0.8	2.2
Health-related quality of life	PF	90	9.0	0.54	18.8	52.1
	RP	100	10	0.67	24.1	66.8
	BP	77	7.7	0.13	22.4	62.1
	GH	75	7.5	0.67	12.1	33.5
	VT	60	6.0	0.25	11.9	32.9
	SF	55.6	5.5	0.69	14.2	39.3
	RE	100	10	0.64	28.9	80.1
	MH	52	5.2	0.79	10.4	28.8
	PCS	64.8	6.4	0.75	9.2	25.5
	MCS	70.7	7.0	0.61	10.4	28.8

rms, root mean square of postural sway movement; AP, anterior-posterior; ML, medio-lateral;MVIC, Maximal Voluntary Isometric Contraction; FSST, Four Square Step Test; TUG, Timed Up and Go test; CSST, Chair Sit to Stand Test; PPT, Physical Performance Test; CV, coefficient of variation; PF; Physical Functioning; RF; Role limited due to physical problems; RE; Role limited due to emotional problems; SF; Social Functioning; MH, Mental Health; VT, Vitality; BP, Bodily Pain; GH, General Health Perception; PCS, Physical Component summary; MCS, Mental Component Summary.

Figure 4.2: Bland and Altman plots of measures of balance in manifest HD

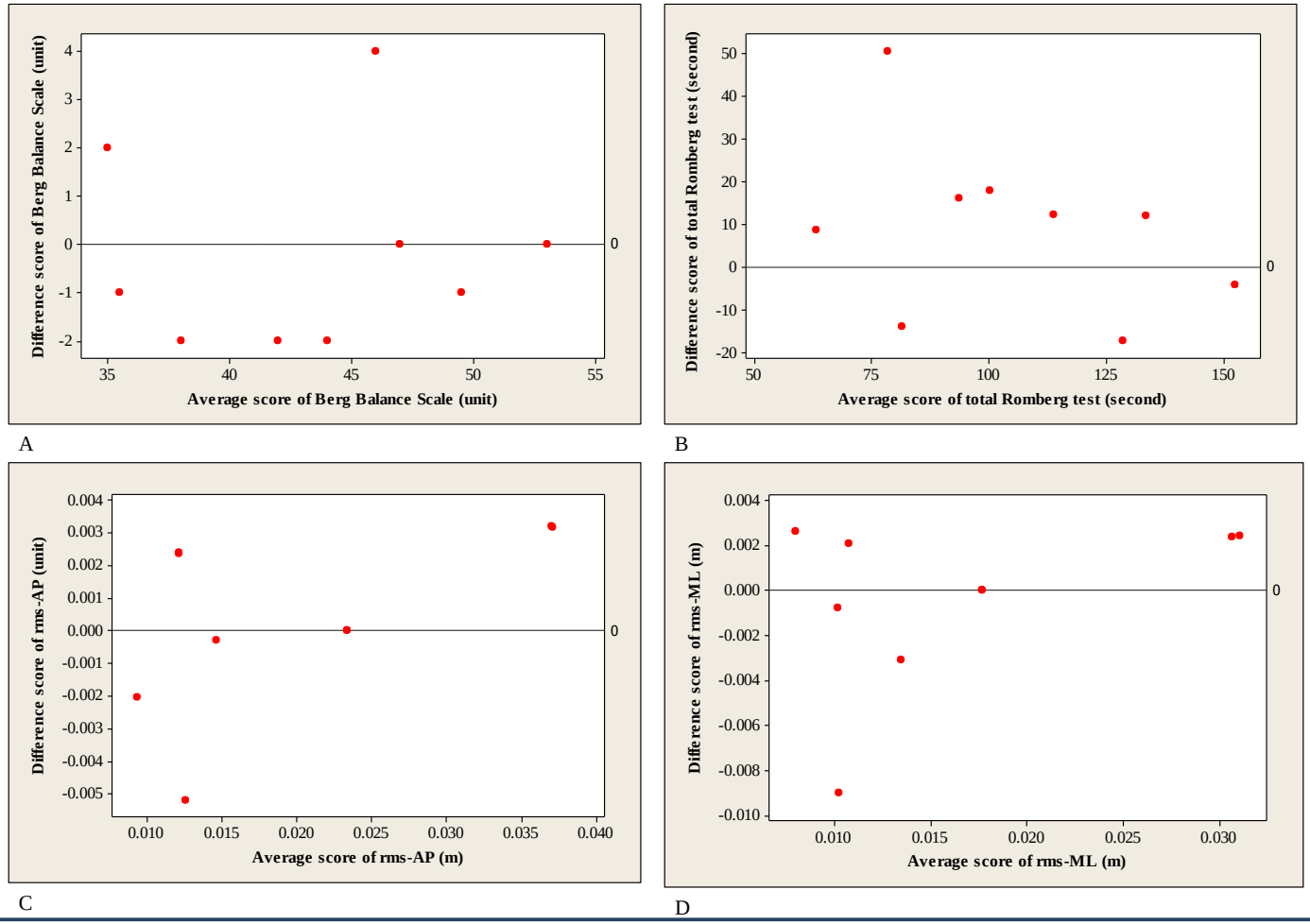
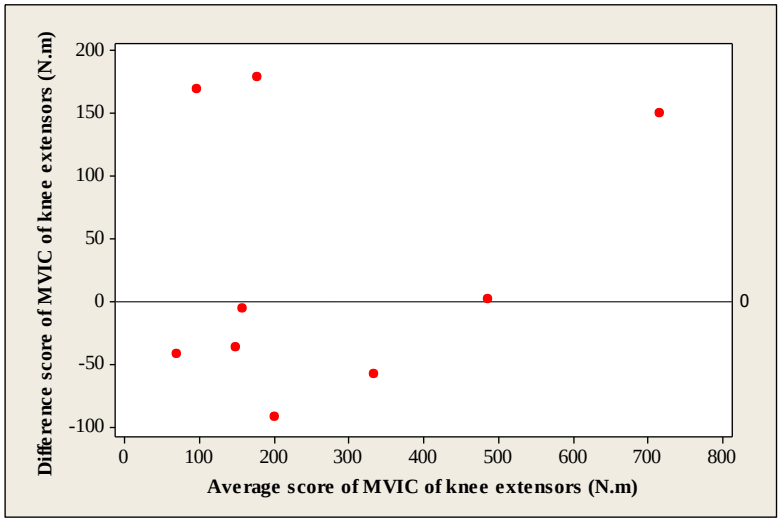
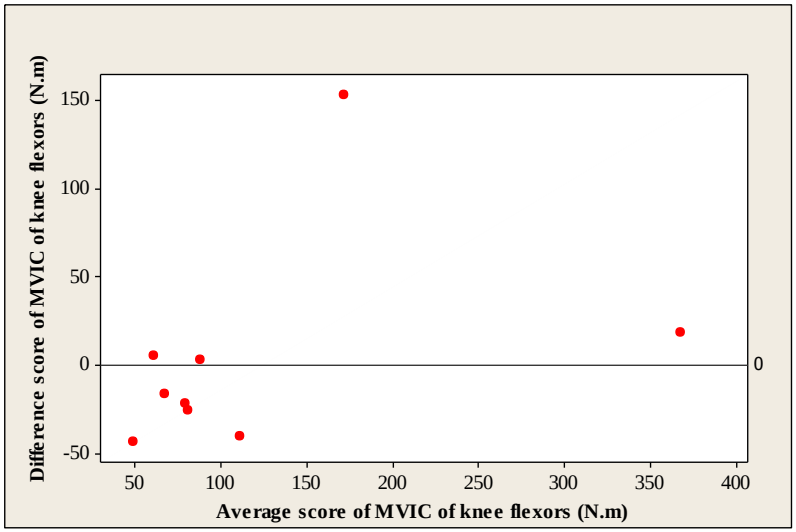


Figure 4.2: Distribution plots of average scores of measures of balance against difference score s(day 2minus day1). Zero line indicates no difference. Positive difference (points above zero line) in A &B indicate better performance at day 2. Positive difference in C &D indicates lower performance at day 2.

Figure 4.3: Bland and Altman plots of measures of muscle strength in manifest HD



A



B

Figure 4.3: Distribution plots of average scores of measures of muscle strength against difference scores (day 2-day1). Zero line indicates no difference. Positive difference (points above zero line) in A & B indicates better performance at day 2. Negative difference (points below zero line) indicates lower performance at day 2.

Figure 4.4: Bland and Altman plots of measures of gait in manifest HD

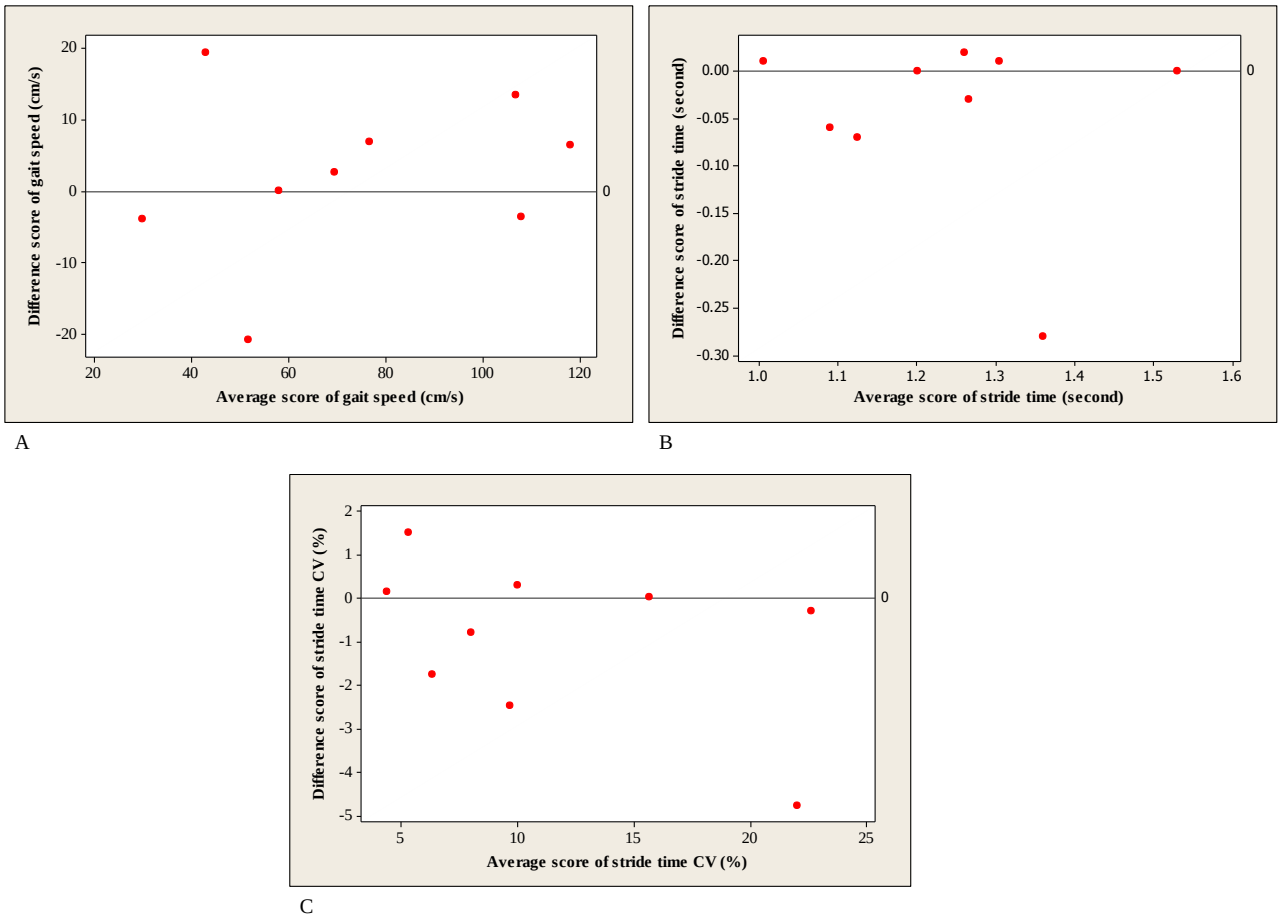


Figure 4.4: Distribution plots of average scores of measures of gait against difference scores (day 2minus day1). Zero line indicates no difference. Positive difference (points above zero line) in A (gait speed) indicates better performance at day 2. Positive difference (points above zero line) in B &C indicates lower performance at day 2.

Figure 4.5: Bland and Altman plots of measures of mobility and functional performance in ADL in manifest HD

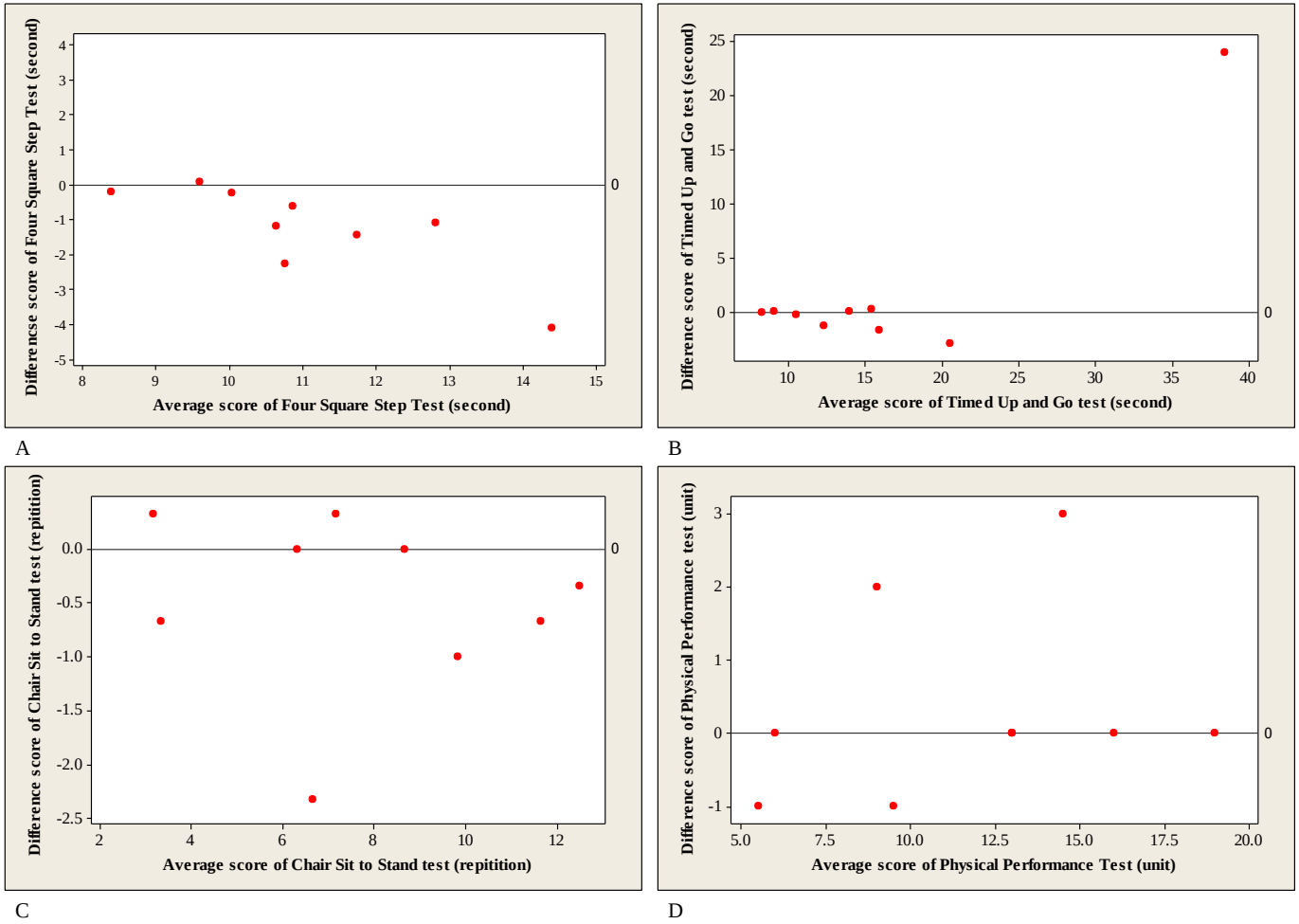


Figure 4.5: Distribution plots of average scores of measures of mobility and function against difference scores (day 2 minus day1). Zero line indicates no difference. Positive difference (points above zero line) in A & B indicates lower performance at day 2. Positive difference (points above zero line) in C & D indicates better performance at day 2.

Figure 4.6: Bland and Altman plots of measures of health-related quality of life in manifest HD

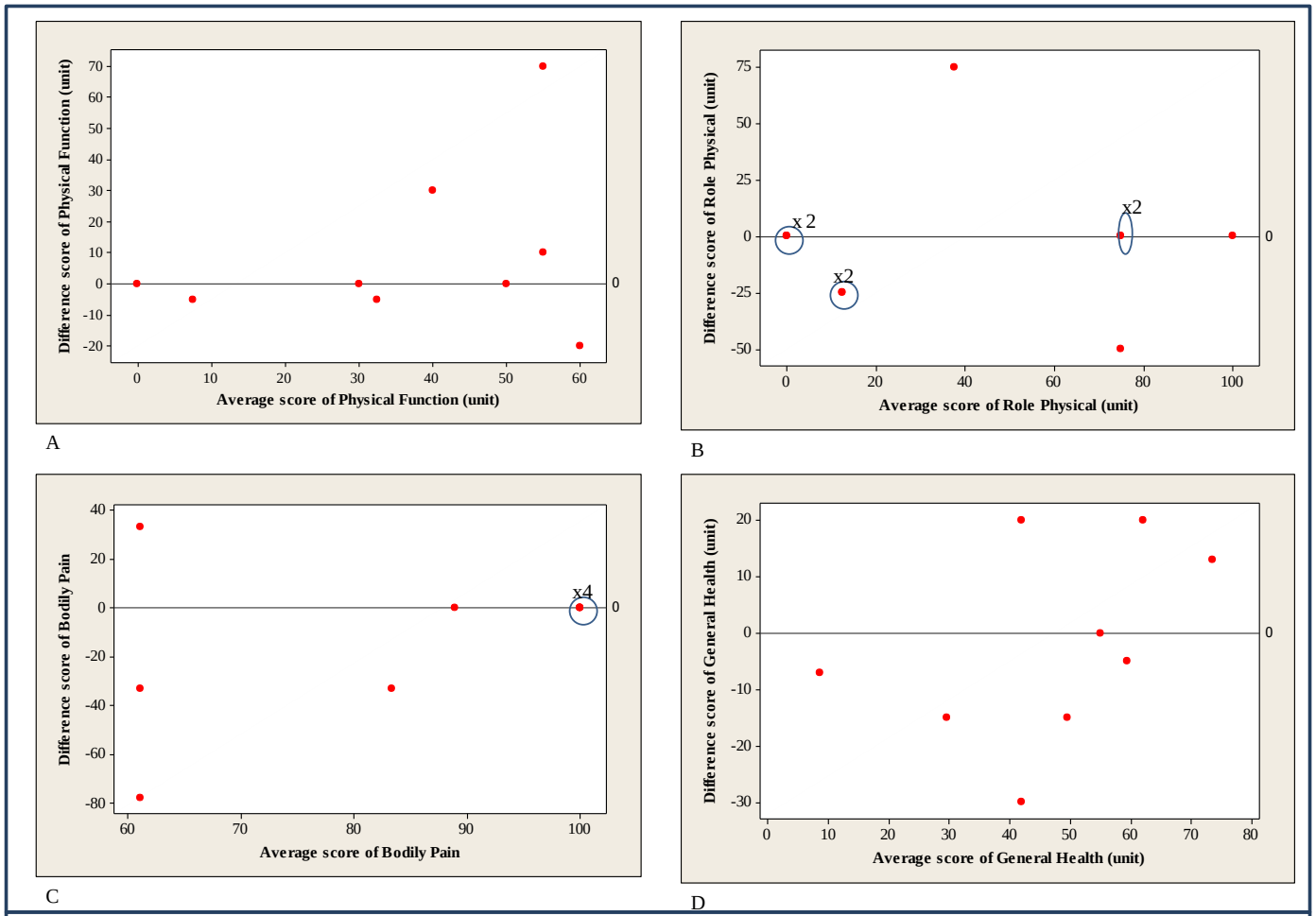
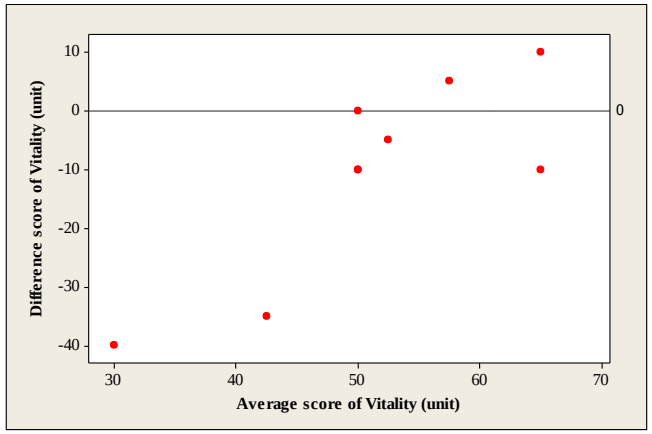
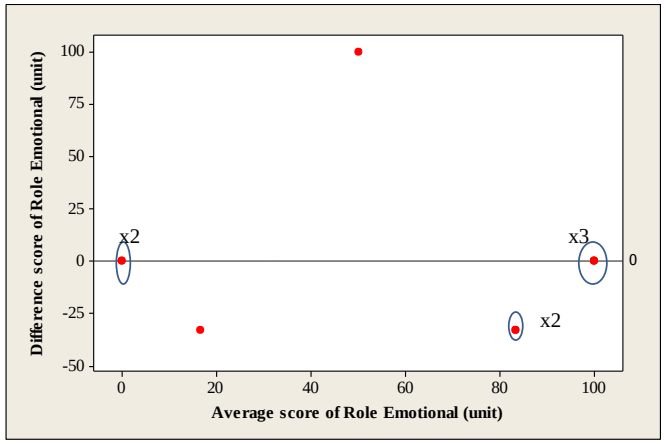


Figure 4.6: Distribution plots of average scores of measures of health related quality of life against difference scores (day 2minus day1). Zero line indicates no difference. Positive difference (points above zero line) in A ,B , C & D indicates better performance at day 2. Negative difference (points above zero line) indicates lower performance at day 2. Blue circles indicate the number of cases on these points.

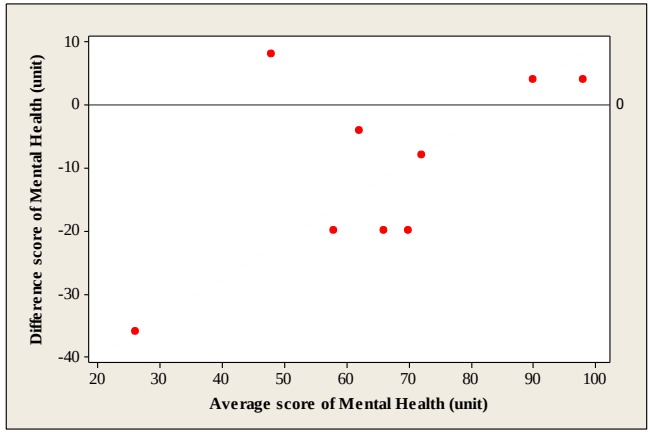
Figure 4.6: *continued* Bland and Altman plots of measures of health-related quality of life in manifest HD



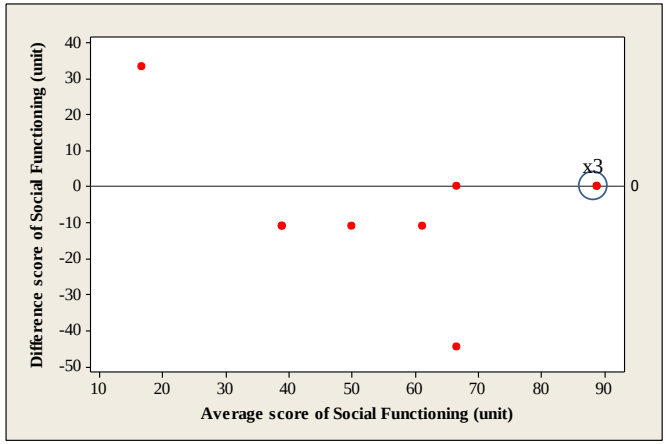
E



F



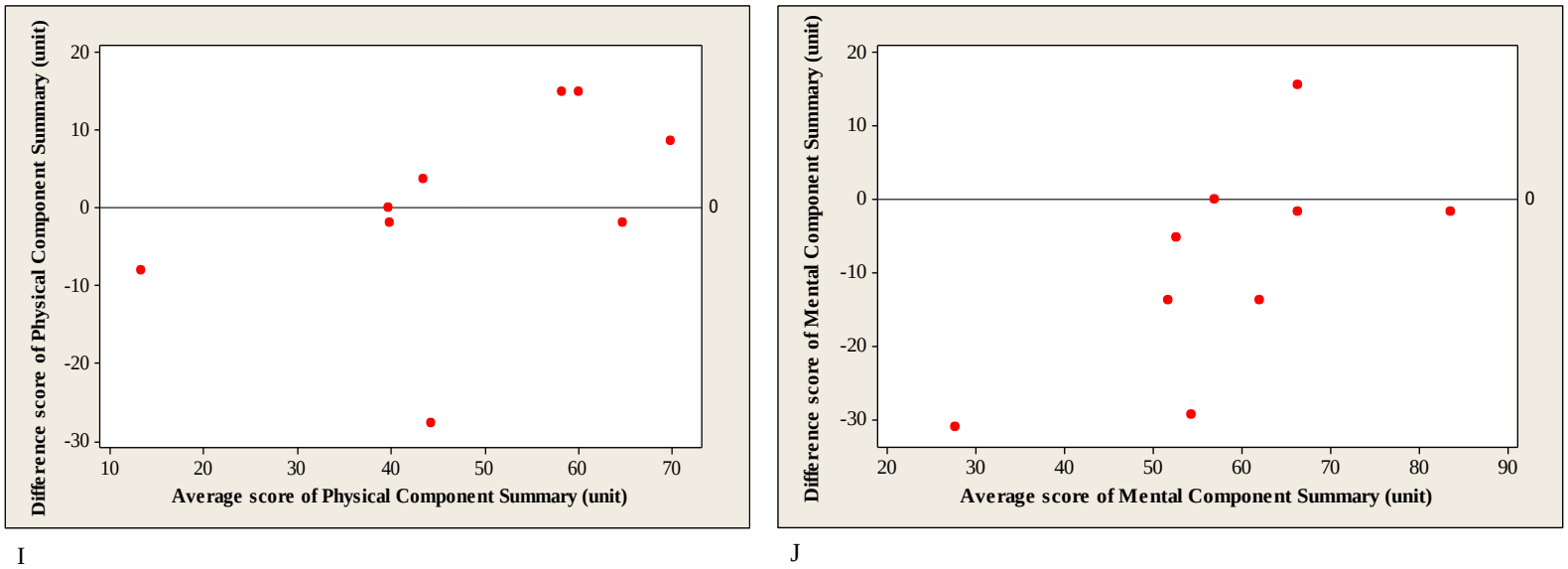
G



H

Figure 4.6: Distribution plots of average scores of measures of health related quality of life against difference scores (day 2minus day1). Zero line indicates no difference. Positive difference (points above zero line) in E , F, G & H indicates better performance at day 2. Negative difference (points above zero line) indicates lower performance at day 2. Blue circles indicate the number of cases on these points.

Figure 4.6: *continued* Bland and Altman plots of measures of health-related quality of life in manifest HD



I J

Figure 4.6: Distribution plots of average scores of measures of health related quality of life against difference scores (day 2 minus day1). Zero line indicates no difference. Positive difference (points above zero line) in I& J indicates better performance at day 2. Negative difference (points above zero line) indicates lower performance at day 2.

4.2.2.2 Reliability of outcome measures in people with pre-manifest HD

Table 4.13 reports average data of the demographic and main clinical characteristics of those who completed reliability assessment and those who did not in the group of participants with pre-manifest HD. Participants who were included in the reliability analysis (n=9) were similar to those who have not been involved in repeated assessments (n=8); no significant differences were found on age, weight and height.

Table 4.15: Characteristics of participants with pre-manifest HD who completed reliability assessment and those who did not

Parameter (mean ± SD)	Participants who completed reliability (n=9)	Participants who did not complete reliability (n=8)	p value
Age in years	44.3 ± 13.3	42.8 ± 11.1	0.8
Weight (kg)	84.3 ± 27.3	79.8 ± 18.3	0.7
Height (cm)	170.1 ± 10.1	169.2 ± 11.6	0.9

Table 4.16 shows the means, standard deviations from the first and second testing days as well as the mean, standard deviation and 95% CI of the differences between the scores obtained from the 2 days. Table 4.17 illustrates the ICCs, the standard error of measurements (SEM) and the minimal detectable change (MDC_{95}) for measures of balance, muscle strength, mobility, and functional performance in ADL and health-related quality of life.

The BBS and the root mean square of postural sway were highly reliable (ICCs ranged from 0.98 to 0.85). The SEM scores of these measures were lower than the 10% of their corresponding total range of measurements that suggests the minimal variability of these measures on repeated testing in people with pre-manifest HD. This was also reflected by the data obtained from Bland and Altman methods; the mean differences for these measures were relatively small and the 95% CIs of the mean differences were very narrow. The graphs in Figure 4.7 provided further insights into this; for example in the BBS, the difference score in 4 cases was zero and in 4 other cases was only 1 unit. In contrast to the BBS and the postural sway measures, the test re-test reliability of the total score of the RT and SRT was lower (ICC=0.77). Furthermore, the SEM of this

outcome was higher than the 10% of the total range of scores which suggests that this test is subject to a higher degree of variability on performing repeated testing in people with pre-manifest HD. Figure 4.7b provided more insight into this; although the difference score in 6 cases was close to zero, there were 3 cases in which the difference score was of at least 17 seconds.

For the measures of muscle strength, the test re-test reliability of the MVIC of both knee flexors and extensors were high (ICC values were of 0.88 and 0.97 respectively). The SEM values were however relatively large (SEM values were larger than the 10% of the total range of scores). This was also reflected by obtaining relatively large standard deviations and 95% CI of the difference scores (Table 4.16). As depicted in Figure 4.8, the ranges of the differences were -100 to 200 N.m and -48 to 57 N.m in MVIC of knee extensors and knee flexors respectively. These results indicate that these measures are subject to some variability in repeated assessments in people with pre-manifest HD.

Measures of gait speed and stride time had the highest test re-test reliability (ICC= 0.96 for both). The small standard deviation at the test and re-test assessment of the stride time CV indicated that the amount of variability between participants was minimal, which may have potentially created smaller test re-test reliability coefficient (ICC= 0.72). However, the SEM values for the 3 variables (gait speed, stride time, stride time CV) were lower than the 10% of their corresponding total range of scores. This suggests that the amount of absolute errors (variability) between test and re-test on these measures within individuals was minimal. These results were consistent with data obtained from Bland and Altman methods seen in Table 4.16; means and standard deviations of the difference scores for all these 3 variables (i.e. gait speed, stride time and stride time coefficient of variation) were relatively small. Figure 4.9 shows that the differences were distributed around zero (i.e. there were no indications of directional biases) and in most cases, the difference was less than 0.05 second in stride time and less than 5 cm/s in gait speed. For stride time coefficient of variation, the difference in all cases was 1 unit or less.

The FSST, TUG, CSST all had good test re-test reliability coefficients; the ICCs of these measures ranged from 0.82 to 0.88. The PPT had a lower test re-test reliability coefficient (ICC=0.62) compared to the other measures. The small standard deviation at

the test and re-test assessment of the PPT indicated that the amount of variability between participants was minimal, which may have potentially created a smaller test re-test reliability coefficient. Of these outcomes only the FSST, CSST and PPT had SEM values that were lower than the 10% of their corresponding total range of scores. This suggests that the amount of absolute errors (variability) between test and re-test on these measures within individuals was minimal. This was also reflected by obtaining relatively small mean, standard deviations and 95% CI of the difference scores for all these measures (Table 4.16). Figure 4.10 shows the differences were distributed around zero in the CSST and PPT (i.e. there were no indications of directional biases). However, as depicted from Figure 4.10 a potential bias is indicated in the TUG and the FSST; most points in the TUG (6/9) and in the FSST (8/9) were below the zero line (i.e. the difference (day 2 minus day 1) had a negative value). This means that in most cases, participants took less time in day 2 relative to the time they took in day 1 to complete TUG and FSST. This directional bias was also reflected in the 95% CI of the FSST for the difference scores (95% CI of differences ranged from -2.2 to -0.23 seconds). Zero did not lie in the interval which indicates a bias between the 2 testing days. Additionally, Figure 4.10a indicates that differences in FSST were potentially related to the size of the mean; there was a tendency of obtaining a larger difference with the increase of the size of the mean score.

The calculated ICC values of the subscales of the SF-36 ranged from 0.5 to 0.91. The subscales of role limited due to physical problems and role limited due to emotional problems had the lowest ICC values (ICC= 0.61 and 0.50 respectively) and the subscales of physical component summary and mental component summary had the highest ICC values (ICC=0.88 and 0.91 respectively). The SEM was higher than the 10% of the respective range of each of the subscales; however the SEM of the physical and mental component summaries just fell short below this criterion (Table 4.16). This suggests that in the absolute terms, the physical and mental component summaries of the SF-36 may be the least susceptible to variability on repeated assessment in the pre-manifest HD. As depicted in Figure 4.11 points are distributed around zero in both the physical and mental component summaries and differences are less than 10 units in 7 cases in the physical component summary and less than 10 units in all cases in the mental component summary. Although the mean difference is small in majority of the other subscales (Table 4.16), outliers of differences were identified in 5 of the subscales

(physical function, role physical, general health, social functioning and role emotional (Figure 4.11). These outliers may have therefore influenced the variability of these subscales in repeated assessments in people with pre-manifest HD.

Table 4.16: Descriptive data for test re-test reliability for outcome measures in pre-manifest HD

Category	Outcome measure	Day 1	Day 2	Difference between day 1 and day 2	
		mean ± SD	mean ± SD	mean ± SD	95% CI
Balance	BBS (unit)	55.1 ± 1.2	**55.4 ± 0.7**	**0.3 ± 0.5**	**0.05, 0.71**
	Romberg test total score (s)	163.6 ± 12.5	**170.0 ± 10.8**	**6.7 ± 10.1**	**-1.0, 14.5**
	rms-AP of postural sway (m)	0.007± 0.002	**0.006 ± 0.002**	**0.005 ± 0.001**	**-0.0007, 0.002**
	rms-ML of postural sway (m)	0.005 ±0.002	**0.003 ± 0.003**	**0.009 ± 0.002**	**0.001,0.003**
Muscle strength	MVIC of knee extensors (N.m)	356 ± 136.8	**374.7 ± 148.6**	**19.5 ± 101.7**	**-58.7, 97.7**
	MVIC of knee flexors (N.m)	221 ± 105.9	**223.1± 116.5**	**-1.6 ± 34.1**	**-27.8, 24.7**
Mobility-measures of gait	Gait speed (cm/s)	122.5 ± 13.4	**125.6 ± 11.7**	**1.8 ± 5.6**	**-2.5, 6.1**
	Stride time (s)	1.1 ± 0.07	**1.1 ± 0.09**	**-0.02 ± 0.03**	**-0.04,0.008**
	Stride time CV (%)	3.0 ± 1.4	**2.6 ± 0.9**	**-0.4 ± 0.7**	**-0.9, 0.19**
Other measures of mobility	FSST (s)	10.4 ± 3.4	**11.5 ± 2.2**	**-1.2 ± 1.2**	**-2.2, -0.23**
	TUG (s)	8.9 ± 1.3	**8.5 ± 1.1**	**0.5 ± 0.8**	**-1.1, 0.2**
	CSST (number of repetitions)	10.8 ± 3.2	**11.3 ± 2.2**	**0.6 ± 2.3**	**-1.1, 2.2**
Functional performance in ADL	PPT (unit)	24.0 ± 2.8	**23.7 ± 1.7**	**-0.2 ± 1.0**	**-0.9, 0.5**

Table 4.16: *Continued* for descriptive data for test re-test reliability for outcome measures in pre-manifest HD

Category	Outcome measure	Day 1	Day 2	Difference between day 1 and day 2	
		mean ± SD	mean ± SD	mean ± SD	95% CI
Health-related quality of life	PF	88.9 ± 22.6	92.2 ± 12.8	3.3 ± 10.6	-4.8, 11.5
	RP	88.9 ± 33.3	75.0 ± 43.3	-13.9 ± 33.3	-39.5, 11.7
	BP	85.2 ± 24.8	82.7 ± 23.6	-2.5 ± 13.4	-12.7, 7.8
	GH	67.3 ± 14.3	69.8 ± 14.1	2.4 ± 9.4	-4.7, 9.6
	VT	67.8 ± 14.6	66.7 ± 14.8	-1.1 ± 9.3	-8.2, 6.0
	SF	74.1 ± 21.5	74.1 ± 22.2	0 ± 14.7	-11.3, 11.3
	RE	100.0 ± 0.0	92.6 ± 22.2	-7.4 ± 22.2	-24.5, 9.7
	MH	78.6 ± 11.3	79.6 ± 12.4	1.3 ± 7.7	-4.6, 7.3
	PCS	78.6 ± 18.9	79.3 ± 12.4	0.7 ± 8.5	-5.8, 7.2
	MCS	73.8 ± 10.8	73.6 ± 11.3	-0.19 ± 4.2	-3.4, 3.0

rms, root mean square of postural sway movement; AP, anterior-posterior; ML, medio-lateral;MVIC, Maximal Voluntary Isometric Contraction; FSST, Four Square Step Test; TUG, Timed Up and Go test; CSST, Chair Sit to Stand Test; PPT, Physical Performance Test; CV, coefficient of variation; PF; Physical Functioning; RF; Role limited due to physical problems; RE; Role limited due to emotional problems; SF; Social Functioning; MH, Mental Health; VT, Vitality; BP, Bodily Pain; GH, General Health Perception; PCS, Physical Component summary; MCS, Mental Component Summary.

Table 4.17: Intra Class Correlation Coefficients (ICCs) for test re-test reliability, standard error of measurements (SEM) and minimal detectable changes (MDC_{95}) for outcome measures in pre-manifest HD

Category	Outcome measure	Day 1		ICC	SEM	MDC_{95}
		Range	Range (10%)			
Balance	BBS (unit)	4.0	0.4	0.85	0.3	0.9
	Romberg test total score (s)	25.6	2.6	0.77	7.1	19.7
	rms-AP of postural sway (m)	0.006	0.0006	0.98	0.00004	0.0001
	rms-AP of postural sway (m)	0.005	0.0005	0.87	0.00007	0.0002
Muscle strength	MVIC of knee extensors (N.m)	438.3	43.8	0.88	73.2	203
	MVIC of knee flexors (N.m)	269.7	26.9	0.97	28.2	78.2
Mobility-measures of gait	Gait speed (cm/s)	42.3	4.2	0.96	3.4	9.7
	Stride time (s)	0.2	0.02	0.96	0.01	0.03
	Stride time CV (%)	4.7	0.5	0.75	0.4	1.1
Other measures of mobility	FSST (s)	8.9	0.9	0.88	0.8	2.2
	TUG (s)	3.9	0.4	0.84	0.5	1.6
	CSST (number of repetitions)	7.9	0.8	0.82	0.7	2.1
Functional performance in ADL	PPT (unit)	8.0	0.8	0.69	0.7	1.9
Health-related quality of life	PF	70.0	7.0	0.83	7.5	20.8
	RP	100.0	10.0	0.63	23.6	65.4
	BP	77.8	7.8	0.85	9.4	26.1
	GH	42.0	4.2	0.78	6.6	18.3
	VT	40	4.0	0.8	6.6	18.3
	SF	55.6	5.6	0.77	10.4	28.8
	RE	0	0	0.50	15.7	43.5
	MH	36.0	3.6	0.79	5.5	15.2
	PCS	60.0	6.0	0.88	6.0	16.6
	MCS	31.0	3.1	0.91	2.9	8.0

rms, root mean square of postural sway movement; AP, anterior-posterior; ML, medio-lateral;MVIC, Maximal Voluntary Isometric Contraction; FSST, Four Square Step Test; TUG, Timed Up and Go test; CSST, Chair Sit to Stand Test; PPT, Physical Performance Test; CV, coefficient of variation; PF; Physical Functioning; RF; Role limited due to physical problems; RE; Role limited due to emotional problems; SF; Social Functioning; MH, Mental Health; VT, Vitality; BP, Bodily Pain; GH, General Health Perception; PCS, Physical Component summary; MCS, Mental Component Summary.

Figure 4.7: Bland and Altman plots of measures of balance in pre-manifest HD

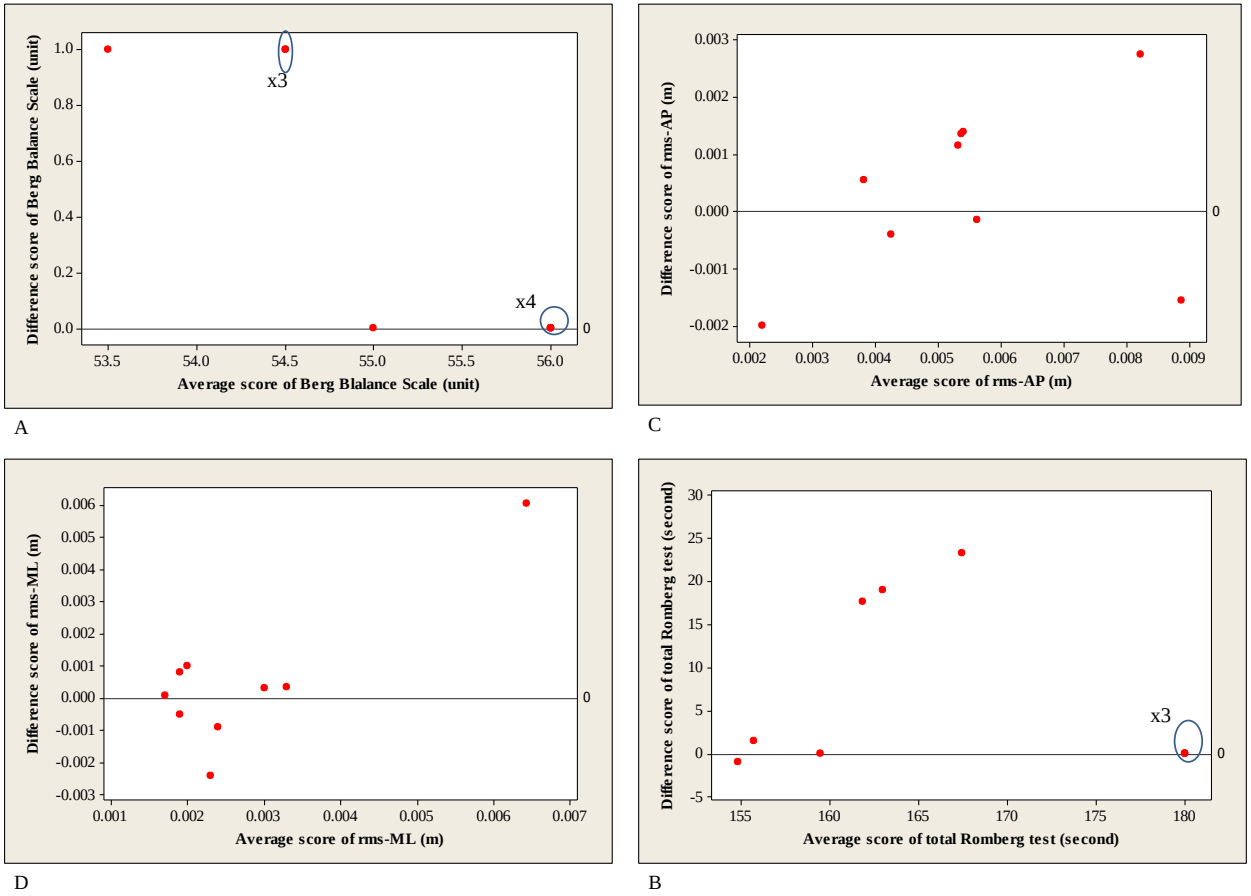


Figure 4.7: Distribution plots of average scores of measures of balance against difference scores (day 2minus day1). Zero line indicates no difference. Positive difference (points above zero line) in A &B indicate better performance at day 2. Positive difference in C &D indicates lower performance at day 2. Blue circles indicate the number of cases scored on these points.

Figure 4.8: Bland and Altman plots of measures of muscle strength in pre-manifest HD

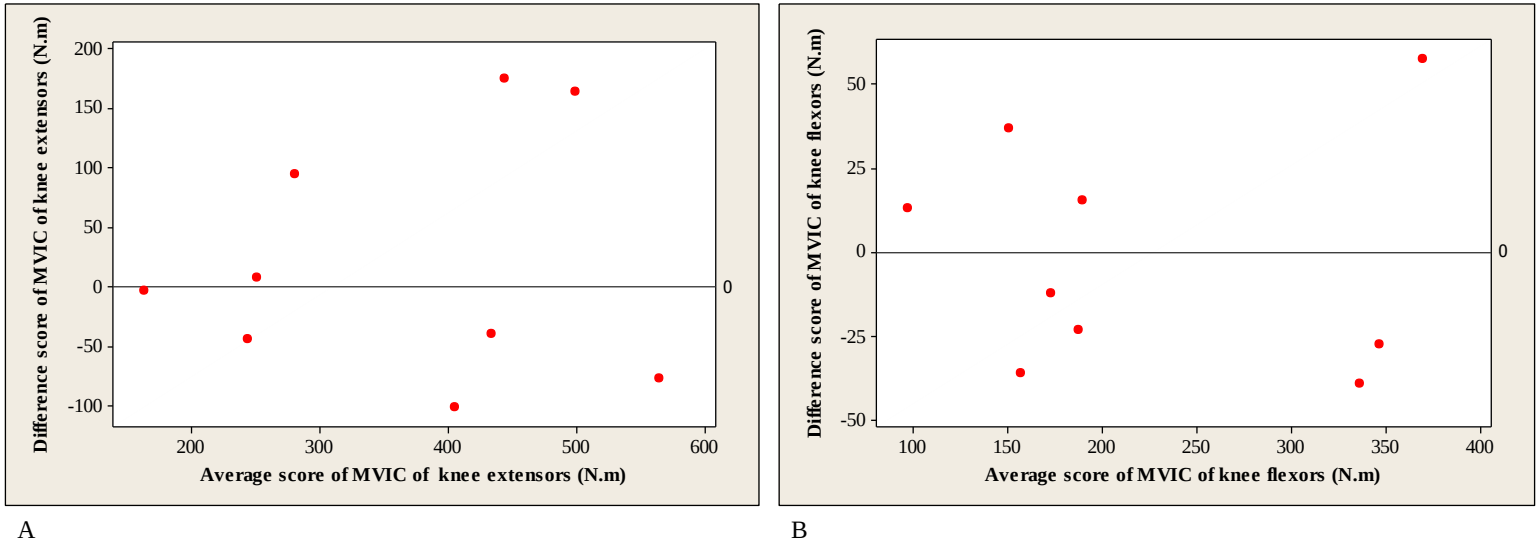


Figure 4.8: Distribution plots of average scores of measures of muscle strength against difference scores (day 2 minus day1). Zero line indicates no difference. Positive difference (points above zero line) in A & B indicates better performance at day2. Negative difference (points below zero line) indicates lower performance at day 2.

Figure 4.9: Bland and Altman plots of measures of gait in pre-manifest HD

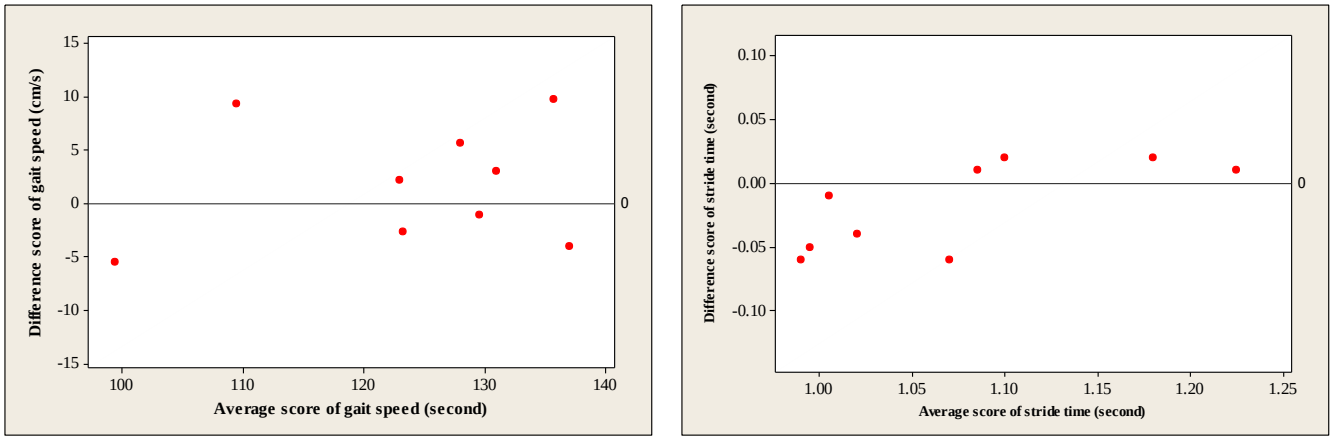


Figure 4.9: Distribution plots of average scores of measures of gait against difference scores (day 2 minus day1). Zero line indicates no difference. Positive difference (points above zero line) in A (gait speed) indicates better performance at day 2. Positive difference (points above zero line) in B &C indicates lower performance at day 2.

Figure 4.10: Bland and Altman plots of measures of mobility and functional performance in ADL in pre-manifest HD

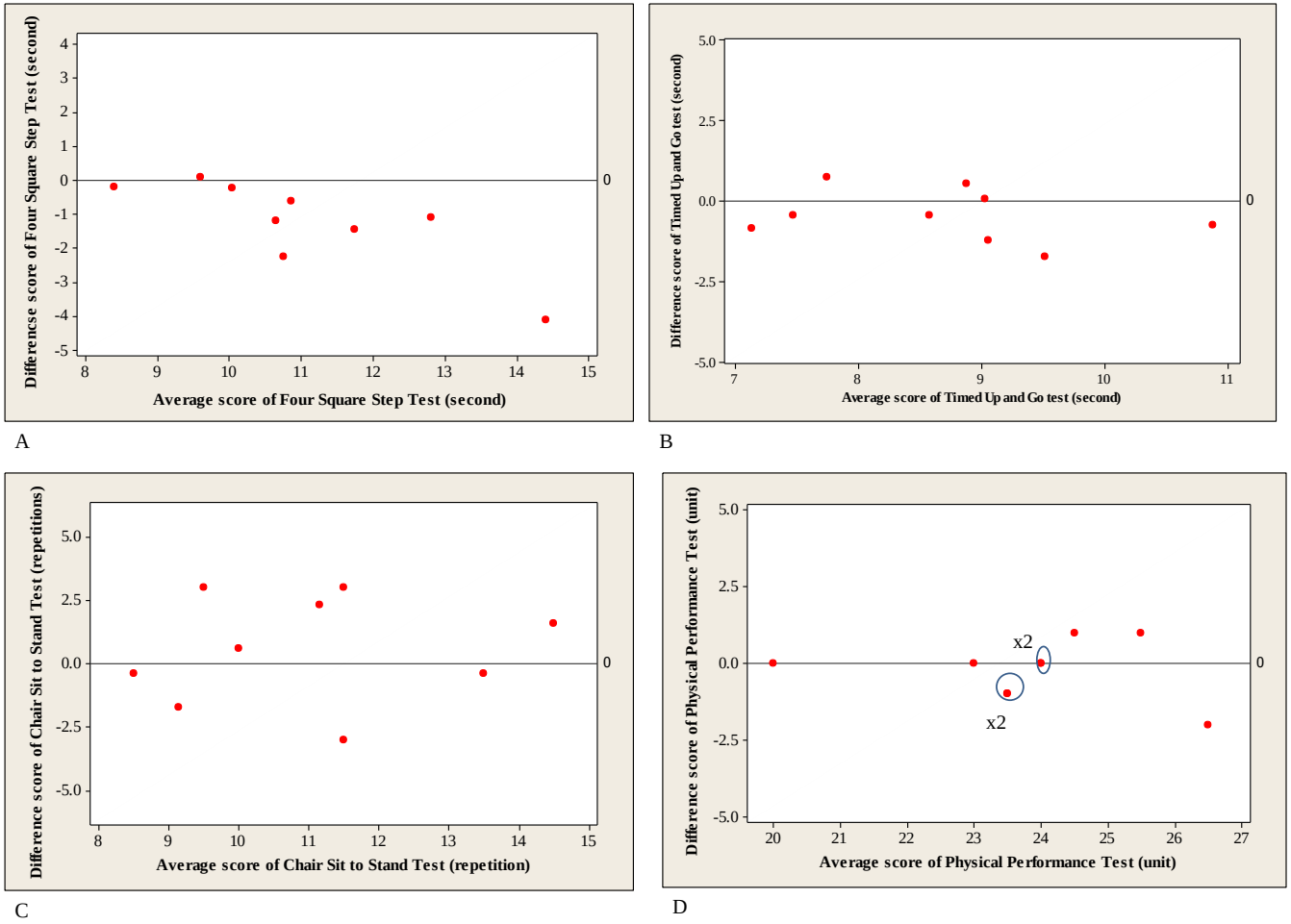


Figure 4.10: Distribution plots of average scores of measures of mobility and function against difference scores (day 2 minus day1). Zero line indicates no difference. Positive difference (points above zero line) in A & B indicates lower performance at day 2. Positive difference (points above zero line) in C & D indicates better performance at day 2. Blue circles indicate the number of cases on these points.

Figure 4.11: Bland and Altman plots of measures of health-related quality of life

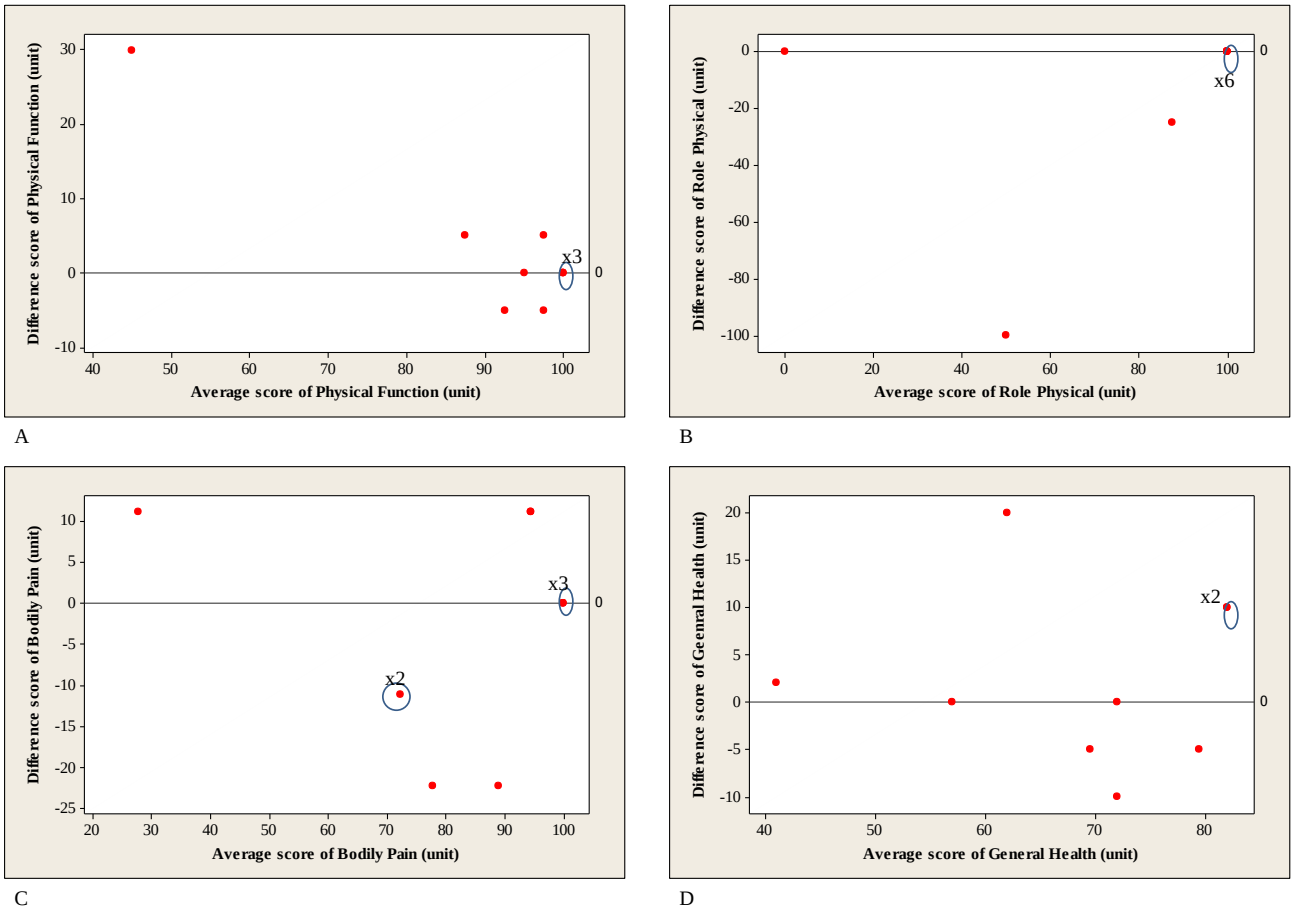


Figure 4.11: Distribution plots of average scores of measures of health related quality of life against difference scores (day 2 minus day1). Zero line indicates no difference. Positive difference (points above zero line) in A ,B , C & D indicates better performance at day 2. negative difference (points above zero line) indicates lower performance at day 2. Blue circles indicate the number of cases on these points.

Figure 4.11: *continued* Bland and Altman plots of measures of health-related quality of life in pre-manifest HD

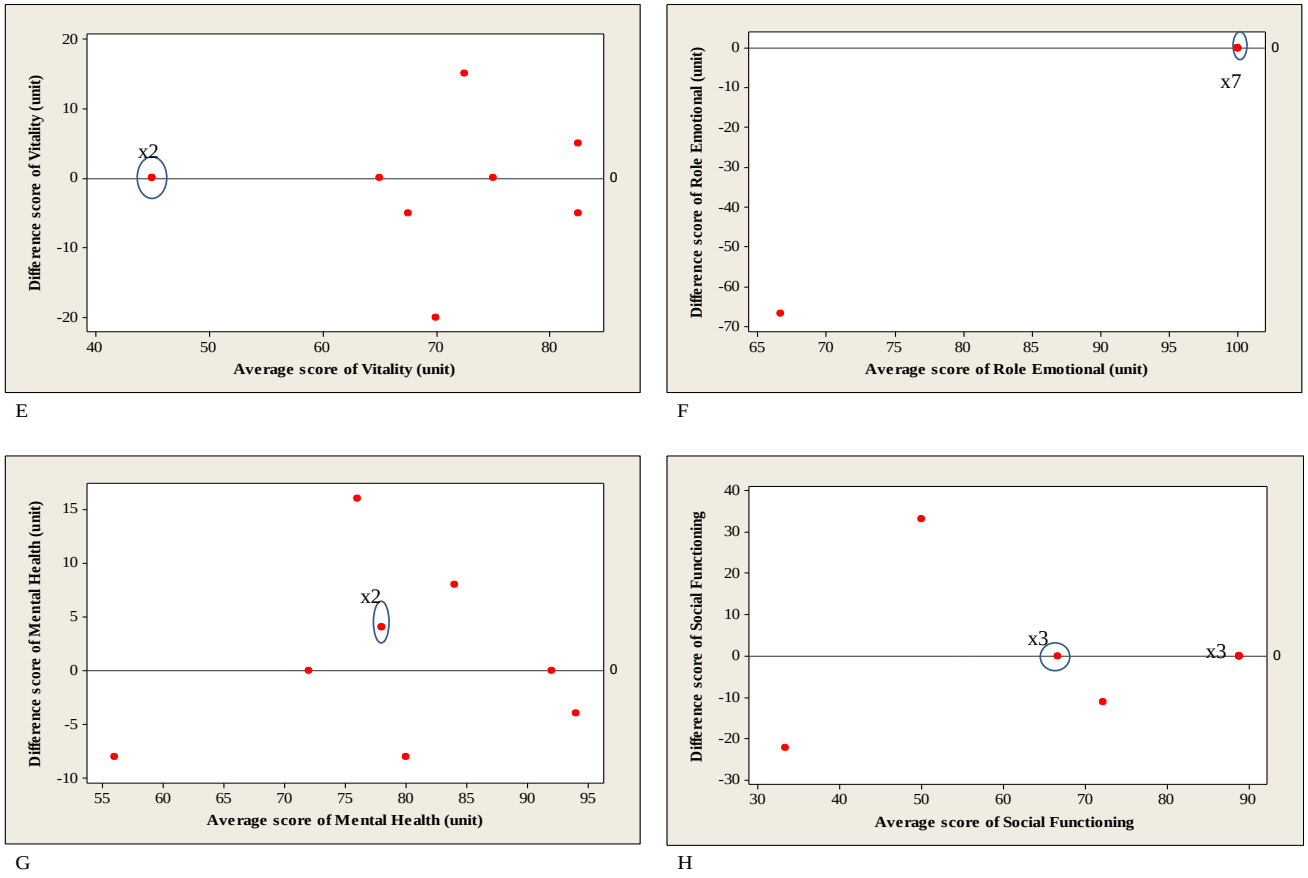
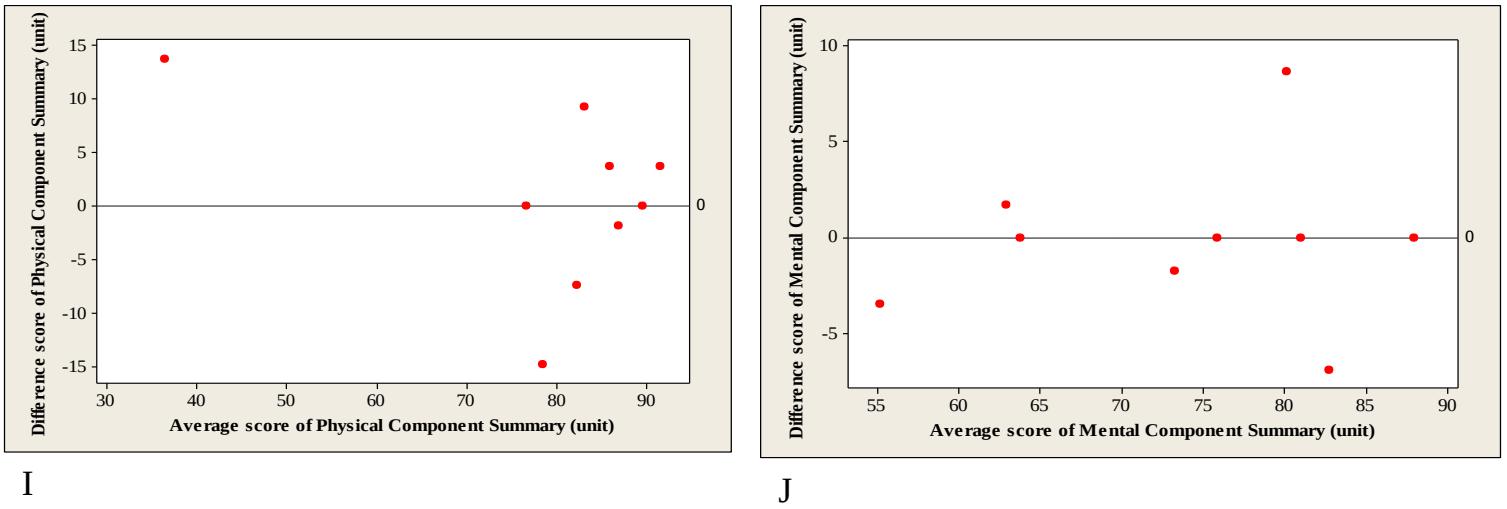


Figure 4.11: Distribution plots of average scores of measures of health related quality of life against difference scores (day 2 minus day1). Zero line indicates no difference. Positive difference (points above zero line) in E , F, G & H indicates better performance at day 2. Negative difference (points above zero line) indicates lower performance at day 2. Blue circles indicate the number of cases on these points.

Figure 4.11: *continued* Bland and Altman plots of measures of health-related quality of life in pre-manifest HD



I J

Figure 4.11: Distribution plots of average scores of measures of health related quality of life against difference scores (day 2 minus day1). Zero line indicates no difference. Positive difference (points above zero line) in I& J indicates better performance at day 2. Negative difference (points above zero line) indicates lower performance at day 2.

4.2.3 Summary of results

Data presented in this chapter relating to the properties of each of the outcome measures in participants with manifest HD and those with pre-manifest HD are summarized in Table 4.15 and Table 4.16. These findings on the characteristics of each of the outcomes in both manifest and pre-manifest HD will be discussed in detail in the sections below.

The results presented in this chapter suggest that deficits in pre-manifest HD may be well represented by measures at the activity level of the ICF model. The PPT as well as the vast majority of the mobility measures which included the gait variability measure, the FSST, the CSST and the peak activity index were all sensitive to early changes in the pre-manifest HD. In addition, the gait variability, the PPT and the CSST were all considered to be highly repeatable.

The data presented in this chapter also demonstrated that the outcomes were sensitive to changes in the manifest HD at each of the levels of the ICF. Taking into account the test re-test reliability values and the calculated SEM, balance is best assessed with the BBS, and activity limitations are well represented by measures of gait variability as well as the CSST and the PPT. The psychometric properties of these measures suggest that they are potentially useful outcomes to detect change over time in individuals with manifest HD. The test re-test reliability data and the MDC_{95} values presented in this chapter further help to explain whether changes reported for the exercise intervention (Chapter 5) can be attributed to the intervention, rather than to natural variability or testing errors.

Table 4.18: Summary of the psychometric properties of outcome measures in subjects with manifest HD

Category	Outcome measure	Discriminant validity	Concurrent validity	Relative reliability (ICC)	Absolute reliability (SEM and Bland and Altman data)*	Indications of directional bias
Balance	BBS	Yes	Yes	Yes	Acceptable	No
	Total score of RT and SRT	Yes	No	Yes	Not acceptable	Yes
	Root mean square of postural sway	Yes	No	Yes	Not acceptable	No
	Excursion of postural sway	No	No	NR	NR	NR
Muscle strength	MVIC of knee flexors and extensors	Yes	No	Yes	Not acceptable	No
Gait	Gait speed	Yes	NA	Yes	Acceptable	No
	Stride time	Yes	NA	Yes	Acceptable	No
	Stride time CV	Yes	NA	Yes	Acceptable	No
Community walking	Daily average of step count	Yes	No	NR	NR	NR
	Percentage of time at levels of PA	Yes	No	NR	NR	NR
	Peak activity index	Yes	Yes	NR	NR	NR
Other measures of mobility	FSST	Yes	Yes	Yes	Not acceptable	Yes
	TUG	Yes	Yes	Yes	Not sure	No
	CSST	Yes	Yes	Yes	Acceptable	No

NA, not applicable; NR, not reported; BBS, Berg Balance Scale; FSST, Four Square Step Test; CSST, Chair Sit to Stand Test; CV, coefficient of variation; PA, physical activity

* "acceptable" means acceptable level of variability between the 2 test sessions

* "not sure" means the variability of the test is influenced by the presence of outliers.

Table 4.18: *continued* Summary of the psychometric properties of outcome measures in subjects with manifest HD

Category	Outcome measure	Discriminant validity	Concurrent validity	Relative reliability (ICC)	Absolute reliability (SEM and Bland and Altman data)*	Indications of directional bias
Functional performance in ADL	PPT	Yes	Yes	Yes	Acceptable	No
Health-related quality of life	PF	Yes	Yes	Yes	Not acceptable	No
	RP	Yes	No	No	Not sure	Yes
	BP	No	No	Yes	Not acceptable	Yes
	VT	Yes	No	Yes	Not acceptable	Yes
	GH	Yes	No	Yes	Not acceptable	Yes
	SF	Yes	No	Yes	Not sure	No
	RE	Yes	No	No	Not sure	No
	MH	Yes	No	Yes	Not acceptable	Yes
	PCS	Yes	Yes	Yes	Not acceptable	No
	MCS	Yes	No	Yes	Not acceptable	Yes

PPT, Physical Performance Test; PF; Physical Functioning; RF; Role limited due to physical problems; RE; Role limited due to emotional problems; SF; Social Functioning; MH, Mental Health; VT, Vitality; BP, Bodily Pain; GH, General Health Perception; PCS, Physical Component summary; MCS, Mental Component Summary.

* "acceptable" means acceptable level of variability between the 2 test sessions.

* "not sure" means the variability of the test is influenced by the presence of outliers.

Table 4.19: Summary of the psychometric properties of outcome measures in subjects with pre-manifest HD

Category	Outcome measure	Discriminant validity	Relative reliability (ICC)	Absolute reliability (SEM and Bland and Altman data)*	Indications of directional bias
Balance	BBS	No	Yes	Acceptable	No
	Total score of RT and SRT	Yes	Yes	Not sure	No
	Root mean square of postural sway	Yes	Yes	Acceptable	No
	Excursion of postural sway	No	NR	NR	NR
Muscle strength	MVIC of knee flexors and extensors	No	No	Not acceptable	No
Gait	Gait speed	Yes	Yes	Acceptable	No
	Stride time	Yes	Yes	Acceptable	No
	Stride time CV	Yes	Yes	Acceptable	No
Community walking	Daily average of step count	No	NR	NR	NR
	Percentage of time at levels of PA	No	NR	NR	NR
	Peak activity index	Yes	NR	NR	NR
Other measures of mobility	FSST	Yes	Yes	Acceptable	Yes
	TUG	No	Yes	Not acceptable	Yes
	CSST	Yes	Yes	Acceptable	No
Functional performance in ADL	PPT	Yes	Yes	Acceptable	No

NA, not applicable; NR, not reported; BBS, Berg Balance Scale; FSST, Four Square Step Test; CSST, Chair Sit to Stand Test; CV, coefficient of variation; PA, physical activity

* "acceptable" means acceptable level of variability between the 2 test sessions

* "not sure" means the variability of the test is influenced by the presence of outliers.

Table 4.19: *continued* Summary of the psychometric properties of outcome measures in subjects with pre-manifest HD

Category	Outcome measure	Discriminant validity	Concurrent validity	Relative reliability (ICC)	Absolute reliability (SEM and Bland and Altman data)*	Indications of directional bias
Functional performance in ADL	PPT	Yes	Yes	Yes	Acceptable	No
Health-related quality of life	PF	Yes	Yes	No	Not sure	No
	RP	Yes	No	No	Not sure	No
	BP	No	No	No	No	No
	VT	Yes	No	No	No	No
	GH	Yes	No	No	Not sure	No
	SF	Yes	No	No	Not sure	No
	RE	Yes	No	No	Not sure	No
	MH	Yes	No	Yes	No	No
	PCS	Yes	Yes	Yes	Not sure	No
	MCS	Yes	No	No	No	No

PPT, Physical Performance Test; PF; Physical Functioning; RF; Role limited due to physical problems; RE; Role limited due to emotional problems; SF; Social Functioning; MH, Mental Health; VT, Vitality; BP, Bodily Pain; GH, General Health Perception; PCS, Physical Component summary; MCS, Mental Component Summary.

* "acceptable" means acceptable level of variability between the 2 test sessions

* "not sure" means the variability of the test is influenced by the presence of outliers.

4.3 Discussion

4.3.1 Measures of physical impairments in body structures and functions

4.3.1.1 Measures of balance

4.3.1.1.1 Berg Balance scale

The BBS includes a number of items that test static and dynamic balance and response to internal perturbation. The BBS was previously used in HD and was demonstrated to be valid in identifying people with HD at risk of falls [45] and in differentiating between stages of the disease in people with manifest HD [94]. Results presented here provide further information about the validity and reliability of this test in people with

HD. Out of the 4 measures of balance evaluated in this study; the BBS has the best psychometric profile in the manifest HD. The test has good discriminant and concurrent-convergent validity in individuals with manifest HD and high test re-test reliability coefficient with indications of minimal variability on repeated testing (SEM<10% of the total range of scores as well as mean and standard deviation of difference scores were relatively very small). The test re-test value calculated here (ICC=0.95) is similar to values reported in the literature for elderly people [181] and people with various other disabilities [182, 185, 190, 191, 243, 244]. The MDC_{95} of 4 in this study was within the range of 2.8 to 5 reported/ or calculated from previous studies of subjects with stroke [185], traumatic brain injury [244] and Parkinson's disease (PD) [182, 191]. The good discriminant and concurrent-convergent validity as well the high test re-test reliability and the indications of minimal variability on repeated testing make the BBS a potentially useful test to monitor disease progression and response to therapeutic interventions in people who are affected with HD.

Whilst the data presented here suggest that the BBS is a potentially useful test in the manifest HD, its use in the pre-manifest stage may be limited. The results presented here demonstrated that the BBS did not have good discrimination ability to detect changes in balance impairments in the pre-manifest HD. This suggests that the test may be inappropriate for measuring balance deficits in the pre-manifest stage. The test includes items (e.g. standing from a chair, sitting on a chair, standing still with eyes open) that may lack the sensitivity to detect changes in the pre-manifest stage. This is supported by the fact that 47% of participants in the pre-manifest HD group reached the ceiling score of 56 on this test, which suggests that the BBS includes tasks which are easy for people who do not have noticeable mobility deficits. More importantly, the scale is based on ordinal measures and therefore it may lack the sensitivity to capture mobility related deficits such as balance impairments in this population at this very early stage of the disease. Ratio or interval measures based on timing activities, as suggested based on observations from other neurological populations, are potentially more sensitive and specific than the ordinal measures to a wide spectrum of severity of impairments [245]. The observations in this study that mobility measures that were based on timing activities, such as the FSST and the CSST, were in contrast with the BBS sensitive to changes across the spectrum of the disease lend further support to this idea.

4.3.1.1.2 Romberg and Sharpened Romberg tests

The Romberg (RT) and Sharpened Romberg (SRT) are tests of static balance that measure the ability to maintain balance or equilibrium with a narrowed base of support during standing. From the data presented here, it can be seen that performance on the RT and SRT decreased with increasing task complexity, from standing feet apart with eyes open, to tandem standing with eyes closed, across all subject groups. These results are in agreement with previous studies [246, 247]. It was interesting to note that many subjects in the healthy controls and pre-manifest groups reached the 30 second- ceiling on the RT with eyes open and eyes closed. In addition, there was a floor effect on the SRT with eyes closed in the vast majority of the subjects with manifest HD. This observed floor effect on this specific task has also previously been reported in people with Parkinson's disease [182] and in elderly women who were healthy [248].

No hierarchical order was applied (i.e. the test was not stopped if a participant failed a lower level of the test). To overcome the effect of the observed ceiling and floor results on the individual subtasks of the RT and SRT tests, the total score of all tasks was used for analysis in this study. This allowed for the assessment of wide variations in ability levels of the included participants. This total score was sensitive to detect change differences between the subjects with manifest HD and healthy controls and between those with pre-manifest HD and healthy controls. This provided indications of the discriminant validity of this score along the spectrum of the disease. In particular, the finding that the test has good discrimination power at the pre-manifest HD is interesting. Noting the average values of the individual subtasks of the test, it can be suggested that inclusion of the SRT tasks added to the complexity of the tests and potentially enhanced the sensitivity of the overall test to detect balance changes at this very early stage of the disease.

Data presented here demonstrated that although the total score of the RT and SRT had good discriminant validity in both manifest and pre-manifest HD, it did not obtain as good concurrent-convergent validity as the other measure of balance (BBS). The BBS correlated highly with the measure of gait variability (stride time CV), whilst the total score of the RT and SRT correlated only moderately with the measure of gait variability. The fact that the BBS involves items of dynamic balance and internal protrusion in addition to the items of static balance may explain this result. It seems that

static balance alone, specifically "standing still" as per the RT and SRT tests may be less important to the functional performance needed during walking, which may partly explain its moderate correlation with gait variability in this study. Findings from previous studies in elderly subjects in which measures of static balance were not strong predictors of measures related to gait, such as gait speed and gait variability [230, 249], is in agreement with results reported here and lend further support to the idea that static balance may be less necessary to the functional performance needed during walking.

In terms of reliability, the test re-test reliability values of the total score obtained in this study for both the pre-manifest and manifest HD were high (ICCs; 0.88 and 0.77). These values fell within the range of 0.7 to 0.9 reported in the literature for the individual tests of Romberg and Sharpened Romberg in healthy individuals [248] and in people with vestibular disorders [250] and PD [182]. The absolute reliability of the Romberg and Sharpened Romberg in these studies was not reported. However, in this study and in the absolute terms of reliability, there were indications that the total score of the RT and SRT is subject to a high degree of variability on repeated testing in people with both manifest and pre-manifest HD (SEM>10% of total range of scores and the mean and standard deviation of difference scores were relatively large). Obtaining a high ICC for this measure in the presence of a high degree of variability can be explained by the observed wide range of scores at the test and re-test assessments, particularly in the manifest HD group. As indicated earlier, the ICC is strongly affected by the range of scores used to calculate the coefficient; ICC is high when the difference in scores between measurements is small in comparison with the range of scores between the studied participants [178], which explains in part the obtaining of high ICC values in this case in the presence of a potentially variable measure. Furthermore, it was interesting to note in Figure 4.2b that this test is susceptible to bias in the manifest HD as most participants (6/9) performed better on this test on day 2. This observation suggests that this test in the manifest HD is prone to a learning effect on repeated assessment. Such a bias effect may confound gains attributed to interventions and therefore needs to be taken into account in future clinical trials. This bias was not evident from the ICC result but further explains the presence of a high degree of variability indicated by the other tests such as the SEM.

High variability within subjects on repeated assessments as reflected by SEM scores has an impact on the MDC calculations [141]. This indicates that the MDC_{95} value of 39.1 seconds in the manifest HD group for the total score, although within the range of 10 to 39 reported from a previous study in PD for individual tasks of Romberg and Sharpened Romberg tests [182], would be larger than desired. The mean score of 100.4 seconds on the total score of RT and SRT would make a change score of 39 or better on repeated testing unrealistic for the majority of the group. Overall, the possibility that this score is prone to variability on repeated measurements may limit its applicability as a measure of responsiveness to change over time in individuals with HD.

4.3.1.1.3 Measures of postural sway

The results presented here demonstrated that measures related to the root mean square of the COP movement were sensitive to differences between people with manifest HD and healthy controls. This result provides indications of the discriminant validity of the root mean square measures in the manifest HD group. In contrast, measures related to excursion of the centre of pressure (COP) during quiet standing both in the anterior-posterior and medio-lateral directions were not sensitive to group differences between people with HD and healthy controls. The inability of the excursion measures to detect differences in balance between people with HD may be related to the force platform test used in this study. Force platform tests are usually done with pre-determined position of the feet and stance width. The required stance as such may result in excess of movement of the COP. In the present study, the participants themselves were allowed to determine the stance width. It was considered that self selected stance width better reflects actual performance of an individual. However, it is possible that some of the participants in this study compensated for their balance deficits by increasing their support base with a wider stance position, and thus this test was unable to capture deficits in the excursion measures. Indirect support for this explanation comes from the observation cited earlier that most of the participants in the manifest HD group were unable to complete the Sharpened Romberg test in which balance can be compromised by a narrow base of support.

The ability of the root mean square measures, but not the excursion, to capture deficits in balance may be related to the construct of these measures and may also reflect the

standing strategy that subjects with HD adopt. Measures of root mean square provide indications of the variability of the movement of COP in a certain direction; whilst excursion represents the distance taken by the COP over the duration of the test. It can only be speculated that subjects with manifest HD may begin the test swaying around one target as a home base. As the test progresses in time, subjects may move and start to sway around another home base. With each different home base, the variability in the COP movement increases. Thus the captured changes in the root mean square may reflect true variability of the COP movement, and therefore balance. This in turn may also explain the calculated correlations between these measures and gait variability (i.e. stride time CV). Whilst the excursion correlated poorly with the measure of gait variability, the root mean square measures had correlated moderately with stride time CV. The correlation coefficients of the root mean square measures fell just short of the criterion for good concurrent convergent validity (correlation coefficients of 0.5 is lesser than the criterion correlation of 0.6). However, it must be noted that these outcomes were susceptible to outliers that seemed to have influenced their associations with the measure of gait variability. Therefore, further validation of these outcomes in future work using a larger sample is required.

In terms of reliability, the test re-test reliability values of the root mean square measures were high. However, it should be noted that in the absolute term of reliability, there were indications that these measures are subject to a certain degree of variability on repeated testing in the manifest HD that may be more than desired (SEM>10% of total range of scores). Obtaining a high ICC for this measure in the presence of a high degree of variability can be explained by the observed wide range of scores at the test and re-test assessments particularly in the manifest HD group. As discussed earlier, the ICC is strongly affected by the range of scores used to calculate the coefficient; ICC is high when the difference in scores between measurements is small in comparison with the range of scores between the studied participants [178] which explains in part the obtaining of high ICC values in this case in the presence of a potentially variable measure. High variability within subjects on repeated assessments as reflected by SEM scores may be related to the protocol of testing used here. In this study the average of only 2 trials were used for analysis. The duration of each trial was 30 seconds. Data available from the literature suggests that minimal variability on measures of root mean square measures of COP requires averaging at least 4 trials of 2 minutes [251]. Future

research may need to examine the reliability of these measures using different protocols of testing by incorporating more trials with longer durations. Overall, the possibility that these measures are prone to variability on repeated testing may limit their applicability to measure change over time in individuals with HD.

4.3.1.2 Measures of muscle strength

The data presented here demonstrated that the MVIC measures of the knee flexors and extensors had good discriminant validity only in the manifest HD; significant differences on these measures were detected only between manifest HD and healthy controls but not between the pre-manifest HD and healthy controls. The discriminant validity of these measures in the manifest stage is consistent with data from a previous study in which the MVIC values of 6 muscle groups of the lower limb were able to distinguish between people with mid-stage HD and healthy controls [96]. The lack of the discriminant validity of these measures in the pre-manifest stage, however, may be related to the suggestion that muscular deficits are subtle in the pre-manifest stage [97, 98] and thus are difficult to detect through clinical assessment.

The MVIC measures, although showing good discriminant validity in the manifest HD, did not obtain good concurrent-convergent validity; these measures correlated poorly with the gait variability measure (stride time CV). The fact that all the subjects with manifest HD that were included in this study were at an early to mid stage of the condition may partially explain this result. In general, one may expect weaker muscles of lower limbs in the presence of higher gait variability. However, it should be noted that the relationship between these 2 variables may not be linear. Evidence available from other populations lends support to this idea. For example, muscle strength was associated with measures of gait only at the lower range of muscle strength in a group of older women, resulting in a curvilinear relationship between muscle strength and performance of gait [252]. This can be equivalent in people with HD and muscle weakness at an early to mid stage, such as that seen in the subjects included in this study, may not have a dramatic effect on the measures of gait. This may explain the lack of concurrent-convergent validity of the MVIC measures that were observed here. Further investigations to examine the validity of these measures among a sample with a

wider range of subjects, including subjects who are more advanced in the disease stage are indicated.

In terms of the reliability of the MVIC measures, the test re-test reliability coefficients were very high in both the manifest and pre-manifest (ICC=0.94 for both groups). This calculated test re-test reliability fell within the range of 0.8 to 0.96 reported in previous studies of subjects with stroke [183], lower motor neuron disease [253] and healthy adults aged between 20 and 69 years [254]. None of these studies, however, assessed individuals with HD. Although results from this study showed high ICC values of the MVIC measures, these measures seemed to be subject to a high degree of variability in the absolute figure; the SEM values were larger than the 10% of the total range of scores and the mean as well as the standard deviation of the within subject's difference scores were relatively large. The wide range of scores observed at the test and re-test assessment of MVIC indicated that the amount of variability between participants was high, which may have potentially created a high test re-test reliability coefficient in the presence of a high degree of variability within participants on repeated testing [141]. Every effort was made to standardize the testing procedure to minimise variability in this study. The test, however, still needs good understanding of instructions, and a very cooperative participant. Furthermore, it is possible that participants with manifest HD in this study may have experienced co-activation of the knee extensor and/ or flexor musculature (secondary to dystonia) during performance of the test [35]. In addition, difficulties in movement initiation and movement execution as well as the deficits in force generation seen in this population may also influence the performance of this test [37, 255]. Any or all of these factors may have contributed to increased variability of the test in the present study. Thus, the susceptibility of these measures to high degree of variability may limit its use as a measure of responsiveness to change over time in this population.

4.3.2 Measures of activity

4.3.2.1 Measures of mobility

4.3.2.1.1 Walking- measures of gait

The present data demonstrates that measures of gait variability derived from the GAITRite walkway have good discriminant validity in both manifest and pre-manifest

HD. Participants with both manifest and pre-manifest HD had higher stride time coefficient of variations (CV) when compared with healthy controls. These results are consistent with previous studies that examined gait pattern in people with HD. Rao et al [40] in a study that investigated the spectrum of gait impairments in HD subjects, demonstrated significant differences in step time CV analogous to the data presented here. These results also align with those presented in a study of 17 subjects with pre-manifest HD and 57 healthy controls by Devlal et al [107].

In contrast to the gait variability, other measures of gait which included gait speed and stride time demonstrated good discriminant validity in the manifest HD participants but not in those with pre-manifest HD. Significant differences were found in gait speed and stride time between the manifest HD subjects and healthy controls, but not between those with pre-manifest HD and healthy controls. This finding is in contrast with data reported in both Devlal and Rao et al studies [40, 107] in which gait speed and step time were found to be significantly different across all subject groups. The finding in this study that the gait variability, but not the parameters describing properties of average measures such as gait speed and stride time, was sensitive to capture change differences between the subjects with pre-manifest HD and healthy controls, is interesting. The fact that gait as a functional task is controlled by an array of physiological and neurophysiological systems may provide an explanation for this observation. Performance of gait relies on neural, motor and sensory inputs and therefore, gait variability can be viewed as a final integrated output of the locomotor system [104]. This dependence on a host of factors suggests that gait variability may act as a sensitive measure, perhaps revealing deficits in gait, even when the other measures of gait such as stride time and gait speed only show more subtle changes.

Data from the present study suggests that the GAITRite walkway is a reliable instrument in quantifying gait measures in manifest and pre-manifest groups. The test re-test reliability coefficients of gait speed and stride time for both manifest and pre-manifest groups were excellent (ICC above 0.8 for both variables). These coefficients were also in agreement with the values previously reported by Rao et al [140] in a sample of individuals with manifest HD, and fell within the range reported in previous studies of older adults and subjects with Alzheimer disease and Parkinson's disease (ICC range from 0.75 to 0.99) [140, 199-204]. The test re-test reliability obtained in this

study for the stride time coefficient of variations (CV) was also surprisingly high in both the manifest and pre-manifest HD groups (ICC=0.98, 0.75 respectively). The small SEM values relative to the range of the scores at the test re-test assessments (SEM<10% of the total range of scores) as well as the small mean and standard deviation of the within subject's difference score for all the gait measures included in this analysis suggest highly repeatable parameters. This provides indications that despite observable variability in motor performance, there is some underlying consistency in the pattern of gait deficits in HD. The MDC_{95} obtained in this study for the gait speed and stride time were lower in comparison to those calculated from a previous study by Rao et al [140], indicating a lesser amount of variability in the data presented in this study. One possible explanation for this result is that analysis of the data presented here was based on a larger number of trials; the average of 10 walking trials was used in this study compared to only 2 trials in the study by Rao et al [140]. Hence, the use of a larger number of trials may potentially help in providing an adequate sampling of a subject's motor performance.

Overall, out of the 3 measures of gait evaluated here, gait variability as reflected by the stride time CV, was the most sensitive to detect changes across the broad spectrum of the disease. This measure as well had high test re-test reliability with indications of exposing minimal variability on repeated testing. This makes gait variability a potentially useful measure to monitor disease progression and response to therapeutic interventions in people with HD, even at the very early stages of the disease.

4.3.2.1.2 Walking-measures of community walking

The StepWatch Activity Monitor, which consists of an accelerometer and microprocessor was used in this research for the purpose of monitoring the actual walking in the community setting; thus providing an indication of an individual's performance of walking. The main advantage of this monitor is that it can be worn for extended periods and has a range of outputs available. Total step count is the most commonly used output, but peak activity index is also available. The peak activity index represents the average step rate of the fastest sustained 30 minutes. The percentage of time spent at high (above 40 steps/min), medium (between 15 and 40 steps/min) and low (below 15 steps/min) rates can also be calculated.

As expected, all measures derived from the activity monitor demonstrated good discriminant validity in the manifest HD group. Individuals with manifest HD (although all were able to walk independently), demonstrated significantly lower average daily step counts and activity levels than healthy controls. Furthermore, high correlation was found between the peak activity index and the stride time coefficient of variations which gives an indication of the good concurrent-convergent validity of this measure. This high correlation suggests that the associated motor deficits in HD such as increased gait variability may limit individuals with HD by restricting the actual number of steps that they are able to maintain for an extended period of time. In contrast to peak activity index, there were no significant correlations between the average daily step count, the percentages of time spent at different levels of physical activity and the stride time coefficient of variation. The fact that besides the physical capacity there are other potential influential factors on the total steps an individual with HD would take in one day may explain this result. It is likely that behavioural, personal, environmental and social factors also impact the number of steps taken in 1 day [256]. Highest step rate in 30 minutes (peak activity index) is based on rate rather than amount of stepping or percentage of time and may be therefore more reflective of maximal physical performance in this population. This result is consistent with previous reports from current literature in which peak activity indices were found to best correlate with gait speed in individuals with stroke [257] and with the Rivermead Mobility Index in individuals with other neurological disorders [208]. The peak activity index was also found to be the most reliable compared to average daily step counts and the percentage of time spent at different levels of activities in stroke [186] and other neurological conditions [208].

Interestingly, data presented here suggests that individuals with pre-manifest HD had a trend toward spending less time participating in medium and high activities than healthy controls, although these differences were not significantly different. In contrast, individuals with pre-manifest HD demonstrated significantly lower peak activity index when compared to healthy controls; providing an indication of the good discriminant validity of this measure in the pre-manifest HD. This finding suggests that people with pre-manifest HD may have reduced ability to maintain activity levels for a longer period of time. The origin of this is unknown and further investigations are required to determine factors that may potentially contribute to restricted activity levels in pre-

manifest HD. Issues related to fatigue (if any) or the tendency toward having a sedentary life style as a consequence of apathy can be contributing factors. In addition, the possibility that subtle deficits in mobility and balance may limit individuals with HD at this very early stage of the disease by restricting the actual number of steps that they are able to maintain for an extended period of time is indicative. This warrants further investigation. Overall, the good concurrent-convergent and discriminant validity across the spectrum of the disease, as well the high test re-test reliability (based on data available from current literature) make the peak activity index in particular a potentially useful measure to monitor responsiveness to change over time in people with HD.

4.3.2.1.3 Other measures of mobility

4.3.2.1.3.1 Four Square Step Test

Performance on the FSST was significantly different in both manifest HD participants and those with pre-manifest HD when compared to healthy controls. This provides indications of the good discriminant validity of this test in both manifest and pre-manifest HD groups. The good discriminant validity of this test in the pre-manifest HD in particular is interesting and can be understood in the context of the nature of this test. The FSST requires the individual to comprehend, plan, organise, and incorporate the stepping sequence that requires combination of movement and weight shift from one foot to another while changing direction [210], thereby making the test more cognitively challenging. The fact that deficits in executive cognitive functions such as planning, organising and sequencing a motor task start to appear from the pre-manifest stage [22, 23] and may therefore add to the difficulty of performing this test, explains its sensitivity to capture differences in the pre-manifest when compared to healthy controls.

In addition to the good discriminant validity, the FSST had good concurrent-convergent validity with the primary measure (stride time CV). This test has not been previously used in HD; however data presented here are consistent with reports from the literature on using the FSST in other populations such as the elderly [187], vestibular disorders [211] and stroke [209]. In these populations, the FSST was found to have good concurrent validity with walking speed [211] and other measures of balance [187, 209] as well as being sensitive in identifying people who are at risk of falls [187, 210, 211].

In terms of reliability, the test re-test reliability coefficients obtained for the FSST in both manifest and pre-manifest HD were high and similar to values found in previous studies of subjects with stroke [209], vestibular disorders [211] and older adults [187]. None of these studies assessed the absolute reliability of this measure. In this study, the calculated SEM provided indications of minimal variability of the test in the pre-manifest HD in the absolute term. The SEM value however, suggested that this test in the manifest stage is prone to a high amount of variability on repeated assessments (SEM> 10% of the total range of scores in the manifest HD). The fact that this test requires the performance of a coordinated motor task that is cognitively challenging may partly explain the high variability in the manifest HD.

Overall, data obtained from the Bland and Altman methods suggest that this test is prone to a learning effect (i.e. directional bias) in both manifest and pre-manifest HD; most manifest (7/9) and pre-manifest (8/9) individuals performed better in day 2 on this test compared to day 1 (Figure 4.5a and 4.10a). This bias was not evident from the ICC results and potentially was not big enough to produce a high value of SEM in the pre-manifest. However, this is an interesting observation to note and it may disappear on re-testing when more trials of the test are included; FSST score in this study was based on the average of 3 trials, however future studies may need to incorporate a larger number of trials to overcome the observed learning effect.

In addition to a learning effect, data presented here revealed that there was a potential bias toward the larger values on this test (i.e. there was a tendency for a relationship between the difference score and the size of the mean). For example, in the manifest HD group, the 3 participants who took on average 30 seconds or more to complete the test were the ones who showed the largest differences in performing the test on repeated assessment. Taking into account the complexity of this test and its cognitive demands, this bias towards a larger value suggests that participants who were more impaired potentially both physically and cognitively may find it more difficult to perform this test at the baseline and this in turn may have contributed to a highly variable performance on repeated testing.

In addition to its subjectivity to a higher degree of variability and to directional biases particularly in the manifest HD, the FSST has some other disadvantages that need to be

considered. The test requires a high level of skilled physical supervision on the part of the tester in order to ensure the subject's safety. In addition, the test can be described as an "all-or-nothing" test, in that a score cannot be given to a subject who does not complete the test, which may result in obtaining a floor effect. In this study, a floor effect was observed in 20% of the participants with manifest HD (i.e. 20% of the participants in the manifest HD group could not perform the test).

In summary, the test was sensitive to early mobility changes in pre-manifest HD; however its susceptibility to a learning effect on repeated assessment may limits its use as a measure to monitor disease progression in this early stage of HD. Furthermore, its use in the manifest HD stage may be limited due to its susceptibility to floor effects, a higher degree of variability on repeated testing and directional biases.

4.3.2.1.3.2 Timed Up and Go test

The TUG evaluates mobility during transfer from sit- to stand, walking and turning. The TUG was also previously used in HD [93] and was demonstrated to be useful in identifying people with HD who are at risk of falls [45]. Results obtained from this study demonstrated that although the test had good discriminant as well as concurrent-convergent validity in manifest HD, it did not obtain good discriminant validity in the pre-manifest HD. The test was unable to distinguish between individuals with pre-manifest HD and healthy controls. This result is consistent with findings reported by Rao et al [94] in which the TUG was also found to be not sensitive in detecting mobility deficits in the pre-manifest HD. As indicated earlier, a likely explanation for this result is that mobility deficits in the pre-manifest HD are subtle and therefore tests of mobility that include more complex patterns of movement are required to detect such changes at this very early stage of the disease [92].

In terms of reliability, the test re-test reliability coefficients in both the manifest and pre-manifest HD groups were high (ICC=0.74, 0.84 respectively). The test re-test reliability values obtained in this study, although relatively high, are lower than the values previously reporting test re-test reliability of TUG in the elderly [212], people with peripheral arthritis [258] and in people with Parkinson's disease [182, 191]. This can be explained in the context of the data presented here about the absolute reliability

of this test in HD. The calculated SEM was higher than the acceptable limit in both groups (SEM> 10% of the total range of scores). This indicates that the test is potentially susceptible to a high degree of variability between 2 test sessions in people with HD. Data obtained from Bland and Altman plots provided further insight into this. For example in the pre-manifest HD it seems that the variability between the 2 testing sessions occurred in one direction (i.e. bias); most individuals with pre-manifest HD (6/9) performed better on this test on day 2 compared to day 1. This suggests that this test is prone to a learning effect in the pre-manifest HD.

In the manifest HD, although in most cases (7/9) differences between day 1 and day 2 were relatively minimal (Figure 4.5b), there was an outlier. The presence of the outlier may have inflated the degree of variability in people with manifest HD. It was also interesting to note that this outlier (i.e. the case that showed the largest difference) is the case that had the largest average score. This suggests that the TUG in manifest HD stage is susceptible to the bias toward the larger value (i.e. differences between repeated assessments increases when average score increases). This observation needs to be further investigated in a larger sample with a wider range of levels of impairments. Overall, the high variability of the TUG in individuals with the manifest HD who are more impaired can be attributed to a number of factors. First, despite the fact that the TUG consists of basic everyday movements, its various components for individuals with mobility deficits can be particularly complicated; performing the test involves an interaction between multiple systems, such as sensory input, neuromuscular function and cognitive processes. For example, to be able to rise from a sitting position to a standing position requires both strength and technique. Walking a path for 3 meters includes both acceleration and deceleration as participants prepare for a turn. The turning sequence is challenging for people with HD. Finally, turning around to sit down challenges both balance and orientation in adapting the body position to the chair. Second, as the test requires understanding of instructions as well as an ongoing adaptation to tasks, anticipation, and planning, cognitive impairments as seen in HD may influence performance of the test [212]. This, in particular, is important to consider as there is some supportive evidence from other populations that cognitive impairments may influence the measures of the TUG assessment [212].

In summary, the TUG as suggested on previous research may be useful as a screening tool to identify people who are at risk of fall in this population. However, its use to measure responsiveness to change over time may be limited as it seems to lack the sensitivity to early mobility changes in HD and it is susceptible to directional biases on repeated testing.

4.3.2.1.3.3 Chair Sit to Stand Test

The CSST is a simple and common method of assessing postural control in the community or in a clinic setting [188]. The test protocol has 2 versions. In the first version, the test measures the time the participant takes to complete a given number of sit- to- stand repetitions, usually either 5 or 10 [259]. While this version of the test has good concurrent validity relative to other measures of interest, such as walking speed and risk of falls [214, 260], it can result in a floor effect. As an example, a floor effect was observed even on a 5-stand version of the chair stand test in a study of elderly people, when 22% of a population of over 5,000 community individuals could not complete the required 5 repetitions [261]. The 30-second Chair Stand test is an alternative protocol that has been introduced by Jones et al [188], with the aim of assessing the older adult population specifically. In the 30-s Chair Stand test the examiner quantifies the maximum number of chair stands completed within 30 seconds instead of measuring the time taken to complete a specific number of repetitions. This allows for the assessment of a wide range of abilities and for this reason this version of the test was used in this study.

The results in this study demonstrated that the version of the 30 seconds CSST test was able to distinguish between manifest HD and healthy controls as well as between pre-manifest HD and healthy controls. This provides indications of the discriminant validity of this test in people with HD along the spectrum of the disease. The test also has good concurrent-convergent validity with gait variability measure (stride time CV). These results are consistent with the literature, which has shown that this test provides a valid indication of measures of mobility and has good discrimination power in detecting expected differences in age categories and physical activity level groups in community dwelling older adults [188, 262].

The finding in this study about the good discrimination validity of the CSST to capture changes in the mobility performance in the individuals with pre-manifest HD is particularly interesting. This result can be understood in light of available information from the literature about sit to stand performance in people with HD; subtle deficits in the slopes and durations of Sit to Stand transitions were previously recorded in the pre-manifest HD group using a kinematic sensor when compared with healthy controls [116]. Considering these subtle deficits in sit to stand performance and taking into account that the 30 seconds CSST is a stress type of test in which the maximum number of Sit to Stand transitions is recorded in a certain amount of time, it is likely to find a difference in the performance of this test between the groups of pre-manifest and the healthy controls.

In terms of reliability, the test re-test reliability coefficient obtained for the CSST in both manifest and pre-manifest HD was high and comparable to the value reported in a previous study of elderly adults [188]. The calculated SEM provided indications of minimal variability of the test on repeated testing in both the manifest and pre-manifest HD (SEM<10% of the total range of scores in both groups). The difference between the 2 test sessions in both manifest and pre-manifest HD groups was 2 repetitions or less in most cases (Figure 4.5d and 4.10d) which further confirms the minimal variability of this test on repeated testing in this population. These results provide the suggestion of a highly repeatable test. Overall, the good discriminant validity as well as the high test re-test reliability of this test in both the manifest and pre-manifest HD suggests that this test is potentially a useful test in monitoring disease progression and response to therapeutic interventions across the broad spectrum of the disease.

4.3.2.2 Measures of functional performance in ADL

The 7-item PPT was used in this study to assess the functional performance in ADL. The PPT was chosen because its items reflect different dimensions of function, specifically upper fine motor function and upper "coarse" motor function, as well as mobility [189, 263]. The PPT was previously demonstrated to have good concurrent validity with other functional performance measures, such as the Katz ADL scale and Tinetti gait score [189], as well as predictive validity for institutionalization or mortality in a sample of older adults [263]. The results of this study were consistent with these

previous reports and demonstrated that the PPT correlated highly with the measures of gait variability. This provided indications of the concurrent-convergent validity of this test and suggests that functional decline in HD is associated with related motor deficits seen in this population.

In addition, results from this study demonstrated that the test was sensitive to distinguish between individuals with manifest HD and healthy controls. Furthermore, this test was able to differentiate between people with pre-manifest HD and healthy controls. These results provided indications of the discriminant validity of this test in both manifest and pre-manifest HD. The finding that the test was sensitive to early changes in the pre-manifest HD is important and provides the suggestion of pre-clinical decline in function in this population. Brach et al [206] previously used the PPT as a performance-based measure to identify early decline in physical functioning in community-dwelling older people. Similarly Landgraff et al [216] used the PPT to detect early changes in functional performance in a sample of individuals with asymptomatic carotid artery disease. These studies provide additional supporting evidence that the PPT is useful in identifying early decline in functional performance.

Functional decline in the pre-manifest HD was not previously documented in pre-manifest HD using the routine measure of function used to assess the functional performance in this population (the Total Functional Capacity scale (TFC)) [137, 139]. This is in agreement with what is reported in this study in which all the pre-manifest subjects scored on the ceiling on the Total Functional Capacity scale (TFC). However, none of the pre-manifest HD scored on the ceiling in the PPT test. The fact that the TFC and the PPT use different methods to measure functional performance may explain this result. The TFC is a self reported measure of functional performance, whereas the PPT is a direct observational test that assesses individuals' performance based on time to completion of certain tasks. It is therefore likely that preclinical deficits in physical performance can affect function by increasing time to complete the task as indicated by a lower score on the PPT which have not been routinely identified clinically using the TFC scale, or perceived and communicated by individuals with pre-manifest HD. This is in agreement with available evidence which found that early deficits in physical function are often not reported by individuals but can be observed using performance-based measures [206].

Considering the reliability, the test re-test reliability value of 0.95 obtained for the PPT in the group of manifest HD fell within the range of 0.8 to 0.96 reported in previous studies of subjects with the elderly [189] and PD [217]. The small SEM relative to the total score of measurements indicated that the test is highly repeatable in the absolute term in the manifest HD group. The calculated MDC_{95} value of 2.5 in this study was comparable to the value calculated from a previous study for subjects with PD [217]. Although the ICC value of 0.69 for the PPT was lower in the pre-manifest group, the very small SEM relative to the range of the scores indicates that the test is highly repeatable even in the pre-manifest HD group. The difference between the 2 testing sessions in the pre-manifest HD groups was 1 unit or less in the vast majority of cases (8/9) (Figure 4.10d) which further confirms the minimal variability of this test on repeated testing in this population at this very early stage. This result (obtaining low ICC values whilst observing minimal variability in the absolute figure), as indicated earlier, can be explained in light of the homogeneity of the tested sample. The ICC value is known to be strongly influenced by the magnitude of the observed variance between subjects [141, 178]. The lower the magnitude of the range or spread of the scores therefore, the lower the magnitude of ICC even in the presence of a highly repeatable measure [178]. In this study, the small range of PPT scores in the pre-manifest group indicates the low variability of this test among the subjects being tested which may explain the low ICC value calculated for this test in this group. Overall, the good discriminant validity of this test in both manifest and pre-manifest HD as well as the high test re-test reliability suggests that the PPT can be useful as a measure of responsiveness to change in this population along the spectrum of the disease.

4.3.3 Measures of participation

4.3.3.1 Measures of health-related quality of life

Health-related quality of life can be assessed using a generic or a disease-specific tool. As there is no disease-specific tool available yet for assessing health-related quality of life in HD, the 36-Item Short-Form Health Survey (SF-36), which is a generic tool commonly used in research, was used in this study. Data presented here demonstrated that all the subscales of the SF-36 except the bodily pain have good discriminant validity in individuals with manifest HD; scores obtained from all subscales except the bodily pain were able to distinguish between people with manifest HD and healthy

controls. This result is consistent with reports from previously conducted studies in which individuals subjects with HD had poorer health- related quality of life than healthy controls [117-120]. In particular, the profiles of quality of life demonstrated here in the manifest HD were similar to those reported in a previous study and in which significantly reduced health related quality of life was demonstrated on several dimensions of the SF-36 including physical function, role physical, social function, and general health perceptions [119]. Thus data presented here provides further support for the reduced health-related quality of life in manifest HD as identified by the SF-36. The inability of the bodily pain subscale to distinguish between manifest HD and healthy controls in this study is also consistent with reports from a previously conducted study in which scores obtained from bodily pain subscales in people with manifest HD were not significantly different from the scores obtained from their carers [119].

In addition to the good discriminant validity of the majority of the SF-36 subscales, some of the dimensions appeared to have good concurrent criterion validity in the manifest HD. In this study, the physical function subscale as well as the aggregate physical score (i.e. the physical component summary) correlated significantly and substantially with the primary measure of gait variability (stride time CV). This suggests that motor aspects of the disease and, in particular, walking difficulties may be a key factor associated with health-related quality of life in this population. This is in agreement with available evidence, which found that the physical dimension of the SF-36 in HD correlates significantly with the TFC score [117], the UHDRS-motor score [119, 120], the disease duration and the patient's self-rated score on their level of functioning or independence level [118, 119].

The test re-test reliability coefficient obtained in this study for the subscales of the SF-36 were fair to substantial in the manifest HD and were moderate to high in the pre-manifest HD (ICC vales ranged from 0.13 to 0.79 in the manifest HD and from 0.5 to 0.91 in the pre-manifest HD). The lower limits of these values were lower than those reported in a previous study of subjects with HD [119]. The upper limits of the ICC values reported here, however was within the range reported in a previous study in HD [119] and were also similar to values reported in studies of subjects with vestibular disorders [264], stroke [265] and PD [182]. The absolute reliability of the SF-36 in HD has not been evaluated in previous studies. In this study, the calculated SEM values of

all the in the manifest HD were much higher than the criterion (SEM> 10% of total respective range of scores (Table 4.14)). Similarly in the pre-manifest HD, the SEM values were much higher than the criterion in the vast majority of the subscales; only the SEM of the physical component summary and the mental component summary just fell short below the criterion in the pre-manifest HD. This provides an indication that the SF-36 is susceptible to a high degree of variability. The data obtained from Bland and Altman plots provided further insights into this. It seems that reliability of the SF-36 subscales in pre-manifest HD is affected by outliers; in some of the subscales, mainly the physical function, role limited due to physical problems, social functioning and role limited due to emotional problems, although differences in most cases were close to zero, there were some outliers (i.e. big differences in few cases) (Figure 4.11). These outliers may have inflated the degree of variability in these subscales; thus there is a need to confirm findings reported here with a larger sample in future studies.

Data obtained from the Bland and Altman methods have also highlighted two interesting observations about the reliability of the SF-36 subscales in the manifest HD. Firstly, in some of the subscales such as the physical function and the bodily pain, there were a tendency toward bias to greater value. For example in the role physical subscale, largest differences were observed in cases where the mean is greater than 40 (Figure 4.11). Secondly, there were indications of directional bias in at least 4 of the subscales (i.e. mental health, vitality, general health, mental component summary). In all of these subscales, most participants had a lower score on day 2 compared to day 1. This observation in particular is interesting and one possible explanation of it is the occurrence of a response shift bias. Response shift is common in population in which individuals live with a chronic illness [266] and there are preliminary indications that it does occur in the HD population [118]. Response shift refers to the fact that subject's views, values and expectations may change over time [267]; thus influencing the assessment of quality of life. Spangers and Schwarts [266] suggest that coping; social support, goal reordering, reframing expectations, and social comparison may all be active mechanisms in response shift. Although it is not clear if response shift has occurred or not in this study, one might hypothesise that reframing expectations is an important factor in the observed directional bias; being a participant in a study that evaluate physical abilities and fitness levels may made some participants to view their situations at the re-test assessment (i.e. day 2) as being worse compared to what they

previously thought (i.e. at day 1). It should be noted however, that these are only speculations and further research is required to confirm of whether response shift occurs in HD and how it would affect the assessment of health-related quality of life. This is an important area of investigation as response shift bias will have implications for the design of future studies; subject's shift in rating quality of life over time may mask treatment gain.

Although a response shift bias in HD is possible, the susceptibility of the SF-36 subscales in general to a high degree of variability could reflect a distortion that is secondary to the cognitive impairments seen in this population. The majority of the questions in the survey are asked by inquiring if the participant is doing better, worse or the same. These types of questions involve implicit or explicit comparisons to the past and retrospective judgement of health-related quality of life; thus answering these questions can be cognitively demanding particularly in individuals with cognitive deficits as in people with HD.

Overall, although the vast majority of the SF-36 subscales seem to have good discriminant validity and the physical function and physical summary component subscales in particular have a good concurrent-convergent validity in the manifest HD, the susceptibility of the subscales to higher degree of variability may limit their use as measures of responsiveness of change over time in people with HD.

Chapter Five

Results and Discussion: Part 2

5 Results and discussion: Part 2

5.1 Overview

This chapter presents the quantitative results of Part 2 of the study, which aimed to evaluate the feasibility and potential benefits of a home-based exercise programme. A repeated measures design was used. Twenty-five participants with early to mid-stage HD were randomly assigned to the exercise intervention group or to the control group who received delayed intervention (Figure 5.1). Participants who completed the study were assessed 3 times over the study duration (at baseline; at 8 weeks and at 16 weeks) using a battery of outcome measures whose psychometric properties were evaluated in the first part of the study (Chapter 4). The primary outcome was gait variability (stride time coefficient of variation (CV)). Secondary outcomes included other measures of gait as well as measures of balance, muscle strength, mobility, community walking, functional performance in ADL and health-related quality of life.

Results in this chapter relating to the feasibility and potential benefits of the exercise programme are presented in 4 sections. In the first and second sections, the flow of participants through the study, baseline characteristics and adverse events are described. In the third section data related to comparison of follow- up scores at the 8-week period (i.e. the primary end point of the study was at 8 weeks) across groups, after adjustment for differences at baseline using analysis of covariance (ANCOVA), are provided. In addition scatter plots of individual responses for all outcomes in which scores at baseline were plotted against the change scores, categorized by group allocation are illustrated. Furthermore, effect sizes which were calculated for outcome measures at 8 weeks based on differences in change scores between groups are reported in this section. Descriptive data which was used to compare follow-up scores on the primary outcome only at 16 weeks are provided in the fourth section of the results.

The result sections will be followed by discussion of the data. Data obtained from the previous chapter relating to the psychometric properties of the outcome measures are used to aid in providing interpretations of findings from this part of the study. In

particular, the values of the minimal detectable change (MDC_{95}) of each of the outcomes that are presented in the previous chapter are used here to determine whether any statistically significant changes on the outcomes in the exercise intervention are clinically significant. Changes in the outcomes in the intervention group that exceed the MDC95 are 95% likely to be admitted as a real change in the outcome rather than being a result of random error or natural variations in testing [141, 178] and therefore can be interpreted as meaningful in practice [178].

5.2 Results

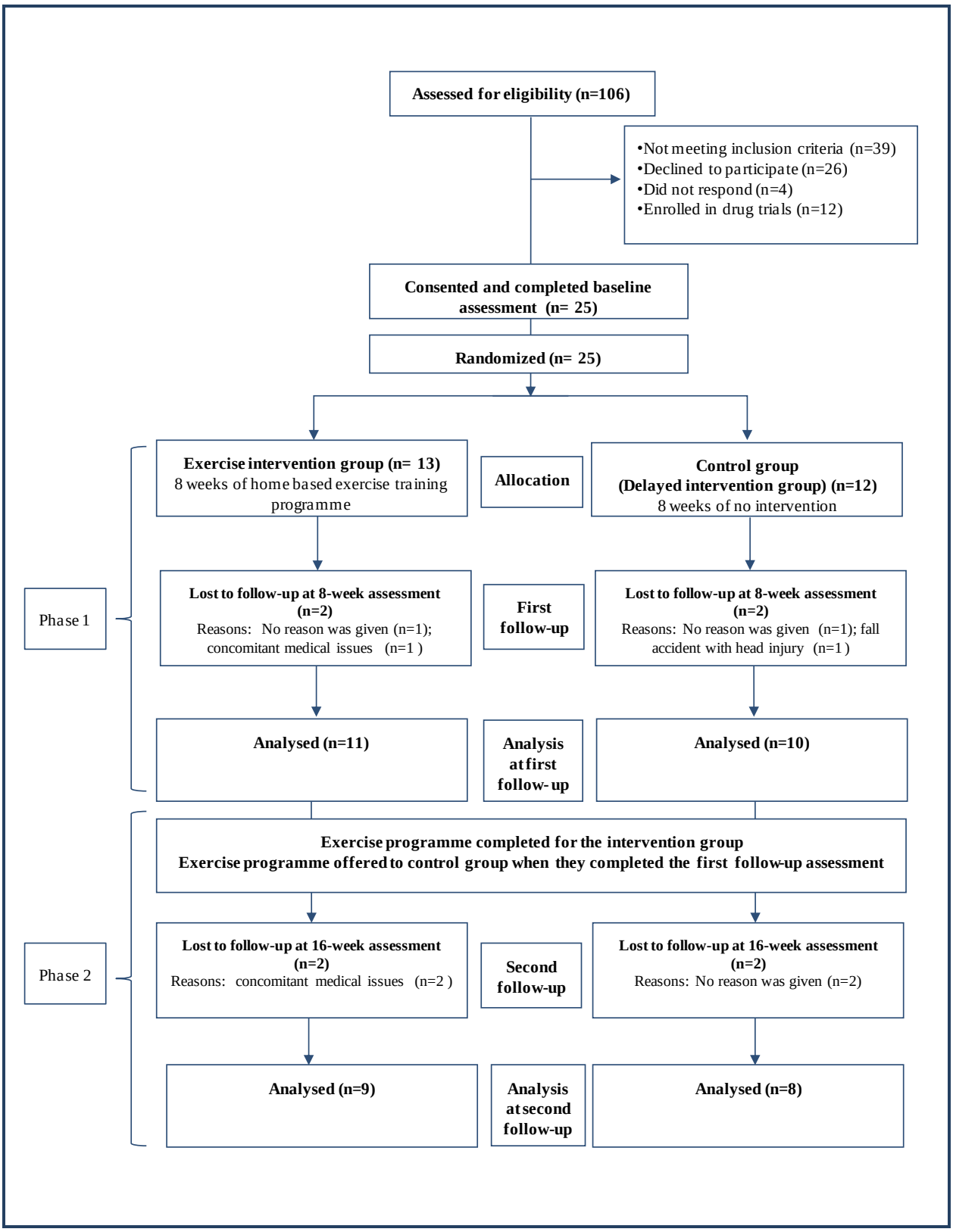
5.2.1 Participants' flow

A flowchart detailing the flow of participants through each stage of the trial is presented in Figure 5.1. In accordance with the Consolidating Standards of Reporting Trials (CONSORT) guidelines [268, 269], this figure provides details for each group on the number of participants randomised, receiving treatment, completing the study and analysed for primary outcomes at each stage of the study. Over the study recruitment period, 25 participants were recruited into the study, 13 to the early intervention group (home-based exercise intervention) and 12 to the delayed intervention group (i.e. control). Of the 106 sequential subjects who attended the recruiting clinic during the recruitment period, 39 (36.8%) were ineligible. The reasons for ineligibility fell into 3 main categories: 1) at an advanced stage of the disease (wheelchair dependent) (n=13); 2) having co-morbidities that prevented participation in regular physical activity (n=8); or 3) having cognitive or behavioural symptoms that would have limited participants from co-operating with the intervention (n=18). In addition, 12 individuals (11.3%) were considered ineligible due to their enrolment in concurrent drug trials. Of the 55 eligible subjects, 25 (45.5%) agreed to participate, which represents an overall recruitment rate of 23.6%.

Of the 25 participants allocated into either exercise or control, 21 participants (84%) attended for the first follow-up assessment at 8 weeks. Two participants from the exercise intervention (early intervention group) and 2 participants from the control (delayed intervention group) did not attend the 8- week assessment (i.e. dropped out). At the 16-week review (second follow-up) 17 (68% of allocated participants) attended for re-assessment on the primary outcome measure, with a total of 4 participants being

lost from the exercise intervention group and 4 participants from the control group. Four of the participants who did not attend the follow-up assessments (i.e. dropped out), did not give a reason for non- continuing (n = 1 exercise intervention group, n = 3 control group). The other 4 participants who have been lost to follow-up developed concomitant medical issues that prevented them from continuing the study (n=4). This included 3 participants in the exercise intervention group in which one had progressive depressive symptoms, one had progressive vocal spasm symptoms and one was hospitalized for an insertion of a percutaneous endoscopic gastrostomy tube. In addition, a participant in the control group had an accidental fall which was unrelated to the study.

Figure 5.1: Flow of participants through the study



5.2.2 Baseline characteristics of participants and adverse events

The baseline characteristics of participants who enrolled in the study are shown in Table 5.1. Nine participants (69.2%) in the early intervention exercise group and 8 participants (66.7%) in the delayed intervention group were prescribed medications for depression or mood disorders (diazepam, citalopram or olanzapine). In addition, 5 participants (38.5%) in the exercise intervention group and 6 participants (50%) in the control group were prescribed medications for managing chorea (see Appendix 6 for more details).

None of the participants in either study group reported a change in their medication type or dose during the study period. None of the participants in the control group reported any changes in their usual routine related to performing physical activities in the first 8 weeks of the study. Participants who completed the exercise programme from both arms of the study reported no incidences of falls, no increases in sustained fatigue levels or pain (there were some reports of mild muscle discomfort on initiation of the programme), and no other adverse events related to the exercise programme.

Table 5.1: Baseline characteristics for control and intervention groups (Mean ± SD)

Category	Outcome measure	Control group (n=12)	Exercise group (n=13)
Age	Age (years)	51.3 ± 16.9	54.2 ± 9.9
Gender	Gender: male, n (%)	5 (41.7)	7 (53.8)
TFC	TFC	6.0 ± 1.8	6.9 ± 2.8
Medication	Anti-psychotic drugs n (%)	8 (66.7)	9 (69.2)
	Anti-choreic drugs n (%)	6 (50)	5 (38.5)
	Others, n (%)	5 (41.6)	8 (61.5)
Disease-specific motor scale	mMS^ (unit)	22.9 ± 6.4	25.6 ± 9.6
Balance	BBS (unit)	44.9 ± 7.4	39.8 ± 12.1
	Total score of RT and SRT (s)	104.7 ± 33.8	98.9 ± 45.4
	rms-AP (m)	0.012 ± 0.006	0.013 ± 0.004
	rms-ML (m)	0.011 ± 0.005	0.011 ± 0.004
Muscle strength	MVIC of knee extensors (N.m)	235.5 ± 200.1	213.5 ± 136.4
	MVIC of knee flexors (N.m)	122.3 ± 1013.3	113.6 ± 68.2
Gait	Gait speed (cm/s)	83.1 ± 21.5	63.3 ± 37.1
	Stride time (s)	1.2 ± 0.2	1.3 ± 0.5
	Stride time CV (%)	9.8 ± 10.9	11.2 ± 6.2
Community walking	Average of daily step count	3346 ± 1838	3622 ± 2034
	Percentage of time spent at no PA	78.1 ± 10.2	78.2 ± 9.6
	Percentage of time spent at low PA	16.0 ± 8.4	16.0 ± 6.8
	Percentage of time spent at moderate PA	5.4 ± 3.1	5.3 ± 4.2
	Percentage of time spent at high level of PA	0.5 ± 0.5	0.5 ± 0.09
	Peak activity index (unit)	29.7 ± 8.4	30.2 ± 10.1
Other measures of mobility	FSST (s)	30.2 ± 20.2	30.6 ± 19.8
	TUG (s)	12.7 ± 4.5	19.4 ± 11.1
	CSST (number of repetitions)	8.2 ± 3.3	6.4 ± 3.5
Functional performance in ADL	PPT (unit)	13.5 ± 4.6	11.3 ± 6.1

TFC, Total Functional Capacity scale; mMS, modified motor score of the Unified Huntington's Disease Rating Scale; BBS, Berg Balance Scale; RT, Romberg test; SRT, Sharpened Romberg test; rms, root mean square of postural sway movement; AP, anterior-posterior; ML, medio-lateral;MVIC, Maximal Voluntary Isometric Contraction; FSST, Four Square Step Test; TUG, Timed Up and Go test; CSST, Chair Sit to Stand Test; PA, Physical Activity; CV, coefficient of variation.

Table 5.1: *continued* Baseline characteristics for control and intervention groups (Mean ± SD)

Category	Outcome measure	Control group (n=12)	Exercise group (n=13)
Health-related quality of life	PF	38.5 ± 31.5	33.3 ± 28.6
	RP	157.5 ± 48.7	129.2 ± 39.6
	BP	81.1 ± 22.9	78.7 ± 30.9
	VT	52.0 ± 14.8	47.9 ± 14.8
	GH	51.7 ± 16.9	45.3 ± 21.0
	SF	55.6 ± 31.4	59.3 ± 21.4
	RE	156.7 ± 49.8	147.2 ± 48.1
	MH	72.8 ± 15.5	62.3 ± 15.1
	PCS	58.6 ± 21.8	51.8 ± 19.5
	MCS	66.0 ± 14.0	60.2 ± 11.4
PF; Physical Functioning; RF; Role limited due to physical problems; RE; Role limited due to emotional problems; SF; Social Functioning; MH, Mental Health; VT, Vitality; BP, Bodily Pain; GH, General Health Perception; PCS, Physical Component summary; MCS, Mental Component Summary.			

5.2.3 Eight-week study outcomes

Data analysis was carried out on complete cases; data from all participants who completed the first follow-up assessments (n=11 exercise intervention group, n=10 control group) were included in the analysis. The sections below provide data from scatter plots of individual responses, categorized by group allocation followed by data obtained from statistical comparisons between study groups.

5.2.3.1 Scatter plots of individual-case responses

Figure 5.2 below shows how subjects responded to the intervention in all balance outcomes. The vast majority of participants in the intervention group (10/11) improved in the berg balance scale. However, only 5/11 subjects in the intervention group demonstrated improvement in the total score of Romberg and Sharpened Romberg tests. Similarly, only 3/11 subjects in the intervention arm of the study demonstrated some improvements in the measures of postural sway.

Figure 5.3 shows that 6/11 participants in the intervention arm demonstrated improvements in the modified UHDRS-motor score (mMS). In addition, only few participants demonstrated some improvements in measures of muscle strength.

Most of the participants in the intervention group improved in their gait characteristics (9/11 subjects improved in gait speed and stride time and 8/11 subjects improved in stride time CV) (Figure 5.4). Similarly most of participants in the intervention group (10/11) demonstrated improvements the Chair Sit to Stand Test as well as in the measure of functional performance in ADL (i.e. the Physical Performance Test) (Figure 5.6). In term of community walking, Figure 5.5 shows that all participants in the intervention group took more daily steps after the intervention period and tended to spend less time being inactive and more time being active at moderate and high levels of physical activities.

In term of health-related quality of life, most of the participants in the intervention group (10/11) demonstrated improvements in the physical function subscale. Similarly, most participants in the intervention group (6/11) demonstrated improvements in the general health perception subscale as well as the physical component summary (Figure 5.7). There were lesser trends toward improvements in the intervention group in the other subscales of the SF-36.

Figure 5.2: Scatter plots of individual cases on measures of balance

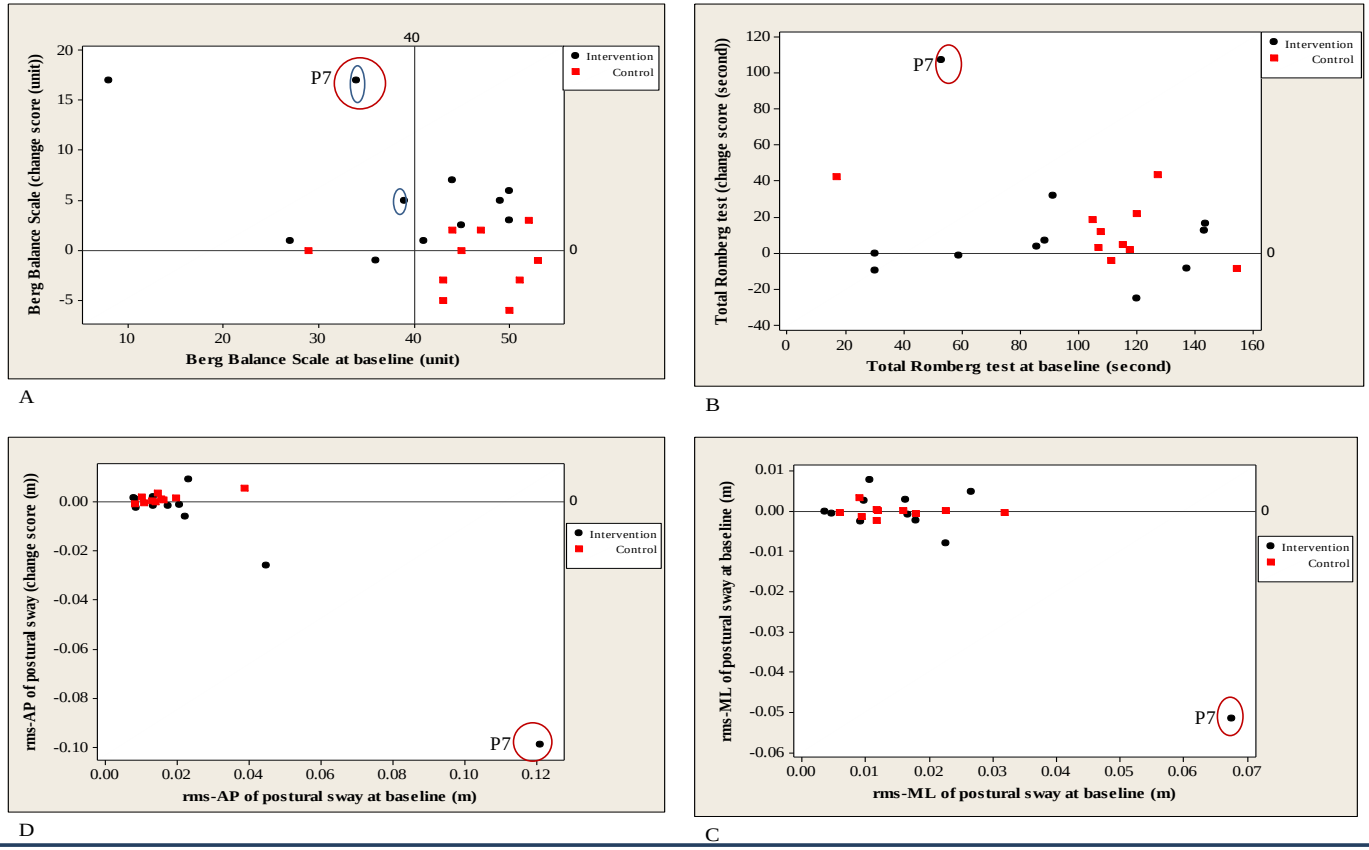
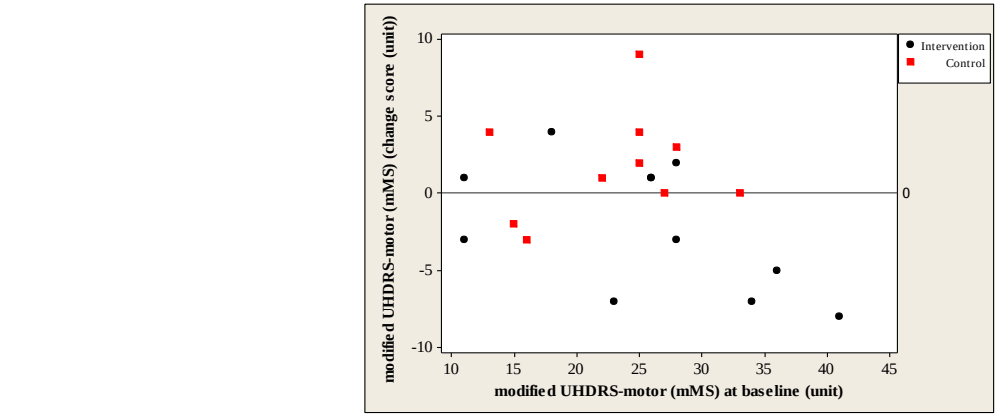
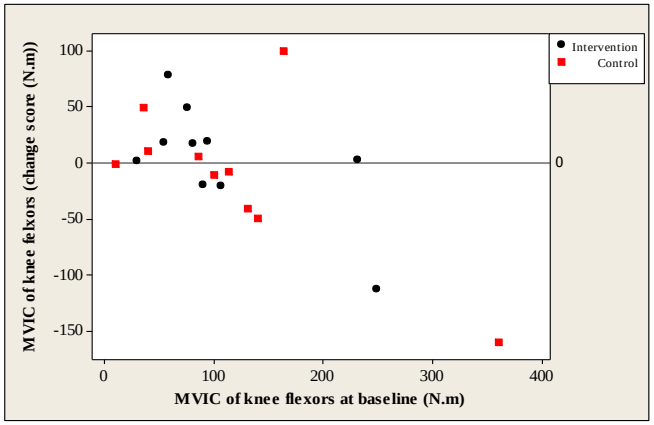


Figure 5.2: Distribution plot of balance measures at baseline against change score, categorized by group allocation. Change score is the difference between baseline and follow-up score (follow-up minus baseline). Zero line indicates no difference (i.e. no change from baseline to follow-up). Positive change in A & B (i.e. change above zero) indicates improvement in these measures at follow-up. A positive change in C & D indicates deterioration in these measures at follow-up. The score of 40 in BBS at baseline indicates those who were at risk of falls. The 2 cases in intervention group circled in blue changed from a score below 40 to above 40. Case coded P7 (in the intervention group; circled in red) showed the large change in in all outcomes.

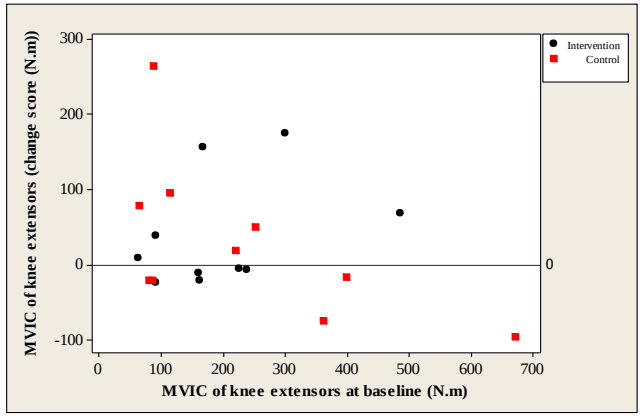
Figure 5.3: Scatter plots of individual cases of disease-motor score (mMS) and measures of muscle strength



A



C



B

Figure 5.3: Distribution plot of mMS and measures of muscle strength at baseline against change score, categorized by group allocation. Change score is the difference between baseline and follow-up score (follow-up minus baseline). Zero line indicates no difference (i.e. no change from baseline to follow-up). Positive change in A (i.e. change above zero) indicates deterioration in mMS at follow-up. A positive change in B & C indicates improvements measures of muscle strength at follow-up.

Figure 5.4: Scatter plots of individual cases of gait measures

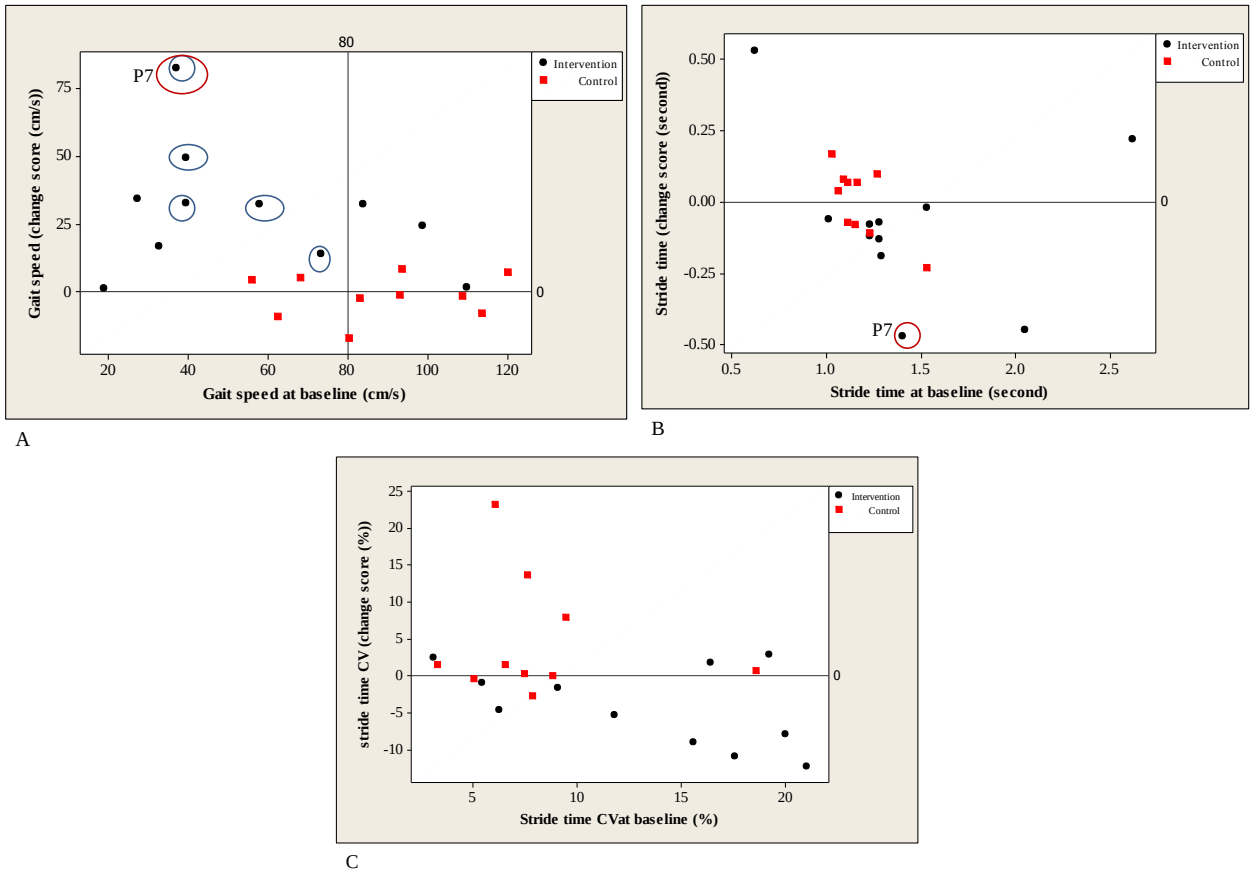


Figure 5.4: Distribution plot of gait measures at baseline against change score, categorized by group allocation. Change score is the difference between baseline and follow-up score (follow-up minus baseline). Zero line indicates no difference (i.e. no change from baseline to follow-up). Positive change in A (i.e. change above zero) indicates improvement in gait speed at follow-up. A positive change in B & C indicates deterioration in stride time and stride time CV at follow-up. The score of 80 cm./s is the minimum gait speed required for community mobility. The 5 cases in intervention group circled in blue changed from a score below 80 to above 80 cm/s. Case coded P7 (in the intervention group; circled in red) showed the large change in in all outcomes.

Figure 5.5: Scatter plots of individual responses of community walking measures

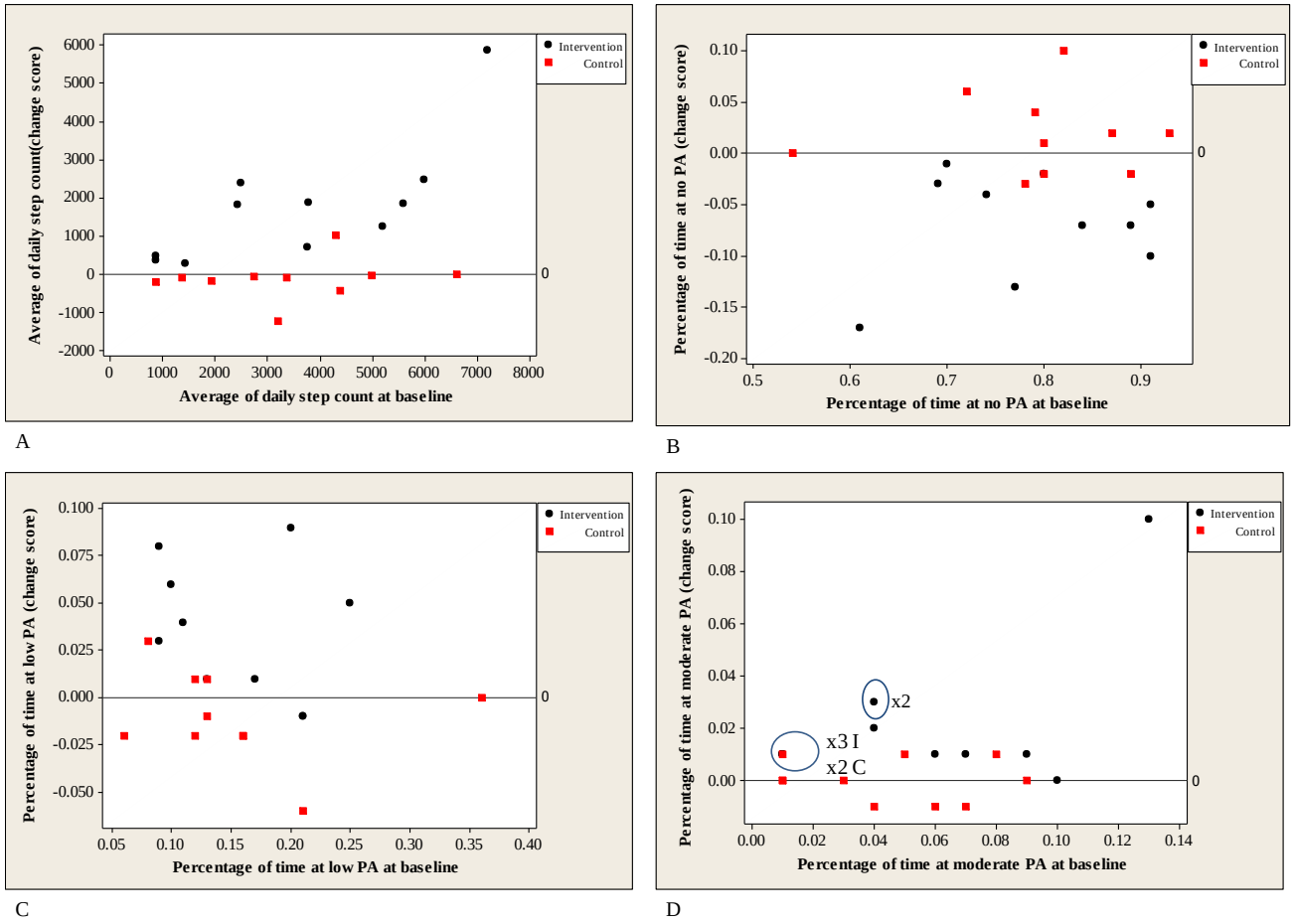
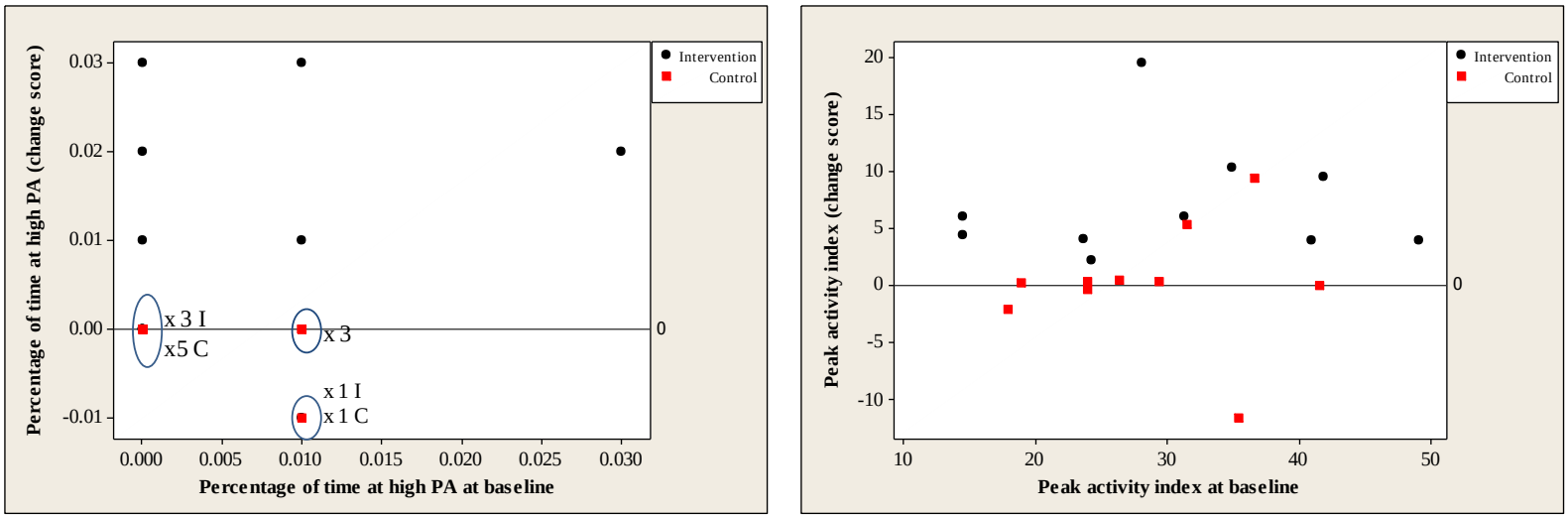


Figure 5.5: Distribution plot of community mobility measures at baseline against change score, categorized by group allocation. Change score is the difference between baseline and follow-up score (follow-up minus baseline). Zero line indicates no difference (i.e. no change from baseline to follow-up). Positive change in A, C & D (i.e. change above zero) indicates improvement at follow-up. A positive change in B indicates deterioration at follow-up. Blue circles indicate the number of cases scored on these points. I; Intervention group/ C; Control group.

Figure 5.5: *continued* Scatter plots of individual responses of community walking measures



E F

Figure 5.5: Distribution plot of community mobility measures at baseline against change score, categorized by group allocation. Change score is the difference between baseline and follow-up score (follow-up minus baseline). Zero line indicates no difference (i.e. no change from baseline to follow-up). Positive change in E & F (i.e. change above zero) indicates improvement at follow-up. Case coded P7 (in the intervention group; circled in red) showed the large change in these outcomes. Case coded P7 (in the intervention group; circled in red) showed the large change in in these outcomes. Blue circles indicate the number of cases scored on these points. I; Intervention group/ C; Control group.

Figure 5.6: Scatter plots of individual cases of mobility measures and function

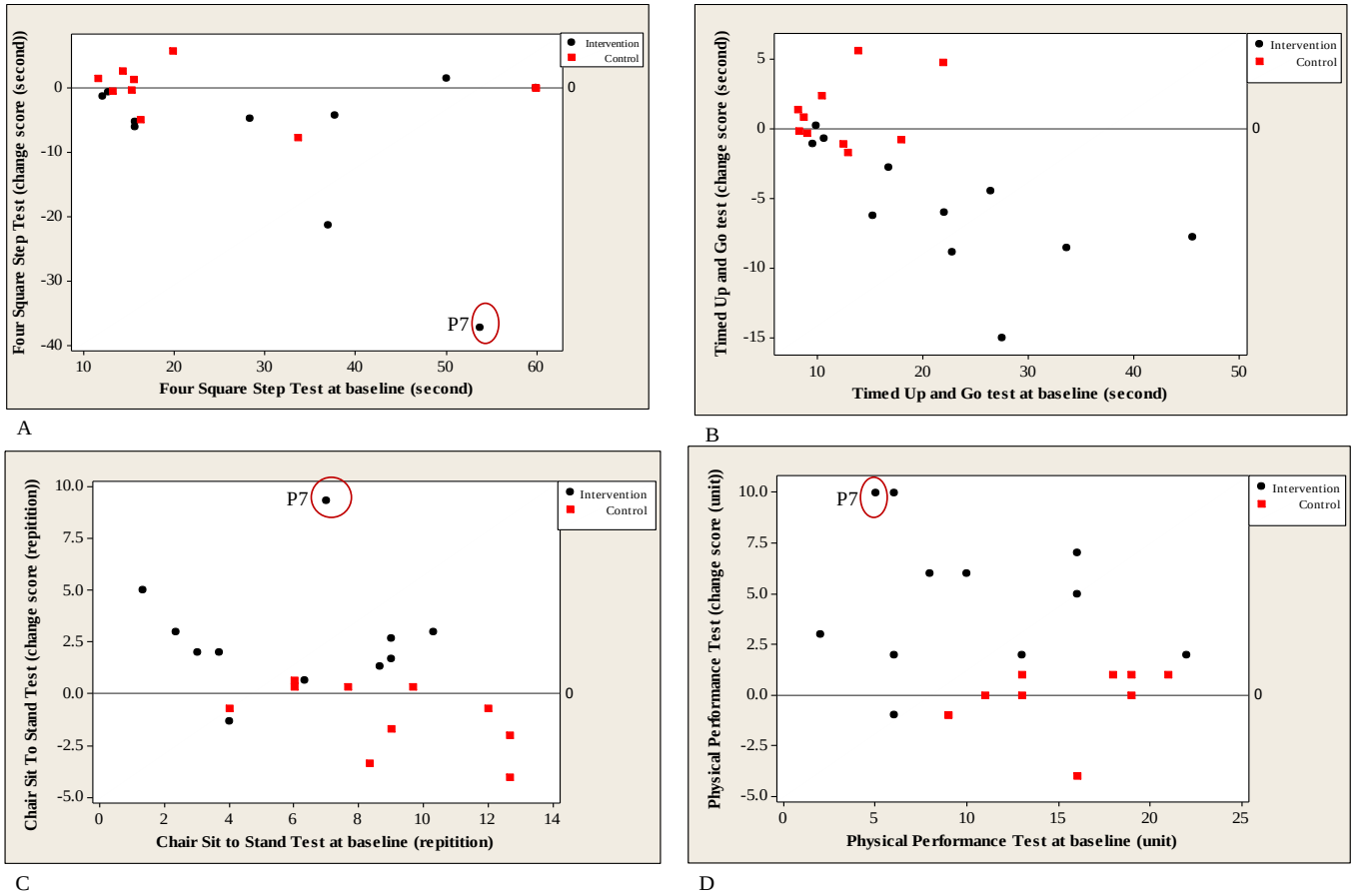
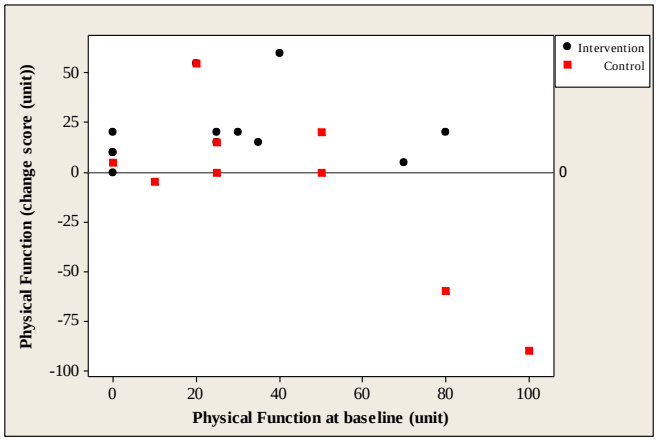
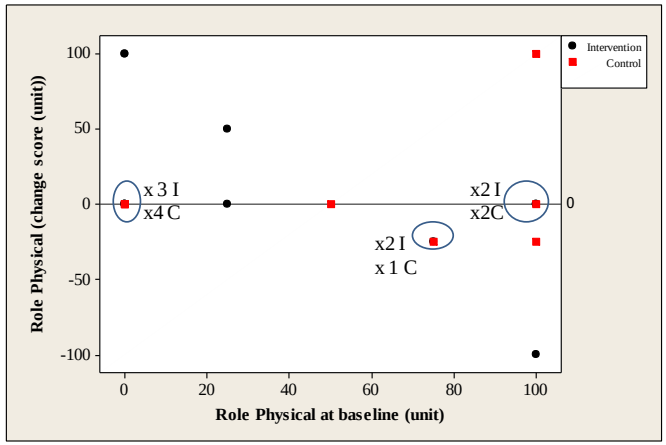


Figure 5.6: Distribution plot of mobility measures and function at baseline against change score, categorized by group allocation. Change score is the difference between baseline and follow-up score (follow-up minus baseline). Zero line indicates no difference (i.e. no change from baseline to follow-up). Positive change in A & B (i.e. change above zero) indicates deterioration in FSST and TUG at follow-up. A positive change in C & D indicates improvement in CSTS and PPT at follow-up. Case coded P7 (in the intervention group; circled in red) showed the large change in in most outcomes.

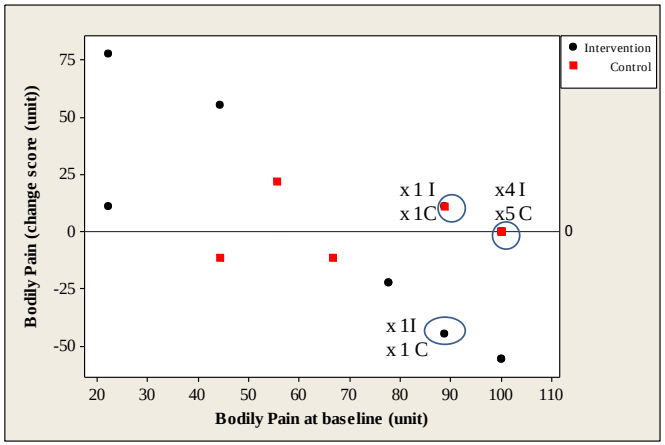
Figure 5.7: Scatter plots of individual responses of measures of health-related quality of life



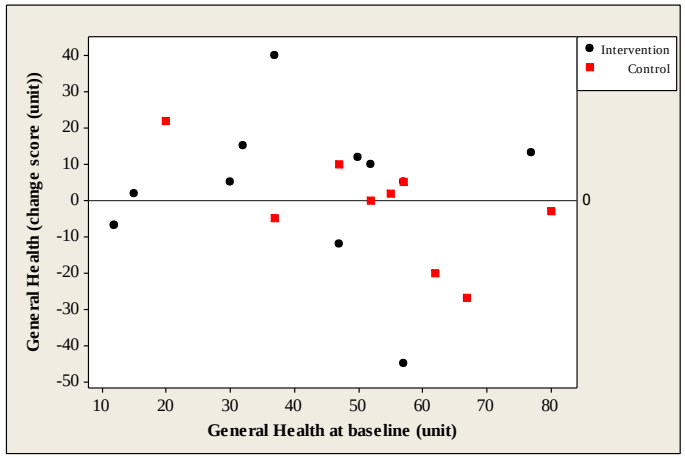
A



B



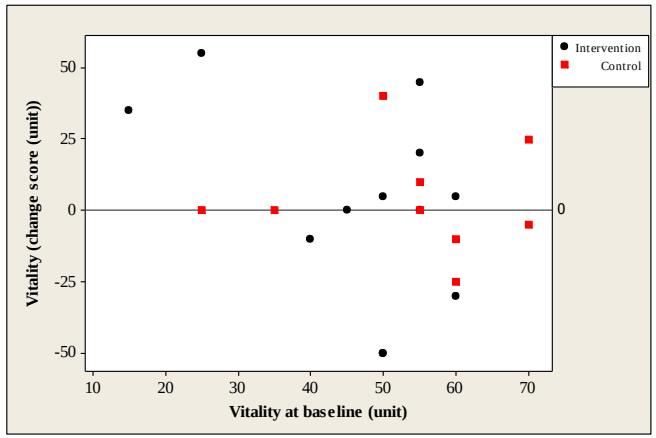
C



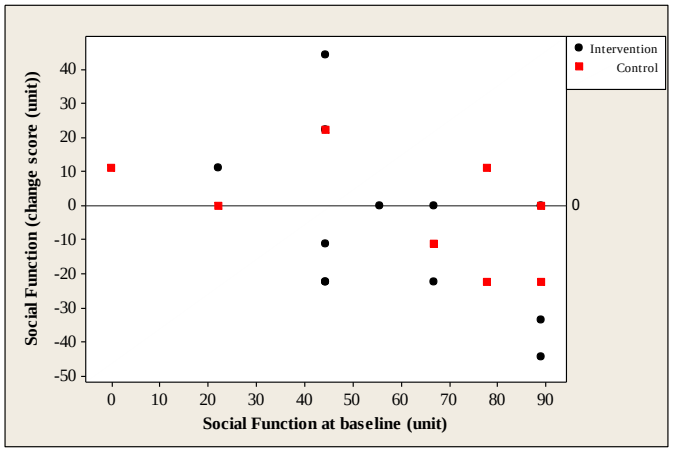
D

Figure 5.7: Distribution plot of health-related quality of life measures at baseline against change score, categorized by group allocation. Change score is the difference between baseline and follow-up score (follow-up minus baseline). Zero line indicates no difference (i.e. no change from baseline to follow-up). Positive change in A,B,C & D (i.e. change above zero) indicates improvement at follow-up. Blue circles indicate the number of cases scored on these points. I; Intervention group/ C; Control group.

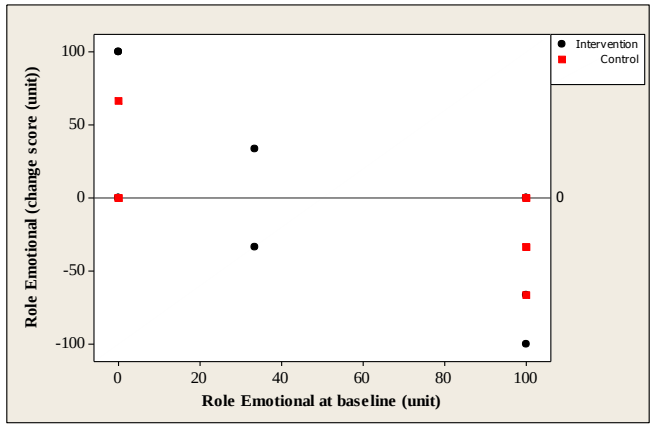
Figure 5.7: *continued* Scatter plots of individual responses of measures of health-related quality of life



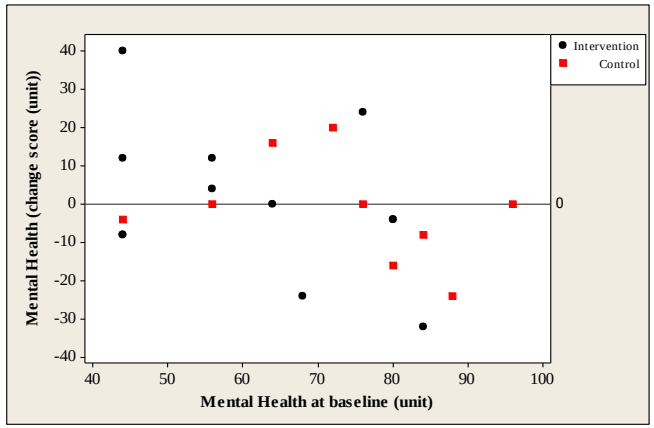
E



F



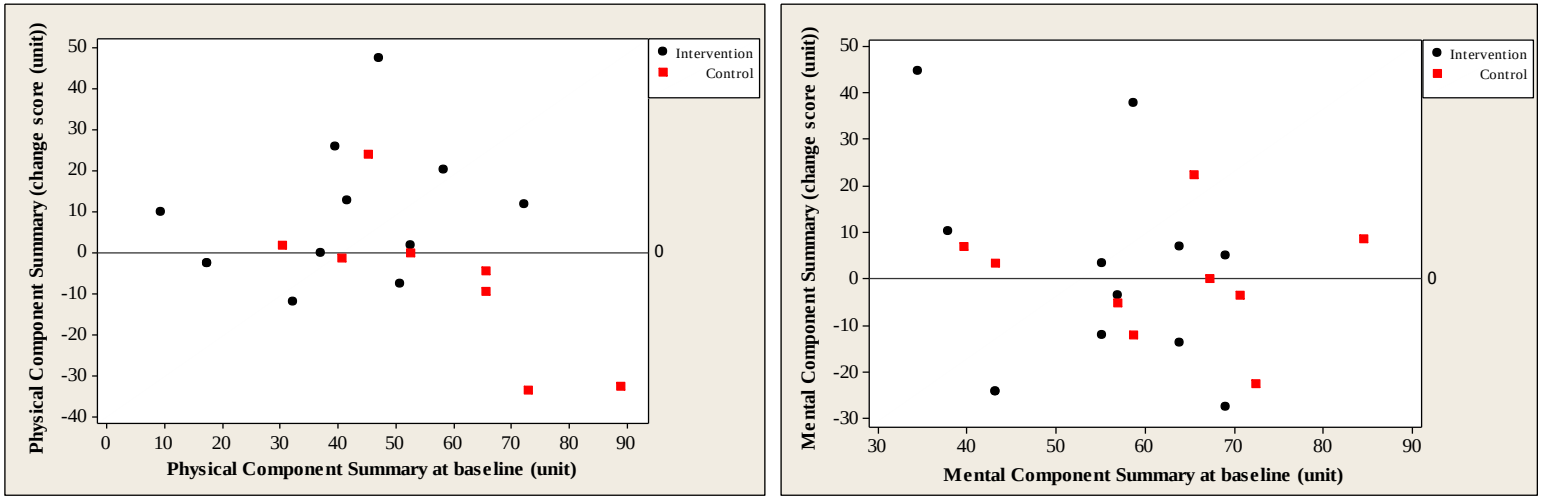
G



H

Figure 5.7: Distribution plot of health-related quality of life measures at baseline against change score, categorized by group allocation. Change score is the difference between baseline and follow-up score (follow-up minus baseline). Zero line indicates no difference (i.e. no change from baseline to follow-up). Positive change in E,F,G & H (i.e. change above zero) indicates improvement at follow-up. Blue circles indicate the number of cases scored on these points. I; Intervention group/ C; Control group.

Figure 5.7*: continued* Scatter plots of individual responses of measures of health-related quality of life



I J

Figure 5.7: Distribution plot of health-related quality of life measures at baseline against change score, categorized by group allocation. Change score is the difference between baseline and follow-up score (follow-up minus baseline). Zero line indicates no difference (i.e. no change from baseline to follow-up). Positive change in E,F,G & H (i.e. change above zero) indicates improvement at follow-up. Blue circles indicate the number of cases scored on these points. I; Intervention group/ C; Control group.

5.2.3.2 Group comparisons

5.2.3.2.1 Primary outcome

At the first follow-up assessment, there was a significant difference between groups on the mean adjusted score of stride time CV (mean difference - 6; 95% CI (-11.5, -0.6); effect size=1.2) (Table 5.2).

Table 5.2: The primary outcome measure (stride time CV) at baseline and first follow-up for complete cases (n=21)

Baseline scores (Mean ± SD)			**First follow-up (Mean ± SD)**		**Differences between groups at first follow-up adjusted for baseline measures**		
Outcome measure	Control group (n=10)	Exercise intervention group (n=11)	Control group (n=10)	Exercise intervention group (n=11)	Mean difference (95% confidence interval)	p-value	Effect size
Stride time CV (%)	6.4 ± 2.6	11.6 ± 5.6	9.9 ± 5.8	9.7 ± 7.9	-6 (-11.5, -0.6)	0.03	1.2
CV; coefficient of variation.							

5.2.3.2.2 Secondary outcomes

5.2.3.2.2.1 Measures of physical impairments in body structures and functions

5.2.3.2.2.1.1 The disease-specific motor scale

Significant differences were observed between groups on the mean adjusted scores of the modified motor score of the UHDRS (mMS) (mean difference -4.5 units; 95% CI (-8.8, -0.2); effect size= 1.1) (Table 5.3).

Table 5.3: Disease-specific motor score at baseline and first follow-up upon complete cases

Baseline scores (Mean ± SD)			**First follow-up (Mean ± SD)**		**Differences between groups at first follow-up adjusted for baseline measures**		
Outcome measure	Control group (n=10)	Exercise intervention group (n=11)	Control group (n=10)	Exercise intervention group (n=11)	Mean difference (95% confidence interval)	p-value	Effect size
mMS (unit)	23.6 ± 6.5	23.8 ± 10.5	25.9 ± 7.6	21.5 ± 8.7	-4.5 (-8.8, -0.2)	0.04	1.1
mMS; modified motor score of the Unified Huntington's Disease Rating Scale.							

5.2.3.2.2.1.2 Measures of balance

Significant differences between groups were observed on some of the measures of balance at the first follow-up (Table 5.4). Significant differences between groups were observed on the mean adjusted score of the Berg Balance Scale (BBS) (mean difference 5.4 units; 95% CI (1.0, 9.9); effect size= 1.4). However, there was no significant difference between groups on the adjusted mean scores of the total score of the Romberg and Sharpened Romberg (RT & SRT) tests (mean difference; -5.5 s; 95% CI (-31.7, 20.7); effect size=0.1), the root mean square of postural sway in the anterior-posterior direction (mean difference; 0.001 m; 95% CI (-0.001, 0.004); effect size=0.4) and the root mean square of postural sway in the medio-lateral direction (mean difference; 0.001 m; 95% CI (-0.004, 0.005); effect size=0.3).

Table 5.4: Measures of balance at baseline and first follow-up for complete cases (n=21)

Baseline scores (Mean ± SD)			**First follow-up (Mean ± SD)**		**Differences between groups at first follow-up adjusted for baseline measures**		
outcome measure	Control group (n=10)	Exercise intervention group (n=11)	Control group (n=10)	Exercise intervention group (n=11)	Mean difference (95% confidence interval)	p-value	Effect size
BBS (unit)	45.7 ± 6.9	38.5 ± 12.4	44.7 ± 7.5	44.2 ± 10.7	5.4 (1.0, 9.9)	0.01	1.4
Total score of RT and SRT (s)	108.3 ± 35.2	89.2 ± 42.9	122.1 ± 29.2	101.5 ± 49.9	-5.5 (-31.7, 20.7)	0.7	0.1
rms-AP (m)	0.012 ± 0.006	0.013 ± 0.004	0.014 ± 0.006	0.013 ± 0.004	0.001 (-0.001, 0.004)	0.3	0.4
rms-ML (m)	0.011± 0.005	0.011± 0.004	0.014 0.006	0.013 0.004	0.001 (-0.004, 0.005)	0.8	0.3
BBS, Berg Balance Scale; RT and SRT, Romberg and Sharpened Romberg tests; rms, root mean square of postural sway movement; AP, anterior-posterior; ML, medio-lateral.							

5.2.3.2.2.1.3 Measures of muscle strength

There were no significant differences between groups on the mean adjusted scores of the Maximal Voluntary Isometric Contraction (MVIC) of knee extensors (mean difference; 16.1N.m; 95% CI (-179, 211.2); effect size= 0.1) and for the MVIC of knee flexors (mean difference; -3.1 N.m; 95% CI (-88.3, 82.2); effect size=0.3) (Table 5.5).

Table 5.5: Measures of muscle strength at baseline and first follow-up upon complete cases (n=21)

Baseline scores (Mean ± SD)			**First follow-up (Mean ± SD)**		**Differences between groups at first follow-up adjusted for baseline measures**		
Outcome measure	Control group (n=10)	Exercise intervention group (n=11)	Control group (n=10)	Exercise intervention group (n=11)	Mean difference (95% confidence interval)	p-value	Effect size
MVIC of knee extensors (N.m)	245.5 ± 209.4	198.1 ± 125.7	243 ± 136.3	292.1 ± 204	16.1 (-179, 211.2)	0.8	0.1
MVIC of knee flexors (N.m)	117.8 ± 113.3	105.9 ± 70.1	94.2 ± 76.1	111.7 ± 35.5	3.1 (-88.3, 82.2)	0.9	0.3
MVIC, Maximal Voluntary Isometric Contraction.							

5.2.3.2.2.2 Measures of Activity

5.2.3.2.2.2.1 Walking- other measures of gait

Significant differences between groups were also observed on the mean adjusted scores of gait speed (mean difference; 26.2 cm/s; 95% CI (7.2, 45.3); effect size=1.7) (Table 5.6). There were no significant differences, however, between groups on the adjusted mean scores of stride time (mean difference; 0.05 s; 95% CI (-0.3, 0.2); effect size=0.7).

Table 5.6: Measures of gait at baseline and first follow-up for complete cases (n=21)

Baseline scores (Mean ± SD)			**First follow-up (Mean ± SD)**		**Differences between groups at first follow-up adjusted for baseline measures**		
Outcome measure	Control group (n=10)	Exercise intervention group (n=11)	Control group (n=10)	Exercise intervention group (n=11)	Mean difference (95% confidence interval)	p-value	Effect size
Gait speed (cm/s)	87.8 ± 21.9	56.5 ± 30.7	86.5 ± 24.1	85.4 ± 32.5	26.2 (7.2, 45.3)	0.01	1.7
Stride time (s)	1.2 ± 0.1	1.4 ± 0.5	1.2 ± 0.1	1.3 ± 0.5	0.05 (-0.3,0.2)	0.7	0.7

5.2.3.2.2.2.2 Walking- measures of community walking

Significant differences were observed on all the measures of community walking at the first follow-up (Table 5.7). Significant differences were observed between groups on the mean adjusted scores of the average daily step count (mean difference1805; 95% CI (890, 2720); effect size=1.6), and the peak activity index (mean difference 6.7; 95% CI (1.4, 12.1); effect size=1.0). Similarly, significant differences between groups were also observed on the adjusted mean scores of the percentage of time spent inactive (mean difference -0.08; 95% CI (-0.14, -0.04); effect size=1.3) and on percentages of time spent at low (mean difference 0.05; 95% CI (0.01, 0.08); effect size=1.1), moderate (mean difference 0.02; 95% CI (0.001, 0.04); effect size=1.0) and high level of physical activities (mean difference 0.01; 95% CI (0.002, 0.02); effect size=0.9).

Table 5.7: Measures of community walking at baseline and first follow-up for all complete cases (n=21)

Baseline scores (Mean ± SD)			**First follow-up (Mean ± SD)**		**Differences between groups at first follow-up adjusted for baseline measures**		
Outcome measure	Control group (n=10)	Exercise intervention group (n=11)	Control group (n=10)	Exercise intervention group (n=11)	Mean difference (95% confidence interval)	p-value	Effect size
Average of daily step count	3376 ± 1758	3596 ± 2176	3249 ± 1940	5355 ± 3511	1805 (890, 2720)	0.001	1.6
Percentage of time spent at no PA	79.1 ± 11.0	79.2 ± 10.0	79.9 ± 12.0	71.8 ± 12.1	-8.0 (-14.0, -4.0)	0.001	1.3
Percentage of time spent at low PA	15.9 ± 9.0	15.8 ± 6.0	14.1 ± 9.0	2.2 ± 6.0	5.0 (1.0, 8.0)	0.007	1.1
Percentage of time spent at moderate PA	5.0 ± 3.0	6.0 ± 4.0	5.0 ± 3.0	8.0 ± 6.0	2.0 (1.0, 4.0)	0.04	1.0
Percentage of time spent at high level of PA	0.4 ± 0.5	0.6 ± 0.9	0.3 ± 0.5	2.0 ± 2.0	1.0 (0.2, 2.0)	0.03	0.9
Peak activity index (unit)	29.1 ± 8.0	30.3 ± 11.6	29.3 ± 10.2	37.3 ± 12.9	6.7 (1.4, 12.1)	0.02	1.2
PA, Physical Activity.							

5.2.3.2.2.2.3 Other measures of mobility

Significant differences between groups were observed on the mean adjusted scores of the chair sit to stand test (CSST) (mean difference 3.4; 95% CI (1.0-5.7); effect size= 1.7) (Table 5.8). However, there were no significant differences between groups on the mean adjusted scores of the four square step test (FSST) (mean difference; -6.3 s; 95% CI (-14.8, 2.2); effect size= 0.8) and the Timed Up and Go (TUG) test (mean difference; -2.6 s; 95% CI (-6.9, 1.7); effect size=0.9).

Table 5.8: Other measures of mobility at baseline and first follow-up for complete cases (n=21)

Baseline scores (Mean ± SD)			**First follow-up (Mean ± SD)**		**Differences between groups at first follow-up adjusted for baseline measures**		
Outcome measure	Control group (n=10)	Exercise intervention group (n=11)	Control group (n=10)	Exercise intervention group (n=11)	Mean difference (95% confidence interval)	p-value	Effect size
FSST (s)	25.9 ± 18.9	34.8 ± 19.1	25.7 ± 18.7	27.6 ± 20.4	-6.3 (-14.8, 2.2)	0.1	0.8
TUG (s)	12.8 ± 4.7	20.6 ± 11.6	13.7 ± 5.9	16.8 ± 9.2	-2.6 (-6.9, 1.7)	0.2	0.9
CSST	8.8 ± 3.0	5.9 ± 3.1	7.7 ± 2.5	8.6 ± 4.2	3.4 (1.0-5.7)	0.008	1.7
FSST; Four Square Step test; TUG, Timed Up and Go test; CSST; Chair Sit to Stand test.							

5.2.3.2.2.2.4 Measures of functional performance in ADL

Significant differences were observed between groups on the mean adjusted scores for the physical performance test (PPT) (mean difference 4.8; 95% CI (2.0, 7.7); effect size=1.8) (Table 5.9).

Table 5.9: The measures of functional performance in ADL at baseline and first follow-up upon complete cases (n=21)

Baseline scores (Mean ± SD)			**First follow-up (Mean ± SD)**		**Differences between groups at first follow-up adjusted for baseline measures**		
Outcome measure	Control group (n=10)	Exercise intervention group (n=11)	Control group (n=10)	Exercise intervention group (n=11)	Mean difference (95% confidence interval)	p-value	Effect size
PPT (unit)	14.8 ± 4.4	10.0 ± 6.0	14.6 ± 5.1	14.7 ± 6.6	4.8 (2.0,7.7)	0.002	1.8
PPT, Physical Performance Test.							

5.2.3.2.2.3 Measures of participation

5.2.3.2.2.3.1 Measures of health-related quality of life

No significant differences were observed in any of the subscales of the SF-36 (effect sizes ranged from 0.08 to 0.9) (Table 5.10).

Table 5.10: Measures of health related quality of life at baseline and first follow-up upon complete cases (n=21)

Baseline scores (Mean ± SD)			**First follow-up (Mean ± SD)**		**Differences between groups at first follow-up adjusted for baseline measures**		
Outcome measure	Control group (n=10)	Exercise intervention group (n=11)	Control group (n=10)	Exercise intervention group (n=11)	Mean difference (95% confidence interval)	p-value	Effect size
PF	40.0 ± 33.1	40.0 ± 30.3	36.9 ± 26.4	51.4 ± 33.7	21.0 (-8.9, 51.0)	0.15	0.8
RF	63.9 ± 54.6	54.5 ± 53.4	41.7 ± 43.3	40.9 ± 45.1	9.9 (-33.7, 53.4)	0.63	0.6
BP	53.0 ± 17.3	75.8 ± 28.0	85.2 ± 24.8	74.7 ± 29.4	-8.2 (-33.9, 17.5)	0.50	0.1
VT	53.3 ± 15.0	48.2 ± 18.9	57.2 ± 24.3	53.2 ± 27.4	-0.9 (-26.3, 24.4)	0.90	0.1
GH	83.9 ± 22.9	48.4 ± 19.4	51.2 ± 13.8	45.8 ± 27.5	2.4 (-15.7, 20.6)	0.70	0.3
SF	59.0 ± 30.9	56.6 ± 30.0	56.8 ± 26.3	54.5 ± 21.9	-2.4 (-20.5, 15.6)	0.80	0.4
RE	55.6 ± 52.7	51.5 ± 50.3	48.1 ± 41.2	54.5 ± 47.8	7.9 (-31.8, 47.7)	0.70	0.08
MH	73.3 ± 16.4	72.0 ± 14.9	71.6 ± 17.6	65.1 ± 18.4	-1.3 (-17.7, 15.3)	0.80	0.2
PCS	53.2 ± 22.5	49.4 ± 21.8	50.9 ± 12.6	51.5 ± 27.4	13.8 (-6.1, 32.5)	0.10	0.9
MCS	62.1 ± 14.2	59.1 ± 14.5	61.9 ± 18.2	51.7 ± 21.4	-0.2 (-19.8, 19.3)	0.90	0.2

PF; Physical Functioning; RF; Role limited due to physical problems; RE; Role limited due to emotional problems; SF; Social Functioning; MH, Mental Health; VT, Vitality; BP, Bodily Pain; GH, General Health Perception; PCS, Physical Component summary; MCS, Mental Component Summary.

5.2.3.2.3 Summary of results of 8-week study outcome

A summary of the adjusted mean differences between groups at the first follow-up assessment is presented in Table 5.11 along with the minimal detectable change (MDC_{95}) values which were previously calculated in Chapter 4. Significant differences between groups on the BBS, stride time CV, gait speed, CSST and PPT were larger than their corresponding MDC_{95} values. This suggests that the observed differences on these outcomes are likely to be attributed to real changes in the outcomes rather than to measurement errors or natural variations in the testing.

It should be noted, however, that the MDC_{95} values have not been calculated in this study for the mMS and the measures of community walking. Therefore, conclusions about whether changes in these outcomes are clinically significant cannot be confirmed.

Table 5.11: Summary of results of the adjusted mean differences at first follow-up along with the minimal detectable change (MDC_{95}) values calculated in Chapter 4

Domain	Category	Outcome measure	MDC_{95}	Adjusted mean differences at first follow-up
Body structure and function	Disease-specific motor score	mMS (unit)*	NR	4.5
	Balance	BBS (unit)*	3.9	5.4
		Total score of RT and SRT (s)	39.6	5.5
		rms-AP (m)	0.008	0.001
		Rms-ML (m)	0.005	0.001
	Muscle strength	MVIC of knee extensors (N.m)	155.5	16.1
		MVIC of knee flexors (N.m)	98.8	3.1
Activity	Gait	Gait speed (cm/s)*	22.5	26.2
		Stride time (s)	0.22	0.05
		Stride time CV (%)*	3.6	6.0
	Community walking	Average of daily step count*	NR	1805
		Percentage of time spent at no PA*	NR	8.0
		Percentage of time spent at low PA*	NR	5.0
		Percentage of time spent at moderate PA*	NR	2.0
		Percentage of time spent at high level of PA*	NR	1.0
		Peak activity index (unit)*	NR	6.7
	Other measures of mobility	FSST (s)	19.3	6.3
		TUG (s)	16.3	2.6
		CSST (number of repetitions)*	2.2	3.4
	Functional performance in ADL	PPT (unit)*	2.2	4.8

*Statistically significant differences between groups at follow-up adjusted for baseline differences ($p<0.05$); NR, Not Reported.

mMS, modified motor score of the Unified Huntington's Disease Rating Scale; BBS, Berg Balance Scale; RT, Romberg test; SRT, Sharpened Romberg test; rms, root mean square of postural sway movement; AP, anterior-posterior; ML, medio-lateral;MVIC, Maximal Voluntary Isometric Contraction; FSST, Four Square Step Test; TUG, Timed Up and Go test; CSST, Chair Sit to Stand Test; PA, Physical Activity.

Table 5.11*: continued* Summary of results of the adjusted mean differences at first follow-up along with the minimal detectable change (MDC95) values calculated in Chapter 4

Domain	Category	Outcome measure	MDC_{95}	Adjusted mean differences at first follow-up
Participation	Health-related quality of life	PF	52.1	21.0
		RF	66.8	9.9
		BP	62.1	-8.2
		VT	32.9	-0.9
		GH	33.5	2.4
		SF	39.5	-2.4
		RE	80.1	7.9
		MH	28.8	-1.3
		PCS	25.5	13.8
		MCS	28.8	-0.2

PF; Physical Functioning; RF; Role limited due to physical problems; RE; Role limited due to emotional problems; SF; Social Functioning; MH, Mental Health; VT, Vitality; BP, Bodily Pain; GH, General Health Perception; PCS, Physical Component summary; MCS, Mental Component Summary.

5.2.4 Sixteen-week study outcomes

Data for the primary outcome (stride time CV) were collected at the second follow-up (16-week assessment). These data were collected from 17 of the participants (9 from the exercise intervention group (the early intervention group) and 8 from the control group. Descriptive data in the primary outcome are shown in Table 5.12.

Table 5.12: Mean scores of primary outcome (stride time CV) for different periods upon complete cases at the second follow-up assessments (n=17)

	Baseline (Mean ± SD)	First follow-up (8-week assessment) (Mean ± SD)	Second follow-up (16-week assessment) (Mean ± SD)
Exercise intervention group (n=9)	10.6 ± 5.2	6.9 ± 4.9	6.5 ± 3.4
Control group (n=8)	6.3 ± 2.7	8.7 ± 5.0	5.9 ± 2.9

After the initial 8 weeks, 5 subjects out of the 9 in the exercise intervention group (i.e. the early intervention group) reported continuing to do the exercise programme for another 8 weeks after the first follow-up assessment (i.e. after formal input was ceased). Descriptive data in the primary outcome for those who continued to exercise and those who stopped

the exercise programme are shown in Table 5.13. Descriptive data suggest that participants who continued to exercise have a greater overall reduction in the stride time CV relative to the participants who stopped the exercise programme.

Table 5.13: Within-group differences in the primary outcome (stride time CV) at the first and second follow-up assessments

	Mean ± SD			**Baseline to 8-week (i.e. baseline to first follow-up)**	**8 to 16-weeks (i.e. first to second follow-up)**
	Baseline	8 weeks	16 weeks	Difference (95% CI)	Difference (95% CI)
Exercise intervention group CE (n=5)	9.7 ± 6.3	6.8 ± 3.9	4.8 ± 4.5	-2.7 (-10.9, 3.7)	-1.6 (-5.8, 5.4)
Exercise intervention group DE (n=4)	11.5 ± 5.7	7.9 ± 4.5	7.0 ± 5.3	-3.6 (-8.8, 5.4)	-0.9 (-3.1, 9.7)
Control group (n=8)	6.3 ± 2.7	8.7 ± 5.0	5.9 ± 2.9	2.4 (0.08, 4.7)	-2.7 (-4.9, -0.67)
CE, Continued to exercise; DE, Discontinued exercise					

5.3 Discussion

5.3.1 Eight-week study outcomes

5.3.1.1 Measures of physical impairments in body structures and functions

5.3.1.1.1 The disease-specific motor scale

In this study, 6 /11 participants in the intervention group improved in the disease-specific motor score (mMS) (see Figure 5.3). The effect size was large and a significant difference between groups was observed on this outcome. It should however be noted that the amount of deterioration in the control group in this outcome was unusually high given the duration of the study (i.e. 8 weeks); hence this results should be interpreted with some caution. Future research is required to further explore this finding.

The possible improvement in the mMS reported here is consistent with the data obtained from a previously conducted single-case study of a home-based exercise programme in which there was an improvement in the total score of the UHDRS-motor (MS) [2]. Taking into account the progressive neurodegenerative nature of HD particularly in the motor domain (i.e. annual decline in the total MS is evident in HD [270, 271]), the finding of

possible motor improvements reflected by improvement in the mMS score in most of the participants in the exercise intervention group is important. This finding has implications and provides indications that exercise interventions may play a role in addressing motor impairments, maintaining independence in activity of daily living and potentially enabling the subjects with HD to achieve a longer period of stabilization.

The possible improvement reported in the mMS in the intervention group may be better understood in the context of the items of the mMS and their relationship to the content of the exercise programme. The mMS includes items that evaluate dynamic balance, timing of movement, coordination and rigidity. The use of the exercise DVD provided demonstrations that were augmented by visual and verbal cues. These cues may have been useful in helping subjects to control their speed of movement[2]; thus improving muscle timing and coordination. The performance of the task-specific activities included in the exercise programme may have been useful in addressing impairments in dynamic balance [152]. Additionally, the range of flexibility and general strengthening exercises which were crucial parts of the exercise programme may have been beneficial in improving overall fitness level and enhancing sensory feedback from proprioceptive which may have further improved balance [2, 37]. The combination of the flexibility and strengthening exercises may also have provided a beneficial effect in reducing rigidity by producing centrally neural adaptations in the excitability of the α- motor neurons and the magnitude of the output from descending central pathways [272].

Overall the reported improvements in the mMS in the intervention group provide indications that disease-specific motor impairments, such as deficits in timing of movement and balance and lack of coordination, are potentially modifiable by exercise interventions in people with HD. Ameliorations in any or some of these impairments may improve accuracy and reduce variability of movement [2, 37, 111] which in part explains the large observed effects in improving the gait variability, the other measures of mobility and some measures of balance that were reported in this study.

5.3.1.1.2 Measures of balance

Out of the 3 measures of balance evaluated in this study, the vast majority of participants (10/11) improved in the berg balance scale but not on the total score of Romberg and sharpened Romberg tests and measures of postural sway (Figure 5.2). In addition,

statistical analysis revealed significant differences between groups were only for the Berg Balance Scale (BBS). The improvement in the BBS reported here is consistent with data obtained from 2 previous studies that have examined the effects of exercise on BBS in people with HD [2, 76]. In an individual-case control study of 12 subjects with early to mid stage HD, a 6-week clinic-based exercise programme resulted in significantly higher scores on the BBS after the exercise programme when compared to the baseline scores [76]. Similarly, in a single case report of an individual with mid stage HD, a 14-week home-based exercise programme demonstrated an improvement in the BBS of 9 points [2].

The reported mean change in the BBS of 5.4 in this study is larger than the Minimal Detectable Change (MDC_{95}) value of 4 (Chapter 4). This suggests that the improvement reported on this measure of balance is more likely to be due to real change as a consequence of the exercise intervention, rather than to measurement error. This result is particularly important in that improvement in the BBS may reflect a better ability to remain independent and mobile in HD. The BBS has been found previously to be useful in predicting the probability of falls in HD, with a score of less than 40 identified as the threshold for risk of falls [45]. In this study, two participants in the intervention group who were below this threshold of risk of falls (i.e. BBS score was less than 40) increased scores on the BBS from below 40 to above 40 corresponding to a change from the 'at risk of fall' category to that of 'low risk for falls' (Figure 5.2). This finding highlights the potential role of exercise in improving some of the disease underlying impairments which could be linked to obtaining a better functional status despite the presence of a degenerative neurological disease.

Although subjects in the exercise programme improved significantly in their BBS scores, there were no significant improvements on the other measures of balance (the total score of the Romberg (RT) and Sharpened Romberg (SRT) tests and the root mean square values of postural sway during quiet standing). The effect sizes for these outcomes (i.e. total score of the RT and SRT and root mean square of postural sway) were small. This was further reflected by the plots of individual cases particularly in the case of root mean square of postural sway in which only 3 subjects in the intervention group improved (Figure 5.2).
Two factors may explain the significant improvement in the BBS but not in the other measures of balance (i.e. total score of RT and SRT and root man square of postural control during quite standing). Firstly, the smaller effect observed in the total score of the

RT and SRT and the measures of postural sway can be viewed in the light of their psychometric properties. As demonstrated previously (Chapter 4), the RT and SRT tests are subject to ceiling and floor effects. Furthermore both the total score of the RT and SRT and the measures of postural sway are susceptible to a high degree of variability on repeated assessments. In particular the total score of the RT and SRT is subject to a learning effect (Chapter 4). This learning effect in part may explain the observed improvement reported here on this outcome in most of the participants in the control group (8/10) in addition to the improvement was seen in some of the participants in the intervention group (6/11) on this measure (Figure 5.2). Any or all of these factors (i.e. susceptibility to ceiling, floor and learning effects and high degree of variability on repeated assessment) may limit the ability of these outcomes to detect any improvement as a result of the intervention. Secondly, whilst the BBS evaluates both dynamic and static balance as well as internal protrusion, RT and SRT, as well as measures of postural sway during quiet standing, are indicative only of static balance. Thus it can only be speculated that the exercise programme in this study had a marked improvement in the other aspects of balance but it did not affect the components of static balance. The exercise programme in this study was designed to improve overall function and focused on practicing task-specific activities but it was not targeted to specifically train balance. This may have resulted in an improvement in balance needed to perform activities (dynamic balance) but not necessarily for static balance. In fact, static balance may not be the correct variable to examine; maintaining balance while performing functional activities such as walking may be more important for people with HD than simply standing still [249]. This can be viewed in light of the data that suggest better association between measures of walking (reflected by gait variability) and measures that evaluate dynamic balance (i.e. BBS) when compared with measures of static balance (Chapter 4). This is also supported by available evidence which suggests that static balance is not a strong predictor of measures related to functional performance of daily activities such as walking [230, 249]. Thus future research may need to shift the emphasis from simply improving static balance to restoring or maintaining functional balance needed during performing activities of daily living.

5.3.1.1.3 Measures of muscle strength

Whilst there were significant improvements in the BBS and the disease-specific motor score (the mMS) in the intervention group when compared to control, there were no significant improvements in the measures of the isometric muscle strength (the Maximal

Voluntary Isometric Contraction (MVIC) of the knee flexors and extensors). The lack of significant improvement in the isometric muscle strength can be explained by a number of factors. For example, the sample size in this study was small. A study with a larger sample may reveal significant differences. Furthermore, the MVIC outcomes as measured using isokinetic dynamometry are subject to a high degree of variability (Chapter 4) which limits their responsiveness to detect change in muscle strength over time. The isometric muscle strength test requires that the participant is co-operative and able to follow fairly complex instructions. It is also possible that the strength test is affected by co-activation of the knee extensor and/ or flexor musculature (potentially secondary to dystonia) [35]. In addition, the difficulties in movement initiation and movement execution as well as deficits in force generation seen in this population may also influence the performance of this test [37, 255]. Any or all of these factors may contribute to increased variability of the output; hence reducing its responsiveness to measure changes over time.

In addition to the factors cited above, the lack of improvement on measures of muscle strength can be related to the specificity and the setting of the exercise programme used in this study. Although the exercise programme included general strengthening exercises, it was designed to improve function and it did not specifically target muscle strengthening; progressive resistance exercise training was not included in the exercise programme. Progressive resistance training with high intensity has been shown to improve the muscle strength of people with other neurodegenerative diseases [163, 273-276]. The majority of these studies however, have utilised specialised strength training equipment, requiring participants to attend and be supervised, at a gym facility or clinic to participate [273, 274, 276]. Other studies have shown that progressive resistance training using weighted vests in the participant's home, but with close supervision from a therapist, is a safe and effective alternative form of resistance training in improving muscle strength [275]. These methods of delivering exercise in HD may be equally beneficial in improving muscle strength in HD and therefore further investigations in this field are required. An exercise study with closer supervision where the strength of the intervention is more readily tailored and the dose is controlled more precisely, may enable further study to determine if and how exercise can affect muscle strength in people with HD.

5.3.1.2 Measures of activity

5.3.1.2.1 Measures of mobility

5.3.1.2.1.1 Walking- measures of gait and community walking

Improvements in gait parameters including walking speed, stride time and stride time variability were observed in the majority of subjects in the intervention group (see Figure 5.4 for change scores in individual cases in intervention group). The effect size for all these parameters was large (≥0.7) and a significant difference between the study groups was observed on gait speed and stride time variability.

Substantial significant reduction in stride time variability was observed in the intervention group when compared to the control group. However, it should be noted that the amount of deterioration in 3 cases in the control group in this outcome was unusually high (Figure 5.4c) given the duration of the study (i.e. 8 weeks). This may have overinflated the effect calculated in this study on this outcome; hence this result should be interpreted with some caution. Future research is required to further explore this finding.

Whilst there are no previous studies in HD examining the effect of exercise on gait variability to compare the reported results here with, findings from this study about possible improvements in gait variability are consistent with data available in the literature on other populations such as PD and older adults. For example, participation in a 6-month home-based exercise programme that aimed to improve balance in the elderly demonstrated improvement in stride time variability [277]. Similarly, a study of a 4 week clinic-based exercise programme that focused on gait training and the use of rhythmic sound cues demonstrated improvement in gait speed and step time variability in people with PD [278].

The finding of possible improvement in gait variability in this study is important. Gait variability can be considered as a key indicator of general mobility in this population [38], even at the very early stages of the disease [39, 40, 108], hence it being chosen as the primary outcome measure in this study. Critically, gait variability can be viewed as a major determinant of overall physical impairment and activity limitations in people with HD (Chapter 4) and puts them at greater risk of falls [38], thus there is a rationale to maintain and improve this component of gait.

High fall rates are the number one predictor of admission to a nursing home in people with HD [43]. The optimal goal of exercise interventions in HD would be to reduce the actual number of falls. However, fall rates were not measured directly in this study and only reliance on quantifying gait measures such as gait variability was used. Whilst gait variability serves as an objective measure in the evaluation of the risk of falls in HD [38] and in other populations, direct measures of falls relies on participant's self report. Fall rates can either be recorded prospectively using diaries or retrospectively using self-reported questionnaires [279]. Both methods are subject to bias and failure to recall or report fall events. For these reasons, the choice of gait variability as a primary outcome may be more appropriate than measuring actual fall events.

In addition to improvements in measures of gait variability, a significant difference between groups was also identified for gait speed in this study. The reported mean change in gait speed of 26.2 cm/s is larger than the MDC_{95} value of 19.4 cm/s (Chapter 4). This suggests that the improvement in the gait speed in the intervention group in this study is "clinically significant". This finding is in agreement with data obtained from a previously conducted single-case study of an individual with mid stage HD in which a home-based exercise programme demonstrated improvement in gait speed. This result is also consistent with data available from exercise studies in other neurodegenerative diseases. A number of home based exercise programmes in people with PD and AD which aimed to improve mobility revealed positive effects of exercise in improving gait speed [74, 160, 163, 165, 167].

Although the exercise programme in this study revealed a significant improvement in gait speed, there were no significant differences between groups for stride time. Stride time correlates well with gait speed (Appendix 6), however, the fact that many other diverse factors such as balance, confidence, exercise capacity and muscle strength also contribute to gait speed [280-282] may further explain this result. The reliance of gait speed on a multiplicity of components may make it a more sensitive measure, perhaps revealing improvements in gait, even when the other measures of gait, such as stride time, show fewer changes. The effect sizes presented in this study lend further support to this idea. Whilst the effect size for stride time of 0.7 is still fairly large [178], the effect size for gait speed of 1.7 is much larger. These effect sizes suggest that a study with a slightly larger

sample may also reveal differences in the measure of stride time. For example, using an effect size of 0.7, a power of 80%, and an alpha (α) level of 0.05, a sample of 52 participants (26 per arm) will be required to demonstrate differences in the stride time measure.

Adding to the improvements in gait speed and gait variability, data presented here revealed significant differences between groups in the measures of community walking. The average daily step count significantly increased in the exercise group over the 8-week period. Additionally, the time spent doing no walking activity decreased and the time at low, moderate and high levels of physical activities increased. This was reflected by improvements on the peak activity index. The significance improvements in all measures of community walking were further reflected by data obtained from the change scores on individual cases (Figure 5.5). Whilst most participants in the control group had a fairly similar physical activity profile at follow-up relative to their physical activity profile at baseline (i.e. change score in most cases in control group was close to zero), the majority of participants in the intervention group improved in the various measures of community walking (Figure 5.5). This improvement in community walking levels was consistent with participants' perceived benefits on mobility status (see Chapter 6 for qualitative feedback from participants on their involvement in the programme) and further provides an objective measure that levels of community mobility improved in the intervention group.

Exercise training has been shown to increase overall community walking levels consistently in previous studies of other populations including cancer survivors and healthy young adults [283-285]. In this study, the changes in levels of community walking, and in particular in the peak activity index, in the intervention group are important as they provide an indication of the improvements in the participants' usual walking performance in the community rather than only capacity. In fact these changes may reflect the carryover effects of the gain in subjects' capacity reflected by improvements in gait speed and gait variability into subjects' performance in their actual environment. In term of gait speed, a minimum of 80 cm/s as a walking speed is required for independent community walking [286]. In this study, 5 participants in the intervention group increased their walking speed from below 80 cm/s to above 80 cm/s corresponding to moving from the need assistance in community walking category into the category of no need assistance in community walking. In term of gait variability, stride time CV is strongly associated with the actual

number of steps that subjects with HD are able to maintain for an extended period of time (i.e. peak activity index) (Chapter 4). Thus ameliorations in gait variability, as observed here, may have positively influenced the ability of the subjects to sustain activities at higher levels for longer periods of time, which improved the peak activity measure and the other measures of community walking.

The changes in levels of community walking also raise a number of clinical questions about what constitutes an optimal exercise intervention that can influence usual walking performance. Although performing the exercises from the exercise DVD at home in this study included task-oriented postural control tasks and attempted to simulate environments encountered outside the home (e.g. stepping, turning activities), it was nevertheless a safe environment, which may not adequately represent the complexity of walking in community settings [287]. However, the added progressive walking programme outside participants' homes might have added value in improving levels of community walking. Within this context, it must be noted that although the target of the walking programme was to achieve a 30 minute walking per week in the neighbourhood, most participants (7/11) in the intervention group reported walking more than once a week in their immediate environment (i.e. walking into shops, leisure and community centres) (see Chapter 6 for process evaluation). Walking in the immediate environments involves walking in different conditions (i.e. walking on uneven surfaces, crossing roads, negotiating obstacles as well as walking in different weather conditions). Thus the walking component may have added to the value of the programme. The potential of the added value of the walking programme into the benefits in mobility status reported here is consistent with evidence that suggests transferability of functional improvement is most noticeable in the setting in which the intervention is delivered [160]. Furthermore, the fact that the walking programme in this study was progressive with a defined goal (achieving 30 minutes of walking with minimal amount of breaks) may have further helped in improving the community walking. Studies of exercise interventions in other populations suggest that daily walking activity is likely to improve only when realistic goals are pre-defined [284].

5.3.1.2.1.2 Other measures of mobility

In addition to assessing benefits in measures of walking, this study evaluated the potential benefits of exercise in improving other aspects of mobility that are believed to be limited in people with HD. Out of the 3 mobility measures that were used (FSST, TUG, CSST), a

significant difference between groups was found only on the CSST. This was reflected by data obtained from change score on individual cases in which majority of the participants in the intervention group (10/11) improved on this test (Figure 5.6). The reported mean change in the CSST of 3.4 is larger than the MDC_{95} value of 2.2 (Chapter 4), which suggests that the improvement in this measure is "clinically significant". An improvement in the CSST reflects a better ability to rise from a seated to standing position. This transitional task (the sit to stand) is one of the most common activities of daily living, it is a prerequisite for walking, and it is particularly important to maintain physical independence [131], which makes it an important activity to be improved or maintained in people with mobility deficits such as people with HD.

Whilst a significant improvement in the exercise group was demonstrated on the CSST, there were no significant differences between groups on the FSST and the TUG tests. There are a number of factors that can provide some explanations for these findings. For example, the susceptibility of both the FSST and TUG to a higher degree of variability on repeated assessments (Chapter 4) may have influenced this result. However, based on the data presented here both the FSST and the TUG exerted large effects; the calculated effect sizes for the FSST and TUG were of 0.8 and 0.9 respectively. This was also reflected by data obtained from change scores on individual cases; most of the participants in the intervention group improved in the TUG (8/11) and FSST (6/11) (Figure 5.6). The amount of improvements may however not have been enough to reveal statistically significant differences in this small sample. Thus a study with a larger sample may also reveal some differences in these outcomes. Furthermore, whilst the effect size calculated for the CSST was larger than those calculated for the FSST and the TUG test, it should be noted that the CSST test as an outcome was closely aligned to what the exercise group practiced during the exercise programme. The exercise programme included exercises that required participants to specifically practice the sit to stand performance. This factor in part may explain the large effect size obtained from the CSST.

5.3.1.2.2 Measures of functional performance in ADL

In addition to improvement in gait speed and gait variability characteristics and some of the measures of mobility, improvements in the measure of functional performance in ADL (i.e. the PPT) were observed in the majority of participants (10/11) in the intervention group (Figure 5.6c). The effect size for the PPT was large (effect size=1.8) and a

significant difference between the study groups was observed on this measure. The PPT is a global measure that assesses both basic and complex ADL tasks which include writing, lifting, picking up a small object from the floor, dressing, simulated eating, walking and turning. Whilst the exercise programme in this study focused on targeting mobility aspects such as walking; most of the tasks included in the PPT test were not trained or practiced as part of this exercise programme. The significant improvement in the PPT test is therefore interesting and can be viewed in the light of its relationship with the measures of gait variability. The strong association between measures of walking performance (represented by gait variability) and the ability to perform ADLs (represented by the PPT test) (Chapter 4) may reflect a common reliance of these 2 domains of activity on the same physiological components [230]. Therefore, interventions that have effects on 1 of these 2 domains may also have a parallel effect on the other. This is consistent with reports from the literature in which exercise interventions focusing on enhancing gait aspects have been shown to improve function (measured by the PPT) in older adults [288, 289]. The reported improvement in the PPT in this study is also consistent with a previously conducted study in HD in which an inpatient intensive rehabilitation programme with an exercise component resulted in a significant improvement in the PPT [78]. The reported mean change in the PPT of 4.5 in this study is larger than the Minimal Detectable Change (MDC_{95}) value of 2.4 (Chapter 4). This suggests that the improvement reported on this measure is more likely to be due to real change as a subsequent of the exercise intervention, rather than due to measurement error; giving indications that this change is potentially clinically significant.

5.3.1.3 Measures of participation

Although the exercise programme in this study was found to significantly improve measures of gait, balance, levels of community walking and function, there was no significant improvement on health-related quality of life as measured by the SF-36. It is possible that the improvements of gait, postural control and physical functioning observed in this study were too small to carry over to perceived quality of life. However, judging by the magnitude of the improvements seen and the perceptions of patients and carers (see Chapter 6 for more details); this is unlikely to be the case. It is possible that this result is related to the susceptibility of the various subscales of the SF-36 to floor and ceiling effects as well as its susceptibility to a certain degree of variability on repeated testing (Chapter 4).

Although there were no significant differences between groups on any of the subscales of the SF-36, it was interesting to notice the large effect sizes on the physical function subscale as well as the aggregate score of the physical domain (i.e. the physical component summary). These large effects were reflected by data from the change score on individual cases in which most participants in the intervention group improved in the physical function subscale as well as the physical component summary (Figure 5.7). The physical function subscale as well as the aggregate score of the physical domain both assesses the perception of an individual on their ability to perform some physical activities of daily living such as walking, lifting an object and climbing stairs. Thus, the finding that effect sizes on these subscales were large is important as it suggests that the improvement on mobility status reported here using objective outcomes is also possibly subjectively perceived by participants. The large effect sizes on these subscales suggest that significant quality of life improvements using the SF-36 would have emerged with longer intervention or with a larger sample. The effect size of 0.8 that was calculated for the physical function subscale suggests that a sample size of 42 participants is needed to sufficiently power the study on this variable [178].

5.3.1.4 General points for consideration of study outcome at 8-week

In all measures of balance, gait and mobility there was one case that showed the largest amount of improvement relative to the other cases in the vast majority of outcomes (see the case circled on red in Figures 5.2-5.6). The qualitative feedback revealed that this participant was highly motivated to engage in the exercise programme (see Chapter 6 for qualitative feedback from participant coded as P7). As part of the exercise programme, participants were asked to undertake a progressive walk for a maximum of 30 minutes once a week for the 8-week period of the study. This participant, however, reported walking of at least an hour daily for 6 weeks of the exercise programme. Taking this into account, the remarkable improvement that was observed on this participant in most of the outcomes raises a number of questions: 1) did the data from this participant unduly influence the analyses conducted; 2) could this be explained by the exercise dose and 3) could regression towards the mean (RTM) explain the changes. In the realm of the influence of this case on obtained data, exploratory analyses of the dataset excluding this participant did not result in different outcomes. Regarding exercise dose, this observation raises a number of questions rated to what constitutes the optimal exercise dose and type that can best influence mobility status in this population. It can be argued that an exercise

programme with a higher frequency and intensity of walking outside home in particular is more beneficial in improving mobility in HD; this however needs to be further explored in future studies.

In term of RTM, it should also be noted that this participant was rather impaired at baseline (i.e. the participant had a poor performance in the majority of outcomes at baseline). Although being more impaired at baseline suggests having a bigger window for improvements and this participant self report indicates a true change (see Chapter 6 for qualitative feedback), the possibility of RTM cannot be ruled. The RTM is a statistical phenomenon that happens when extremely large or small measurements tend to be followed at second assessment by measurements that are closer to the mean [290]. Thus in this case RTM may in part explain the large changes that were observed on this participant.

The potential for RTM becomes clearer in two of the outcomes: the modified UHDRS-motor score (mMS and the stride time CV. On inspecting the plots of change score of individual cases on these outcomes, it was apparent that subjects whose baseline scores were low tended to increase and those whose baseline scores were high tended to decrease. In both of the mMS and the stride time CV the amount of deterioration in three cases in the control group was unusually high given the duration of the study (i.e. 8 weeks) (Figure 5.3a and 5.4c) which further provides indications of potential RTM. This was reflected by unusually high amounts of deterioration in the mean score of the control group in each of these outcomes. The possibility of RTM in the mMS and the stride time CV suggest that effects on these outcomes are potentially were overinflated; hence results obtained on these measures should be interpreted with some caution and further investigations are required to confirm these findings. Further studies needs also to accommodate for the potential of RTM in their design [290].

5.3.2 Sixteen-week study outcomes

The descriptive data obtained from this part of the study suggest that the stride time coefficient of variation (CV) decreased in the control group who then received the intervention following the first 8-week period (i.e. at the second follow-up) with scores compared to the first follow-up. This suggests that participants who received the intervention later in the study also improved in the primary outcome measure. In addition, the stride time CV continued to decrease in the early intervention group, both in subjects

who continued to exercise (n=5) and those who stopped exercising (n=4) after the initial 8 week study period. The descriptive data presented here, also suggest that those who continued exercising had a greater overall improvement in their stride time CV. This observation would be in agreement with results previously reported in other neurodegenerative disease such as PD about the potential carry-over effects of exercise interventions. Lun et al [161] reported a greater improvement in the Unified Parkinson's Disease Rating Scale (UPDRS) scores in those who continued exercising at 4 months relative to the baseline, compared to those who stopped exercising after the initial 2 months exercise period. Similarly Comella et al [291] reported that the UPDRS scores of subjects who stopped exercising after a 4-week exercise programme returned to baseline value after 6 months. These findings are important and emphasize the importance of regular engagement in physical activities and that the benefits may be short lived if not maintained.

5.3.3 Recruitment

In this study, recruitment difficulties acted as the main barrier to achieving the targeted number of participants. The initial power calculation determined that 40 participants were needed for the study (see Chapter 3). However, the study was stopped before reaching this targeted number due to the difficulty in finding subjects who met the inclusion criteria. Only 25 (23.6%) were enrolled in the study out of the 106 subjects who were seen in the HD clinic. In particular, the concurrent drug trials made recruitment to the study more difficult (all subjects enrolled in concurrent clinical drug trials were excluded from this study). It is reasonable for people with HD who face a long-term disease to choose a pharmaceutical trial that has potential disease modifying properties rather than an exercise intervention that may influence function in the short term. However, it should also be noted that it is important to improve all modes of available management with a view to combining effective symptom management with disease modification once it is available.

In general, it should be remembered that difficulties in recruitment are a common problem in clinical research [138]. This issue may be of even greater concern when recruiting individuals with HD, taking into consideration that the sample selection is limited to a small subset of the population. Furthermore, there are certain barriers, such as lack of motivation and the need to obtain support from the carer, which may limit opportunities for participation in clinical research in this population [292]. The difficulties encountered in

recruiting subjects in this study highlight the need to re-examine the best way to conduct clinical studies. Innovative strategies for recruiting individuals must become high priority in future clinical trials in HD. For example, multicenter exercise trials may be necessary in the future to achieve adequate statistical power. Intervention fidelity in such cases become extremely important part of the study conduct. However, with the use of video and broadband technologies, the host site could oversee an intervention at another location to ensure that the trial protocol is adhered to [138].

In addition to the need to consider multisite trials, Goodman et al [292] suggested a number of strategies that have been used in HD and found to enhance recruitment rate in this population. According to the authors, using web alerts for notification of new clinical trials, as well as providing education to individuals with HD and their families about clinical trials, in support group are mechanisms that have the potential to enhance participation in HD research. Within education in a support group strategy, community advocates can provide educational sessions to groups of HD individuals and their families about a clinical trial, its importance, rationale of the intervention, potential risks and benefits and inclusion and exclusion criteria. This strategy in particular seemed to boost recruitment rate in a previously conducted trial and therefore needs to be considered in future research.

Chapter Six

Results and Discussion: Process Evaluation of Part 2

6 Results and discussion: Process evaluation of part 2

6.1 Overview

This chapter presents the results of the process evaluation for part 2 of the study. Specifically an exploration was carried out to investigate: 1) if participants would adhere to the home-based exercise programme, 2) how the exercise programme was perceived by the participants and their carers, and 3) what factors impacted on the adherence to the home-based exercise programme. Data presented here were gathered from 19 participants who were offered the intervention in both arms of the study and were followed up on completion of the 8 week period of the exercise programme (i.e. early intervention group (n=11) and delayed intervention group (n=8)).

Results presented in this chapter are divided into 3 sections. In the first section, participants' characteristics are provided. In the second section, data about adherence to the exercise programme based on participant's self report are illustrated. This includes the adherence rate of each participant which was calculated as the number of exercise sessions reported as a percentage of potentially expected exercise sessions prescribed for the 8 weeks. For the purposes of data interpretations, participants were considered to have good adherence if they reported performance on at least 50% of the prescribed sessions.

Data related to adherence rate in the second section of the results are presented along other data related to disease-specific factors and participants' perceptions of the exercise programme. In this section, participants' self report about their perceptions of their involvement in the exercise program which was assessed using the short form of the Intrinsic Motivation Inventory (IMI) scale is firstly illustrated. Secondly, differences between those who adhered and did not adhere to the exercise programme for stride time coefficient of variation (CV) and UHDRS-cognitive scores and all the IMI subscales are provided. Thirdly, correlations between adherence rate, stride time CV, UHDRS-cognitive scores and IMI subscales, are presented.

In the third section of the results, data from semi-structured interviews which were conducted on completion of the exercise programme are presented. These data provide further explorations of factors that would have impacted on performance of the exercises in this study. Results presented in this section were derived from interviews that were conducted with participants in both arms of the study who were offered the exercise intervention and subsequently followed up (n=19).

6.2 Results

6.2.1 Participants

Characteristics of those participants who were interviewed on completion of the exercise programme (n=19; 11 from the early intervention group and 8 from the delayed intervention group) are shown in Table 6.1. The data presented are coded as P1-P19; this adds to the transparency of the process whilst protecting the anonymity of the participants and allows the reader, at the same time, to gain an understanding of the source of the information [293]. Most of the participants (n=14) had a full time carer. The participants (10 females and 9 males) varied in their age, stage of the disease and their physical and cognitive status. The ages ranged from 25 to 69 with an average of 52.7 years (SD ±13.3). The mean of the stride time CV was 9.2 (SD ± 4.7). One of the participants was at stage I (TFC 11-13), 5 participants were at stage II (TFC 7-10) and 13 participants were at stage III (TFC 3-6). Six participants had high scores on the UHDRS-cognitive scores (UHDRS-cognitive >200), 6 had moderate scores (UHDRS-cognitive ≥ 100 but less than 200) and 7 had very low scores (UHDRS-cognitive < 100).

Table 6.1: Characteristics of participants who completed the intervention

ID	General information	Carer's involvement	Group allocation	Stride time CV	UHDRS Cognitive scores	TFC score	Stage of the disease
P1	Female; aged 69 at interview	Yes*^	Delayed intervention	8.7	160	3	Stage III
P2	Female; aged 41 at interview	Yes*^	Early intervention	10.3	197	6	Stage III
P3	Male; aged 25 at interview	Yes*^	Delayed intervention	5.5	128	5	Stage III
P4	Female, aged 55 at interview	Yes^	Early intervention	11.3	76	5	Stage III
P5	Female; aged 59 at interview	Yes*^	Delayed intervention	6.2	63	5	Stage III
P6	Female; aged 67 at interview	No	Early intervention	9.3	201	9	Stage II
P7	Male; aged 42 at interview	Yes*^	Early intervention	17.1	84	5	Stage III
P8	Male; aged 78 at interview	Yes*^	Delayed intervention	11.7	50	5	Stage III
P9	Female, aged 51 at interview	Yes^	Early intervention	4.1	221	11	Stage I
P10	Male, aged 38 at interview	No	Delayed intervention	4.3	233	9	Stage II
P11	Female, aged 72 at interview	Yes*^	Early intervention	10.3	88	3	Stage III
P12	Male, aged 41 at interview	Yes*^	Delayed intervention	3.3	198	5	Stage III
P13	Male, aged 51 at interview	Yes*^	Early intervention	17.6	57	4	Stage III
P14	Male, aged 64 at interviews	Yes*^	Early intervention	7.4	73	5	Stage III
P15	Male, aged 51 at interview	Yes*^	Delayed intervention	10.1	130	6	Stage III
P16	Female, aged 42 at interview	No	Early intervention	5.6	206	8	Stage II
P17	Male, aged 60 at interview	No	Early intervention	7.5	200	10	Stage II
P18	Female, aged 41 at interview	Yes*^	Early intervention	19.8	192	6	Stage III
P19	Female, aged 54 at interview	No	Delayed intervention	5.3	230	8	Stage II

UHDRS, Unified Huntington's Disease Rating Scale; CV, coefficient of variation; TFC, Total Functional Capacity Scale; *, carer was involved in supporting the participant during the exercise programme; ^, carer was involved in the interview.

UHDRS-cognitive >200 indicates high cognitive score, UHDRS-cognitive ≥ 100 indicates moderate cognitive score, UHDRS-cognitive < 100 indicates very low cognitive score.

A categorical classification of disease severity is based on the Total Functional Capacity (TFC) score, grouped into 5 stages as the following: (TFC 11-13); stage II (TFC 7-10); stage III (TFC 3-6); stage IV (TFC 1-2).

6.2.2 Exercise adherence

Characteristics of adherence and frequency of completion of the prescribed exercises from the DVD and the walking programme during the 8-week period is shown in Table 6.2. The total expected number of exercise sessions in the 8-week period was 32 (24 exercise sessions and 8 walking sessions). Adherence rates were high for most of the participants who completed the study (based on analysis of the exercise diaries): 15 of the 19 (78.9%) performed at least 75% of the prescribed sessions (mean adherence was 28.4 ± 3.1 of the 32 prescribed sessions). Four participants (21.1%) (P4, P5, P8, P13) did not adhere well to the exercise programme and performed less than 50% of the prescribed sessions (mean adherence was 8.5 ± 4.7 of the 32 prescribed sessions). For the total 19 participants who were followed up after being offered the exercise programme, mean adherence was 24.2 ± 8.9 (76.5% ± 27.8%) of the 32 prescribed exercise sessions. The reasons for non-adherence to some of the exercise sessions in those who adhered well to the overall exercise programme (performed more than 50% of the exercise sessions; n=15) were acute illness (n=4; 26.7%), inability to walk outside home due to bad weather conditions (n=2; 13.3%), timing of the exercise sessions (overlapping with holiday or special occasions at home) (n=5; 33.3%), lack of motivation (n=1; 6.7%), absence of the carer (n=5; 33,3%). In all participants who did not adhere to the exercise programme (n=4) (i.e. performed less than 50% of the prescribed sessions), reasons for adherence were related to the commitment of the carer or carer-participant interpersonal relationship.

Table 6.2: Characteristics of adherence to the exercise programme

ID	Reported participation in the home use of the exercise DVD (Max adherence 24 sessions)	Reported participation in the walking programme (Max adherence 8 sessions)	Total reported participation in the programme (Max adherence 32 sessions) n (%)	Reasons for non-adherence (if applicable)
P1	24	4	28 (87.5%)	Two walking sessions were missed both due to bad weather conditions and an additional 2 sessions were missed due to holiday.
P2	21	8	29 (90.6%)	Three sessions were missed due to illness
P3	22	6	28 (87.5%)	Two sessions were missed due to the absence of carer and 2 walking sessions were missed due to bad weather conditions.
P4	2	8	10 (31.3%)	Most of the sessions at home were missed due to the lack of support from the carer.
P5	6	3	9 (28.2%)	Carer-participant interpersonal relationship
P6	22	8	30 (93.8%)	Two sessions were missed due to holiday
P7	22	8	30 (93.8%)	Two sessions were missed due to illness
P8	10	3	13 (43.3%)	Carer-participant interpersonal relationship
P9	23	8	31 (96.9%)	One session was missed as busy with a special occasion at home
P10	23	7	30 (93.8%)	One session was missed due to illness and one walking session was missed due to lack of motivation.
P11	20	5	25 (78.1%)	Eight sessions were missed due to the absence of the carer.
P12	21	7	28 (87.5%)	Four sessions were missed due to absence of the carer
P13	2	0	2 (6.3%)	Carer-participant interpersonal relationship and participants behavioural problems.
P14	24	8	32 (100%)	None
P15	20	5	25 (78.1%)	Seven sessions were missed due to illness and absence of the carer.
P16	21	8	29 (90.6%)	Three sessions were missed due to holiday
P17	21	8	29 (90.6%)	Three sessions were missed as busy with a special occasion at home
P18	19	6	20 (75%)	Five sessions were missed due to the absence of the carer
P19	24	8	32 (100%)	None

Table 6.3 reports the descriptive data of stride time CV and the UHDRS-cognitive scores as well as the scales of the IMI on both those participants who adhered to the programme (n=15) and those who did not (n=4). The mean score on the UHDRS-cognitive and the tension/pressure scores were significantly different between those who adhered and those who did not adhere. There were no significant differences in the stride time CV scores as well as for all the other subscales of IMI.

Table 6.3: Data of stride time coefficient of variation (CV), UHDRS cognitive scores and Intrinsic Motivation Inventory (IMI), of participants who adhered and participants who did not adhere to the exercise programme (mean ± SD)

Subscale	Participants who adhered (n=15)	Participants who did not adhere (n=4)	p-value
Stride time CV	8.5 ± 4.9	12.7 ± 5.7	0.09
UHDRS cognitive score	169.4 ± 54.9	61.5 ± 11.0	0.001
IMI-Interest/enjoyment	5.3 ± 1.5	4.7 ± 1.0	0.5
IMI-Perceived competence	5.9 ± 1.2	3.8 ± 2.3	0.1
IMI-Effort/importance	6.4 ± 0.8	5.8 ± 0.8	0.3
IMI-Pressure/tension	2.5 ± 1.1	4.5 ± 1.4	0.03
IMI-Value/usefulness	6.7 ± 0.6	6.7 ± 0.6	0.7
For each item of IMI scale, a response on a scale of 7 points indicating how true the statement of the item is given (1 indicates not true at all and 7 indicates very true). Lower scores of the pressure tension subscale and higher scores of all the other subscales indicate positive outcome. Analysis for all parameters is based on using the Mann-Whitney-U test for independent samples.			

Correlation scores between adherence rates, stride time CV, UHDRS-cognitive and the IMI subscales are reported in Table 6.4. Adherence rate was significantly correlated with the stride time CV, the UHDRS-cognitive subscale, perceived competence and pressure/tension subscales. There were no significant correlations between adherence and interest/enjoyment, effort/importance and value/usefulness subscales.

The stride time CV score was significantly correlated with perceived competence subscale; correlations with interest/enjoyment, effort/importance, pressure/tension and value/usefulness subscales were not significant. In addition, the UHDRS-cognitive

score was significantly correlated with the perceived competence and pressure/tension subscales.

Table 6.4: Correlations between adherence rates, stride time coefficient of variation (CV), UHDRS-cognitive score and Intrinsic Motivation Inventory (IMI) subscales

Subscale (n=19)	Correlation with stride time CV	Correlation with UHDRS-cognitive	Correlation with adherence
Adherence	-0.5*	0.6**	-------
IMI-Interest/enjoyment	-0.2	0.3	0.2
IMI-Perceived competence	0.4*	0.5*	0.5*
IMI-Effort/importance	-0.2	0.2	0.3
IMI-Pressure/tension	0.2	-0.5*	-0.6**
IMI-Value/usefulness	0.3	-0.2	-0.2
Correlations were calculated using the Spearman correlation coefficient *p<0.05 **p<0.01			

6.2.3 Semi- structured interviews

All participants who adhered to the programme (n=15) agreed that the prescribed exercises were suitable for them. In particular, participants agreed that the exercise DVD was simple and easy to follow and was a supportive mechanism that helped them to perform the exercises at home without a close supervision from a therapist. Analysis of the interviews revealed perceived benefits as well as perceived barriers and facilitators to performing the exercise programme. The following sections describe these aspects of the interview analyses.

6.2.3.1 Perceived benefits

All participants who adhered to the programme perceived benefits from participating in the exercise programme. Participants perceived improvements in muscle strength (n=3), balance (n=5), motor control (n=4), mobility (n=8), quality of life (n=6) and a reduction in falls (n=2). Illustrative quotes are demonstrated in Table 6.5 below.

As depicted in Table 6.5, the vast majority of the participants who reported perceived improvements in balance, motor control and mobility demonstrated improvements on

the corresponding objective outcome measure. These participants had higher scores on the Berg Balance Scale (BBS), the Chair Sit to Stand test (CSST), or lower stride time CV at the follow-up assessment when compared to the baseline. This suggests that there is an agreement between the subjective perceived improvement reported by participants and the objective change evaluated using the outcome measures.

In addition to the above, most of the participants (n=3/4) who perceived improvements on quality of life had a better scores on the physical function subscale of the SF-36 at the follow-up, relative to what they had scored at the baseline (Table 6.6). Furthermore, some participants (2/4) had a better score on the aggregate score of physical domain at the follow-up, relative to what they had scored at the baseline. This indicates that on the objective outcome (i.e. SF-36), participants demonstrated improvements on some of the physical domains of the health related quality of life.

Table 6.5: Some illustrative quotes for the perceived benefits on the participation of the exercise programme along with the change scores on the objective outcomes of muscle strength, balance and mobility

Perceived benefits	Illustrative quotes	Objective outcome	Participant	Change of scores on objective measures	Comment
Muscle strength	P1: "The exercises with the weights are quite good. They strengthen the arms and the muscles that I have not used often."	MVIC of quadriceps	P1	Not recorded	-------
			P2	-3.0	Did not improve
			P3	Not recorded	-------
Balance	P3: "This programme has helped my balance particularly. I think it was very important to do this programme because I always thought that my problem is the balance. I think it strengthened me around the waist as well which is important for my balance."	BBS	P3	Not recorded	-------
			P6	5.0	improved
			P9	3.0	improved
			P10	Not recorded	-------
			P16	5.0	improved
Overall mobility status	P7: "I can walk for much longer now. I did not used to walk for long distances before I started this programme but now I do this quite frequently. We went to a wedding last week and I had to walk for about an hour and a half, something that I have never done before."	Stride time CV	P1	1.7	Did not improve
			P2	-2.1	improved
			P3	-1.5	improved
			P7	-10.9	improved
			P16	-4.0	improved
			P17	-3.4	improved
			P18	0.85	Did not improve
			P19	-2.4	improved
Control of movement	P11: "The sitting down is getting better. A lot of the time I just tended to lump my self down but now I am controlling this a bit better. I noticed with controlling sitting down that instead of lumping I now think about it more and get a bit more control over it."	CSST	P3	Not recorded	-------
			P11	5.0	improved
			P6	2.0	improved
			P15	Not recorded	-------
Reduction of falls	P2: "I have just noticed that I am not falling as many times since I've been doing the exercises. I had falls a couple of times in the first couple of weeks, but probably in the last four or five weeks, I have not fallen over at all."	Number of falls	P2	Reported reduction in falls	-------
			P18	Reported reduction in falls	-------
Quality of life	P5: "I think that doing this programme would really improve the quality of life because instead of sitting and watching the TV for about seven hours a day I can move and do something else; something that it is advantageous. So doing this programme gives more variety to life."				

MVIC, Maximal Voluntary Isometric Contraction; BBS, Berg Balance Scale; CV, coefficient of variation; CSST, Chair Sit to Stand Test.

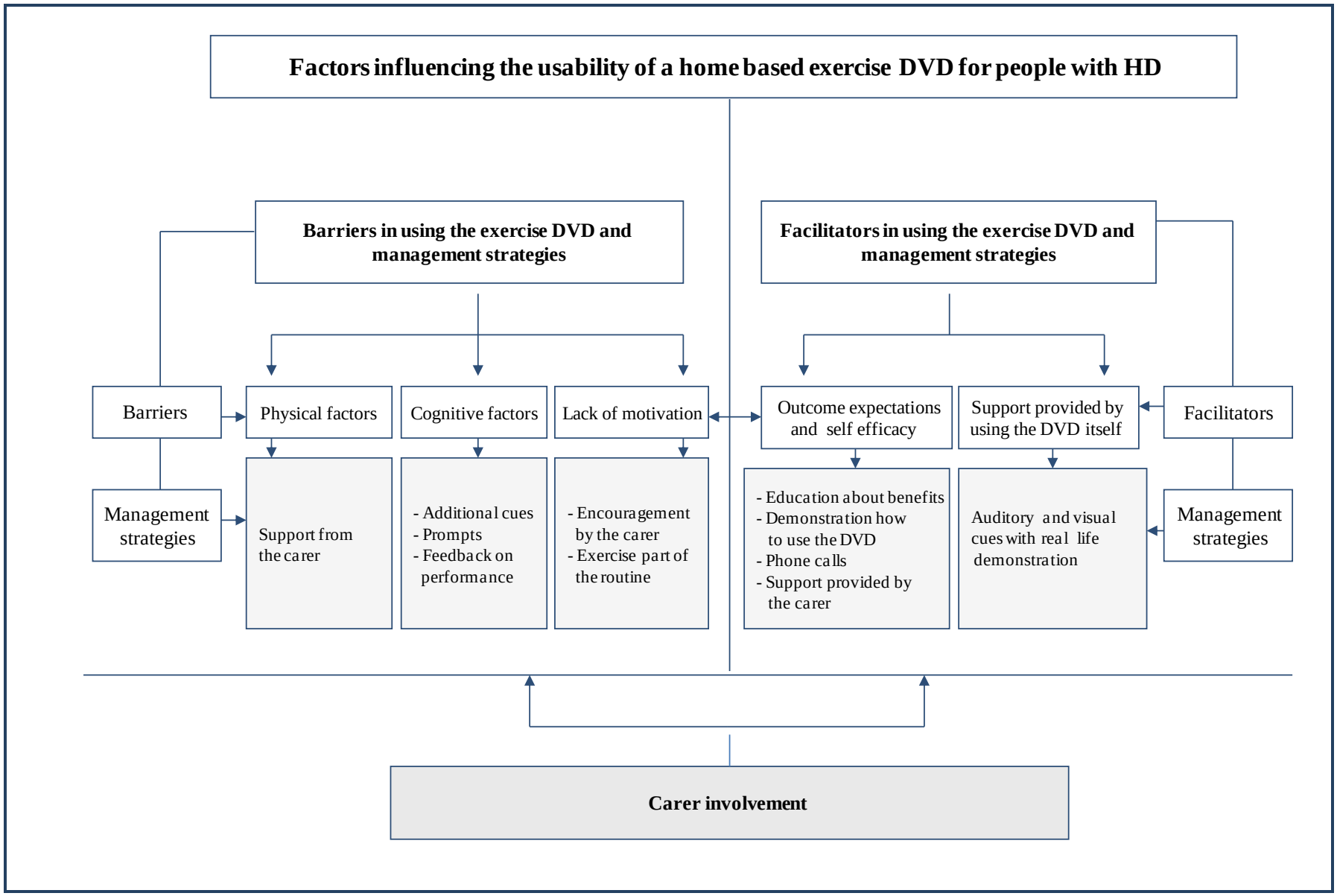
Table 6.6: *S*ome illustrative quotes for the perceived benefits on the participation of the exercise programme on quality of life along with the change scores on the subscales of the SF-36

Quality of life quotes					
P5: "I think that doing this programme would really improve the quality of life because instead of sitting and watching the TV for about seven hours a day I can move and do something else; something that it is advantageous. So doing this programme gives more variety to life."					
P6: ''I think doing the exercises not only helped me physically but mentally too. I just feel much better when I do them.''					
Change scores on the subscales of SF-36					
Participant	**PF**	**RF**	**BP**	**GH**	**VT**
P2	10.00	0.0	-22.22	-7.00	-50.00
P3	NR	NR	NR	NR	NR
P6	15.00	0.0	-11.1	15.00	-5.00
P11	0.0	0.0	-44.44	-12.00	-10.00
P12	NR	NR	NR	NR	NR
P14	15.00	-100.	0.0	10.00	0.0
Participant	**SF**	**RE**	**MH**	**PCS**	**MCS**
P2	-22.22	0.0	-8.00	-2.59	-24.14
P3	NR	NR	NR	NR	NR
P6	0.0	33.3	0.0	12.96	-3.45
P11	-22.22	-100	-4.00	-11.85	-13.79
P12	NR	NR	NR	NR	NR
P14	-33.33	-66.6	12.00	1.85	-3.45
PF; Physical Functioning; RF; Role limited due to physical problems; RE; Role limited due to emotional problems; SF; Social Functioning; MH, Mental Health; VT, Vitality; BP, Bodily Pain; GH, General Health Perception; PCS, Physical Component summary; MCS, Mental Component Summary. On each subscale, a negative change indicates deterioration at follow-up and a positive change indicates an improvement at follow-up.					

6.2.3.2 Perceived barriers and facilitators

Analysis of the interviews revealed barriers and facilitators to using the exercise DVD. The barriers fell mainly into 3 categories: physical factors, cognitive factors and lack of motivation. Participants discussed strategies that they used to address these barriers, which improved adherence to the programme. The facilitators could be categorized as primarily related to the cues provided by the DVD, a person's self-efficacy, and their belief that performing the exercises would yield positive outcomes. The sections below describe these barriers and facilitators, and the participants' management strategies, with some illustrative quotes that are provided. A summary of the categories and subcategories and their relationship to each other are provided in Figure 6.1 below.

Figure 6.1: Summary of main areas, categories and subcategories of barriers and facilitators from interview analysis



6.2.3.2.1 Barriers in performing the exercise programme and management strategies

6.2.3.2.1.1 Physical factors

The majority of participants felt that HD-related physical problems limited to some extent their ability to perform the exercises from the DVD independently. Most of the participants (n=9) who completed the exercise programme felt that some of the exercises were difficult to perform, due to the interference of choreic movements and/or secondary to their perceived balance problems. Some participants at mid stage (n=5) needed their carers to assist with the actual exercises shown in the DVD but participants at earlier stages were able to do the exercises independently without the carer being involved. Participant 3 said:

> "I needed my husband actually to be with me. I do not think I would manage to do them by myself, because of the choreic movement, balance problems and because of the power and things like that..".

In terms of the walking programme, some of the participants at stage II and stage III (n=5) reported the need to have a lot of breaks due to fatigue on the initiation of the exercise programme. Participants, however, commented that this aspect was improved on continuing the exercise programme. In addition, some of the participants at stage 3 (n=6) needed close supervision from their carers while walking to avoid tripping or falling over. Participant 4 said:

> "In the first couple of weeks, I was not able to walk the fifteen minutes without having plenty of breaks. Every three to four minutes I was stopping to have a little break and then continue. Simply I was feeling tired. It is something that I did not used to do. We were setting targets, saying for example; today we will walk from these chairs to the parked cars. I needed to hold onto the hands of my husband for the first couple of weeks as well. We've noticed however that in the last three weeks I am walking the same distance without holding onto him and without taking as many breaks as I used to take"

6.2.3.2.1.2 Cognitive factors

In addition to physical factors, cognitive problems were a main issue that had the potential to limit participants' ability to independently perform the exercise programme. Participants who were moderately to severely cognitively impaired were unable to do the exercises from the DVD on their own; this included the 4 participants who did not adhere to the programme. The participants believed that this was not necessarily due to their physical limitations, but rather because at times they were unable to understand what they were required to do from the DVD. Participant 4 said:

> "I watched the people - what they were doing on the DVD- but I could not actually see if I was doing it right."

6.2.3.2.1.3 Lack of motivation

Participants also discussed issues related to lack of motivation as another main issue that impacted on their initiation to the exercise programme. The use of strategies such as trying to fit the programme into a daily routine also helped to maintain motivation and influenced adherence. Participant 6 said:

> "It was just difficult to get myself into it. Obviously people with HD do have difficulties to start new activity. However, making these exercises part of the routine would make it easier to maintain…''

6.2.3.2.2 Facilitators in performing the exercise programme and management strategies

6.2.3.2.2.1 Cues provided by using the DVD

All participants who completed the exercise programme felt that the DVD was a supportive mechanism to help them initiate and adhere to a home exercise programme. Participants discussed the advantages of using the DVD as an approach to demonstrate the exercises versus using drawings of the exercises in a paper format. They commented that the main advantage of using the DVD was that it provided additional visual and verbal cues, to ensure correct execution of the exercises. Participant 1 said:

> "The visual thing of using the DVD makes it much easier to do it because to do things that have to be committed to memory, particularly as in my case

> memory is a problem, is impossible. So the visual cues of the DVD make it easy to do."

The DVD was used in different ways by participants to derive the support that they needed. The more advanced participants of those who completed the exercise programme (TFC<9; 15/19) needed to play the DVD at each session to do the exercises; the vast majority of the less advanced participants (TFC≥9; 3/19; P6, P9, P10) used the DVD at the beginning of the programme and then were able to integrate the exercises into their daily routine and refer back to the DVD or the exercise booklet only if needed.

6.2.3.2.2.2 Self efficacy and outcome expectations

Expectations of outcome and self-efficacy were 2 important concepts that emerged from the discussion with the participants that positively influenced their motivation and consequently facilitated their adherence to the exercise programme. In terms of the outcome expectations, most participants who adhered to the exercise programme (n=11/15) believed that their involvement in this programme would help them to manage their condition. Participant 10 said:

> "What I was just saying to myself - this is an important kind of thing and I have to do it. I have to do it because it can be beneficial for my balance and my walking."

In terms of self-efficacy, some of the participants who adhered to the programme (n= 8/15) believed that feeling confident about how to use the DVD and how to do the exercises safely helped their adherence. Participant 9 said:

> "I felt that I had to do something to regain my balance but I was not sure how to go about it and having this programme just helped because I felt that I am doing the right thing in the right way."

Participants felt that the weekly telephone calls were an important component of maintaining adherence to the programme, positively affecting their belief in their own ability to affect meaningful change. Participant 9 said:

> "The phone calls were very important to keep me on the programme. We kept communicating and you were answering my questions so I felt I was on the right track. I do not know how well motivated I would be without them."

In addition, all participants who adhered to the programme agreed that the education session provided at home at the beginning of the programme was important to help them to initiate the exercise programme and to promote their self-efficacy. Participant 3 said:

> "The home visit was very useful because I can only see what people on the DVD are doing, so it is good that you saw how I was doing things. This gave me assurance that I was doing it right from the beginning."

While those participants who adhered to the programme thought that 1 session was enough to feel fully confident about how they should progress their exercises, others felt that providing more sessions during the first few weeks of the programme would have been beneficial. One participant suggested that providing feedback from a distance using web-based technology would be useful, rather than having a face to face session which would require either patient or therapist to travel.

6.2.3.2.3 Master theme

All categories of barriers and facilitators related to a master theme that emerged from the analysis; namely that commitment of the carer was a key to the success of the programme. Reasons for non-adherence were mostly attributed to the commitment of the carer or carer-participant interpersonal relationship. Participant 5 and her carer discussed how the carer-participant interpersonal relationship would affect a participant's adherence to the programme. The participant said:

"We could not agree on how to do things." The carer of this participant clarified by saying:

> "She did the exercises with you when you visited us at home but she would not do them with me because mentally she has authoritarian issues, she is more likely to do things with other people who've got medical authority rather than if it is someone from the family."

The carer of one participant (P13) commented that the participant's behavioural aspects prevented her from continuing the exercise programme after the training session at home with the therapist. The carer of this participant said:

> "He did the exercises very well with you when you visited us at home. I could not get him to do them with me though. Whenever I asked him to start doing them, he was getting very irritable and agitated and I could not handle his behaviour, so I stopped asking him to do that."

As noted earlier, some participants needed their carers to help on the actual performance of the exercises because of some physical limitations. In cases of cognitive impairments, the use of strategies such as prompts, verbal cues, and feedback on the participant's performance provided by the carer was vital to help participants accomplish the exercises from the exercise DVD successfully. Participant 3 said:

> "I always needed my nurse…". The carer of this participant clarified by saying:
> "He always needed his nurse to be there to do the exercises. She was providing him with occasional prompts like 'make sure your hands on the chair' when he was using them during standing on the balance things. It tells him put your arm out and touch the chair, move closer or put the chair closer."

For the majority of the participants who adhered to the programme (n=12/15), involvement of the carer was necessary to manage motivation by providing continuous encouragement. Participant 11 said:

> "Motivation was a big issue.…" The carer of this participant added some clarification. The carer said "If I was not there, she would think –'Do I need to do my exercises?'. The problem is that she needed to be prompted to do it."

Support provided by the carer seemed also to influence self-efficacy. Participant 4 who did not adhere to the programme explained how the lack of support from the carer influenced her adherence negatively. The participant said:

> "I was panicking. I do not know why myself. I just felt that 'I would be OK' if there was somebody sitting there while I was doing the exercises."

6.3 Discussion

6.3.1 Exercise adherence

This is the first study that documents the adherence rates to unsupervised home-exercise programmes in people with HD. Adherence is defined as the extent to which people follow the prescribed components of their exercise programme [294]. In this study, most of the participants adhered to the exercise programme; 15 participants reported adherence to at least 75% of the prescribed sessions, while only 4participants reported adherence on a maximum of 41.7% of the prescribed sessions.

Participants' adherence is crucial when using a home programme with self-report as part of a treatment intervention. In an attempt to increase adherence to the exercise programme, the researcher made weekly phone calls to offer encouragement, answer questions, and check on progress. This study's overall adherence rate of 76.5% is within the range of 70% to 95% of adherence rates reported in previous home-based exercise studies in other neurodegenerative diseases [161, 163, 167, 295, 296]. Furthermore, the reported overall adherence rate of 76.5% in this study is slightly better than rates cited in a recent review which concluded adherence rates to medical treatments using self-report as 71.8% and adherence rates of 72% when exercise was the treatment choice [297]. A number of factors including the home visit at the beginning of the exercise programme, the frequent telephone contacts and attempts to involve the carer in supporting participants were well received by the participants and may have contributed to their adherence rate.

Interestingly reasons for non-adherence in all those with low adherence rates were all attributed to the commitment of the carer or to the carer-patient relationship. It was evident that the successful involvement of the carer was a key to the success of the programme, particularly with subjects who were more advanced in the disease process. Participants did not adhere to the programme if they lacked the support of a carer, or if they had a negative relationship with their carer about the carer's role in supporting them in completing the programme. In 1 case, behavioural problems associated with HD, namely agitation, also acted as a main barrier and affected the carer's ability to support the participant effectively on continuing the exercise programme at home. This finding suggests that health-care professionals should work co-operatively with the carer, supporting the carers' self efficacy and building their confidence about the

important role that they can play in supporting the subject with HD to engage in an independent exercise programme.

Data from the IMI subscales indicated positive results in terms of how participants who adhered perceived the participation in the exercise programme. The pressure/tension subscale resulted in a relatively low score, which indicates that; overall, participants did not experience pressure during the use of the exercise DVD or during performing the walking sessions. Effort/importance and value/usefulness subscales resulted in very high scores, which suggest that the participants felt that they produced a good amount of effort when doing the exercises from the DVD and/ or the walking sessions; they believed that it was important for them to do the exercises and they were satisfied with the results.

Significant differences between those who adhered and those who did not adhere were seen on the cognitive scores and on the pressure/tension subscale of the IMI. There was a trend towards higher stride time CV scores in those who did not adhere to the programme, but this was not significant. The small sample may have influenced this result and further investigation on a larger sample is indicated. The significant correlations between the adherence rate, stride time CV, cognitive scores and perceived competence (and the significant differences in pressure tension and cognitive scores) suggest that participants who were more impaired both physically and cognitively may have found it more difficult to perform the exercises and felt less competent, which may have had a negative influence on their adherence to the programme. Furthermore, the significant correlation between the cognitive scores and pressure/tension subscales suggests that participants who were more cognitively impaired experienced more pressure on performing the exercises which may have also adversely influenced their adherence. This quantitative correlation analysis is consistent with the qualitative feedback obtained from the participants in which both physical and cognitive factors were perceived to impact on the ability to do the exercises independently.

6.3.2 Perceived benefits

Data from the interviews extend the available knowledge relating to how participants perceived the exercise programme. The success of an exercise programme is not only based on therapists' evaluations but also on subjects' personal experiences and

perception. It was therefore important to evaluate the perceptions of participants who took part in this study about their involvement in the home-based exercise programme in order to ensure the suitability and acceptability.

All the participants who adhered to the programme perceived benefits to their participation in the programme. The vast majority of participants reported perceived improvements in mobility, balance, control of movement and a reduction in falls. This reported perception was consistent with data obtained from the objective measure in most cases and with the overall quantitative analysis that was provided in the previous chapter (Chapter 5). Furthermore, these reported perceptions about obtaining benefits from the programme exercises is in agreement with reports from the literature [80, 81]. In a previously conducted qualitative study, both therapists and people with HD believed that exercise was beneficial for managing motor symptoms related to HD [80]. While the research is still limited, it appears that people with HD can be effectively involved in a home-based exercise programme and that such an exercise programme may be beneficial in improving various measures of impairment, activities and participation.

In addition to the reported improvements in balance and mobility, a number of participants perceived benefits from their participation in the programme on their quality of life. This reported perception, was consistent with data obtained from the objective outcome measure (i.e. SF-36) in which some participants demonstrated improvements on the physical function subscale as well as the aggregate score of the physical domain (Table 6.6). This provides further indications that that the magnitude of improvements on mobility status recorded in this study using objective outcomes were also perceived by participants.

In addition to perceived improvements on mobility status, some participants reported improvements on other elements such as mood that may relate to other aspects of health related quality of life. This, however, was not captured by the other subscales of the SF-36. Within this context, it was interesting to note that most of the subjects who reported perceived improvements in their quality of life, scored lower in the vast majority of the other subscales of SF-36 at the follow-up (i.e. post- intervention) relative to what they scored at the baseline (i.e. apart from the physical function subscale, most participants

demonstrated deterioration on all other subscales). This response can be traced back to the susceptibility of the SF-36 to a certain degree of variability on repeated testing in general (Chapter 4) and to the possibility of response shift bias in particular. People with HD may change their perception about their quality of life overtime [118]. Thus, the negative change on the majority of SF-36 subscales suggests that these participants may have judged their quality of life using the SF-36 at the baseline as being better than was actually the case. This may reflect a coping mechanism that allowed participants to view their situation at that time as being better, compared to prior circumstances. Alternatively, this observed response on the SF-36 could reflect a distortion that is secondary to cognitive impairments; given that answering the SF-36 questions requires implicit thinking and retrospective judgment which can be cognitively challenging particularly in the presence of cognitive impairments, as per in the HD population [118].

6.3.3 Perceived barriers and facilitators

Although most participants used the exercise DVD successfully and managed to adhere to the prescribed intervention very well, a number of barriers that could impact on the performance of the exercises and adherence to the use of the exercise DVD were reported. Each of these barriers was a disease-specific factor and included physical impairments, cognitive impairments and lack of motivation. This is in agreement with what has been identified about barriers to independent exercise in people with HD [80]. This is also in agreement with what is known about barriers to engagement in independent exercise programmes in other populations. Research carried out in elderly individuals, and people with stroke and spinal cord injury indicated that a change in health status as well as impairments related to the pathology in cases of stroke and spinal cord injury, are the main barriers to engaging in an independent exercise programme [298-300].

In terms of physical impairments, participants in this study, particularly those in more advanced stages, felt that balance deficits and choreic movements had an impact on their independent performance of the exercise programme. These participants needed their carers to help with the actual performance of the exercises from the DVD, but were still able to gain benefit from participation. In terms of the walking sessions, these participants needed close supervision from their carers to avoid tripping or falling. Involving the carer in supporting these participants to perform the exercise programme

at home minimised the risk to safety. This suggests that an independent exercise programme in a home setting is feasible for people with HD at a more advanced stage of HD who may have a good carer support.

In contrast to the physical impairments, cognitive problems were reported to act as a main barrier to independent participation in the exercise programme, particularly at the more advanced stages. Cognitive symptoms are an early sign in HD in which difficulties in maintaining attention to a task, manipulating information and planning can be recognized [2]. These symptoms may progress to include disorders of memory retrieval and eventually global dementia [13]. Given that both the number and severity of cognitive impairment increases with the progression of the disease, they have greater impact on the ability to learn new motor tasks, including the performance of new exercises at the more advanced stages of the disease. However, participants in this study indicated that strategies such as prompts, verbal cues, and feedback on the participant's performance provided by the carer helped to successfully support the accomplishment of the exercises and minimised the effect of cognitive impairment on the ability to perform the exercises from the DVD. Additional verbal cues and prompts provided by the carer were crucial in enhancing usability of the exercise DVD in the presence of cognitive impairment.

The DVD itself was perceived to be a supportive mechanism that helped in completion of the exercises, particularly in the presence of cognitive impairments. The DVD provided a real-life demonstration, and this was viewed by participants as being superior to the written instructions or printed illustrations. The DVD approach augments the information provided by the provision of attention-focusing verbal and visual cues. The literature has illustrated that such cues are important to maintain correctness of performance of an imitative motor task; the visual feedback is important to guide the imitation of the performance and the verbal description is important to assist with processing the visual information of the task [86, 301]. Using these cues is particularly important in people with HD, considering that individuals with HD often do not spontaneously adopt active strategies for learning but when external cues are provided, performance can improve [155]. One of the mechanisms underlying the potential improvement in motor learning in HD, using the external auditory or visual cueing, may stem from the conscious activation of the motor cortex overriding the loss of basal

ganglia function. Research has suggested that over-activity in the unaffected cerebellar and lateral premotor routes may signify an adaptive mechanism through which subjects can use sensory or attentional guidance to overcome their movement disorders [135]. This supports the further potential of modes of exercise that are augmented with sensory cues, such as an exercise DVD, in supporting people with HD to engage in unsupervised exercise programmes.

Lack of motivation was also reported to act as another barrier to adhering to the regular performance of the exercises. Lack of motivation is a main feature of the disease that could act as a barrier to initiate a new life routine such as an exercise programme [81]. Particularly in the realm of exercise training, people with HD may feel helpless, hopeless and reluctant to participate in any exercise programme [143], considering the progressive and degenerative nature of the disease and the number of losses that they might experience as a result.

Since motivation is vital to adherence [168], finding strategies to improve motivation is a key to the success of any provided therapy programme. In this study, outcome expectations and self-efficacy were the 2 main factors reported by participants that helped them to maintain their motivation and therefore facilitated their adherence to the exercise programme. There is a clear link in the literature between outcome expectations, self efficacy and adherence to an exercise programme [302, 303]. In a study that examined factors promoting adherence to a walking programme in a group of elderly adults, participants' belief in their ability to do the exercises safely (self efficacy) and the recognition of the benefits of the exercises (outcome expectations) were key factors [304]. Outcome expectation relates to the belief that specific consequences will result from specific personal actions [298, 304]. In this study, this concept seemed to be important in the initial adoption of the exercise programme; most of the participants who adhered to the programme indicated that their involvement was because of their belief that the performance of the exercises would be beneficial to manage their condition. In terms of self-efficacy, people need to believe that they have the ability to affect their own health and that they have the tools to do that. High self-efficacy infers that the person is capable of controlling his/her own behaviour [298, 304]. In this study, factors that contributed to participants' self-efficacy and therefore to

their motivation to continue with the exercise programme included the belief in their ability to use the exercise DVD appropriately and to do the exercises safely.

Carer's involvement and providing participants with home visit support and phone calls to monitor progress were factors that were perceived by participants to promote self efficacy and facilitate their engagement in the exercise programme, which in turn contributed to adherence. Factors that would promote self-efficacy in this population need further investigation. Behavioural motivation techniques, which have been used successfully in patients with PD to promote self efficacy and consequently engagement in physical activities can be explored to engage people with HD in exercise programmes [169]. Within this strategy, counselling is used to promote a behavioural change through working closely with participants. The strategy includes education about the benefits of physical activity, advice about suitable activities, identifying and overcoming any perceived barriers to engage in physical activity, setting goals, and recruiting social support. This technique can be incorporated with other strategies reported in the literature, such as the motivational interviewing (MI) [305] to help subjects with HD and their carers build their self efficacy; hence facilitating the engagement to an independent exercise programme. The MI has been used in a variety of client populations with a positive effect on exercise adherence [305]. The strategy emphasizes reflective listening and negotiating rather than conflict; hence supporting participant's self efficacy and building confidence so that behaviour change is made possible. Future studies may therefore, need to consider such a strategy to effectively support the subjects with HD and their carers in making a behavioural change such as the engagement in an independent exercise programme.

The suggestion of making use of web-based technology rather than face-to-face sessions merits some consideration. Telemedicine has been successfully applied in other populations such as stroke, cerebral palsy and obstructive sleep apnoea syndrome to monitor the delivery of therapeutic interventions [306-309]. Although further investigation in this area is required, the use of telemedicine technology could be beneficial to people with HD to support their engagement in the independent use of the exercise DVD, or in any other unsupervised exercise programmes.

6.3.4 Trustworthiness of data

In qualitative interviews, there is the possibility that the researchers' views may influence interpretation of the data. To avoid this and to ensure rigour of the obtained results and conclusions, the Krefting framework [234] for analysing qualitative data was used. According to Krefting [234], credible results for a study with a qualitative design need to focus on testing its finding in the group of people from whom the data were obtained (member checking) and from people who are aware of the phenomenon being studied (peer checking) and testing the findings against other sources of data (triangulation). To ensure credible data in this study, different strategies were used as follows: first, full transcribing of the data from the interviews enhanced the credibility of the results by avoiding the selective recording of the information. Second, the accuracy of all the interview transcripts and their analytic categories, interpretations and conclusions were confirmed by the participants (member checking). Third, for accuracy, all the transcripts and their analytic categories were reviewed and debriefed by an independent researcher who was very knowledgeable about the topic of the research (peer checking). Fourth, data that was presented from the interviews were used to cross check against data obtained from the literature as well the data obtained from the quantitative analysis reported here (triangulation). The triangulation in particular provided multidimensional information in order to see a more complete and holistic context about how participants perceived their involvement in home-based exercise programme and factors that might affect participation and adherence [293].

Chapter Seven

Limitations of the Current study

7 Limitations of the current study

7.1 Possible limitations of the current study

This work is not without its limitations. A possible limitation of the first part of the study is the use of a single assessor who was aware of the subjects' diagnostic status. The assessor was not blinded to whether the subjects were HD gene positive or negative which may have been a factor in introducing bias. Knowledge of exposure status by the assessor can influence the scoring; thus producing biased results [310]. However, it should be noted that the vast majority of the outcomes were objective measures (scoring was based on timed tasks or automated process) and standardized procedures were used throughout all assessment sessions (see Appendix 4 for SOPs procedure) which may have helped in reducing bias.

For the second part of the study (i.e. the exercise intervention), it was not possible to blind participants to group allocation as person would know if they were asked to exercise or not. It should be further noted that a potential weakness of this study was the lack of formal blinding of the main assessor; follow-up assessments were undertaken by the same researcher who was involved in recruitment and that the same researcher also provided the intervention to the participants. The lack of blinded assessment may potentially have allowed the introduction of a systematic bias [311, 312]. Every effort therefore was made to overcome this limitation by strictly following the practical guidelines set for independent assessment in randomised clinical trials [311]. Standard operating procedures (SOPs) were used for all components of the assessment protocol (see Appendix 4 for SOPs). All tests were based on objective measures (i.e. tests were based on timed measures and the primary outcome involved an automated process for determining the primary outcome) or were self-administered (i.e. SF36). Tests that were potentially affected by examiner bias (i.e. BBS and mMS) were videotaped and rated by a blinded assessor using an established methodology [231]. The blinded assessor had no previous connection with the participants and acted purely as a video assessor. Practice and training of all assessments, including instructions and methods of scoring, was

undertaken before the commencement of the study which allowed the development of standardized data collection routines.

In terms of randomization, a minimisation method was used in this study to allocate participants into their groups. One of the concerns regarding the use of minimisation is the fact that next assignment can be anticipated in some situations [227]. The knowledge of which allocation is more likely to occur can result in selection bias. This issue however, can be handled using a probability of assignment to the "optimal" treatment group of less than one; hence the next assignment can never be predicted with certainty [228]. In this study, the randomisation was carried out with the aid of MINIM software in which the next participant was allocated to the group that would best minimise imbalance with a probability of 0.7 [229].

There were also some observable differences noted in the primary and secondary outcomes at baseline which have been accounted for in the analysis [147]. The 2 groups, however, were well matched at baseline for age and function (TFC) and additionally in the level of motor impairment, as reflected by the mMS scores. In small studies, such as this study, perfect balance is difficult to achieve even when using a balanced randomisation method (namely minimisation) as has been performed in this study. The strategy taken in this study is in line with the CONSORT guidelines for reporting, and the PSI and ICH directives on statistical analysis of clinical trials [269, 313, 314], which recommend that baseline differences should not be tested for significance but rather that these should be accounted for using proper statistical measures such as ANCOVA. Furthermore, individual responses in this study have been illustrated so as to aid interpretations of the data.

In terms of the process evaluation, the reported rate of adherence of people with HD to the home-based exercise programme in this study was very good. However, it must be remembered that the actual exercise dose was not measured. This study relied on self-report for the measurement of adherence. Without the use of costly accelerometers or cycle ergometers, it is not possible to measure frequency and intensity of home-based exercise interventions objectively [315, 316]. The reliance on participants' self report on recording adherence has its limitations; there is a possibility that participants might have over-reported their exercise activity, although the relatively large effect size of the

intervention and the specificity of the results suggest that participants' reports were reliable. Every effort was made by the researcher in this study to confirm the reported participation; reported adherence was confirmed with the carers (if applicable) and with participants during the weekly phone calls and at the time of the interviews.

Given the cognitive issues and communication difficulties in this population, structured interviews were considered to be the most appropriate method to gather meaningful responses regarding the subjective perceptions of participants and their carers in the involvement in the exercise programme. Although the highly structured format of the interview schedule provided mostly survey type data, the interviews included some open questions to which qualitative analysis was applied. A limitation of this qualitative work of the study is that only subjects who had consented to take part in the study and were followed up, and who were therefore expecting to have to exercise and were offered the intervention, were interviewed. Therefore, findings from this study may not be transferable to the subjects who declined to take part in the study or who dropped out, who may have been less willing or less able to exercise. Although many of the barriers identified in the interviews for non-adherence may also apply to the non-participants in the trial, it is likely that the non-participants had less support from their carers or were less motivated or less able to exercise and make lifestyle changes.

Overall, findings from this study might not be transferable to the general HD population because of the small sample that was used. The sample was one of convenience in that people who were recruited came from a clinic that was actively involved in the exercise type of intervention research, and in which subjects were committed to research in general, which might influence the findings presented in this study. Furthermore, whilst the home exercise was found to be feasible, the recruited subjects were relatively able participants so the results may apply to a limited range of people with HD. The exercise programme in this study was designed for people at early to mid stage HD. Whilst this programme did have the ability to be modified based on an individual's level of impairments and functioning, it was not designed for all people with HD. The vast majority of the enrolled subjects had good support from their carer; however, there were barriers to participation which suggests that this intervention might not be appropriate for all people with HD, and that other systems of delivering exercise need investigation in this population. Future studies should include a larger number of participants with a

wider range of impairments and also recruit participants from different regions. The advantage of such trials is that by recruiting consecutive individuals from multi-regional centres, the sample is likely to represent the characteristics of the entire population for which the intervention was designed [138], hence generalising the findings would be more appropriate.

Chapter Eight

Clinical implications, Recommendations for Future and Conclusions

8 Clinical implications, recommendations for future work and conclusions

8.1 Clinical implications

An important finding of this study is the potential of exercise interventions in improving gait variability in this population. Deficits in gait variability in HD exist early in the life cycle of the disease; they are associated with higher risk of falls as well as more nursing home admissions [38, 40, 43]. Regular participation in an exercise programme that has the potential to influence walking ability is therefore of great importance as it may reduce the risk of falls and postpone the need for institutionalization in this population.

Overall, given the degenerative nature of HD and the relatively short duration of the exercise programme (i.e. 8 weeks); positive findings reported here on multiple domains are clearly encouraging and have some important implications. The disease to date has no cure and all the current pharmacological managements remain symptomatic [31]. Thus, exercise interventions in HD may have a useful, adjunctive role in managing this condition. In view of the data presented here, exercise interventions may help in delaying the progression of motor deficits and improve independence by potentially addressing some physical impairments and limitations in activity. This in turn may have some economic benefits by potentially reducing the number of required medications and the number of visits to clinicians as well as delaying the need for nursing home admission.

In addition to the above, the positive findings reported here about the potential benefits of exercise in HD has some implications on future therapeutic trials in this population. Firstly, in the light of data obtained from this study exercise can confound with the effects would be obtained from drug trials; thus future pharmacological studies need to control for the subject's level of physical activity and receipt of exercise prior and during the period of the study. Secondly, future studies may need to examine the

combined effects of exercise training with the other potential therapeutic procedures in HD such as neural-transplantation; exercise training may be important to enhance recovery and functional gain following transplantation [317]. This is particularly important to be established in the HD population as evidence from animal models of HD [317] implies the need for task retraining following grafting.

On the whole, the exercise programme in this study was perceived to be suitable. In particular, the exercise DVD was perceived to be a supportive mechanism in helping people with HD to engage in an independent home-based exercise programme. Although the home-based setting limits social interaction to some extent, the convenience of doing the exercises when one is able, not having to travel to an exercise facility may outweigh this limitation and possibly result in a reduction on direct costs to the patient [161]. It seems therefore that an innovation such as a DVD can play a supporting role in the provision of exercise interventions for this population, offering a choice in the way that exercises can be delivered outside of therapy sessions or between consultations. The developed DVD has the potential to provide a sustainable exercise intervention for people with HD, and may ultimately contribute to an integrated management service for people with neurodegenerative diseases, facilitating individual management of this disabling condition. Given that there are a number of factors that would impact on the adherence to an independent exercise programme in a home setting (Chapter 6); this study suggests that therapists should work in collaboration with subjects with HD and their carers, evaluating their specific considerations on delivering such an exercise DVD to ensure feasibility and acceptability.

8.2 Recommendations and directions for future work

8.2.1 Issues related to methods and study designs

In the realm of outcome measures, this study additionally examined the psychometric properties of the core set of outcomes across the spectrum of the disease. Within this context, data and methods presented here revealed 3 main issues that need to be addressed in future research. Firstly, in this study, the stride time coefficient of variation was calculated based on pooled left and right strides. This method was used mainly to allow for adequate comparisons between data obtained from this study and data reported in previous HD research where which a similar method for gait variability

calculation was used [41, 42, 106, 107]. One of the concerns, however, regarding the use of this method (i.e. the use of averaged data from right and left strides) is the possibility that effects reported here are inflated due to the duplication of steps in consecutive strides. Thus, future studies needs to calculate effects on this parameter using data from right and left strides separately. Another approach that could be used in future research to calculate gait variability is to use step time CV instead of stride time CV. Step time CV can be calculated using the standard deviation from the residuals of each step around the mean of its respective limb. The advantage of such approach is that it allows an increased number of steps to be included in the analysis; thus providing a more precise measure of gait variability but at the same time ensures that there are no duplications of steps included in the calculation of the gait variability parameter [207].

Secondly, taking into account the test re-test reliability, a number of outcomes which included the TUG and the total score of the RT and SRT were susceptible to outliers (i.e. the difference score was large in a few cases relative to the difference score observed in the other cases). The presence of these outliers may have influenced the results by inflating the magnitude of variability calculated for these outcomes. Interestingly, the existence of these outliers was related to an observation of bias toward the larger values; in these measures there was a tendency that differences increases when average score increased. The bias toward larger values was also observed on the FSST. Larger value on the TUG and the FSST indicates more impairment. The bias toward larger values on these measures, therefore, suggests that movement disorders in the more impaired individuals would be expected to result in an increased variability of performance; hence reducing the reliability of repeat measurements. Thus, replicating this part of the study (i.e. reliability study) using a larger sample of subjects and stratifying subjects into groups by the stage of the disease to create sample homogeneity is warranted. Test re-test reliability studies with larger samples by the stage of the disease will help further defining the Minimal Detectable Changes (MDC) of the outcome measures that were used in this study and in generalizing the findings into the HD population.

Thirdly, in the realm of test-retest reliability, it should be noted that in this study all the subscales of the SF-36 were susceptible to a high degree of variability on repeated assessment. The source of variability reported here in the SF-36 subscales is not clear.

However, the occurrence of response shift is one possibility [118]. Response shift is common in populations in which individuals live with a chronic illness [266] as it is the case in HD. The possibility of response shift bias in HD is important in two lines of investigation. Observational studies of the natural course of HD may benefit from studying response shift explicitly. Such studies could describe whether and how quality of life change over time and how response shift affects these changes. Response shift may also be important in the design of future clinical trials in HD; the classic pre-test/ post-test designs may mask treatment effects if a subject's standard for rating of quality of life shifts over time. Designs that accommodate potential response shift may need to be considered in this population [318]. However, the concept of response shift warrants particular investigation in HD in the first instance.

In addition to the above, it should be noted that in the intervention study (Chapter 5), there were indications of regression toward the mean (RTM) in a number of outcomes. This included the primary outcome (i.e. gait variability) and some of the secondary outcomes such as the modified UHDRS-motor score (mMS); in each of these outcomes some subjects in the control group whose baseline performance was good tended to have unusual deterioration at the follow-up. Although in this study the use of ANCOVA accounts in part for the potential of RTM (i.e. ANCOVA has good statistical power to adjust subject's follow-up scores according to their baseline measurements) [290], it is important to highlight the possible impact that RTM may have on future studies. The main concern regarding RTM is that natural variation in repeated data can look like a real change. Thus, future work needs to take the potential of RTM into account at the study design stage. One of the possible approaches that can be adopted in future studies to minimise the possible effect of RTM is to include two or more baseline measurements. The RTM effect is thought to decrease with multiple measurements [290, 319]. Thus the advantage of taking extra-baseline measurements is that it gives better estimates of each subject true score before the intervention as well as a better estimate of within subject variation [319].

8.2.2 Issues related to evaluating mobility-related outcome measures

In the realm of outcome measures, this study examined the psychometric properties of the core set of outcomes in a group of pre-manifest HD. The results presented here

suggest that deficits in pre-manifest HD may be well represented by measures at the activity level of the ICF model. The PPT as well as the vast majority of the mobility measures which included the gait variability measure, the FSST, the CSST and the peak activity index were all sensitive to early changes in the pre-manifest HD and were considered to be highly repeatable. These findings are important and have major implications for future research as these outcomes have the potential to serve as tools to monitor disease progression in HD. Further validation of these outcomes using longitudinal design however is required. Furthermore, due to the sensitivity of these outcomes to early changes in HD, they have the potential to measure change in response to exercise interventions in the pre-manifest stage. Further validation, however is required in future research.

Whilst the vast majority of the outcomes in this study that were sensitive to changes in the pre-manifest HD were at the activity level, it is still not known what optimal outcomes would represent impairments and participation restrictions at the pre-manifest stage of HD. In terms of impairments, this study focused on evaluating measures of physical impairments such as balance and muscle strength. There is some evidence to suggest that subtle changes in these categories (i.e. balance and muscle strength) are present in pre-manifest individuals [92, 97, 98] and therefore further investigations validating outcomes that reflect these constructs and their relations to function at this early stage of the disease are required. Furthermore, subtle cognitive impairments that develop at the pre-manifest stage also need to be considered when validating functional outcomes in future studies. In fact, the combination of the subtle physical and cognitive changes is the one that may explain the early limitations on the functional abilities such as walking, as seen in this study. Future studies should provide in depth evaluation of the interaction between physical and cognitive impairments and their relationships to the activity and participation levels in the pre-manifest HD.

The data presented in chapter 4 confirm that the outcomes were sensitive to changes in the manifest HD at each of the levels of the ICF. Taking into account the test re-test reliability values and the calculated SEM as well as the responsiveness data to the exercise intervention (Chapter 5), balance is best assessed with the BBS, and activity limitations are well represented by measures of gait speed and gait variability as well as the CSST and the PPT. The psychometric properties of these measures suggest that they

are potentially useful outcomes to detect change over time and in response to exercise interventions in individuals with manifest HD.

Overall, from the range of outcomes evaluated here, gait variability appears to have the most potential to serve as a useful primary outcome in future exercise studies, both in manifest and pre-manifest HD. As indicated earlier, this measure is a key indicator of general mobility in HD [38, 93] and it is clear from the data presented here that gait variability has better sensitivity than the other measures of gait in capturing early mobility deficits in HD and in detecting responses to an exercise intervention. Furthermore, as gait variability seems to reflect multiple components of physical impairments, activity limitations and participation restrictions. Measures at each of the 3 levels of the ICF demonstrated correlations with gait variability; measures of balance, the other mobility measures including the levels of community walking and the measure of health-related quality of life correlated highly with gait variability. Gait variability, therefore, can be used as a summary measure that reflects each of the 3 domains of the ICF. Thus its use as a primary outcome in future exercise studies in HD is recommended.

Within the context of outcomes at the participation level (i.e. health-related quality of life measures), the SF-36 was the only outcome used in this study to evaluate quality of life. Data presented here demonstrated that SF-36 is susceptible to floor and ceiling effects across the spectrum of the disease. The SF-36 is a generic measure of health-related quality of life, and possibly may not have sufficiently captured disease-specific aspects of quality of life. Indeed, there is increasing recognition of the poor relevance of the SF-36 to quality of life recording in HD [117], and work is currently being undertaken to validate a more relevant disease-specific quality of life scale HDQoL [318]. Items of this developed scale have been generated from the perspectives of people with HD about disease related problems of daily living and therefore it is likely to be more sensitive than generic scales in capturing the true impact of HD. Furthermore, the scale has disease-specific physical and functional domains which provide the suggestion that it may allow the impact of exercise interventions that aim to improve function to be appropriately and holistically evaluated. Thus future research needs to consider using such a disease-specific health related quality of life measure in conjunction with a generic measure such as the SF-36.

8.2.3 Issues related to evaluating exercise interventions

This study was in the exploratory phase, where the feasibility, acceptability and potential benefits of a home- based exercise intervention in HD were evaluated; whilst the small sample size does prevent generalization of the results to the HD population at large, the approach taken here was in line with the staged approach advocated in the Medical Research Council (MRC) framework for developing and evaluating complex interventions [69, 70]. This step is essential before conducting large-scale trials and the encouraging findings reported here suggest that larger studies are now indicated. Indeed, future studies with larger populations should replicate findings from this study in other contexts and explore variations in intensity, duration as well as mode and type of exercise as part of the exploratory phase before conducting definitive randomised controlled trial. Within the MRC framework [69, 70] a definitive randomized clinical trial should not be undertaken until a variety of doses of therapy are examined at the exploratory stage. This will help in fully refining and defining the variables of interventions that can be evaluated and compared in definitive randomised clinical trials. Furthermore, the best timing of applying exercise interventions as well as effects on both motor and non-motor symptoms in future research should also be examined along with mechanistic evaluations as part of this exploratory phase. A number of future exploratory studies are proposed below to clarify the role of exercise interventions in people with HD.

In terms of the duration of exercise, whilst this study demonstrated that 8 weeks of structured exercise programme influenced mobility aspects in subjects with early to mid stage HD, the descriptive data from the 16 week follow up suggests that participants who continued exercising after the first eight weeks had a greater overall improvement in their gait variability. Although only descriptive data, this provides an indication that benefits from exercise in HD may be short lived if not maintained. Thus future studies exploring the long term effect of exercise interventions with variations in exercise duration are needed.

In terms of mode of exercise delivery, this study focused on an independent home-based exercise programme. The advantages of such a programme are the convenience of doing the exercises when one is able without having to travel to an exercise facility. The

disadvantages, however, include loss of the social aspects of exercising in a group and subjects having to be self-motivated. These aspects, along with the suggestion that people with HD would have different preferences for the location and the way of exercising [80], provide indications that the feasibility of other modes of exercise in HD such as exercise in groups or an independent exercise programmes in a gym setting needs to be examined in future research. Furthermore, it should be noted that there were barriers to participation in an independent exercise programme that were reported here and that safety can be an issue when performing exercises alone if one's symptoms are more advanced. Thus some subjects with HD would benefit from an intensive, one to one training exercise programme that is supervised by a therapist. This may take the form of a supervised exercise programme carried out in the participant's home or at the clinic. In such cases individual progression specific to the individual's particular clinical and social needs can be accommodated. Such a method of service delivery where closer supervision is provided needs further investigation in this population.

Within the realm of mode of exercise and considering the facilitators that were identified here, self efficacy was a main factor that influenced motivation and consequently the initial adoption of the exercise programme and the adherence to it. Strategies such as the weekly phone calls and the initial home visit were perceived to be important to build up participants' confidence and self efficacy and in turn to motivate them to adhere to the exercise programme in a home setting. Future research needs to extend these findings by exploring and examining the most effective strategies to improve self efficacy and other important aspects that would facilitate behavioural change in terms of exercise adoption and adherence in HD. For this purpose, it is advocated that interventions in future research be theory based. Self determination theory (SDT) [320] is a model that has been shown to be useful in enhancing physical activity motivation in healthy adults and can be used in future exercise studies in HD. SDT focuses on the degree to which an individual's behaviour is self-motivated and self-determined; thus behavioural change is made possible and maintained. In the context of exercise adherence, the SDT suggests that self efficacy and autonomy need to be fulfilled in order to enhance self-determined motivation [320]. This means that people need to feel a sense of choice with respect to their exercise goals (autonomy); they need to understand these goals and feel that they can be effective in carrying out the necessary actions to achieve these goals (self-efficacy). As per the data obtained

from this study, addressing barriers and facilitators and eliciting management strategies as well as promoting competence possibly via conducting regular contacts with subjects are strategies that have the potential to be used in future research to enhance autonomy and self-efficacy. These strategies are concordant with Motivational Interviewing (MI) [305], a counselling method that aims to promote behaviour change. MI involves avoiding controlling behaviours such as direct persuasion for change. Instead, this approach seeks to empower participants by eliciting personal reasons for change, addressing barriers, helping participants to become aware of discrepancies between goals and actions and supporting self efficacy. MI therefore can be seen as a method of promoting self determined motivation in and may offer a practical strategy for promoting adherence to exercise interventions in future investigations.

An important finding from this study was that the successful involvement of the carer was a key to the successful of the programme. Participants needed their carers to perform their exercises and to motivate them to adhere to the exercise programme. The main reason cited for non-adherence was the lack of the support from the carer or the carer-participant relationship. Thus future research need to focus on finding strategies to maximize the successful engagement of the carers in supporting people with HD in performing their exercises particularly when an exercise programme is applied at home setting. In the light of results presented here and taking into account self-determination theory (SDT); the role of the carer in future research needs to be considered as an extrinsic source of motivation and an important autonomy supportive mechanism. According to SDT, a person will develop and maintain more self-determined motivation when the personal context around them is autonomy supportive [320]. The idea of autonomy support refers to eliciting and acknowledging individuals' perspectives while minimizing pressure and control [321]. Thus future research needs to examine effective strategies for how the carers can successfully support the subject with HD to engage in independent exercise programmes whilst at the same time minimizing conflict and control. For example, a behavioural management technique, which has been used successfully in supporting carers of people with Alzheimer's Disease (AD) to encourage patients' engagement in home-based exercise programme, could be explored in people with HD [74]. The concept of this technique is based on teaching carers a problem-solving approach with the aim of motivating the patient to exercise and at the same time to avoid potential conflicts. Within this technique, carers are provided with skills on

how to identify and modify precipitants of participants' distress and behavioural problems that would impact on daily function and would adversely affect the subject-carer interactions. Additionally, carers using this technique can be given instructions about how to reduce the occurrence of these problems while also gaining skills on how to offer choices and options, supporting the subject' and making the exercise experience fun and enjoyable. Thus more research investigating the potential role of this approach on helping the carer to support people with HD to engage in an independent programme is warranted.

In terms of exercise type, this study demonstrated the benefits of a structured exercise programme that involved mainly the practice of task-specific activities which aimed to improve balance and functional activities in HD. However, it remains to be seen whether other types of exercises, such as aerobic as well as resistive exercises, can be beneficial in HD without causing undue harm. Aerobic exercises, in other neurological disorders, have been found to have a positive effect on motor and non-motor symptoms including cognitive functions [322, 323]. For example, the effect of aerobic exercise, compared with stretching, in participants with stroke was recorded on several measures of cognitive function in a study by Quaney et al [324]. In this study, participation in regular aerobic exercise resulted in improvement in speed of information, motor learning and implicit learning as measured using the serial reaction timed task (SRTT) and predictive grip force modulation (PGFM) with the less-affected hand. Similarly, significant improvements in the Mini Mental State Examination (MMSE) score were reported in a group of people with dementia after participation in an exercise programme with aerobic and resistive components over 12 months. The improvements in cognitive function reported in this study were also accompanied by improvements in the activities of daily living, cardiopulmonary function, endurance and balance. In another study, participation in 30 minutes of exercise training that included both aerobic and flexibility components significantly decreased depressive symptoms, improved health-related quality of life and decreased the number of hospitalisations among people with Alzheimer's disease (AD) [74]. Taking into account the available evidence from other populations about the benefits of aerobic exercises, their potential effects in HD warrant further investigation. This is particularly important considering the growing body of literature which suggests that exercise which is predominantly aerobic (unlike the intervention in this study) may have a protective effect by stimulating brain

perfusion and improving neurovascular integrity [325]. There is a need, therefore, for well designed trials to establish whether aerobic exercise is a useful intervention to improve or maintain motor and non-motor function in HD. This could be a vital area for investigation in this devastating long-term neurological condition where, to date, no disease-modifying treatment and very little in the way of symptomatic treatment is available.

Resistance training is another type of exercise that needs further investigation in people with HD in future studies. In this study, although the exercise programme included general strengthening exercises, it did not specifically target muscle strengthening. Progressive resistance exercise training was not included in the exercise programme which in part may explain the lack of significant improvements in muscle strength in this cohort. Progressive resistance training has generally been shown to be effective in the elderly and other neurodegenerative diseases such as PD in improving muscle strength and demonstrated a parallel effect in improving mobility [125, 326]. Resistance training may be equally beneficial in improving muscle strength in HD and therefore further investigations in this field are required.

In addition to the potential role in improving function, resistive training may also impede the noticeable decline in bone integrity observed in individuals with HD. Recent investigations have reported low bone mineral density (BMD) in individuals with HD, from an early stage of the disease, at the hip and lumbar spine which may lead to osteoporosis with the progression of the disease [327]. The aetiology of the lower BMD status in HD is still unknown; however it is likely to be related to performing lower levels of physical activity as seen in the data presented here. Whilst, to the knowledge of the researcher, investigations are lacking in the literature regarding bone health outcomes and exercise in HD, there is a strong rationale for why resistive exercises in particular need to be considered. According to the Wolff's law, loads applied to the bone via the muscular system in addition to loading the axial skeleton, which can be accomplished through resistive exercise, have a direct impact on bone formation and remodelling [125]. Furthermore, the American College of Sports Medicine (ACSM) maintains the efficacy of weight bearing exercise programmes in promoting bone health across the life-span [328]. Such programmes are widely used in the prevention and treatment of osteoporosis in healthy adults and in adults with neurodegenerative disease

such as PD [125, 329]. People with HD may stand to derive equal benefit from resistive exercise; however, these potential benefits in improving bone health parameters remain to be determined.

In term of the best time of applying exercise interventions in HD, future exercise studies may need to be initiated in the pre-manifest HD stage. Such studies would aim to target motor deficits early in the disease life cycle, before they begin to impact on a person's ability to participate in the community. This is particularly important as there is a growing body of evidence suggesting that exercise has a neuroprotective effect in other neurodegenerative disease such as AD. A meta-analysis of prospective cohort studies suggests that participation in regular physical activities reduces the risk of dementia and Alzheimer's disease by 28% and 45% respectively [330]. These findings along with a report that a passive lifestyle may potentially influence symptom onset in patients with HD [67] and inferences made from HD animal models suggesting that exercise may have direct effects on disease progression and plasticity, provides theoretical support for exercise interventions in the pre-manifest stage. Thus, future studies examining the effects of exercise in pre-manifest HD and their impact on disease onset and disease progression are indicated.

Investigation of the potential mechanisms underlying the functional gains reported in this study is clearly required. A number of studies have shown that in both intact and brain damaged rodents, structured exercise appears to drive a set of coordinated central nervous system changes, including circuit reorganization [331]. Studies in animals with cortical lesions have shown that repetitive performance of challenging motor tasks promoted neuroplastic changes within the cortical and sub-cortical areas of the brain through increased synaptogenesis [332, 333], and suggested that this may underlie the reported improvements. The increased synaptogenesis, observed with the performance and acquisition of motor tasks, has been related in some studies to the increase of synthesis and release of proteins that promote neuronal survival [334]. Although the specific proteins required for such plasticity are yet to be fully elucidated, brain-derived neurotrophic factor (BDNF) increases in an activity-dependent manner making it a natural candidate to mediate the benefits of exercise on brain health [61]. Furthermore, BDNF is known to be important for the survival of striatal neurons [335]. BDNF levels were specifically shown to be rescued in the striatum of R6/1 HD mice housed in an

enriched environment, and were associated with a delayed onset of HD-like symptoms [64].

8.3 Conclusions

The main aim of this research was to evaluate the feasibility, acceptability and potential benefits of a home-based exercise programme in people with early to mid-stage HD. To the knowledge of the researcher, this is the first systematic controlled trial of a defined exercise intervention in people with HD. There was no safety concerns related to the exercise programme in this sample. In addition, the study demonstrated that a home-based exercise programme was feasible, and that most individuals demonstrated excellent adherence to the programme. The latter is important, as reduced motivation is one of the core features of HD [31], and the capacity of this patient group to adhere to an exercise programme was previously unknown. Furthermore, this short-term exercise programme also resulted in significant at the first follow-up, in a range of measures at the body structure and function as well as activity levels of the ICF model. This included the primary outcome of gait variability and secondary measures of gait speed, balance, mobility and community walking as well as functional performance in ADL. Given the degenerative nature of HD and the relatively short duration of the exercise intervention used in this study, this is clearly an important and highly encouraging finding.

The significant improvement in the primary outcome (i.e. gait variability) is particularly important. In exercise trials, it is important that the deficits targeted by the intervention are not the primary outcome [138]. In this study, although a walking component was part of the intervention, there was no specific gait training protocol incorporated into the exercise programme and this leads to the suggestion that the improvements reported here can be considered a response to the intervention per se.

Although the exercise programme in this study was found to significantly improve measures at the physical impairment and activity levels, there was no significant improvement in the used measure at the participation level. The only outcome used to evaluate participation was the SF-36. It is possible that this result is related to the susceptibility of the SF-36 subscales to a certain degree of variability on repeated

testing. Variability of a measure on repeated testing decreases the power of a study to detect differences between groups because of the random error of measurement that causes an increase in variance. It should be noted however, that large effect sizes were observed on the physical function subscale and the aggregate score of the physical domain (i.e. physical summary component). Taking into account the magnitude of the improvement on the physical functioning subscale and the physical summary component of the SF-36 (i.e. the large effect sizes on these subscales) and the perceptions of the intervention reported by participants (Chapter 6 of process evaluation), lack of significant improvements in these subscales is likely to be related to the small sample size in this study. It can also be related to the use of SF-36 as a generic measure of health-related quality of life. The evaluation of the impact of exercise interventions on health-related quality of life in this population with a larger sample and with the use of disease-specific quality of life measures in conjunction with the SF-36 is required in future studies.

This work is not without limitations. The sample size was small and the main assessor in this study was not blinded to group allocation. However steps were taken to blind as far as possible and limit any assessor bias (for example by employing blinded video-rating and further more by the use of an automated process for determining gait parameters). There were also some observable differences noted on some of the outcomes at baseline. In addition, the potential of regression toward the mean (RTM) was noted on some of the outcome measures. To account for these limitations (i.e. differences at baseline and RTM in the analyses, ANCOVA was used in line with the CONSORT guidelines [269] and further individual responses were illustrated to aid interpretations of the data. However, it is important to highlight the potential impact that such limitations namely baseline differences (people with different levels of impairments at baseline may respond differently to the applied intervention) may have on future trial outcomes. To account for baseline differences, future studies may need to consider evaluating the effects of exercise interventions according to the stage of the disease to ensure homogeneity of groups at the outset, and further to evaluate how people with HD at different stages of the disease respond to exercise interventions. In addition, to minimise the potential effect of RTM, future studies may need to consider the involvement of multiple baseline measurements[290, 319].

The small sample size in this study does prevent generalization of the results to the HD population at large however the approach taken here is in line with the staged approach advocated in the Medical Research Council Framework for Developing and Evaluating Complex Interventions [69]. Establishing, safety and feasibility of an exercise intervention, estimating effects and piloting potential outcome measures are all essential steps before large scale definitive trials can be considered. Thus, findings from this study prepare the ground for future detailed exercise studies in HD. Summary of directions for future research based on the data presented here is provided in Figure 8.1.

Figure 8.1: Summary of proposed future studies in line with the Medical Research Council (MRC) framework for developing and evaluating complex interventions [69].

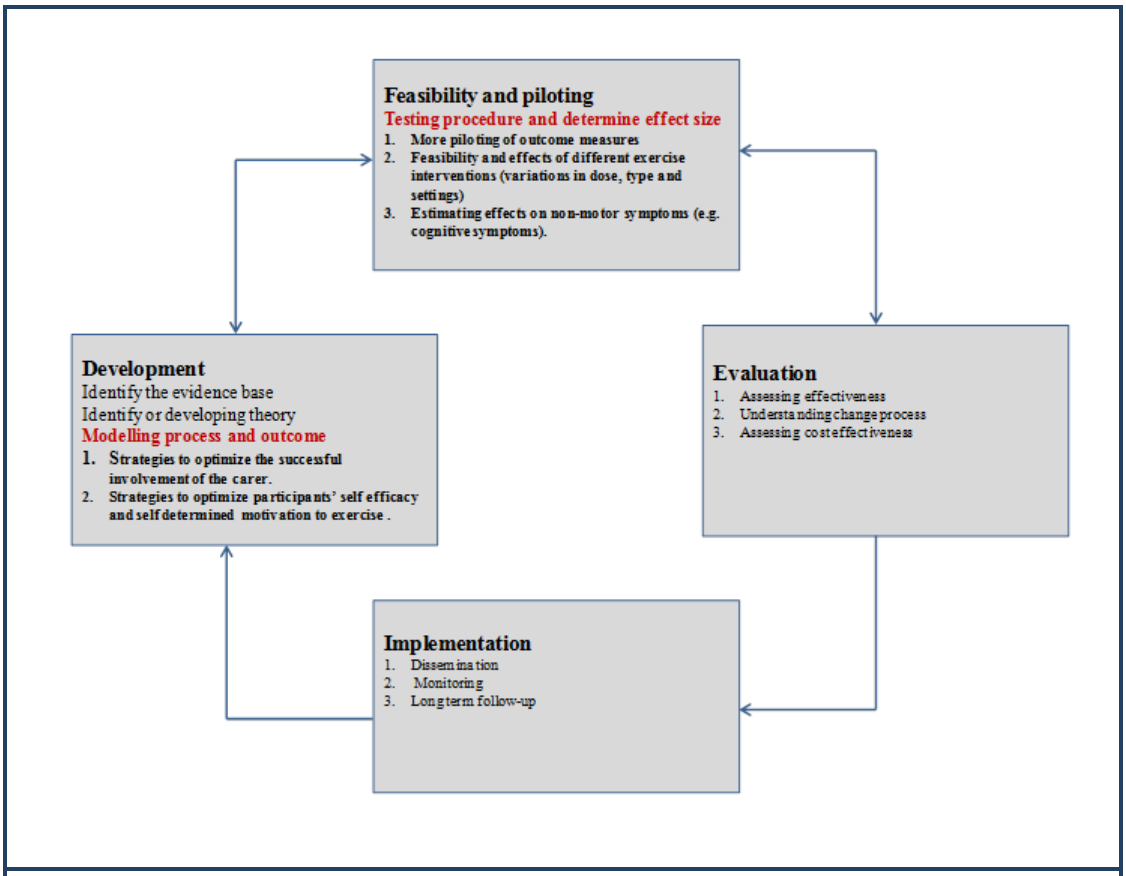


Figure 8.1: Directions for future research includes the following: 1) modelling process to refine the intervention used in this study) feasibility and piloting to additionally pilot outcomes and examine feasibility and effects of variations of exercise dose and type on motor and none motor symptoms.

In the realm of outcome measures, findings from this study suggest that gait variability show the most promise to serve as a primary outcome in future exercise studies both in manifest and pre-manifest HD. In addition, this study suggests that outcomes that were sensitive to changes across the spectrum of the disease and that were highly repeatable on repeated assessment (i.e. Physical Performance Test and Chair Sit to Stand Test) have the potential to measure responsiveness to change in exercise studies and therefore they need to be considered in future work. Further investigations on a larger sample, however, are required to refine the MDC values calculated for these measures.

Within the context of outcomes, all measures related to quality of life that were recorded in this study were highly variable on repeated assessment. Shift response is

one possible mechanism [118] that would explain the high variability and as this may have implications on the designs of future clinical trials, future work needs to adequately evaluate of whether shift response occurs in HD and how it would affect the assessment of health-related quality of life over time in this population.

In term of exercise intervention, one of the main findings of this study is that the successful involvement of the carer was a key to the success of the programme. Self efficacy and motivation were two main determinants for engagement in an independent exercise programme. These findings highlight the importance of further exploring strategies that would enhance self management and ensure behaviour-change in term of adherence to exercise programme as this (i.e. adherence) is very relevant to ensure efficacy of an intervention in future work [336]. In line with the MRC framework for complex interventions, the next step of the research presented here, would be to focus on further modelling the intervention that was used in this study for further future evaluation. To achieve this, a series of qualitative work in form of focus groups and interviews with subjects with HD and their carers needs to be conducted with the aim of refining the theoretical framework underpinning the intervention and determining contents and structures needs to be incorporated in behavioural techniques to optimize subject's self efficacy and motivation as well as the successful involvement of the carer.

In conclusion, this study shows the potential of exercise as a therapeutic intervention to improve mobility in people with HD and justifies further work to evaluate the effects of exercise in this population. Given the inferences made from animal models suggesting that exercise may have direct effects on disease progression and plasticity [65, 66] and the fact that advances in HD are likely to have implications for other neurodegenerative conditions [337], results from this study are important and provide a landmark for future more extensive studies. Future work with a larger sample should replicate this study to confirm findings and additionally explore variations in mode, dose and type of exercise. Examining effects on both motor and non-motor symptoms along with mechanistic evaluations is now indicated. It remains to be seen whether other types of physical interventions, such as aerobic exercise are feasible and can be beneficial in HD without causing undue harm. Aerobic exercise in other neurodegenerative disease, such as Alzheimer's disease, is suggested to have a positive effect on motor and non-motor symptoms including cognitive functions [337] and may have a protective effect by

stimulating brain perfusion and improving neurovascular integrity [325]. This could be a vital area for investigation in this long-term neurological condition where to date no disease-modifying treatment is in existence.

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9 References

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Appendix 1: Information Sheets of the Study and Consent Forms

10 Appendix 1: Information sheets of the study and consent forms

Participant information sheet

(Healthy group)

'' A study of movement deficits and physiotherapy in people with Huntington's disaese''

You are being invited to take part in a research study that is investigating physiotherapy for people with Huntington's disease (HD). Before you make a decision, it is important that you understand why the research is being done and what it will involve.

Part 1 of this information sheet tells you the purpose of this study and what will happen if the participant takes part. Part 2 gives you more detailed information about the conduct of the study.

Please take the time to read the following information carefully and discuss it with others if you wish.

PART 1

What is the reason for the study?

People with Huntington's disease (HD) may have problems with gait and balance (which contribute to mobility difficulties) over the disease period. Little is known about when these impairments might develop and what influence their development. Physiotherapy is presumed to play a role in assisting people with HD to enhance their balance and improve their mobility, but participation in a hospital or clinic-based physiotherapy is sometimes difficult to coordinate as it needs frequent trips outside the

home. Home-based interventions may be easier for people with HD to be involved in. However, research into the delivery of such home-based programs is limited. A better understanding of the factors influencing gait impairments (across the continuum of the disease) as well as the factors influencing success of home based intervention may help us provide an improved standard of care to people with HD.

What is the purpose of the study?

The purpose of this study is to evaluate home-based physiotherapy-led interventions in individuals with Huntington's disease (HD). A further purpose of this study is to investigate factors that influence gait impairments in HD across the disease continuum.

Why was I chosen to take part in this study?

You have been invited to participate in the study as we are recruiting a group of individuals who are healthy and have not been diagnosed with HD. It is important to create a healthy comparison group in order to investigate the differences between people with HD and those without HD.

Do I have to take part?

There is no obligation to take part in the study. We will describe the study and go through this information sheet, which we will then give to you. We will then ask you to sign a consent form to show you have agreed to take part. If you do decide to take part you are free to withdraw at any time and without giving a reason.

What will happen to me if I take part?

If you would like to take part, we will arrange a suitable time for you to participate. This will be at your convenience. You will be asked to sign a written consent form indicating that you are happy to take part in the study and you will then be asked:

1- To visit the Research Centre for Clinical Kinaesiology (RCCK) for assessments. The RCCK is based in the Heath Campus, Department of Physiotherapy, Cardiff University. The total duration of the assessment visit should not exceed 2 hours. During the assessment visit, you will be asked about your medication use, your living circumstances and any falls you might have had in the past 12 months. At the assessment visit we will record your weight, height, balance, strength level, muscle flexibility level, mobility level and walking characteristics. We will ask you to wear a small device on your waist while you perform the following tasks:

a. Walk on a carpet that is embedded with sensors that will enable us to evaluate your walking.
b. Perform a number of movements while measurements are being made. These movements include testing of strength of lower limb muscles, standing up, standing quietly with eyes open and closed, standing placing one foot in front of the other, and walking.
c. As part of the assessment you will be asked to complete a questionnaire about your general physical functionality and general health perception.

Note: A video camera will be used to video tape the assessment sessions.

2- You will be requested to participate in monitoring of your general mobility.

You will be asked to wear two activity monitors at home. You will be asked to wear the monitors 8 consecutive days and not to remove the sensor except for bathing and sleep. At the same time you will be asked to report if you have any falls and comment on the wearability of the monitors.

Expenses:

There will be no special payment for your involvement in this study; however we will refund your travel and parking costs when attending research assessments.

What are the possible benefits of taking part?

There are no specific benefits to you in taking part in this study however, the results of this study may help us to provide better physiotherapy treatment in the future for people with HD.

What are the possible disadvantages and risks of taking part?

The measurements to be taken are routinely used in people with neurological conditions; however any testing is not without some risk. The proposed clinical assessment is however unlikely to cause undue stress to you. The care and comfort will be ensured at all times. Before and during the study you will be given the opportunity to discuss any concerns with the researchers in private.

What if there is a problem?

Any complaint about the way you have been dealt with during the study or any possible harm you might suffer will be addressed. The detailed information on this is given in part 2.

What happens when the research study stops?

After you have participated in the study you are still free to contact any of the researchers with any question or queries you may have regarding the study. If you are interested in the data collected during your participation we would be happy to send you a report.

Confidentiality- Will my taking part in this study be kept confidential?

Yes. We will follow ethical and legal practice and all information about you will be handled in confidence. The details are included in Part 2.

What if you would like extra information or independent advice about participation in research?

You are free to contact the researchers at the contact details provided at the end of this letter if you would like more information. Alternatively, information on taking part in Clinical Research can be obtained from the UK Clinical Research Collaboration (UKCRC). This organisation provides independent advice and information on participating in clinical research. Further details, including access to a patient leaflet concerning clinical trial involvement, can be obtained from the UKCRN website: www.ukcrc.org/publications/informationbooklets or by emailing: info@ukcrn.org.uk

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 new information becomes available?

Sometimes we get new information about the treatment being studied. If this happens, we will tell you and discuss whether you should continue in the study. If you decide to continue in the study we may ask you to sign an updated consent form.

What will happen if I don't want to carry on with the study?

If you withdraw from the study, we will destroy all your identifiable samples, but we will need to use the data collected up to your withdrawal. You are free to withdraw from the study at any time without giving any reason.

What if there is a problem?

If you are harmed by taking part in this research study, there are no special compensation arrangements. If you are harmed due to someone's negligence, then you may have grounds for a legal action but you may have to pay for it. Regardless of this, if you wish to complain, or have any concerns about any aspect of the way you have been approached or treated during the study, the normal National Health Service and University complaints mechanism should be available to you.

Confidentiality- will my taking part in this study be kept confidential?

We would like to reassure you that your personal details would be kept strictly confidential. No one, except the named investigators would have access to these details and no identifying details would appear in our published results.

What will happen to the results of the research study?

The results of the study may be presented at conferences and published in medical or scientific journals. If you would like, we 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 organizing and funding the research?

The study is being organized by the Department of Physiotherapy, School of Healthcare Studies, Cardiff University. The study will be run by Hanan Khalil in collaboration with

Dr Monica Busse, Dr Robert van Derusen, Dr Lori Quinn and Professor Anne Rosser. Part funding for this study is provided by a grant from the Paul Jeffery Waters fund.

Who has reviewed the study?

All research in the NHS is looked at by independent group of people, called a Research Ethics Committee, whose role it is to protect your safety, rights, wellbeing and dignity. This study has been reviewed and given favourable opinion by Research and Development Committee and the South East Wales Research Ethics Committee as well as the joint Cardiff and Vale NHS Trust and Cardiff University Risk Review Committee.

Further information and contact details

If you have any questions or queries please don't hesitate to contact Hanan Khalil using the contact information addressed below.

Hanan Khalil

Department of Physiotherapy, Cardiff University, Ty Dewi Sant, Heath Park, CF14 4XNTel: 0292068773

Participant information sheet

(HD pre-symptomatic group)

''A study of movement deficits and physiotherapy in people with Huntington's disease''

You are being invited to take part in a research study that is investigating physiotherapy for people with Huntington's disease (HD). Before you make a decision, it is important that you understand why the research is being done and what it will involve.

Part 1 of this information sheet tells you the purpose of this study and what will happen if the participant takes part. Part 2 gives you more detailed information about the conduct of the study.

Please take the time to read the following information carefully and discuss it with others if you wish.

PART 1

What is the reason for the study?

People with Huntington's disease (HD) may have problems with gait and balance (which contribute to mobility difficulties) over the disease period. Little is known about when these impairments might develop and what influence their development. Physiotherapy is presumed to play a role in assisting people with HD to enhance their balance and improve their mobility, but participation in a hospital or clinic-based physiotherapy is sometimes difficult to coordinate as it needs frequent trips out side the home. Home-based interventions may be easier for people with HD to be involved in. However, research into the delivery of such home-based programs is limited. A better understanding of the factors influencing gait impairments (across the continuum of the disease) as well as the factors influencing success of home based intervention may help us provide an improved standard of care to people with HD.

What is the purpose of the study?

The purpose of this study is to evaluate home-based physiotherapy-led interventions in individuals with Huntington's disease (HD). A further purpose of this study is to investigate factors that influence gait impairments in HD across the disease continuum.

Why was I chosen to take part in this study?

You have been invited to participate in the study as we are recruiting a group of individuals who have tested gene positive for the disease but are without clinical symptoms (pre-symptomatic HD). You will take part of the study that aims to investigate factors associated with gait impairments according to the disease stage. It is important to understand this component in pre-symptomatic HD. Understanding of gait pattern across the disease continuum will advance our understanding of mobility difficulties in this population and ultimately provide insight for therapeutic interventions.

Do I have to take part?

There is no obligation to take part in the study. We will describe the study and go through this information sheet, which we will then give to you. We will then ask you to sign a consent form to show you have agreed to take part. Your decision will not affect your future care. If you do decide to take part you are free to withdraw at any time and without giving a reason.

What will happen to me if I take part?

If you would like to take part, we will arrange a suitable time for you to participate. This will be at your convenience. You will be asked to sign a written consent form indicating that you are happy to take part in the study and you will then be asked:

1- To visit the Research Centre for Clinical Kinaesiology (RCCK) for assessments up to 2 times over the study duration. The RCCK is based in the Heath Campus, Department of Physiotherapy, Cardiff University. The total duration of each visit should not exceed 2 hours.

During the assessment visit you will be asked about your medication use, your living circumstances and any falls you might have had in the past 12 months. At the assessment visit we will record your weight, height, balance, strength level, muscle flexibility level, mobility level and walking characteristics. We will ask you to wear a small device on your waist while you perform the following tasks:

a. Walk on a carpet that embedded with sensors that will enable us to evaluate your walking.
b. Perform a number of movements while measurements are being made. These movements include testing of strength of lower limb muscles, standing up,

standing quietly with eyes open and closed, and standing placing one foot in front of the other and walking.

c. As part of the assessment you will be asked to complete a questionnaire about your general physical functionality and general health perception.

Note: A video camera will be used to video tape the assessment sessions.

2- You will be requested to participate in monitoring of your general mobility. In between assessment visits you will be asked to wear two activity monitors at home. You will be asked to wear the monitors 8 consecutive days and not to remove the sensor except for bathing and sleep. At the same time you will be asked to report if you have any falls and comment on the wearability of the monitors.

Expenses:

There will be no special payment for your involvement in this study; however we will refund your travel and parking costs when attending research assessments.

What are the possible benefits of taking part?

There are no specific benefits to you in taking part in this study however, the results of this study may help us to provide better physiotherapy treatment in the future for people with HD.

What are the possible disadvantages and risks of taking part?

The measurements to be taken are routinely used in with neurological conditions; however any testing is not without some risk. The proposed clinical assessment is however unlikely to cause undue stress to you. The care and comfort will be ensured at all times. Before and during the study you will be given the opportunity to discuss any concerns with the researchers in private.

What if there is a problem?

Any complaint about the way you have been dealt with during the study or any possible harm you might suffer will be addressed. The detailed information on this is given in part 2.

What happens when the research study stops?

After you have participated in the study you are still free to contact any of the researchers with any question or queries you may have regarding the study. If you are interested in the data collected during your participation we would be happy to send you a report.

Confidentiality- Will my taking part in this study be kept confidential?

Yes. We will follow ethical and legal practice and all information about you will be handled in confidence. The details are included in Part 2.

What if you would like extra information or independent advice about participation in research?

You are free to contact the researchers at the contact details provided at the end of this letter if you would like more information. Alternatively, information on taking part in Clinical Research can be obtained from the UK Clinical Research Collaboration (UKCRC). This organisation provides independent advice and information on participating in clinical research. Further details, including access to a patient leaflet concerning clinical trial involvement, can be obtained from the UKCRN website: www.ukcrc.org/publications/informationbooklets or by emailing: info@ukcrn.org.uk

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 new information becomes available?

Sometimes we get new information about the treatment being studied. If this happens, we will tell you and discuss whether you should continue in the study. If you decide not to carry on, your clinical care will not be affected in any way. If you decide to continue in the study we may ask you to sign an updated consent form.

What will happen if I don't want to carry on with the study?

If you withdraw from the study, we will destroy all your identifiable samples, but we will need to use the data collected up to your withdrawal. You are free to withdraw from the study at any time and this will not affect your continuing medical care.

What if there is a problem?

If you are harmed by taking part in this research study, there are no special compensation arrangements. If you are harmed due to someone's negligence, then you may have grounds for a legal action but you may have to pay for it. Regardless of this, if you wish to complain, or have any concerns about any aspect of the way you have been approached or treated during the study, the normal National Health Service and University complaints mechanism should be available to you.

Confidentiality- will my taking part in this study be kept confidential?

We would like to reassure you that your personal details would be kept strictly confidential. No one, except the named investigators, would have access to these details and no identifying details would appear in our published results.

GP notification

We do feel that it is important that your GP is kept informed. We would like to let him/her know if you agree to take part in the study and we will supply him/her with a copy of this information sheet. However, please let us know if you would prefer that your GP is not informed.

What will happen to the results of the research study?

The results of the study may be presented at conferences and published in medical or scientific journals. If you would like, we 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 organizing and funding the research?

The study is being organized by the Department of Physiotherapy, School of Healthcare Studies, Cardiff University. The study will be run by Hanan Khalil in collaboration with Dr Monica Busse, Dr Robert van Derusen, Dr Lori Quinn and Professor Anne Rosser. Part funding for this study is provided by a grant from the Paul Jeffery Waters fund.

Who has reviewed the study?

All research in the NHS is looked at by independent group of people, called a Research Ethics Committee to protect your safety, rights, wellbeing and dignity. This study has been reviewed and given favourable opinion by Research and Development Committee

and the South East Wales Research Ethics Committee as well as the joint Cardiff and Vale NHS Trust and Cardiff University Risk Review Committee.

Further information and contact details

If you have any questions or queries please don't hesitate to contact Hanan Khalil using the contact information addressed below. Hanan Khalil Department of Physiotherapy, Cardiff University, Ty Dewi Sant, Heath Park CF14 4XN Tel: 02920687739

Participant information sheet

(HD symptomatic group)

''A study of movement deficits and physiotherapy in people with Huntington's disease''

You are being invited to take part in a research study that is investigating physiotherapy for people with Huntington's disease (HD). Before you make a decision, it is important that you understand why the research is being done and what it will involve.

Part 1 of this information sheet tells you the purpose of this study and what will happen if the participant takes part. Part 2 gives you more detailed information about the conduct of the study.

Please take the time to read the following information carefully and discuss it with others if you wish.

PART 1

What is the reason for the study?

People with Huntington's disease (HD) may have problems with gait and balance (which contribute to mobility difficulties) over the disease period. Little is known about when these impairments might develop and what influence their development. Physiotherapy is presumed to play a role in assisting people with HD to enhance their balance and improve their mobility, but participation in a hospital or clinic-based physiotherapy is sometimes difficult to coordinate as it needs frequent trips out side the home. Home-based interventions may be easier for people with HD to be involved in. However, research into the delivery of such home-based programs is limited. A better understanding of the factors influencing gait impairments (across the continuum of the disease) as well as the factors influencing success of home based intervention may help us provide an improved standard of care to people with HD.

What is the purpose of the study?

The purpose of this study is to evaluate home-based physiotherapy-led interventions in individuals with Huntington's disease (HD). A further purpose of this study is to investigate factors that influence gait impairments in HD across the disease continuum.

Why was I chosen to take part in this study?

You have been invited to participate in the study as we are recruiting a group of individuals who have been diagnosed with HD.

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Do I have to take part?

There is no obligation to take part in the study. We will describe the study and go through this information sheet, which we will then give to you. We will then ask you to sign a consent form to show you have agreed to take part. Your decision will not affect your future care. If you do decide to take part you are free to withdraw at any time and without giving a reason.

What will happen to me if I take part?

If you would like to take part, we will arrange a suitable time for you to participate. This will be at your convenience. You will be asked to sign a written consent form indicating that you are happy to take part in the study and you will then be asked:

1- To complete a home-based physiotherapy exercise program for 8 weeks at a certain time point during the study. The programme will comprise a series of strength, flexibility, balance and endurance exercises specifically tailored for people with HD. An exercise DVD as well as an educational booklet will be given to you to help you with completing the exercise programme. You will be asked to do the exercises at least 3 times a week. The total duration of the exercises session will not exceed one hour. In addition to the performing the exercises from the DVD, you will be asked to undertake one of the exercises of your preferences or to undergo a walking program once a week for 30 minutes. With assistance from your main carer, you will be asked to keep a diary, indicating the days that you do the exercises and also noting any problems or general observations. We will visit you at home when you first start to do the exercises to ensure that you are managing them and after the initial visits, you will be telephoned weekly by the researcher to discuss the exercises. You will also be provided with a contact telephone number to speak to the researcher if you have any specific problems relating to the exercise programme.

At the end of the exercise programme we will ask you to complete one short questionnaire about the performed exercises. Additionally, we will interview you to obtain your opinion about the involvement in the program. We will also ask that your main carer is present at the interviews to be able to give any additional input, if this is required. The interview will not last more than 30 minutes.

Conversations that take place during the interview and the weekly telephone calls will be audio recorded. The spoken words on the audio tapes will be converted into writing by transcription. The taped conversations will be destroyed on completion of transcription of the tapes. A copy of the transcript will be made available to you for additional comment.

2- To visit the Research Centre for Clinical Kinaesiology (RCCK) for assessments up to 4 times over the study duration. The RCCK is based in the Heath Campus, Department of Physiotherapy, Cardiff University. The total duration of each visit should not exceed 2 hours.

During the first visit you will be asked about your medication use, your living circumstances and any falls you might have had in the past 12 months. At each visit we will record your weight, height, balance, strength level, muscle flexibility level, mobility level and walking characteristics. We will ask you to wear a small device on your waist while you perform the following tasks:

a. Walk on a carpet that embedded with sensors that will enable us to evaluate your walking.
b. Perform a number of movements while measurements are being made. These movements include testing of strength of lower limb muscles, standing up, standing quietly with eyes open and closed, and standing placing one foot in front of the other and walking.
c. As part of the assessment you will be asked to complete a questionnaire about your general physical functionality and general health perception.

Note: A video camera will be used to video tape the assessment sessions.

3- You will be requested to participate in monitoring of your general mobility. In between assessment visits you will be asked to wear two activity monitors at home. You will be asked to wear the monitors 8 consecutive days and not to remove the sensor except for bathing and sleep. At the same time you will be asked to report if you have any falls and comment on the wearability of the monitors.

Expenses:

There will be no special payment for your involvement in this study; however we will refund your travel and parking costs when attending research assessments.

What are the possible benefits of taking part?

There are no specific benefits to you in taking part in this study however, the results of this study may help us to provide better physiotherapy treatment in the future for people with HD .

What are the possible disadvantages and risks of taking part?

The proposed clinical assessment is however unlikely to cause undue stress to you. The care and comfort will be ensured at all times. The proposed exercise program is low intensity and does not involve any heavy load bearing exercise or high intensity cardiovascular intervention and therefore poses minimal risk to you. You will be advised on recognition of any warning signs at which to cease the execution of exercise. You will be provided with a contact telephone number to speak to the researcher if you have any specific problems relating to the exercise intervention. If necessary you will be seen in the HD clinic for review. Before and during the study you will also be given the opportunity to discuss any concerns with the researchers in private.

What if there is a problem?

Any complaint about the way you have been dealt with during the study or any possible harm you might suffer will be addressed. The detailed information on this is given in part 2.

What happens when the research study stops?

After you have participated in the study you are still free to contact any of the researchers with any question or queries you may have regarding the study. If you are interested in the data collected during your participation we would be happy to send you a report.

Confidentiality- Will my taking part in this study be kept confidential?

Yes. We will follow ethical and legal practice and all information about you will be handled in confidence. The details are included in Part 2.

What if you would like extra information or independent advice about participation in research?

You are free to contact the researchers at the contact details provided at the end of this letter if you would like more information. Alternatively, information on taking part in

Clinical Research can be obtained from the UK Clinical Research Collaboration (UKCRC). This organisation provides independent advice and information on participating in clinical research. Further details, including access to a patient leaflet concerning clinical trial involvement, can be obtained from the UKCRN website: www.ukcrc.org/publications/informationbooklets or by emailing: info@ukcrn.org.uk.

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 new information becomes available?

Sometimes we get new information about the treatment being studied. If this happens, we will tell you and discuss whether you should continue in the study. If you decide not to carry on, your clinical care will not be affected in any way. If you decide to continue in the study we may ask you to sign an updated consent form.

What will happen if I don't want to carry on with the study?

If you withdraw from the study, we will destroy all your identifiable samples, but we will need to use the data collected up to your withdrawal. You are free to withdraw from the study at any time and this will not affect your continuing medical care.

What if there is a problem?

If you are harmed by taking part in this research study, there are no special compensation arrangements. If you are harmed due to someone's negligence, then you may have grounds for a legal action but you may have to pay for it. Regardless of this, if you wish to complain, or have any concerns about any aspect of the way you have been approached or treated during the study, the normal National Health Service and University complaints mechanism should be available to you.

Confidentiality- will my taking part in this study be kept confidential?

We would like to reassure you that your personal details would be kept strictly confidential. No one, except the named investigators, would have access to these details and no identifying details would appear in our published results.

GP notification

We do feel that it is important that your GP is kept informed. We would like to let him/her know if you agree to take part in the study and we will supply him/her with a copy of this information sheet. However, please let us know if you would prefer that your GP is not informed.

What will happen to the results of the research study?

The results of the study may be presented at conferences and published in medical or scientific journals. If you would like, we 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 organizing and funding the research?

The study is being organized by the Department of Physiotherapy, School of Healthcare Studies, Cardiff University. The study will be run by Hanan Khalil in collaboration with Dr Monica Busse, Dr Robert van Deursen, Dr Lori Quinn and Professor Anne Rosser. Part funding for this study is provided by a grant from the Paul Jeffery Waters Bequest fund.

Who has reviewed the study?

All research in the NHS is looked at by independent group of people, called a Research Ethics Committee to protect your safety, rights, wellbeing and dignity. This study has been reviewed and given favourable opinion by Research and Development Committee and the South East Wales Research Ethics Committee as well as the joint Cardiff and Vale NHS Trust and Cardiff University Risk Review Committee.

Further information and contact details

If you have any questions or queries, please don't hesitate to contact Hanan Khalil using the contact information addressed below. Hanan Khalil, Department of Physiotherapy, Cardiff University, Ty Dewi Sant, Heath Park, CF14 4XN, Tel: 02920687739

Participant consent sheet

Title of Project: <u>A study of movement deficits and physiotherapy in people with Huntington's Disease</u>

(Healthy group)

Please initial box

I confirm I have read and understood the information sheet, version 3.0 dated 14/05/09, for the above study and have had the opportunity to consider the information to ask questions and to have had these answered.	
I understand that my participation is voluntary and that I am free to withdraw at anytime without giving any reason, this will not affect my legal rights being in any way.	
I agree for the research assessments to be video taped.	
I understand that all information about me will be kept in a secure place and in a confidential way and destroyed once the study is completed.	
I understand that data will not be used for commercial purposes.	
I confirm that data from the study can be used in the final research report and other academic publications. I understand that these will be used anonymously and that no individual respondent will be identified in such report.	
I agree to take part in this study.	

Name of subject _____ Date _____

Signature _____

Name of Researcher _____ Date _____

Signature _____

When completed, 1 for patient, 1 for researcher site file

Participant consent sheet

Title of Project: <u>A study of movement deficits and physiotherapy in people with Huntington's Disease</u>

(HD pre-symptomatic group)

Please initial box

I confirm I have read and understood the information sheet, version 3.1 dated 14/05/09, for the above study and have had the opportunity to consider the information to ask questions and to have had these answered.	
I understand that my participation is voluntary and that I am free to withdraw at anytime without giving any reason, this will not affect my medical care or legal rights being in any way.	
I agree for the research assessments to be video taped.	
I understand that all information about me will be kept in a secure place and in a confidential way and destroyed once the study is completed.	
I understand that data will not be used for commercial purposes.	
I confirm that data from the study can be used in the final research report and other academic publications. I understand that these will be used anonymously and that no individual respondent will be identified in such report.	
I am willing for my GP to be notified that I am taking part in this study.	
I agree to take part in this study.	

Name of subject _____ Date _____

Signature _____

Name of Researcher _____ Date _____

Signature _____

When completed, 1 for patient, 1 for researcher site file

Participant consent sheet

Title of Project: <u>A study of movement deficits and physiotherapy in people with Huntington's Disease</u>

(HD Symptomatic group)

Please initial box

I confirm I have read and understood the information sheet, version 3.2 dated 14/05/09, for the above study and have had the opportunity to consider the information to ask questions and to have had these answered.	
I understand that my participation is voluntary and that I am free to withdraw at anytime without giving any reason, this will not affect my medical care or legal rights being in any way.	
I agree for the research assessments to be video taped.	
I agree for the conversations that take place during the interview and on the telephone to be tape recorded.	
I would like to have a copy of the transcript of the conversations, in order to make comments.	
I understand that all information about me will be kept in a secure place and in a confidential way and destroyed once the study is completed.	
I understand that data will not be used for commercial purposes.	
I confirm that data from the study can be used in the final research report and other academic publications. I understand that these will be used anonymously and that no individual respondent will be identified in such report.	
I am willing for my GP to be notified that I am taking part in this study.	
I agree to take part in this study.	

Name of subject _____ Date _____

Signature _____

Name of Researcher _____ Date _____

Signature _____

When completed, 1 for patient, 1 for researcher site file

Appendix 2: Exercise Diaries

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Exercise and physical activity diary (week 1)

Week start date:
Week end date:

A- Please tick activities that you performed during the week, indicating how many days you did the activity and how much time you spent in one of those days

Activity	Tick	Days/week	Minutes/day
Travelling in a motor vehicle like a train , bus or car			
Walking to go from one place to place			
Bicycling to go from one place to place			

B- Please tick activities that you performed in and around the house during the week, indicating how many days you did the activity and how much time you spent in one of those days

Activity	Tick	Days/week	Minutes/day
Chopping wood			
Heavy lifting			
Digging in the garden or the yard			
Carrying light loads			
Sweeping inside home			
Scrubbing floors			
Washing windows			
Raking in the garden or yard			
Others: (please describe)			

C- Please tick any sporting activities you performed during the week, indicating on how many

days you did the activity and how much time you spent doing the activity

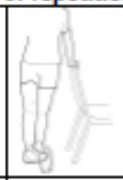
Activity	Tick	Days/week	Minutes/day
Exercise bike			
Going to the gym			
Others: (please describe)			

D- Please record how much time you usually spent sitting (on average over the last week). This may include sitting at a desk, visiting friends, reading or sitting or lying down to watch television.

E- Please record any additional activities that you have done

Exercise Diary (week 1) Week start date: Week end date:

1- Please check when exercise is completed (record the number of repetition for each exercise)

												
Session 1												
Session 2												
Session 3												
												
Session 1												
Session 2												
Session 3												

Appendix 3: Schedules of the Home visit and Weekly Phone Calls

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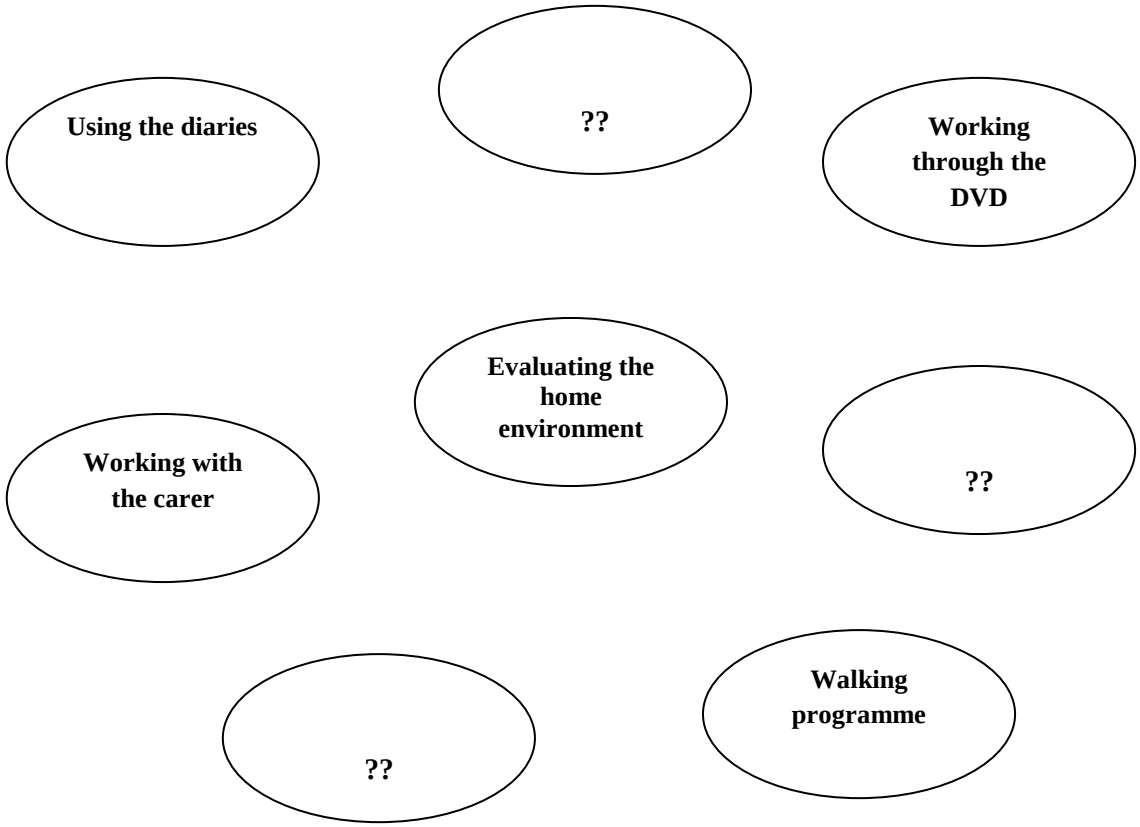
Agenda setting for the home visit



1- Working through the DVD

a- Revising the different sections of the exercise DVD
b- Explaining the use of the counter and the background music
c- Revising the correct posture
d- Revising the list of the precautions
e- While watching the DVD ask the following questions:
- Where in home can you see your self doing this?
- Which chair would you use?
- How might this fit into your every day routine?

f- Making sure that the participant has got enough space and safe environment to perform the exercises
g- Picking up the exercises to start with
h- Ensuring the correct execution of exercises; Performing the chosen exercises with the participant

2- Walking programme

- In addition to the exercises from the DVD, we would like you to walk outside at least once a week, with a walking aid if required, for as long as they can, taking breaks if needed; the goal to achieve at 8 weeks is to walk for 30 minutes with minimal numbers of breaks.

3- Working with the carer

a- Talking to both the participant and the carer "so you will really have to stick together as a team to make this work"
b- Ask the carer "How do you think you can help with this?"
c- Offer options:
- Can you be at home while the patient performing the exercises to help if there is a need?
- Can you help the patient in filling out the diaries?
- Would you both agree a time in the day for doing this?

Phone calls- schedule

A. Performing the exercise

Have you performed the exercises from the DVD this week?

If yes;

- How often?
- What exercises have you performed?
- Have you performed any additional exercises?
- Do you have difficulties with performing the exercises?
- Do you have any concerns would you like to discuss regarding the performed exercises?

If never;

- Why do you think you have not performed the exercises this week?
- What things do you think make it difficult to you to perform the exercises?
- How do you think things can be better for you to perform the exercises?

Appendix 4: Standard Operating Procedures of the Outcome Measures

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Modified motor score of the UHDRS (mMS)

Equipment: a video recorder, standard chair, biro pen to use as moving target.

Requirements: Clear 9 metre walkway marked out for gait component.

Estimated time: 5 minutes

Testing Protocol: While the assessor is carrying out the tests, another member of the research team should be video recording it. Video recording will be digitized, date and time are removed and scoring is completed by a blinded assessor.

1) Tongue protrusion

Suggestion: Please ask your participants to open their mouth wide while you inspect it using a torch. Then ask your participants to protrude their tongue well beyond their front teeth while keeping their mouth wide open and to keep it out as long as it takes you (as the examiner) to count aloud from 1 to 10. Participants should be made aware that they are not allowed to prevent their tongue from slipping back into the mouth by biting on it.

2) Finger taps

Make sure participant is seated comfortably opposite you at the same level. Explain the test to the participant. Demonstrate the movement; tap thumb with index finger in rapid succession with widest amplitude possible, each hand separately. Ask participant to do this.

3) Pronate/supinate-hands

This requires the participant to alternately hit the palmar and dorsal surface of one hand against the palm of the opposite hand. Use the palm of the opposite hand as a target instead of some other surface such as the participant´s leg or the table surface. The participant should do this task as quickly as possible over a **five-second interval**. The task is graded according to the degree of slowing and irregularity.

4) Luria

Fist-hand-palm sequencing

a. Say *'Can you do this?'* Examiner puts hand into fist on flat surface (or in lap) and sequences as follows: fist, side, flat (DO NOT REPEAT THIS OUT LOUD).
b. Watch to make sure that participant can mimic each step.
c. Continue to practice Luria 3-step for 1 - 2 minutes.
d. When participant is able to join you then say *'Very good, now keep going, I am going to stop.'* Rest hand and start timing participant's sequences.
e. A sequence is considered correct only if it is unaided by examiner model and in the correct order. Count completed sequences and score.
f. If participant was unable to complete any sequences over a 10-second period, then continue as follows.
g. Say *'Now lets try it again. Put your hands like this. FIST; SIDE; FLAT'*.
h. Watch to make sure the participant can mimic each step. Using the verbal labels, begin the sequences again and ask the participant to *'Do as I do, Fist, Side, Flat'* (repeat this as you continue).
i. Continue to perform Luria 3-step.
j. When participant is able to join you say *'Very good, now keep going, I am going to stop'*.
k. Rest hand and start timing participant's sequences.
l. A sequence is considered correct if it is unaided by examiner model and in the correct order.
m. Count completed sequences and score as above.

5) Rigidity-arms (NOTE: OBTAIN CONSENT FOR TOUCH)

Rigidity is judged on passive movement of the arms with the participant relaxed in the sitting position.

6) Bradykinesia-body

Observe the participant during spontaneous motion such as walking, sitting down, arising from a chair, and executing the tasks required during the examination. This rating reflects the examiner's overall impression of bradykinesia.

7) Gait

Use cones / tape as a marker on the floor to measure 9 metres (10 yards) prior to the test. Point out the markers to the participant and explain the test. Observe the participant walking approximately 9 meters (10 yards) at normal pace and then turning

and returning to the starting point. Ask them to repeat but walking as briskly as they can.

Instructions to the participant: Please walk along the distance marked out as briskly as you can, turn safely and return to where you started, walking briskly.

8) Tandem walking

The participant is requested to walk ten steps in a straight line with the foot placed (accurately but not quickly) such that the heel touches the toe of the other foot. Deviations from a straight line are counted.

9) Retropulsion pull test

Explain the test to the participant. Ask participant to stand. The participant's response to a sudden posterior displacement produced by a pull on the shoulder while the participant is standing with eyes open and feet slightly apart is assessed. The shoulder pull test must be done with a quick firm tug after warning the participant. The participant should be relaxed with feet apart and should not be leaning forward. If the examiner feels pressure against his/her hands when placed on the participant's shoulders, the examiner should instruct the participant to stand up straight and not lean forward. The examiner should instruct the participant to take a step backward to avoid falling. Examiners must catch participants who begin to fall.

Berg Balance Scale

Description:

14-item scale designed to measure balance of the older adult in a clinical setting.

Equipment needed:

Ruler

2 standard chairs (one with arm rests, one without)

Footstool or step

Stopwatch or wristwatch

15 ft walkway

Testing protocol: While the assessor is carrying out the tests, another member of the research team should be video recording it. Video recording will be digitized, date and time will be removed and scoring will be completed by blinded assessor.

Time: 15-20 minutes

Scoring: A five-point ordinal scale, ranging from 0-4. "0" indicates the lowest level of function and "4" the highest level of function.

Berg Balance Scale

ITEM DESCRIPTION SCORE (0-4)

1. Sitting to standing _____

2. Standing unsupported _____

3. Sitting unsupported _____

4. Standing to sitting _____

5. Transfers _____

6. Standing with eyes closed _____

7. Standing with feet together _____

8. Reaching forward with outstretched arm _____

9. Retrieving object from floor _____

10. Turning to look behind _____

11. Turning 360 degrees _____

12. Placing alternate foot on stool _____

13. Standing with one foot in front _____

14. Standing on one foot _____

Total _____

General instructions

Please document each task and/or give instructions as written. When scoring, please record the lowest response category that applies for each item.

In most items, the subject is asked to maintain a given position for a specific time. Progressively more points are deducted if the time or distance requirements are note met, if the subject's performance warrants supervision, or if the subject touches an external support or receives assistance from the examiner. Subject should understand that they must maintain their balance while attempting the tasks. The choices of which leg to stand on or how far to reach are left to the subject. Poor judgment will adversely influence the performance and the scoring.

Berg Balance Scale

1. SITTING TO STANDING

INSTRUCTIONS: Please stand up. Try not to use your hand for support.

( ) 4 able to stand without using hands and stabilize independently

( ) 3 able to stand independently using hands

( ) 2 able to stand using hands after several tries

( ) 1 needs minimal aid to stand or stabilize

( ) 0 needs moderate or maximal assist to stand

2. STANDING UNSUPPORTED

INSTRUCTIONS: Please stand for two minutes without holding on.

( ) 4 able to stand safely for 2 minutes

( ) 3 able to stand 2 minutes with supervision

( ) 2 able to stand 30 seconds unsupported

( ) 1 needs several tries to stand 30 seconds unsupported

( ) 0 unable to stand 30 seconds unsupported

If a subject is able to stand 2 minutes unsupported, score full points for sitting unsupported. Proceed to item #4.

3. SITTING WITH BACK UNSUPPORTED BUT FEET SUPPORTED ON FLOOR OR ON A STOOL

INSTRUCTIONS: Please sit with arms folded for 2 minutes.

( ) 4 able to sit safely and securely for 2 minutes

( ) 3 able to sit 2 minutes under supervision

( ) 2 able to able to sit 30 seconds

( ) 1 able to sit 10 seconds

( ) 0 unable to sit without support 10 seconds

4. STANDING TO SITTING

INSTRUCTIONS: Please sit down.

( ) 4 sits safely with minimal use of hands

( ) 3 controls descent by using hands

( ) 2 uses back of legs against chair to control descent

( ) 1 sits independently but has uncontrolled descent

( ) 0 needs assist to sit

5. TRANSFERS

INSTRUCTIONS: Arrange chair(s) for pivot transfer. Ask subject to transfer one way toward a seat with armrests and one way toward a seat without armrests. You may use two chairs (one with and one without armrests) or a bed and a chair.

( ) 4 able to transfer safely with minor use of hands

( ) 3 able to transfer safely definite need of hands

( ) 2 able to transfer with verbal cuing and/or supervision

( ) 1 needs one person to assist

( ) 0 needs two people to assist or supervise to be safe

6. STANDING UNSUPPORTED WITH EYES CLOSED

INSTRUCTIONS: Please close your eyes and stand still for 10 seconds.

( ) 4 able to stand 10 seconds safely

( ) 3 able to stand 10 seconds with supervision

( ) 2 able to stand 3 seconds

( ) 1 unable to keep eyes closed 3 seconds but stays safely

( ) 0 needs help to keep from falling

7. STANDING UNSUPPORTED WITH FEET TOGETHER

INSTRUCTIONS: Place your feet together and stand without holding on.

( ) 4 able to place feet together independently and stand 1 minute safely

( ) 3 able to place feet together independently and stand 1 minute with supervision

( ) 2 able to place feet together independently but unable to hold for 30 seconds

( ) 1 needs help to attain position but able to stand 15 seconds feet together

( ) 0 needs help to attain position and unable to hold for 15 seconds

8. REACHING FORWARD WITH OUTSTRETCHED ARM WHILE STANDING

INSTRUCTIONS: Lift arm to 90 degrees. Stretch out your fingers and reach forward as far as you can. (Examiner places a ruler at the end of fingertips when arm is at 90 degrees. Fingers should not touch the ruler while reaching forward. The recorded measure is the distance forward that the fingers reach while the subject is in the most forward lean position. When possible, ask subject to use both arms when reaching to avoid rotation of the trunk.)

( ) 4 can reach forward confidently 25 cm (10 inches)

( ) 3 can reach forward 12 cm (5 inches)

( ) 2 can reach forward 5 cm (2 inches)

( ) 1 reaches forward but needs supervision

( ) 0 loses balance while trying/requires external support

9. PICK UP OBJECT FROM THE FLOOR FROM A STANDING POSITION

INSTRUCTIONS: Pick up the shoe/slipper, which is place in front of your feet.

( ) 4 able to pick up slipper safely and easily

( ) 3 able to pick up slipper but needs supervision

( ) 2 unable to pick up but reaches 2-5 cm(1-2 inches) from slipper and keeps balance independently

( ) 1 unable to pick up and needs supervision while trying

( ) 0 unable to try/needs assist to keep from losing balance or falling

10. TURNING TO LOOK BEHIND OVER LEFT AND RIGHT SHOULDERS WHILE STANDING

INSTRUCTIONS: Turn to look directly behind you over toward the left shoulder. Repeat to the right. Examiner may pick an object to look at directly behind the subject to encourage a better twist turn.

( ) 4 looks behind from both sides and weight shifts well

( ) 3 looks behind one side only other side shows less weight shift

( ) 2 turns sideways only but maintains balance

( ) 1 needs supervision when turning

( ) 0 needs assist to keep from losing balance or falling.

11. TURN 360 DEGREES

INSTRUCTIONS: Turn completely around in a full circle. Pause. Then turn a full circle in the other direction.

( ) 4 able to turn 360 degrees safely in 4 seconds or less

( ) 3 able to turn 360 degrees safely one side only 4 seconds or less

( ) 2 able to turn 360 degrees safely but slowly

( ) 1 needs close supervision or verbal cuing

( ) 0 needs assistance while turning

12. PLACE ALTERNATE FOOT ON STEP OR STOOL WHILE STANDING UNSUPPORTED

INSTRUCTIONS: Place each foot alternately on the step/stool. Continue until each foot has touch the step/stool four times.

( ) 4 able to stand independently and safely and complete 8 steps in 20 seconds

( ) 3 able to stand independently and complete 8 steps in > 20 seconds

( ) 2 able to complete 4 steps without aid with supervision

( ) 1 able to complete > 2 steps needs minimal assist

( ) 0 needs assistance to keep from falling/ unable to try

13. STANDING UNSUPPORTED ONE FOOT IN FRONT

INSTRUCTIONS: (DEMONSTRATE TO SUBJECT) Place one foot directly in front of the other. If you feel that you cannot place your foot directly in front, try to step far enough ahead that the heel of your forward foot is ahead of the toes of the other foot. (To score 3 points, the length of the step should exceed the length of the other foot and the width of the stance should approximate the subject's normal stride width.)

( ) 4 able to place foot tandem independently and hold 30 seconds

( ) 3 able to foot ahead independently and hold 30 seconds

( ) 2 able to take small step independently and hold 30 seconds

( ) 1 needs help to step but can hold 15 seconds

( ) 0 loses balance while stepping or standing

14. STANDING ON ONE LEG

INSTRUCTIONS: Stand on one leg as long as you can without holding on.

( ) 4 able to lift leg independently and hold > 10 seconds

( ) 3 able to lift leg independently and hold 5-10 seconds

( ) 2 able to lift leg independently and hold ≥ 3 seconds

( ) 1 tries to lift leg unable to hold 3 seconds but remains standing independently.

( ) 0 unable to try of needs assist to prevent fall

TOTAL SCORE (Maximum = 56)

Romberg and Sharpened Romberg tests

Romberg Tests

1) Eyes Open

Each subject should stand on a level surface wearing flat shoes (2 trials with his or her feet together, as close as they can be and 2 trials with feet apart); arms crossed over the chest, and the open palm of the hand falling on the opposite shoulder. Once stable, the subject should attempt to maintain that position for 30 seconds. Record the time.

2) Eyes Closed

Each subject should stand on a level surface wearing flat shoes (2 trials with his or her feet together, as close as they can be and 2 trials with feet apart); arms crossed over the chest, and the open palm of the hand falling on the opposite shoulder. Once stable, the subject should attempt to maintain that position for 30 seconds. Record the time.

Sharpened Romberg tests

1) Eyes open

Each subject should stand on a level surface wearing flat shoes with his or her feet aligned in a strict tandem heel-to-toe position, arms crossed over the chest, and the open palm of the hand falling on the opposite shoulder.

Once stable, the subject should attempt to maintain that position for 30 seconds. If the subject fails to maintain the position by movement of either arms or feet or by opening his or her eyes, the time taken to failure should be noted. Each subject is given 2 trials.

2) Eyes closed

Each subject should stand on a level surface wearing flat shoes with his or her feet aligned in a strict tandem heel-to-toe position, arms crossed over the chest, and the open palm of the hand falling on the opposite shoulder.

Once stable, the subject should close his or her eyes and attempt to maintain that position for 30 seconds. If the subject fails to maintain the position by movement of either arms or feet or by opening his or her eyes, the time taken to failure should be noted. Each subject is given 2 trials.

Measures of postural sway

Equipment: Kistler® force platform, 8 channel amplifier, software on a computer for data processing.

Testing protocol: quiet standing on the force platform with eyes open for 30 seconds. Two trials are performed. Two examiners are included. One gives instructions and set the start and the end of the test from the PC. The other stands behind the participant during the test as a safety measure.

Instructions:

1) Stand on the force platform, placing your feet apart.
2) Look straight ahead, with head erect while you fix your vision on the black spot placed on the white screen.
3) Cross over your arms with open palm of the hand are placed over the opposite shoulder.
4) Stand as still as possible for as long as you can for up to 30 seconds.

Isomtric muscle strength testing

Equipment: Kin-com isokinetic testing chair dynamometer unit.

Testing protocol: Participant is seated on the chair. The backrest is adjusted to 110 degrees of posterior incline. Seat belts and pads is used The most inferior portion of the transducer pad is adjusted above the lateral maleolli. The axis of the lever arm is aligned to be at the same level of the inferior part of the lateral epicondyle of femur. The knee is flexed at an angle of 90 degrees. The angle of the knee is determined by using a universal goniometer. Participant performs 3 trials of 3 seconds for each of the right and left knee flexors and knee extensors. Sixty seconds of rest is given between trials. Participants are given verbal coaching during testing. Three progressive sub-maximal warm up repetitions of both knee flexors and extensors are performed prior to testing.

Instructions:

1) Please keep back against the backrest and fold your arm against the chest during the test.
2) Once the test is started please push (or pull) as hard as you can.

Walking test- GAITRite

Equipment: GAITRite walkway, standard chair, software on laptop.

Testing Protocol: Each participant is asked to perform ten trials of walking through the walkway at their comfortable pace. Two familiarisation trials at the beginning of the testing session are performed. A two meters acceleration and deceleration distance on either end of the walkway was included.

Instructions: Walk until the landmark placed after the end of the walkway, turn and walk back. Walk at a pace that is comfortable for you.

Stepwatch Activity Monitor (SAM)

Equipment: SAM, ankle strap, appropriate packaging/ envelope for participant to send back SAM to research team after wearing for 8 days, software on laptop.

Testing Protocol:

1) Explain to the participant in detail what the SAM is and how it is to be used.
2) Setup the software to establish the recording activity of the participant.
3) Put SAM on participant to demonstrate how it should be worn.
4) If recording activity starting straight away, check monitor is flashing with each step the participant takes with right leg.
5) Participant will wear SAM for eight days and then return it in the post in the envelope provided.
6) To be completed at baseline and after the first follow-up assessments.

Instructions:

1) Please wear the step watch for eight days.
2) The SAM must be worn with the rounded end up.
3) It is worn just above the ankle bone on either side of either leg.
4) Adjust the Velcro for comfort and wear an extra sock if you need additional padding.
5) Put the SAM on right away when you get up in the morning and wear it throughout the day. Take it off at night and when you shower or have a bath.
6) Please treat the SAM with reasonable care.

Four Square Step Test

Description: The FSST involves stepping over low objects (2.5cm) and movement in 4 directions.

Estimated time: 5 minutes

Equipment needed: stopwatch, 4 canes, The square is formed by using 4 canes resting flat on the floor. Canes were 90cm long, and the direction and type of handle used is not important.

Testing protocol:

The subject stands in square number 1 facing square number 2. The aim is to step as fast as possible into each square in the following sequence. Square number 2, 3, 4, 1, 4, 3, 2, and 1. This sequence requires the subject to step forward, backward, and sideway to the right and left. The score is recorded as the time taken to complete the sequence. The stopwatch starts when the first foot contacts the floor in square 2 and finishes when the last foot comes back to touch the floor in square 1. The following instructions are given to the subject, "Try to complete the sequence as fast as possible without touching the sticks. Both feet must make contact with the floor in each square. Face forward during the entire sequence." The sequence is then shown to the subject. One practice trial is completed to ensure the subject knows the sequence. Three FSST are completed with the average time taken as the score. A trial is repeated if the subject fails to complete the sequence successfully, loses balance, or makes contact with a cane during the sequence. Subjects who were unable to face forward during the entire sequence and needed to turn before stepping into the next square were given a score of 60 seconds. All subjects wear their preferred shoes. The examiner stood in a position to see all steps taken by the subject, and an assistant provided the subject with close supervision. The entire test, including giving instructions and a practice trial, took less than 5 minutes to complete.

Scoring: Time (in seconds) to complete sequence above.

Comments: (able to stand facing front, multiple reps need)

Timed Up and Go test

Description: For this test, subjects stand up from a chair, walk 3 meters, turn around, and return to the chair.

Estimated time: 10 minutes

Exclude subjects who: are unable to ambulate without physical assistance. Assistive devices can be used.

Equipment: standard height chair (18") with arms (26" to arm height); firm surface; stopwatch

Testing Protocol: The timed "Up and Go" test measures, in seconds, the time taken by an individual to stand up from a standard arm chair (approximate seat height of 46 cm, arm height 65 cm), walk a distance of 3 meters, turn, walk back to the chair, and sit down. The front legs of the chair should be at the start position (0). A cone should be placed at 3 meters distance, to indicate the turn around point for the subject. The subject wears their regular footwear and uses their customary walking aid (none, cane, walker). No physical assistance is given. They start with their back against the chair, their arms resting on the armrests, and their walking aid at hand. The subject walks through the test once before being timed in order to become familiar with the test. Either a stopwatch or a wristwatch with a second hand can be used to time the trial. The test is repeated twice. Turn should be anteclockwise. a demonstration of the test is provided to the subject and one practice trial is performed before the beginning of the test.

Instructions to the patient: "When I say 'go' I want you to stand up and walk to the line, turn and then walk back to the chair and sit down again. Walk at your normal pace."

Scoring: Time is recorded starting from the word "go" until the time the subjects fully sits in the chair. Record the time of both trials. The first trial (test trial) the time is not recorded.

30 seconds Chair Sit to Stand Test

Equipment: standard chair without arms and with a seat height of approximately 17 inches (43.2 cm). Place the back of the chair against a wall to prevent movement during the test.

Testing Protocol:

1) The chair should be placed against a wall to prevent it from moving during the test.
2) The test begins with the participant seated in the middle of the chair, back straight, feet approximately shoulder-width apart and placed on the floor at an angle slightly back from the knees, with one foot slightly in front of the other to help maintain balance when standing. While monitoring the participant's performance to assure proper form, the tester will silently count the completion of each correct stand.
3) Arms will be crossed at the wrists and held against the chest.
4) At the signal "go," the participant rise to a full stand (body erect and straight) and then returned back to the initial seated position.
5) The participant will be instructed to be fully seated between each stand.
6) Following a demonstration by the tester, a practice trial of one repetition will be given to check proper form, followed by the 30-s test trial.
7) The score will be the total number of stands executed correctly within 30 s (more than halfway up at the end of 30-s counted as a full stand).
8) Incorrectly executed stands will not be counted.
9) Repeat twice.

If participants are unable to stand up one time without assistance than they can use their hands to assist them in rising and returning to the seated position while following all other procedures as described above. Make sure that if hands were used make note of this when recording the assessment data.

Estimated time: 1 minute

Instructions:

1) Sit in the middle of the chair, back straight, feet approximately shoulder-width apart and placed on the floor at an angle slightly back from the knees, with one foot slightly in front of the other to help maintain balance when standing.
2) Cross your arms at the wrists and hold against your chest.
3) On the signal “go” rise from the chair and stand fully (body erect and straight) and then return to the seat in the original position.
4) You are to do this as many times as you can in 30 seconds which I will be timing.
5) Between each stand make sure you are fully seated.

Physical Performance Test

Description: The PPT is a compilation of items mimicking basic and complex ADL tasks and is scored by timing the completion of a task. This time then is related to a categorical score of 0 to 4, in which 4 represents people in the fastest 20% at completing the task, 1 represents those in the slowest 20%, and 0 represents those who cannot complete the task. The maximum score on the 9-item PPT is 36. Subjects perform a series of 9 standardized tasks, which are timed. The tasks include writing a sentence, simulated eating, turning 360 degrees, putting on and removing a jacket, lifting a book and putting it on a shelf, picking up a penny from the floor, a 50-foot walk test, and climbing stairs (scored as two items: time for climbing one flight of stairs and counting the number of flights of stairs the subject is able to ascend)

Equipment: pen, piece of paper, 5 kidney beans, empty coffee can, teaspoon, PDR or similar size textbook (5.5 lbs), chair/stool height 59 cm, shelf height 118 cm, cardigan sweater/jacket or lab coat, 50 ft walkway, flight of stairs (12 steps), US penny or UK 1p coin

Estimated time: 20 minutes

Testing Protocol:

Administer the test as outlined below. Subjects are given up to two chances to complete each item. Assistive devices are permitted for tasks 6 – 8.

1) Ask the subject, when given the command to "go" to write the sentence "whales live in the blue ocean." Time from the word "go" until the pen is lifted from the page at the end of the sentence. All words must be included and legible. Period need not be included for task to be considered completed.

2) Five kidney beans are placed in a bowl, 5 inches from the edge of the desk in front of the patient. An empty coffee can is placed on the table at the patient's non-dominant side. A teaspoon is place in the patient's dominant hand. Ask the subject on the command "go" to pick up the beans, one at a time and place each in the coffee can. Time from the command "go" until the last bean is heard hitting the bottom of the can.

3) Place a Physician's Desk Reference or other heavy book on a table in front of the patient. Ask the patient, when given the command "go" to place the book on a shelf above shoulder level. Time from the command "go" to the time the book is resting on the shelf.

4) If the subject has a jacket cardigan sweater, ask them to remove it. If not, give the subject a lab coat. Ask the subject, on the command "go" to put the coat on completely such that it is straight on their shoulders and then remove the garment completely. Time from the command "go" until the garment has been complexly removed.

5) Place a penny approximately1 foot from the patient's foot on the dominant side. Ask the patient, on the command "go" to pick up the penny from the floor and stand up. Time from the command "go" until the subject is standing erect with a penny in hand.

6) With subject in a corridor or in and open room, ask the subject to turn 360 degrees. Evaluate using the scale on PPT scoring sheet.

7) Bring subject to start on a 50 –foot walk test course (25 feet out and 25 feet back) and ask the subject, on the command "go" to walk to the 25-foot mark and back. Time from the command "go" until the starting line is crossed on the way back.

   Scoring: See scoring sheet

PPT Scoring Sheet

			Time	Scoring	Score
1.	Write a sentence. (Whales live in the blue ocean.)	Seconds		≤ 10 sec = 4 10.5-15 sec = 3 15.5 – 20 sec = 2 >20 sec = 1 unable = 0	
2.	Simulated eating	Seconds		≤ 10 sec = 4 10.5-15 sec = 3 15.5 – 20 sec = 2 >20 sec = 1 unable = 0	
3.	Lift a book and put it on a shelf Book PDR 1988: 5.5 lbs Bed height 59 cm Shelf height 118 cm All sitting with feet on floor	Seconds		≤ 2 sec = 4 2.5- 4 sec = 3 4.5 – 6 sec = 2 > 6 sec = 1 Unable = 0	
4.	Put on and remove a jacket 1.Standing 2.Use of bathrobe; button down shirt; hospital gown.	Seconds		≤ 10 sec = 4 10.5-15 sec = 3 15.5 – 20 sec = 2 >20 sec = 1 unable = 0	
5.	Pick up a penny from floor.	Seconds		≤ 2 sec = 4 2.5- 4 sec = 3 4.5 – 6 sec = 2 > 6 sec = 1 Unable = 0	
6.	Turn 360 degrees		Discontinuous steps = 0 Continuous steps = 2		
			Unsteady (grabs, staggers) = 0 Steady = 2		
7.	50-foot walk test. Starting sitting for instructions.	Seconds		≤ 15 sec = 4 15.5- 20 sec = 3 20.5 – 25 sec = 2 >25 sec = 1 unable = 0	
	TOTAL SCORE (maximum 28 for seven-item)				
	(*Round time measurements to nearest 0.5 seconds.)				

Short Form 36 (SF-36)

Equipment: Pencil and paper

Testing Protocol: Ensure the participant is seated comfortably in a chair and has a pencil to fill in the questionnaire. Explain that the questionnaire asks for the participants views about their health. Ask the participant to go through the questionnaire with the carer (if applicable), asking the questions as he/she goes through it. For each of the questions, ask the participant to tick the box that best describes the answer.

Estimated time: 10 minutes

Hints:

During the past 4 weeks how much did pain interfere with your normal work; including both work outside the home and housework.

Had difficulty performing the work or other activities for example it took extra effort.

During the past 4 weeks have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems such as feeling depressed or anxious?

Intrinsic Motivation Inventory questionnaire

For each of the following statements, please indicate how true it is for you, using the following scale:

1	2	3	4	5	6	7
not at all true			somewhat true			very true

A. Interest/Enjoyment

1. I enjoyed doing this exercise program very much
2. This exercise program was fun to do.
3. I thought this was a boring exercise program. (R)
4. This exercise program did not hold my attention at all. (R)
5. I would describe this exercise program as very interesting.
6. I thought this exercise program was quite enjoyable.
7. While I was doing this exercise program, I was thinking about how much I enjoyed it.

B. Perceived Competence

1. I think I am pretty good at this exercise program.
2. I think I did pretty well at this exercise program.
3. After working at this exercise program for awhile, I felt pretty competent.
4. I am satisfied with my performance at this exercise program.
5. This was an exercise program that I couldn't do very well. (R)

C. Effort/Importance

1. I put a lot of effort into exercise program.
2. I didn't try very hard to do well at this exercise program. (R)
3. I tried very hard on this exercise program.
4. It was important to me to do well at this exercise program.

5. I didn't put much energy into this exercise program. (R)

D. Pressure/Tension

1. I did not feel nervous at all while doing this exercise program. (R)
2. I felt very tense while doing this exercise program.
3. I was very relaxed in doing this exercise program. (R)
4. I was anxious while working on this exercise program.
5. I felt pressured while doing this exercise program.

E. Value/Usefulness

1. I believe this exercise program could be of some value to me.
2. I think that doing this exercise program is useful for improving my condition.
3. I think this exercise program is important to do.
4. I would be willing to do this exercise program again because it has some value to me.
5. I think doing this exercise program is helpful.
6. I believe doing this exercise program could be beneficial to me.
7. I think this is an important exercise program.

Appendix 5: Interview Schedule

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Closed questions:	**a priori codes**
Was the training program suitable for you? What do you think about the overall structure of the DVD? Was it easy to navigate and follow?	Suitability of the exercise the exercise programme
Did you have difficulty in performing the exercises? Can you explain?	Barriers
Was the home visit useful? Were the phone calls useful?	Facilitators
Was the exercise programme useful?	Perceived benefits

Open questions:

Please state how you were using the exercises DVD?

Prompts: If yes;

- How often you were using the exercise DVD?
- What exercises have you performed and how long each session was undertaking?
- Can you please explain how you were performing the exercises?

Prompts: If never;

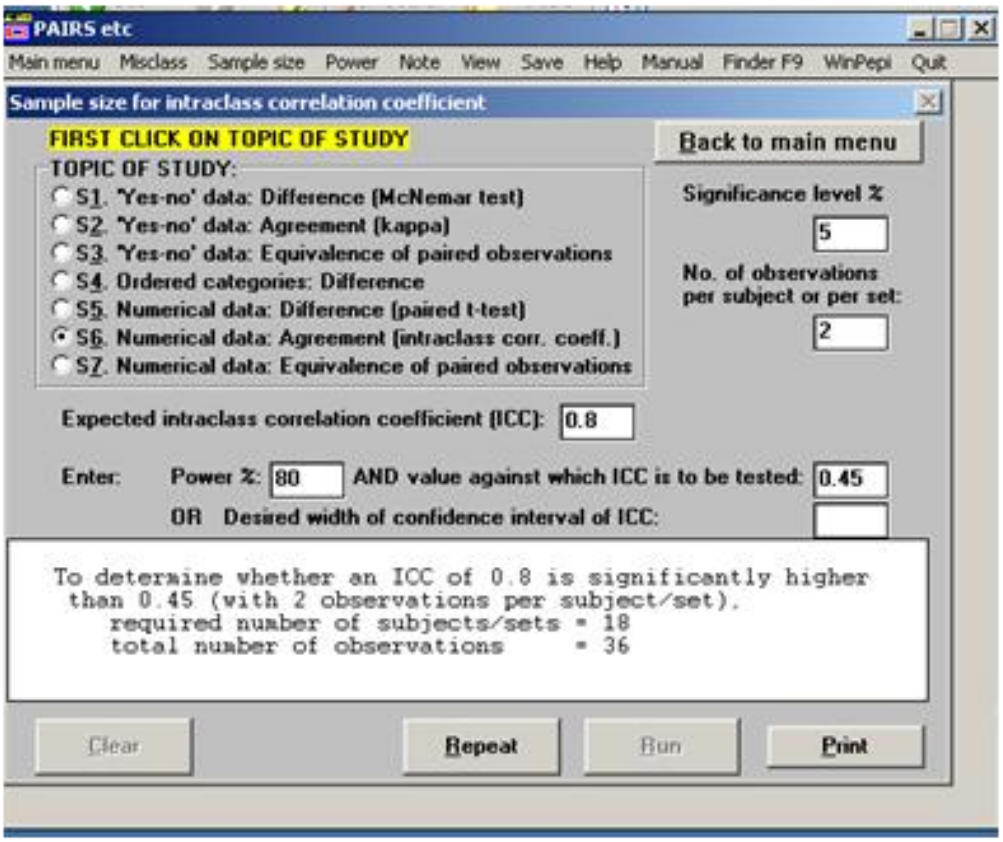
- Can you explain why do you think you have not performed the exercises?

Please state how often you were doing the walking?
Please describe what you have liked most and least about the program?

Appendix 6: Sample size; Correlations between Gait Measures and scatter plots of correlations between outcomes

15 Appendix 6: Sample size; correlations between measures of gait and scatter plots of correlations

A) Sample size calculations for reliability study



B) <u>Correlations between measures of gait</u>

	mMS	Stride length CV	Stride length	Stride time	Gait speed
Stride time CV	0.71**	0.96**	-0.63**	0.50**	-0.65**

	Stride length	Stride time
Gait speed	0.82**	-0.56**

C) Correlations between outcomes and stride time CV

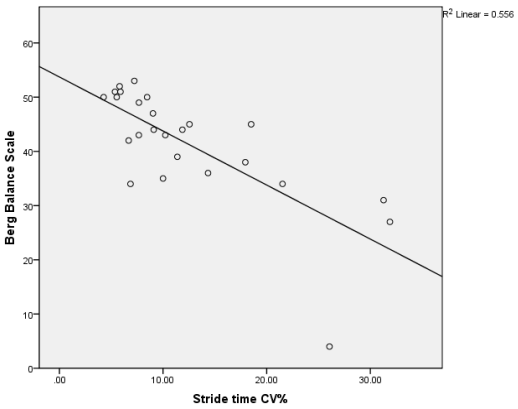
Data were checked for the presence of outliers using casewise diagnostic procedure [219]; cases where standardized residuals (differences between observed and predicted values divided by an estimate of their standard deviation) were greater than 1.96 or lesser than -1.96 were considered to be outliers (i.e. cases where standardized residuals were outside 2 SD of their distribution). Analysis was carried out with and without outliers to estimate effects of outliers on results. Correlation coefficients after excluding outliers are provided in the table below.

The correlation coefficient of 0.6 was used as a cut off point for the interpretation of the results obtained for the concurrent-convergent validity. An outcome considered to have a good concurrent convergent validity if the correlation coefficient with stride time CV was of 0.6 or more [240]. Accordingly, excluding outliers did not influence the obtained results. In all outcomes that had good concurrent-convergent validity, correlation coefficients were still of at least 0.60 even after excluding outliers. Similarly, in all outcomes that did not have good concurrent convergent validity (apart from the root mean square measures of postural sway), correlation coefficients were still lesser than 0.6 even after excluding all outliers from analysis (for more details see table and scatter plots below).

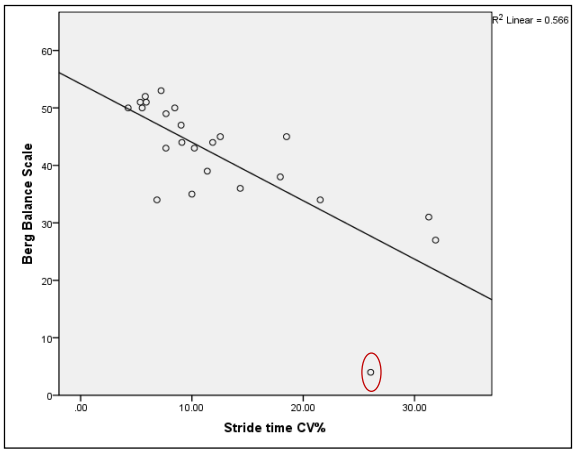
Summary of correlations of outcome measures with stride time coefficient of variations (with and without outliers)

	Correlation coefficient	Correlation coefficient with outliers removed
Berg balance scale	-0.72**	-0.74**
Total score of Romberg test	-0.44*	-0.58*
rms-AP of postural sway	0.50*	0.58*
rms-ML of postural sway	0.51*	0.65*
Total excursion-AP	0.1	0.028
Total excursion- ML	0.19	0.016
MVIC of knee extensors	-0.14	-0.12
MVIC of knee flexors	-0.44	-0.49
Four square step test	0.64**	0.68**
Timed up and go test	0.6*	0.63*
Chair sit to stand test	-0.71**	No outliers
Physical performance test	-0.66**	No outliers
Average of daily step count	-0.32	No outliers
Percentage of time spent at no PA	0.13	0.029
Percentage of time spent at low PA	-0.06	-0.09
Percentage of time spent at moderate PA	-0.21	No outliers
Percentage of time spent at high PA	-0.29	-0.29
Peak activity index	-0.62**	0.65**
Physical function	-0.61**	0.64**
Role physical	-0.38	No outliers
Bodily pain	-0.11	No outliers
Vitality	-0.34	0.46*
General health	-0.33	No outliers
Social Functioning	-0.16	-0.24
Role emotional	0.15	No outliers
Mental health	-0.15	No outliers
Physical Component Summary	-0.6**	-0.65**
Mental Component Summary	-0.04	0.01
Note: an outcome measure was considered to have a good concurrent-convergent validity with gait variability (i.e. stride time CV %) if the correlation coefficient was of 0.6 or more.		

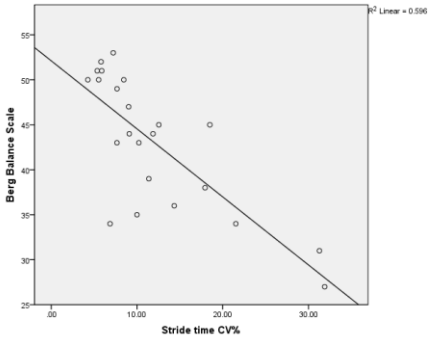
Berg Balance Scale



One case was outside 2SD (i.e. identified by casewise diagnostic)

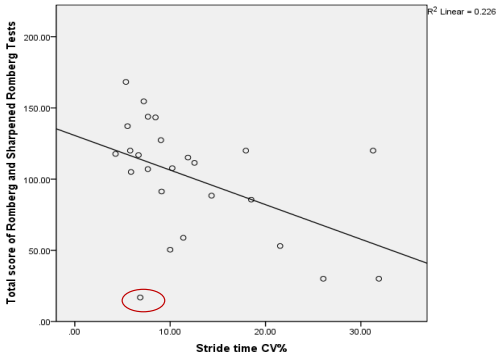


Another case was identified as an outlier by visually checking the scatter plot

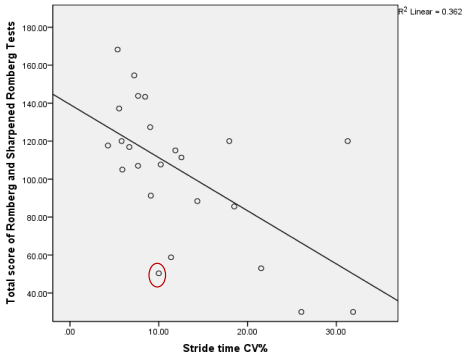


Removing all outliers change r (Pearson) from 0.74 to 0.76 and r spearman from 0.72 to 0.74

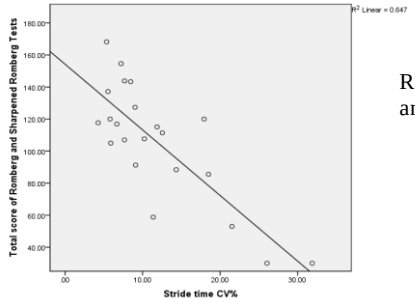
Total score of Romberg and Sharpened Romberg tests



One case was outside 2 SD (i.e. identified by casewise diagnostic).



Removing this case changes r (Pearson) from 0.47 to 0.6 and r (Spear man) from 0.44 to 0.5; another case at this stage was identified as being outside 2SD.



Removing the second outlier changes r (Pearson) from 0.6 to 0.7 and r (Spearman) from 0.5 to 0.58

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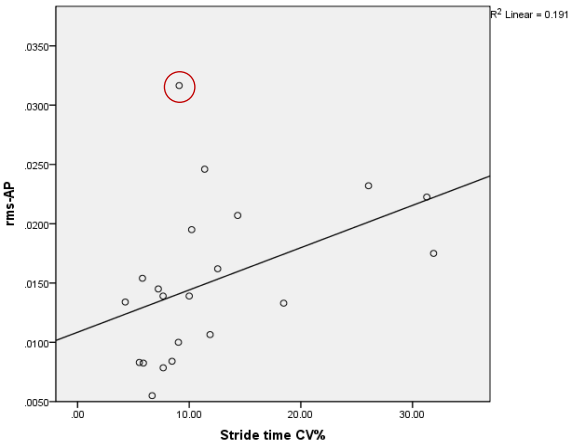
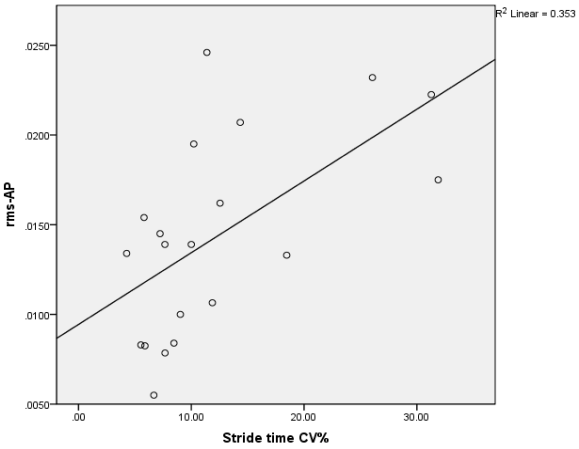
rms-AP of postural sway



One case was outside 2SD (i.e. identified by casewise diagnostic)

Removing outlier changes r (Pearson) from 0.5 to 0.58



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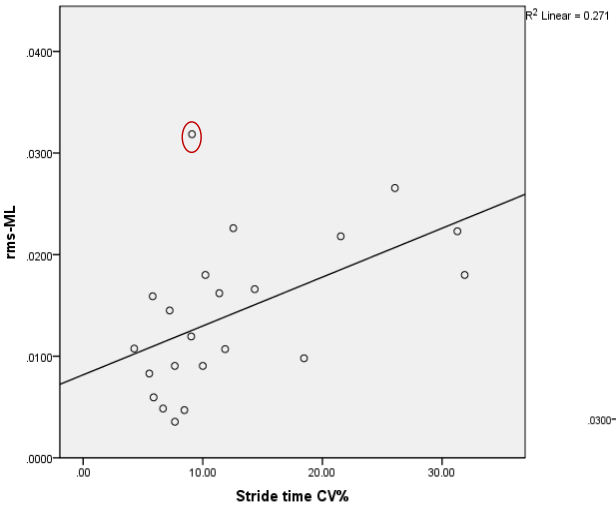
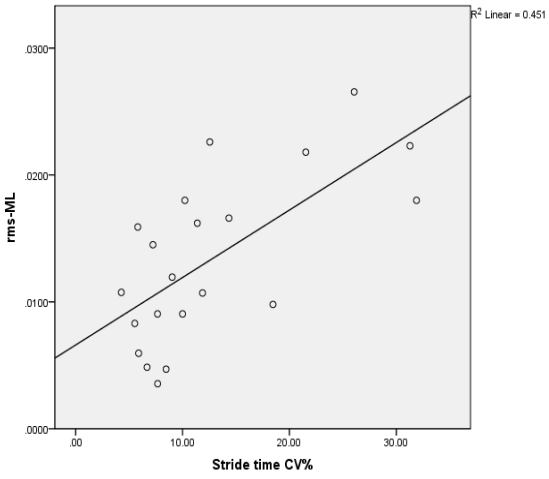
rms-ML of postural sway

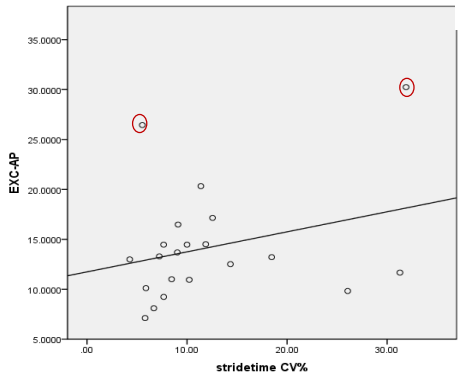


One case was outside (i.e. identified by casewise diagnostic)

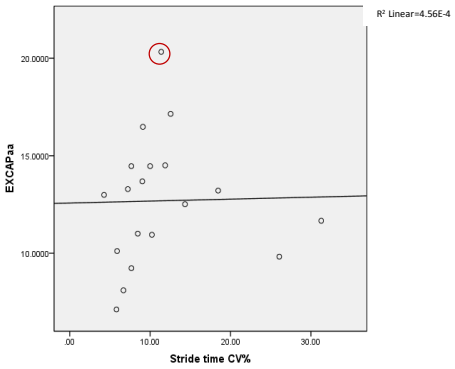
Removing outlier changes r (Pearson) from 0.51 to 0.65



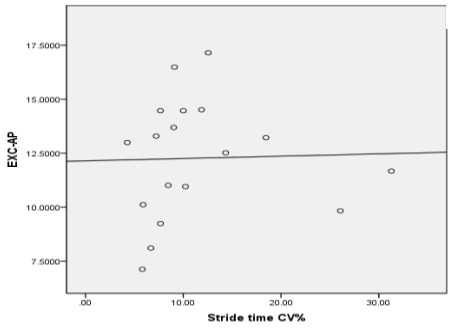
Excursion- AP of postural sway



Two cases were outside 2SD.

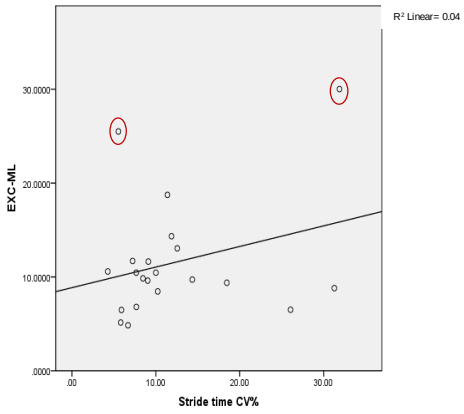


After removing the first 2outlier,s, one more case was further indicated by casewise diagnostic as being outside 2SD.

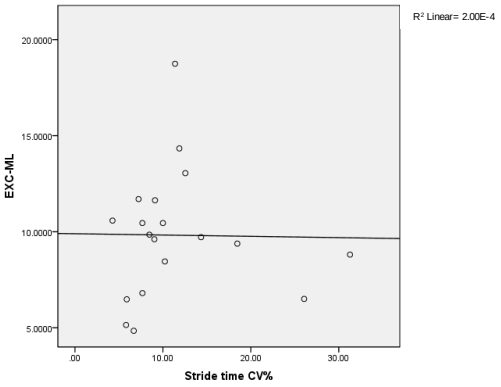


Removing all outliers changes r (Pearson) from 0.1 to 0.028

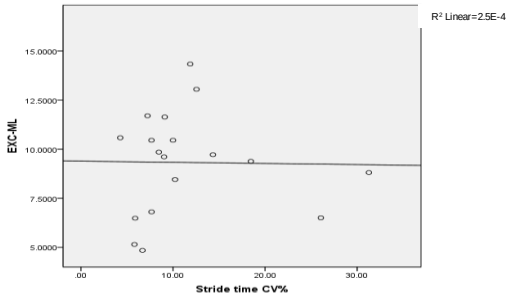
Excursion-ML of postural sway



Two cases were outside 2SD .

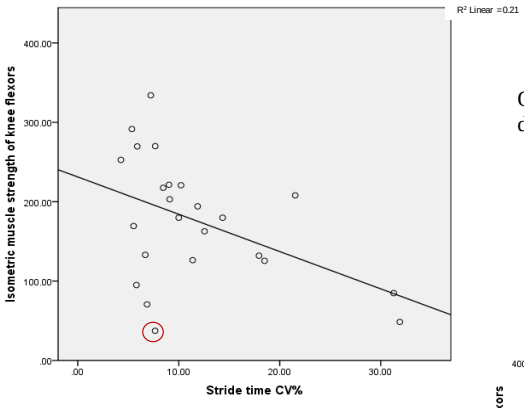


After removing the first 2outliers, one more case was further identified by casewise diagnostic as being outside 2SD.



Removing all outliers changes r (Pearson) from 0.19 to 0.016

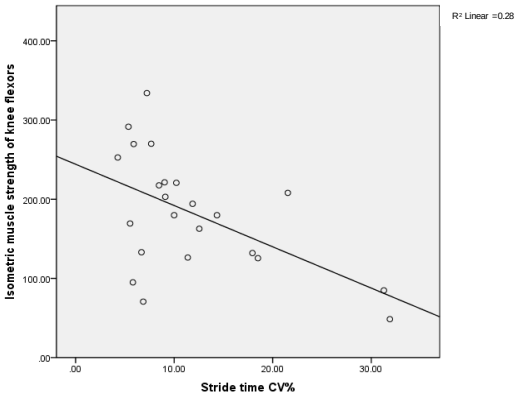
Isometric muscle strength of knee flexors



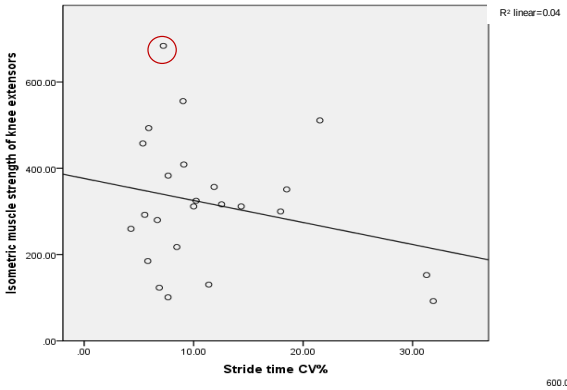
One case was outside 2SD (i.e. identified by casewise diagnostic)

•Removing the outlier changes r (Pearson) from 0. 46 to 0. 53 and r (Spearman) from 0.44 to 0.49.

•After removing the first outlier, no other outliers were further indicated by casewise diagnostic as being outside 2 SD.



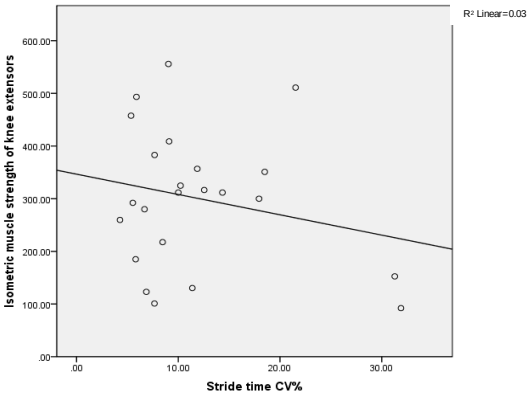
Isometric muscle strength of knee extensors



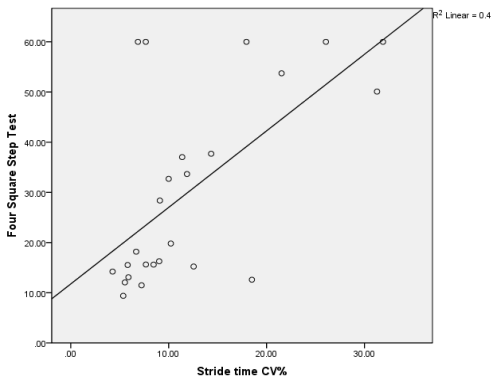
One case was identified as outside 2SD (i.e. identified by casewise diagnostic)

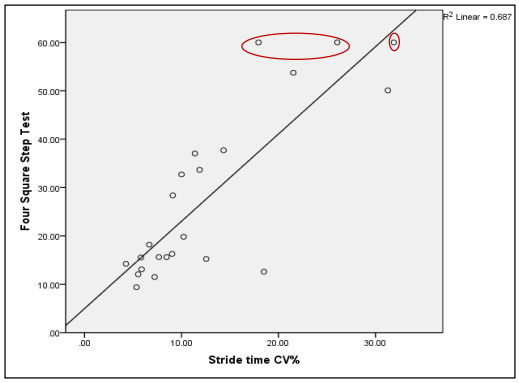
•Removing outlier changes r (Pearson) from 0. 2 to 0. 17 and r (Spearman) from 0.14 to 0.12.

•After removing the first outlier, no other outliers were further indicated by casewise diagnostic) as being outside 2SD.



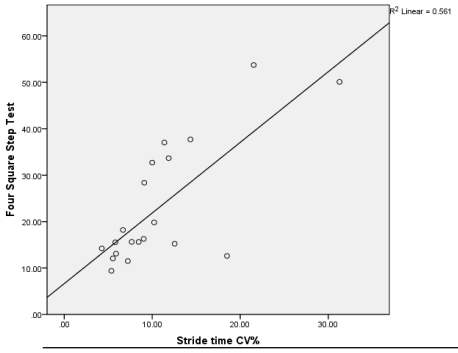
Four Square Step Test





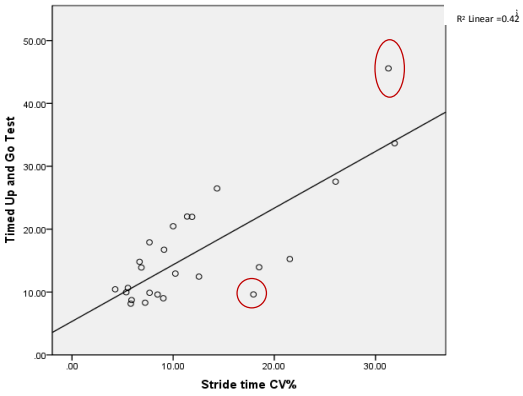
Two cases were outside 2SD (i.e. identified by casewise diagnostic)

Other 3 cases (cases who were given the score of 60 seconds when could not perform the test) were removed.



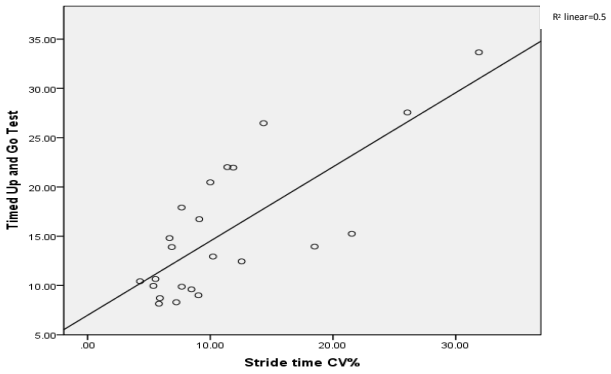
Removing all outliers changes r (Pearson) from 0.63 to 0.74 and r (spearman) from 0.64 to 0.68 .

Timed Up and Go test

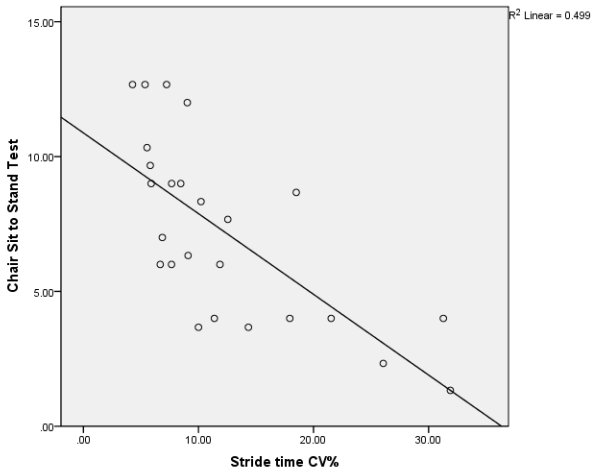


Two cases were outside 2SD (i.e. identified by casewise diagnostic).

Removing outliers changes r (Pearson) from 0.65 to 0.70 and r (spearman) from 0.60 to 0.63.

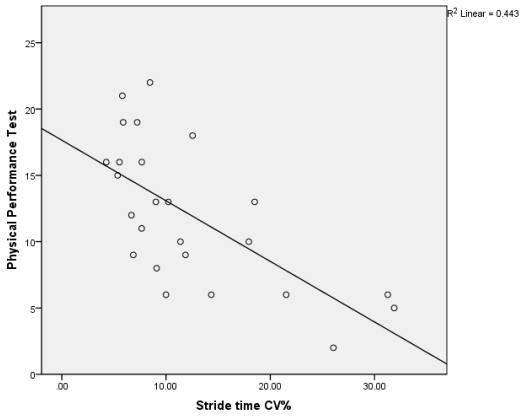


Chair Sit to Stand Test



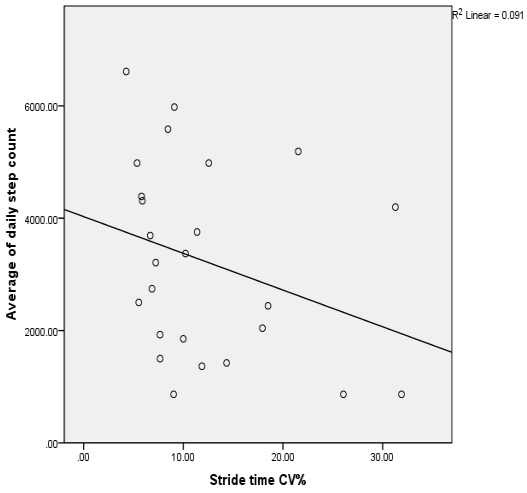
No outliers were identified

Physical Performance Test



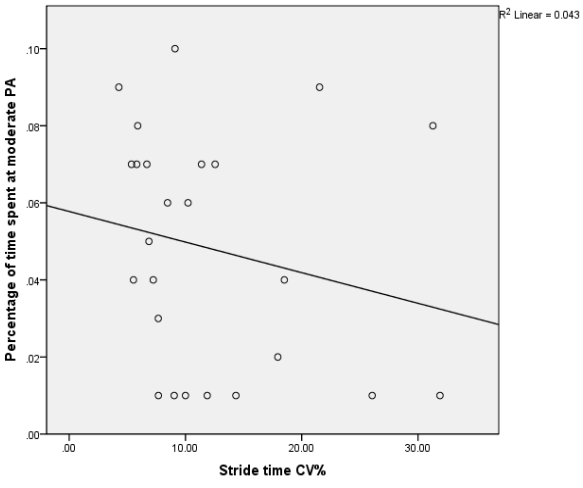
No outliers were identified

Average of daily step count



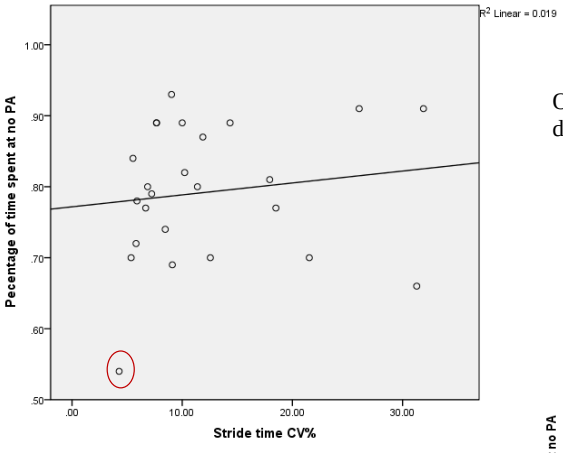
No outliers were identified

Percentage of time at moderate PA



No outliers were identified

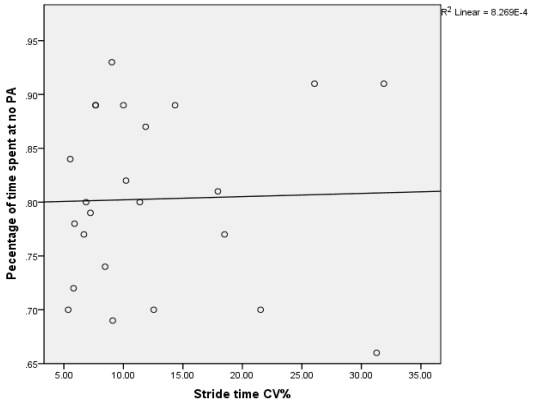
Percentage of time spent at no PA



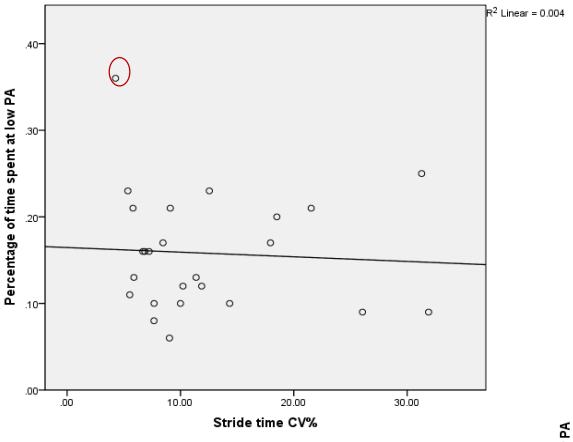
One case was outside 2SD (i.e. identified by casewise diagnostic)

•Removing the outlier changes r (Pearson) from 0.13 to 0.029.

•After removing the first outlier, no other outliers were further indicated by casewise diagnostic as being outside 2 SD.



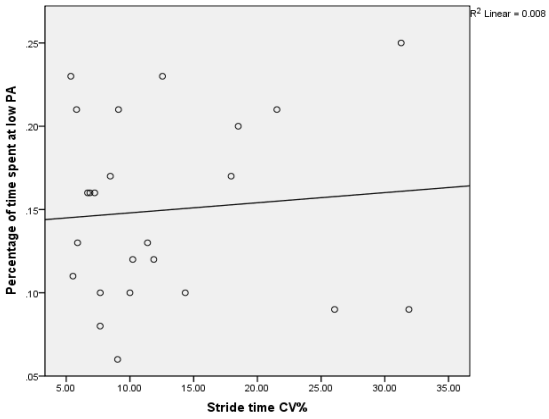
Percentage of time spent at low PA



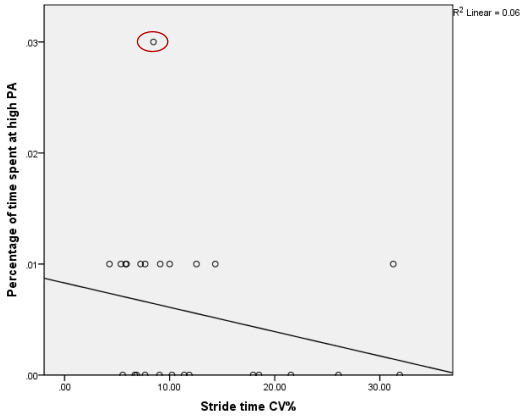
One case was outside 2SD

•Removing the outlier changes r (Pearson) from 0.06 to 0.09.

•After removing the first outlier, no other outliers were further indicated by the diagnostic criteria as being outside 2SD.



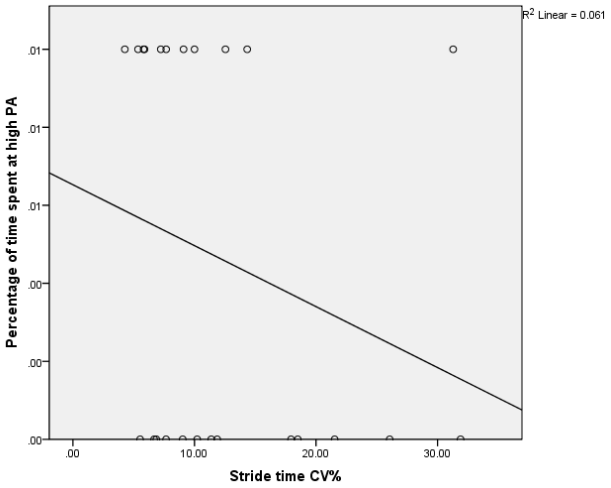
Percentage of time spent at high PA



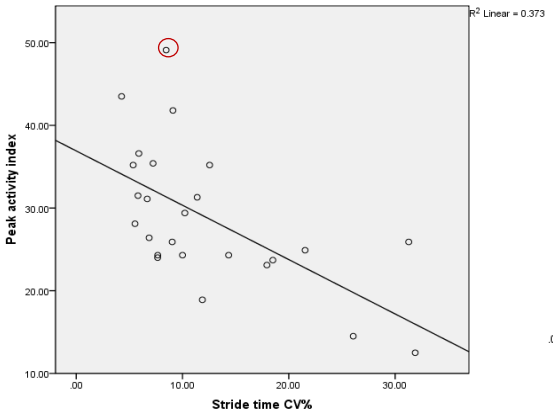
One case was outside 2SD (i.e. identified by casewise diagnostic)

•No change on r on removing the outlier.

•After removing the first outlier, no other outliers were further indicated by casewise diagnostic as being outside 2SD.



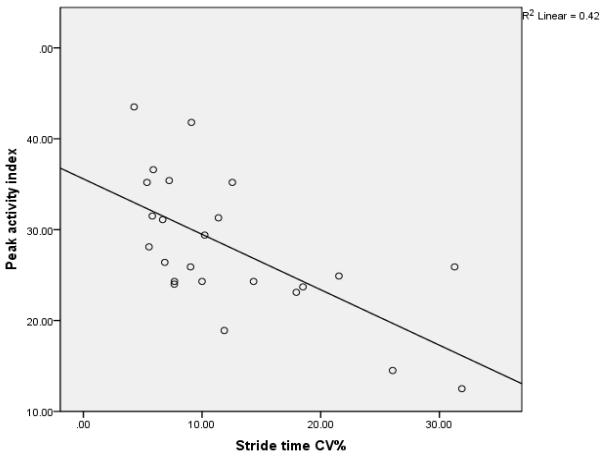
Peak activity index



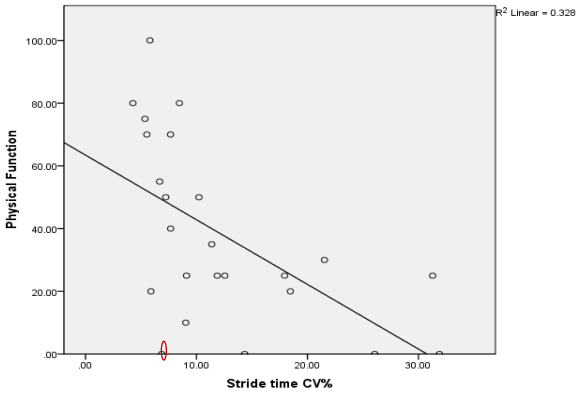
One case was outside 2SD (i.e. identified by casewise diagnostic).

•Removing the outlier changes r (Pearson) from 062 to 0.65.

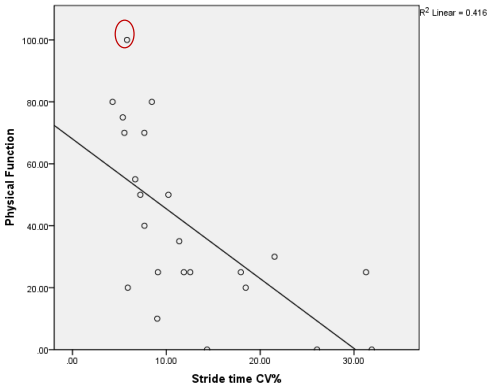
•After removing the first outlier, no other outliers were further indicated by casewise diagnostic as being outside 2SD.



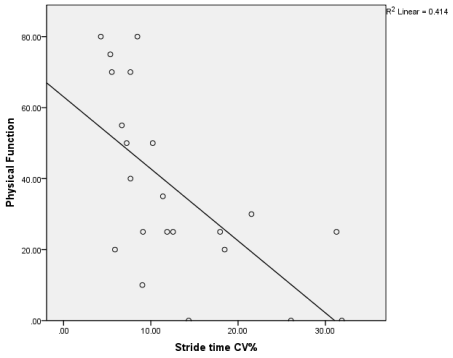
Physical Function



One case was outside 2SD.

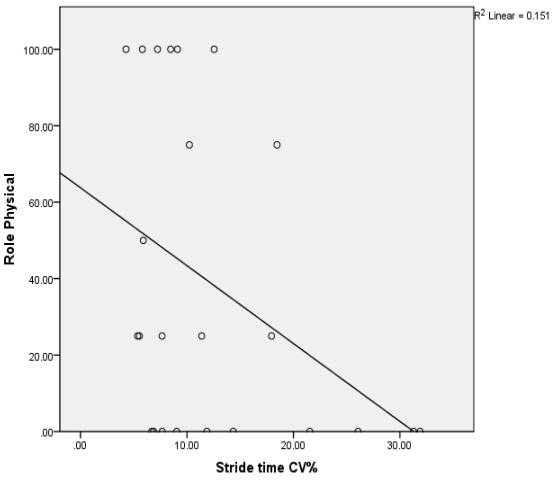


Removing this case changes r (Pearson) from 0.61 to 0.65 and r; another case at this stage was identified as being outside 2 SD.



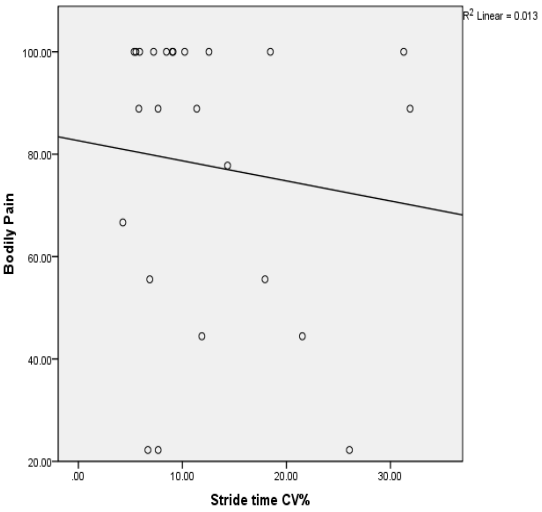
Removing all outliers changes r (Pearson) from 0.61 to 0.64.

Role Physical



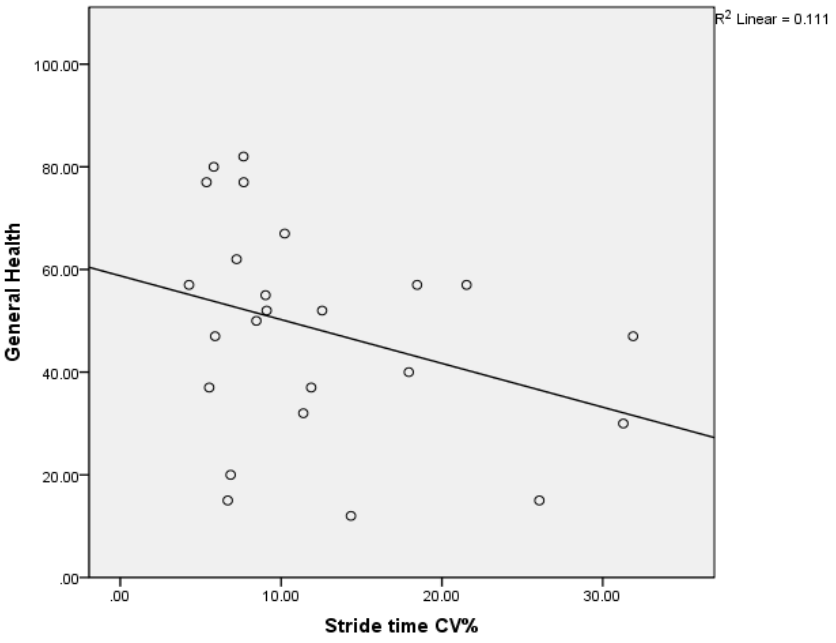
No outliers were identified

Bodily Pain



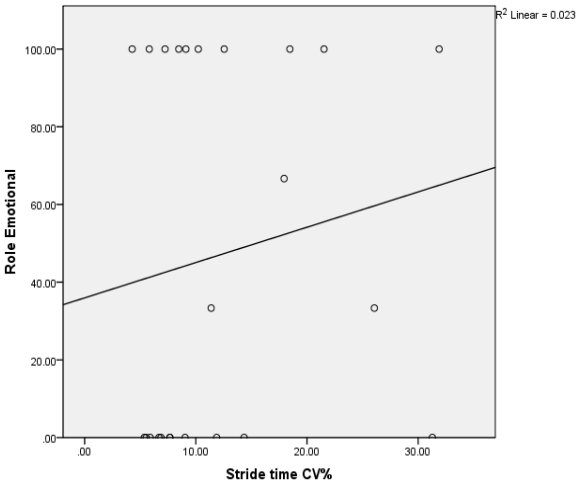
No outliers were identified

General Health



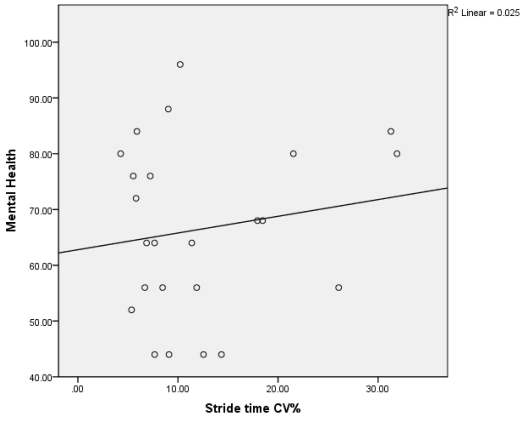
No outliers were identified

Role Emotional



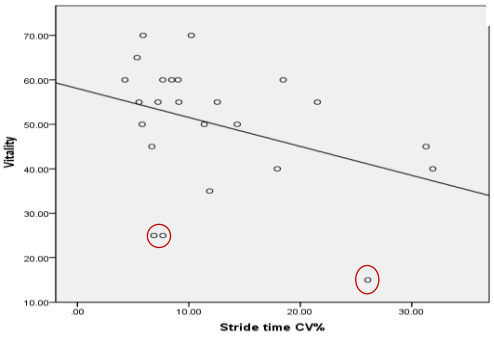
No outliers were identified

Mental Health



No outliers were identified

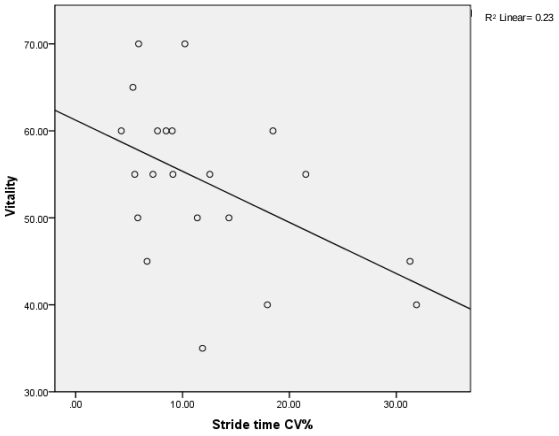
Vitality



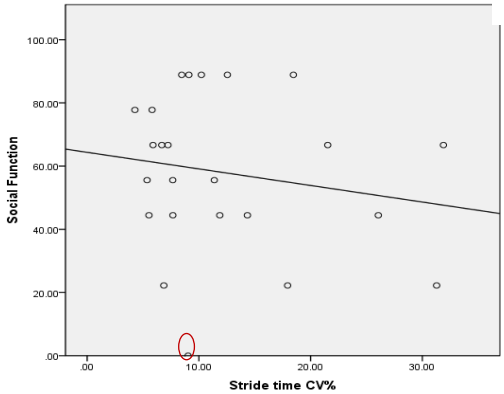
Three cases were outside 2SD (i.e. defined by casewise diagnostic)

•Removing outliers changes r from 0.33 to 0.46

•After removing the first outlier, no other outliers were further identified by casewise diagnostic as being outside 2SD.



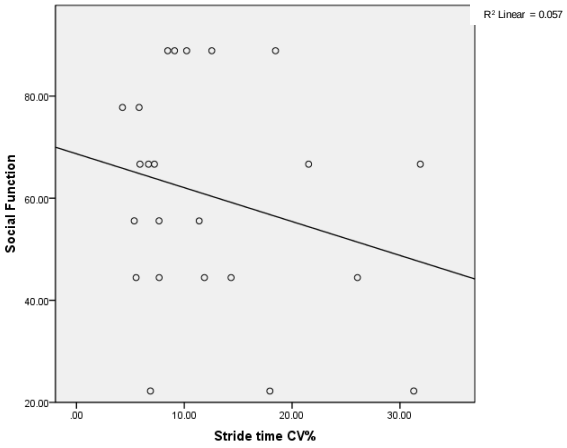
Social Functioning



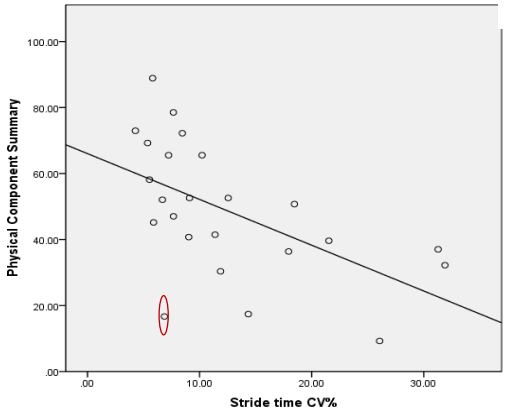
One case was outside 2SD (i.e. defined by casewise diagnostic)

•Removing outliers changes r from 0.16 to 0.24

•After removing the first outlier, no other outliers were further identified by casewise diagnostic as being outside 2SD.



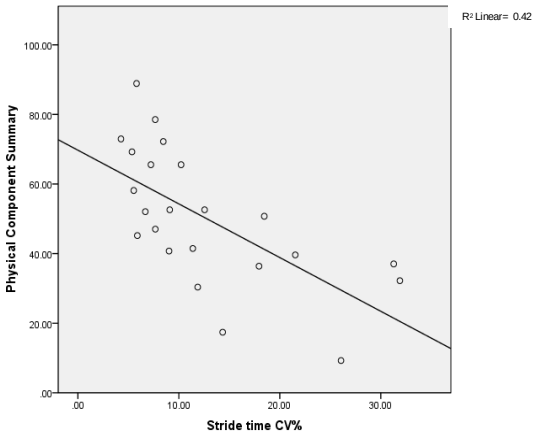
Physical Summary Component



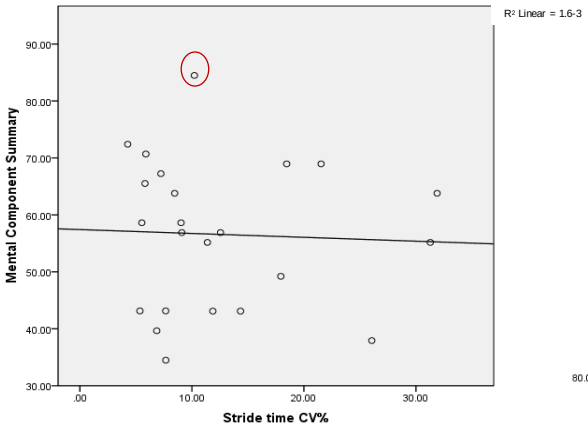
One case was outside 2SD (i.e. identified by casewise diagnostic)

•Removing outliers changes r from 0.61 to 0.65

•After removing the first outlier, no other outliers were further identified by casewise diagnostic as being outside 2SD.



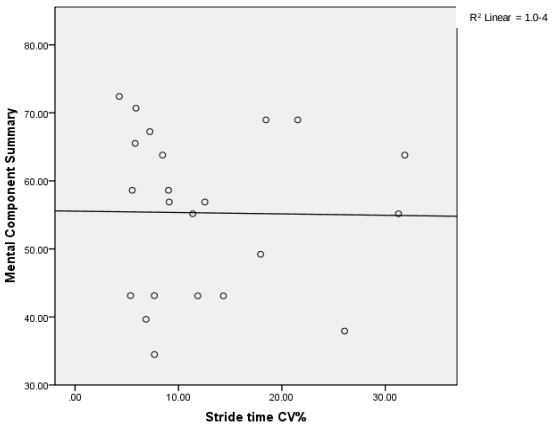
Mental Component Summary



One case was outside 2SD (i.e. identified by casewise diagnostic)

•Removing outliers changes r from 0.04 to 0.01

•After removing the first outlier, no other outliers were further identified by casewise diagnostic as being outside 2SD.



Appendix 7: Medications

16 Appendix 7: Medications

Participant	Group	Medications	Indication
P1	Exercise intervention	1. Clopiramine 2. Diazepam 3. Tetrapenezine	1. Depression 2. Depression 3. Movement
P2	Control	1. Oxybutanin 2. Olanzapine	1. Urinary frequency 2. Movement
P3	Exercise intervention	1. Citalopram	Depression
P4	Control	1. Talopran 2. Olanzapine	1. Depression 2. Movement
P5	Exercise intervention	1. carbimazole 2.paroxetine 3. ramapril 4.propranalol	1. Hyperthyroid 2.depression 3. hypertension 4.hypertension
P6	Control	1. Olanzopine 2.Sulpride 3.Cocodamol	1. Mood disorder 2.Mood disorder 3.Aches and pain
P7	Control	1. MST 2. Olanzapine 3. Lansoprazole 4. Citalopram 5. meloxican 6. fortisip 7. clonazepam	1. back pain 2. movement 3. anti acid 4. depression 5. arthritis 6. food supplement 7. Chorea
P8	Exercise intervention	Insuline	Diabetes
P9	Exercise intervention	1. Citalopram 2. Olanzapine	1. Depression 2. Movement
P10	Control	Lanzoprazotol	acid (stomach)
P11	Exercise intervention	1. Quetiapine 2.Bendrofluendhiazid	 Blood pressure
P12	Control	None	None
P13	Exercise intervention	1. VitB 2. Thiamine 3. Mitrazapine 4.Procyclidine 5. Omeprazole 6. Atorvastatine 7. Aspirine 8.Tetrabenazine	
P14	Control	1. Sorceral capsules 2.Mirtazapine	1. multivitamine 2.depression
P15	Exercise intervention	1. Olanzopine 2. Citalopram	1. Movement 2. depression

P16	**Exercise intervention**	**1. Lanzoprazole 2.Fluxetine**	**1. gastric acid 2. depression**
P17	**Control**	**1. Citalopram**	**1. depression**
P18	**Control**	**1. Temazepam 2. Propranolol 3. Tetrabinzine 4.Cetirizine**	**1. Insomina 2. anxity 3. movement 4.nasal congestion**
P19	**Exercise intervention**	**1. Mitrazapine 2.Chlorphinamine 3.Pramipexole**	**1. Mood disorder 2.antihistamine 3.HD**
P20	**Control**	**None**	**None**
P21	**Exercise intervention**	**1. perindopril 2. erbumine 3. maxalt 4.atrovastatin 5. clopidognel**	**all for cholestrol, preventing re-current heart attack**
P22	**Exercise intervention**	**1. Trihexyphenil 2. Citalopram 3. Alanzopen**	**1. Balance 2. Antidepressant 3. Antichoeric**
P23	**Exercise intervention**	**1. Nystatyin 2. Citalopram 3. Tramadol 4.Gapabentin 5. Simvastatin**	**1. Pain 2. Antidepressant 3. Arthritis 4. Arthritis 5. Arthritis**
P24	**Control**	**1. Ampladine 2.Rampirol**	**1. Blood pressure 2. Blood pressure**
P25	**Control**	**1. Seroxat 2. Desogestnel**	**1. anxity and depression 2. contraceptives**

Appendix 8: Posters and Publications

17 Appendix 8: Posters and publications

Khalil H, Quinn L, van Deursen R, Martin R, Rosser A, Busse M. Adherence to use of a home-based exercise DVD in people with Huntington's disease: participants' perspectives. Physical Therapy, 2012; 92 (1): 69-82.

Khalil H, Quinn L, van Deursen R, Rosser A, Busse M. The use of a home based exercise DVD in people with Huntington's disease: Patients and carers perspectives. World Congress of Physical Therapy. Amsterdam, June 2011.

Khalil H, van Deursen R, Quinn L, Rosser A, and Busse M. Clinical measurement of sit to stand performance in people with Huntington's disease: reliability and validity for 30 seconds chair sit to stand test, in European Huntington's Disease Plenary Meeting. Prague, 2010, Journal of Neurology, Neurosurgery & Psychiatry. p. 81 (Supp. 1)

Khalil H, Dalton A, van Deursen R, Rosser A, Ó Laighin G, Busse M. The Use of an Accelerometer to Evaluate the Performance of Timed Up and Go Test in Pre-symptomatic and Symptomatic Huntington's Disease in European Huntington's Disease Plenary Meeting. Prague, 2010, Journal of Neurology, Neurosurgery & Psychiatry. p. 81 (Supp. 1).

Busse M, Quinn L, **Khalil H**, Rosser A. Move To Exercise: Developing an Exercise DVD for People with Huntington's disease. World Congress on Huntingtons Disease Vancouver: Clinical Genetics 2009. p. 76 (Suppl. 1) 86.