UNIVERSITY OF PLYMOUTH

EVALUATING DIGITAL HEALTH TECHNOLOGIES TO ADVANCE PARKINSON'S DISEASE CARE

by

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Copyright Statement

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Author's Declaration

At no time during the registration for the degree of Doctor of Philosophy has the author been registered for any other University award without prior agreement of the Doctoral College Quality Sub-Committee.

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Publications

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Abstract

Evaluating Digital Health Technologies to Advance Parkinson's Disease Care

Thea Dominey

Parkinson's disease (PD) is a common progressive neurological disorder characterised by a complex range of motor and non-motor symptoms (NMS). Current PD service provision does not meet the needs of patients, and puts pressure on services with limited capacity. Digital Health Technologies (DHTs), including body-worn sensors and portable devices, may provide advantages, by enabling continual and objective monitoring of symptoms, and facilitating patient self-management.

I carried out a series of studies and evaluations of DHTs for use in PD, to evaluate their ability to identify and monitor symptoms in both a clinical and research context. These included:

1. The evaluation of a computerised paced finger tapping task (PFT) that was found to correlate with a measure of verbal fluency, suggesting there may be potential to implement the PFT as part of a wider finger tapping battery to be used as a screening tool for PD executive dysfunction.
2. The iterative, user-centred design and formative evaluation of NMS Assist, a smartphone-based app to enable regular assessment of NMS as well as provide education for patients. The app was found to be highly usable, and key areas of amendment were identified.

3. A clinical service evaluation of the PKG™, a PD remote monitoring device. The findings revealed the PKG™ is useful for identifying patients with unmet treatment need, even in newly diagnosed people with Parkinson's (PwP) who experience more frequent clinic review.
4. A systematic review of neuroprotective trial design in PD. The results demonstrated a wide range of primary outcome measures is used across trials, and there is little evidence of patient stratification. The findings highlighted the potential for DHTs to improve various aspects of clinical trial design.

I discuss the potential value of DHTs, as well as challenges associated with their use, identified as a result of this research.

298 words

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Abbreviations

ADL = Activities of daily living

AIMS = Abnormal Involuntary Movement Scale

AT = Advanced Therapy

BKS = Bradykinesia Score

DBS = Deep brain stimulation

DHTs = Digital Health Technologies

DKS = Dyskinesia Score

EDS = Excessive daytime sleepiness

EF = Executive function

ENS = Enteric nervous system

ESS = Epworth Sleepiness Scale

FDA = Food and Drug Administration

FDS = Fluctuation Score

FU = Follow up

GBA1 = Glucocerebrosidase gene

HD = Huntington's disease

ICD = Impulse control disorder

IPD = Idiopathic Parkinson's disease

IQR = Interquartile Range

ISI = Inter-stimulus interval

ITI = Inter-tap interval

KPPS = The King's Parkinson's Disease Pain Scale

LBD = Dementia with Lewy Bodies

LEDD = Levopdopa equivalent daily dose

LRRK2 = Leucine rich repeat kinase 2

MAO-B = Monoamine Oxidase B Inhibitors

MCI = Mild Cognitive Impairment

MDS = Movement Disorders Society

MDS-UPDRS = Movement Disorders Society Unified Parkinson's Disease Rating Scale

NMS = Non-motor symptoms

NP = New patient

PD = Parkinson's disease

PFT = Paced Finger Tapping Task

PINK1 = PTEN-induced putative kinase 1

PKG™ = Parkinson's Kinetigraph

PROs = Patient Reported Outcome

PTI = Percentage time immobile

PTT = Percentage time with tremor

PUK = Parkinson's UK

QoL = Quality of Life

RBD = Rapid Eye Movement (REM) Sleep Behaviour Disorder

SNCA = a-Synuclein (SNCA) gene

Chapter 1 Overview of Thesis and General Introduction

1.1 Overview of Thesis

This thesis contains a general introduction, followed by four experimental chapters, a general discussion and a conclusion.

Chapter 1 is the general introduction, and provides an overview of Parkinson's disease (PD), PD service provision, and Digital Health Technologies (DHTs).

Chapter 2 details the introduction, methods, results and discussion of the development and evaluation of a digital objective motor (finger tapping) assessment tool to provide information on potential PD cognitive impairment.

Chapter 3 details the development and evaluation of a novel smartphone based app to enable regular remote monitoring of non-motor symptoms (NMS) and provide self-help information for people with Parkinson's (PwP) and carer partners. Chapter 3 has an introduction, and is then split into three parts. Part 1 relates to the identification of app users and uses, Part 2 relates to the iterative design process of a) the app wireframe and b) the self-help materials, and Part 3 relates to the methods and results of the formative evaluation. There is an overall discussion.

Chapter 4 details the introduction, methods, results and discussion of a clinical service evaluation, evaluating the utility of an existing wearable device, The Parkinson's Kinetigraph (PKG^{TM}) to identify patients with unmet treatment needs between clinic appointments.

Chapter 5 details the introduction, methods, results and discussion of a systematic evaluation of PD neuroprotective trial design to evaluate the potential for DHTs to add value.

Finally, prior to the main conclusions, references and appendices, Chapter 6 details the overall discussion.

1.2 General Introduction

1.2.1 Parkinson's disease (PD)

Parkinson's disease (PD) is a chronic progressive neurodegenerative disorder characterised by motor symptoms including slowness of movement (bradykinesia), rigidity and tremor, and non-motor symptoms (NMS) including neuropsychiatric symptoms (e.g. anxiety, depression) sleep disturbances, and autonomic disturbance (e.g. orthostatic hypotension, constipation). The presentation of symptoms varies between patients and throughout the progression of the disease, with symptoms having a significant impact on quality of life for people with Parkinson's (PwP) and their carer partners (Global Parkinson's Disease Survey (GPDS) Steering Committee., 2002; Schrag, Hovris, Morley, Quinn, & Jahanshahi, 2006).

The motor symptoms associated with PD are thought to be caused by the death of dopaminergic neurons in the midbrain, whereas the presence of non-motor symptoms provide evidence of neuronal loss in additional areas of the brain (DeMaagd & Philip, 2015) and autonomic nervous system (Orimo, Ghebremedhin, & Gelpi, 2018). While no drug has been shown to slow or reverse the neurodegenerative process of PD, there are effective treatments for both the motor and non-motor symptoms of PD; however long term use together with disease progression can lead to adverse effects that may limit function or dose.

1.2.2 Epidemiology

Parkinson's disease is a common neurodegenerative disorder. A recent report on the prevalence and incidence of PD in the UK (Parkinson's UK, 2017), estimated that 22 in every

10,000 women and 32 in every 10,000 men are living with PD in the UK . As these figures suggest, PD is more common in men, with men accounting for 57.5% of the PD population in the UK. Prevalence increases with age, doubling roughly every 5 years between 50 and 69 years for both men and women. From 85 onwards, prevalence appears to decrease slightly, however this may be due to mortality, or due to the difficulty in diagnosing PD in very elderly populations, where symptoms may be confused with normal ageing.

Due to an increasing life expectancy and an ageing population, the prevalence for PD in the UK was estimated as 145,519 in 2018 (up 6.4% from 136,816 in 2015) and the incidence 18,461 (up 6.6% from 17,314 in 2015) (Parkinson's UK, 2017). Furthermore, by 2025, the prevalence of PD is expected to have increased by 18%, and by 2065, both the incidence and prevalence of PD in the UK is expected to have doubled (see Figure 1).

The prevalence of PD is also increasing globally (Dorsey et al., 2018). In 2016, 6.1 million people had PD globally, compared with 2.5 million in 1990 (Dorsey et al., 2018). This continual rise in prevalence and incidence of PD in the UK and globally is expected to have significant social, health and economic impacts.

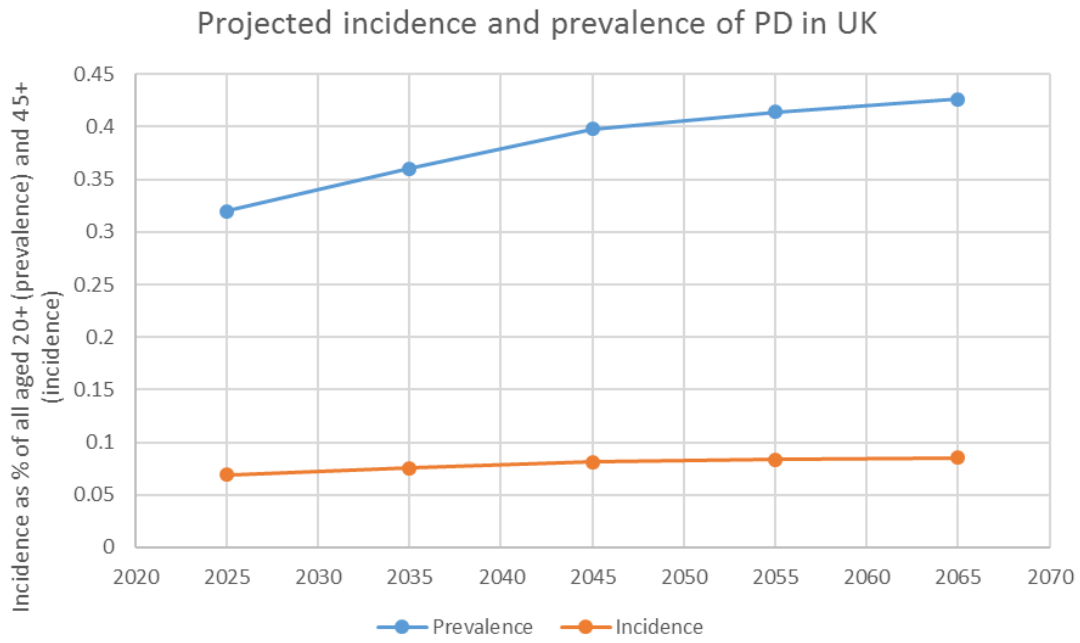


Figure 1 Projected incidence and prevalence of PD in the UK. Based on data from the Parkinson's UK Clinical Practice Research Datalink Summary Report (Parkinson's UK, 2017).

1.2.3 Economic impact of PD

Due to an increasing life expectancy, people are living longer with PD, which, coupled with increased incidence and prevalence of the disease means the economic impact of PD is substantial and complex.

The economic impact of PD can be measured from a variety of different perspectives, as outlined in Figure 2.

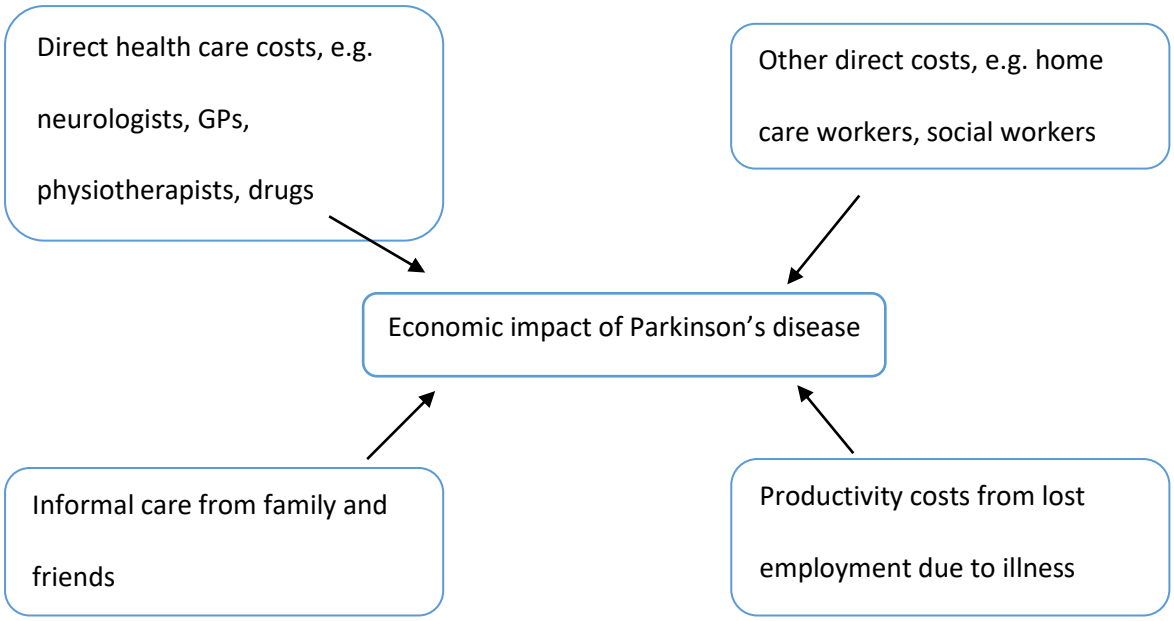


Figure 2 The different economic costs contributing towards the overall economic impact of Parkinson's disease. Figure based on McCrone (2007).

In 2015, Parkinson's UK (PUK) commissioned a national survey to provide an estimate of the economic impact of PD for someone living with the condition in the UK (Gumber et al., 2017). The research revealed that on average, a household in the UK where someone has a diagnosis of PD will incur an annual cost of £16,582, which was broken down as higher health costs (£2,229), higher social costs (£3,622) and loss of income (£10,731).

Of interest, previous research into the economic impact of PD identified several predictors of cost in PD including problems with depression, communication and gait, as well as longer duration of illness (McCrone, Allcock, & Burn, 2007). Gender was associated with total costs, with men having higher costs than women.

This research indicates the overall economic impact of PD for households living with the condition and to services is high. Furthermore, overall societal costs are expected to rise given the increasing age-related prevalence of the disease in the UK.

1.2.4 Aetiology

Despite extensive research, the cause of PD remains elusive. The current view is that both environmental factors and genetic factors contribute to the onset of disease, with genetic predisposition increasingly seen as a major influence to the cause of PD (Schapira & Jenner, 2011). Age is strongly related to the onset of PD, and remains the biggest risk factor for developing idiopathic Parkinson's disease (IPD) (Reeve, Simcox, & Turnbull, 2014). This is thought to be explained by an increased vulnerability of dopaminergic neurons to toxic insult with age (Schapira & Jenner, 2011).

1.2.5 Familial PD

While the cause of PD in the majority of cases remains unknown (IPD) in less than 10% of cases, the cause of PD is thought to be genetic, known as familial PD. In familial cases of PD, if the leucine rich repeat kinase 2 (LRRK2) or a-Synuclein (SNCA) gene is altered, the disorder is inherited in an autosomal dominant manner, whereas if the Parkin, PTEN-induced putative kinase 1 (PINK1), DJ-1 and ATP13A2 genes are altered, the disease is inherited in an autosomal recessive manner (Corti, Lesage, & Brice, 2011). A list of known gene mutations associated with PD are summarised in Table 1.

1.2.6 Genetic associations with IPD

The genetic factors associated with IPD have been extensively studied, in the hope that it may lead to effective treatments and early detection of disease (Schapira, 2015). The accumulation of a-synuclein protein is thought to underlie the pathogenesis of PD, with mutations of the SNCA gene leading to the presence of abnormal protein associated with PD. Despite several gene mutations having been identified in familial PD, these are relatively rare, and account

for approximately less than 10% of all cases (Mullin, Schapira, & Leonard, 2015). Genome-wide association (GWA) studies have allowed for the identification of a number of additional significant genetic associations with PD (Edwards et al., 2010), which include SNCA and MAPT.

Importantly, mutations of the glucocerebrosidase gene (GBA1) have been recently identified as a significant risk factor for PD (Aharon-Peretz, Rosenbaum, & Gershoni-Baruch, 2004) and are substantially more common in PD than other associated genes including LRRK2 or SNCA (Schapira, 2015). The lifetime risk of developing PD for those with a GBA1 mutation has been estimated as 20% for someone at 70 years of age, increasing to 30% at 80 years of age (Beavan & Schapira, 2013). Estimates of the proportion of PwP that carry the GBA1 mutation vary, but is thought to be between 5 to 10% (Schapira, 2015).

The genetic mutations associated with PD are summarised in Table 1 below.

Table 1 Table of genetic mutations associated with Parkinson's disease.

Name	Gene	Inher.-Onset-Type	Function
PARK1	α-synuclein (SNCA), 2% of AD cases	AD-E-PD/PDD	Vesicle tracking
PARK2	Parkin, 50% of AR hereditary cases	AR-J/E-PD	Ubiquitination
PARK3	Unknown – not found since identified 1998	AD-L-PD	Unknown ?risk factor
PARK4	α-synuclein (=PARK1 gene multiplication)	AD-E-PD/PDD	Vesicle tracking
PARK5	Ubiquitin-C-terminal hydrolase L1 (UCH-L1)	AD-L-PD	Ubiquitination
PARK6	PTEN-induced kinase 1 (PINK1)	AR-E-PD	Mitochondrial function
PARK7	DJ-1	AR-L-PD	?apoptosis
PARK8	Leucine-rich repeat kinase 2 (LRRK2), 10% of AD cases	AD-L-PD	?mitochondrial fusion/fission
PARK9	Lysosomal ATPase (ATP13A2)	AR-J/E-PD/PD+	Lysosomal ATPase
PARK10	Unknown	AR-?-PD	Unknown ?risk factor
PARK11	Unknown	AD-?-PD	Unknown ?risk factor
PARK12	Unknown	XR-?-?	Unknown ?risk factor

Name	Gene	Inher.-Onset-Type	Function
PARK13	Serine protease (HTRA2)	AD-?-?	Serine protease
PARK14	Phospholipase A2 (PLA2G6)	AR-E-PD+	Phospholipase A2
PARK15	F-box only protein 7 (FBX07)	AR-E-PD+	Ubiquitination
PARK16	Unknown – identified in GWAS as risk factor	?-?-PD	Unknown
PARK17	VPS35	AD-E/L-PD	Endosome protein trafficking
PARK18	EIF4G1	AD-L-PD	mRNA protein production
PARK19	DNAJC6	AR-J-PD/PD+	Endocytosis
PARK20	SYNJ1	AR-E-PD/PD+	Vesicle recycling
Glucosidase	GBA (Gauchers disease)	AD-L-PD/PD+	Lysosomal enzyme
POLG1	Polymerase gamma	AR-E-PD+	DNA polymerase gamma 1

AD=autosomal dominant; AR=autosomal recessive; J=juvenille (<20yrs); E=early (<50yrs); L=late (>=50yrs);PD=Typical PD; PDD=PD with dementia; PD+=PD with additional neurological features (* of familial cases only)

The discovery of GBA1 as a significant risk factor for PD provides valuable insights into disease pathophysiology, which may help efforts to predict PD prior to the development of symptoms, and help to develop neuroprotective therapies.

1.2.7 Environmental Factors:

There are a variety of known environmental influences that are associated with the occurrence of PD, including bacterial or viral infection, and exposure to chemicals such as carbon monoxide and carbon disulphide (Schapira & Jenner, 2011.). Pesticide exposure has been increasingly identified as a potential environmental influence, however it has not been possible to identify specific pesticide substances that might be responsible (Richardson et al., 2009).

Some environmental factors including caffeine and alcohol have been associated with a decreased risk of developing PD (Lees, Hardy, & Revesz, 2009), with non-smokers twice as likely to develop PD (Hernán et al., 2001) and people who do not consume caffeine daily at a 25% increased risk of disease (Ascherio et al., 2004). Indeed, recent studies have supported the potential use of caffeine (an adenosine A2 receptor antagonist) as an anti-PD drug (Prediger, 2010).

1.2.8 (Patho) physiology of movement

Intentional movement occurs in response to initiation by the cerebral motor cortex that directly (or indirectly via local premotor circuits) reaches the brain stem or spinal motor neurons, and projects to the relevant muscles (Groenewegen, 2003). Several cortical and

subcortical centres including the basal ganglia receive input from the primary motor cortex and send processed information via the thalamus to the descending corticospinal motor pathways that originate in the motor and premotor areas of the cerebral cortex. The basal ganglia thereby influence the final motor output (eg. magnitude and timing of movements) (Groenewegen, 2003).

The basal ganglia are composed of four main nuclei (see Figure 3): the striatum, the pallidum, the subthalamic nucleus and the substantia nigra. The substantia nigra consists of the pars compacta, which contains dopaminergic neurons, and the pars reticula. The basal ganglia receives input from almost all parts of the cerebral cortex, with the striatum being the main input structure. Dopamine neurons stemming from the substantia nigra pars compacta (SNpc) project to the striatum via the nigrostriatal pathway.

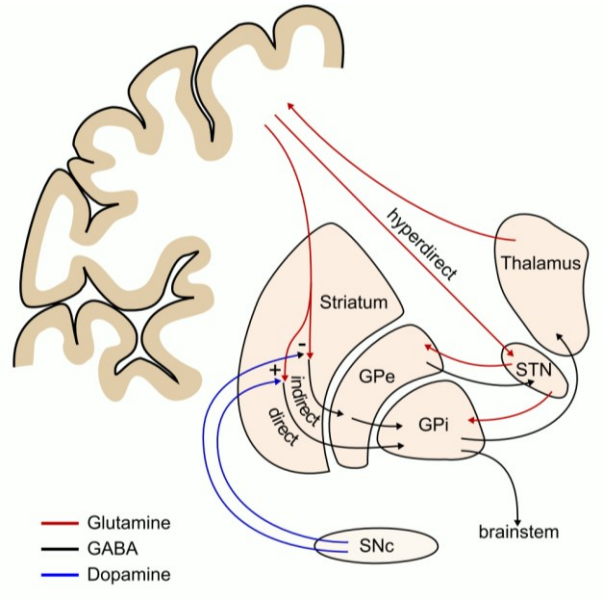


Figure 3 Anatomy of the basal ganglia and major anatomical connections between the basal ganglia and cortex. From Brittain & Brown (2014)

A hallmark feature of PD pathology is the loss of dopaminergic neurons of the substantia nigra pars compacta (SNpc), with neuronal loss estimated to be 60-70% at the onset of symptoms (Lang & Lozano, 1998).

In addition to the selective loss of dopaminergic neurons, pathological confirmation of diagnosis focuses on the finding of Lewy bodies, which are primarily made up of the protein *α*-synuclein (see Figure 4). Despite the presence of Lewy bodies representing a defining feature of PD, the relevance of Lewy bodies to the disease process remains uncertain (Schapira & Jenner, 2011).

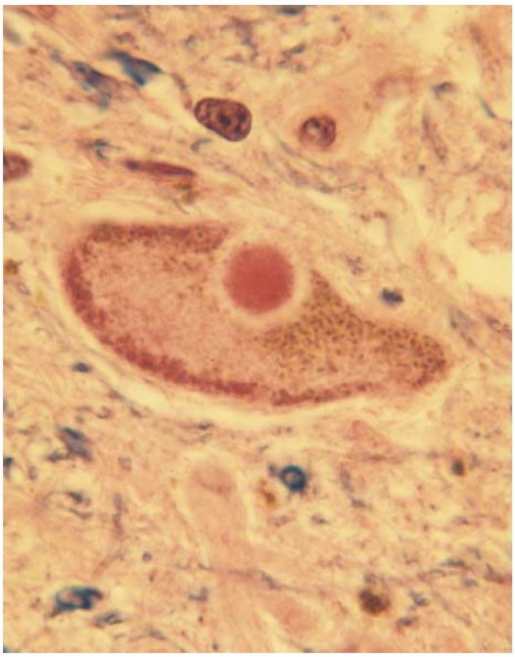


Figure 4 A typical Lewy Body in the cytoplasm of a pigmented dopaminergic neuron in the substantia nigra. Taken from Lang & Lozano (1998).

The effect of this dopaminergic loss is a malfunction of the complex direct and indirect pathways (see Figure 5). A loss of dopaminergic neurons means it is not possible to initiate

more movement in the direct pathway, nor prevent an excessive reduction in movement in the indirect pathway, resulting in a slowness of movement.

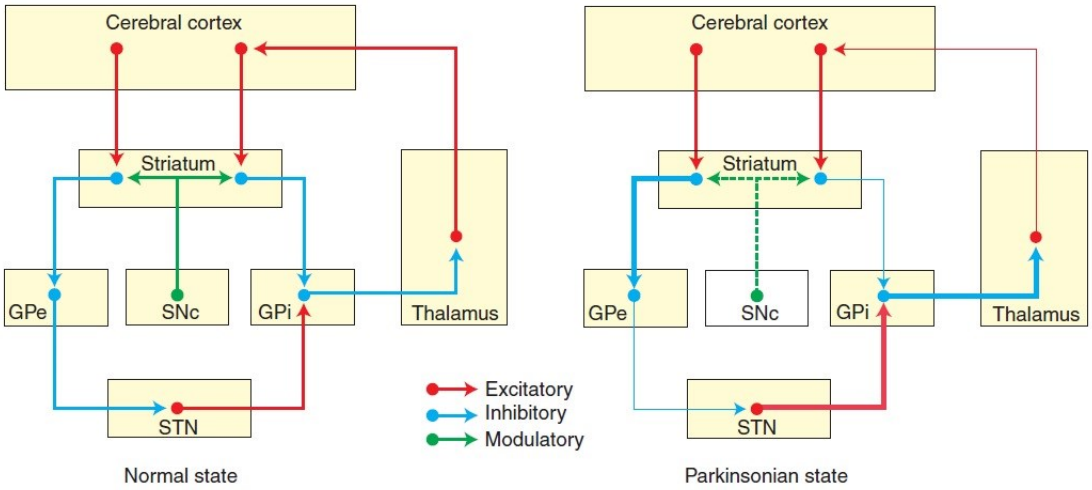


Figure 5 Schematic summary of the basal ganglia model in normal and Parkinsonian State. Thicker arrows illustrate hyperactive pathways, whereas thinner arrows represent hypoactive circuits.

The mechanisms of cell death that contribute to neuronal loss in PD are not fully understood, however considerable advances in understanding have been made in recent years (Schapira & Jenner, 2011). Mitochondrial dysfunction (Gu et al., 1998), oxidative stress (Schapira, 1995), altered protein handling (Schapira et al., 2009) and inflammatory change (Iravani, Kashefi, Mander, Rose, & Jenner, 2002) are all events considered to lead to cell death in PD, however the combination and sequence of these events leading to cell death remains to be ascertained (Schapira & Jenner, 2011).

Braak and collegues (2003) have challenged the traditional view that the degeneration of dopaminergic neurons starts in the substantia nigra (Braak et al., 2003). Instead, Braak (2003) described a pathological process of degeneration comprising six stages (see Figure 6).

In stages 1 and 2, Braak (2003) describes how neurodegeneration may have already begun outside of the substantia nigra, but is not progressed to the point of a formal diagnosis of PD, which is dependent on the presence of motor symptoms. This phase (whereby symptoms and signs are present but not yet sufficient to meet diagnostic criteria for classical PD) is known as prodromal PD (Postuma et al., 2015).

The main brain areas implicated in Stages 1 and 2 of Braak's hypothesis (including the olfactory bulb, the anterior olfactory nucleus and the lower brain stem) are thought to mediate NMS including olfacation, and sleep (Chaudhuri, Healy, & Schapira, 2006). Manifestation of NMS may therefore be indicators of prodromal PD. Indeed, the Movement Disorders Society (MDS) has published diagnostic criteria for prodromal PD (Berg et al., 2015) based on a variety of non-motor manifestations including rapid eye movement (REM) Sleep Behaviour Disorder (RBD), olfactory dysfunction, constipation, excessive daytime sleepiness (EDS), symptomatic hypotension, erectile dysfunction, urinary dysfunction and depression.

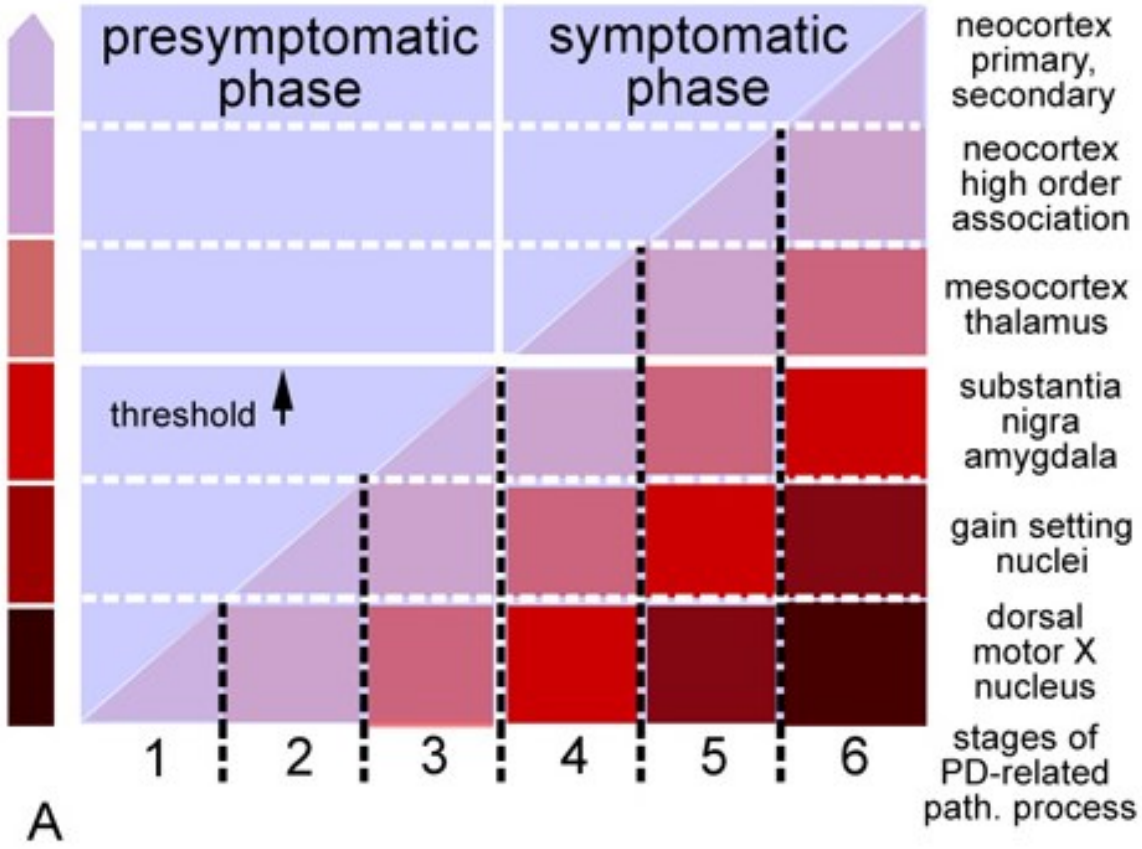


Figure 6 Progression of PD-related pathology in accordance with Braak's staging hypothesis. Taken from Sakakibara, Fowler, & Hattori (2010).

1.2.9 Clinical Features

Parkinson's disease is characterised by a multifaceted picture of motor and non-motor symptoms that varies between patients and throughout the progression of the disease. The marked heterogeneity in the clinical presentation of PD adds to the complexity of managing the condition.

1.2.10 Motor Symptoms

The four cardinal symptoms of PD are:

1.2.10.1 Bradykinesia

Bradykinesia initially manifests as slowness in performing activities of daily living (ADL) and slow reaction times, but also encompasses difficulties with planning and executing movements, and loss of spontaneous movements and/or gestures (Jankovic, 2008). Bradykinesia is the most characteristic clinical feature of PD and its presence is required for a diagnosis of PD to be made (Gibb, 1988). Bradykinesia is typically assessed by asking the patient to perform rapid and repetitive movements of the hand and feet (finger taps, heel taps). The clinician aims to identify slowness of movement and decreasing amplitude.

1.2.10.2 Rigidity

Rigidity is characterised by resistance throughout the range of limb movement and is typically accompanied by the 'cog-wheeling' phenomenon, whereby limbs move with small, jerky motions. PD rigidity can occur distally (wrists, ankles) or proximally (neck, shoulders, hips). Voluntary movements of the contralateral limb can be used to help detect mild cases, by increasing rigidity in the limb being examined (Jankovic, 2008).

1.2.10.3 Rest tremor

Rest tremor is a common symptom in PD and occurs unilaterally at a frequency between 4 and 6 Hz. Rest tremor may appear in the thumb and index finger (often described as "pill-rolling") but can also appear in lips, chin, jaw and legs. The tremor does not generally appear

when the limb is in motion but when at rest, and characteristically disappears with action and during sleep (Jankovic, 2008).

1.2.10.4 Postural Instability

Postural instability usually occurs in the later stages of PD, after the onset of other motor symptoms. It is caused by the loss of postural reflexes and assessed by 'The Pull Test' whereby a clinician pulls the patient sharply backwards by the shoulders. The number of steps taken by the patient to recover indicates the level of instability (>2 or no response indicative of an abnormal response) (Jankovic, 2008).

Other motor symptoms, which are not necessary for a diagnosis of PD include:

1.2.10.5 Gait

Gait disturbances in PD are varied, and can include episodic disturbances, which occur intermittently, as well as continuous disturbances, which are persistent and lead to changes in walking pattern (Hausdorff, 2009). Some examples of episodic gait disturbances are festination, meaning a quickening and shortening of normal strides, and freezing of gait (FOG). FOG typically manifests as a sudden inability to move, and can occur when beginning to walk (hesitation), when turning, or an inability to walk through a doorway or across a street. Freezing is not a symptom experienced by all patients, and typically occurs later in the course of the disease. Patients frequently develop techniques to help overcome this disabling symptom, including stepping over a cane, counting or marching (Jankovic, 2008).

Examples of continuous gait disturbances include slowed ambulation with decreased or absent arm swing, and impaired postural control (Hausdorff, 2009). A key gait problem for PwP is the inability to generate sufficient stride length, leading to a reduced and shortened stride length with increased variability.

Gait disturbances can occur early on in the disease (Rochester et al., 2012), and become more marked as the disease progresses. A significant consequence of disturbed gait is falls, which can have important consequences including hospitalisation or nursing home placement, loss of independence, and increased mortality (Farombi, Owolabi, & Ogunniyi, 2016).

1.2.10.6 Postural Tremor

Postural tremor can be differentiated from rest tremor as it occurs when the patient has their arms outstretched in a horizontal position.

1.2.11 Non Motor Symptoms (NMS)

The range of NMS that can occur in PD fall into 5 groups of symptoms; neuropsychiatric symptoms, sleep disorders, autonomic symptoms, gastrointestinal symptoms and sensory symptoms (Chaudhuri, Healy, & Schapira, 2006). As mentioned previously, the cause of some of the NMS in PD is thought to be associated with the distribution of α-synuclein outside the nigrostriatal system (Dickson et al., 2009), which affects multiple subcortical nuclei including nucleus basalis of Meynert (NBM)(cholinergic), locus coeruleus (LC) (noradrenergic), dorsal raphe nucleus (DRN) (serotonergic) and the dorsal motor nucleus of the vagus nerve (DMV) (Jellinger, 2017). The early loss of innervation from these nuclei and degeneration of

dopaminergic, serotonergic, cholinergic and noradrenergic pathways are thought to contribute to various NMS experienced in PD (Jellinger, 2017). In line with Braak's (2003) staging theory, many of these symptoms are present prior to the emergence of motor symptoms. Indeed, RBD, olfactory dysfunction, constipation, excessive daytime sleepiness (EDS), symptomatic hypotension, erectile dysfunction, urinary dysfunction and depression, all form part of the MDS criteria for prodromal PD (Berg et al., 2015). Additionally, the peripheral autonomic nervous system and enteric nervous system are affected at early stages in PD, and underlie some of the NMS experienced (Ferrer, 2011).

Figure 7 displays the different pathways affected in PD that may contribute towards the relevant motor and non-motor symptoms listed beneath each image.

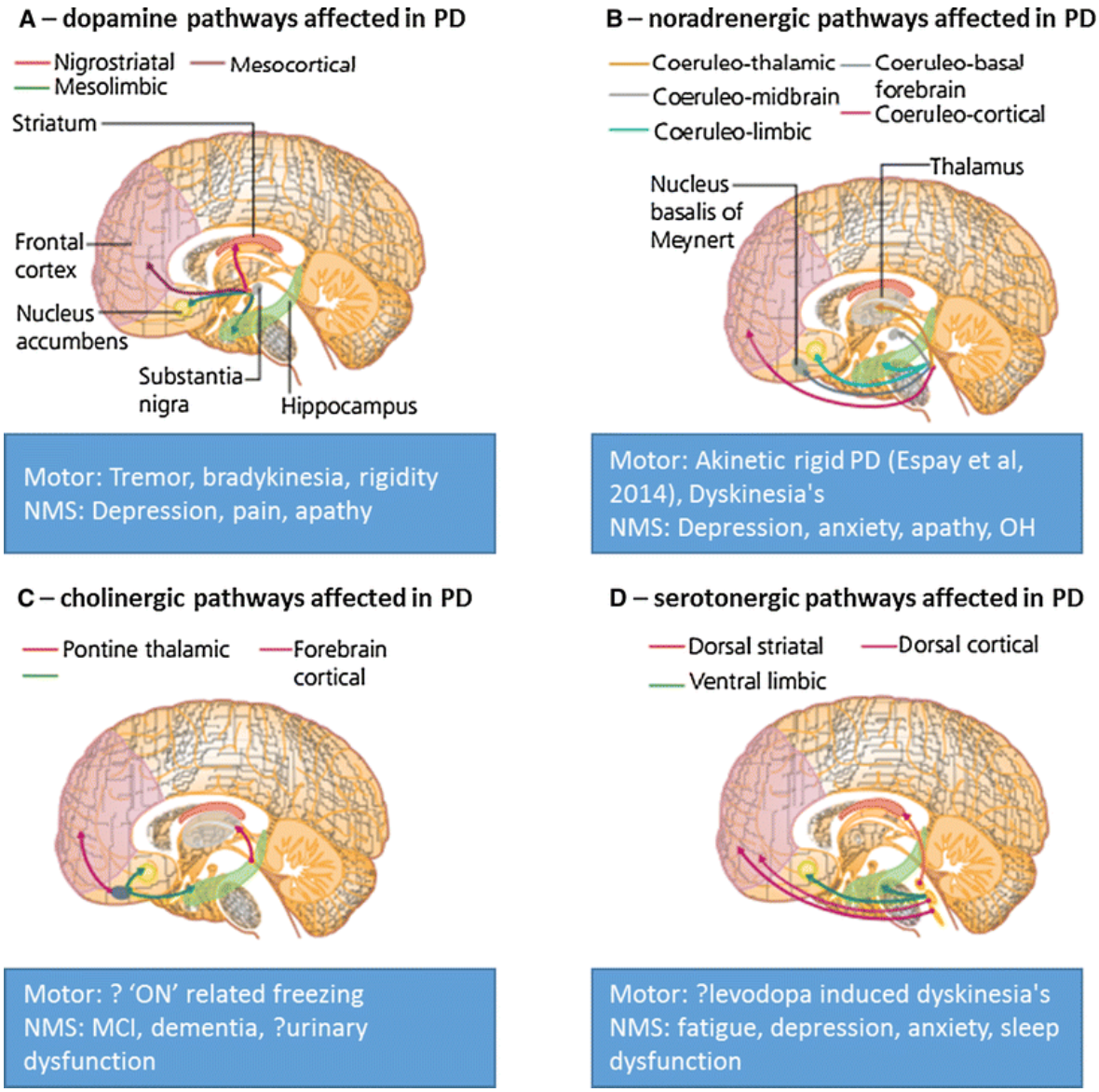


Figure 7 The various pathways affected in PD, with corresponding motor and non-motor symptoms taken from Titova, Padmakumar, Lewis, & Chaudhuri (2017)

A brief description of the NMS experienced in PD is given below, with relevant treatment recommendations summarised in Table 2.

1.2.11.1 Neuropsychiatric Symptoms:

1.2.11.1.1 Depression:

Depression is experienced in up to 45% of PwP, and amongst other signs, can manifest as pessimism about the future, a sense of guilt and heightened irritability (Pellicano et al., 2007). Depression has been identified as the most significant predictor of quality of life in PD (GDPS, 2002), and is highly comorbid with anxiety (Menza, Robertson-Hoffman, & Bonapace, 1993). As outlined in a review by Dickson (2009), the anatomic substrate of depression in PD is not well defined, although norepinephrine and serotonin deficiencies are well documented in PD, and PD depression responds well to drugs that enhance noradrenergic or serotonergic neurotransmission (Dickson et al., 2009). As mentioned previously, the LC and DRN are examples of neurons that use these transmitters, and are targets of PD pathology (Dickson et al., 2009).

1.2.11.1.2 Psychotic Symptoms (Visual Hallucinations and Delusions):

Up to 40% of PD patients experience visual hallucinations of varying intensity (Diederich, Goetz, & Stebbins, 2005), whereas delusions become more frequent as the disease progresses (Chaudhuri et al., 2006). Visual hallucinations are commonly viewed as treatment related, although some research has suggested neuronal degeneration of the pedunculopontine nucleus, locus coeruleus, and the dopaminergic raphe nuclei may play a causative role (Diederich et al., 2005). Visual hallucinations can be distressing for patients and their families, and psychotic symptoms including paranoid ideation and delirium have been found to

strongly correlate with nursing home placement for people with PD, and with morality (Fénelon, Mahieux, Huon, & Ziégler, 2000). These symptoms can also be distressing for families due to their paranoid and accusatory nature.

1.2.11.1.3 Cognitive impairment:

Cognitive impairment is common in PD, with Mild Cognitive Impairment (MCI) occurring in up to 50% of PwP (referred to as PD-MCI) (Litvan et al., 2011). The cognitive deficits experienced in PD are heterogeneous with regards to the domains affected, including executive dysfunction (attention, planning, monitoring, and inhibition), memory and visuospatial impairment (Kehagia, Brandt, Antoniades, Collins, & Williams-Gray, 2016).

Additionally, the type of cognitive deficits experienced is thought to contribute to the rate at which PwP with MCI are likely to progress to dementia. For instance, in a 10 year follow up study, (Williams-Gray et al., 2013) patients with early deficits on tests with a posterior cortical basis (eg. semantic fluency) were found to progress to dementia more quickly than patients with frontostriatally based executive deficits, as displayed in Figure 8.

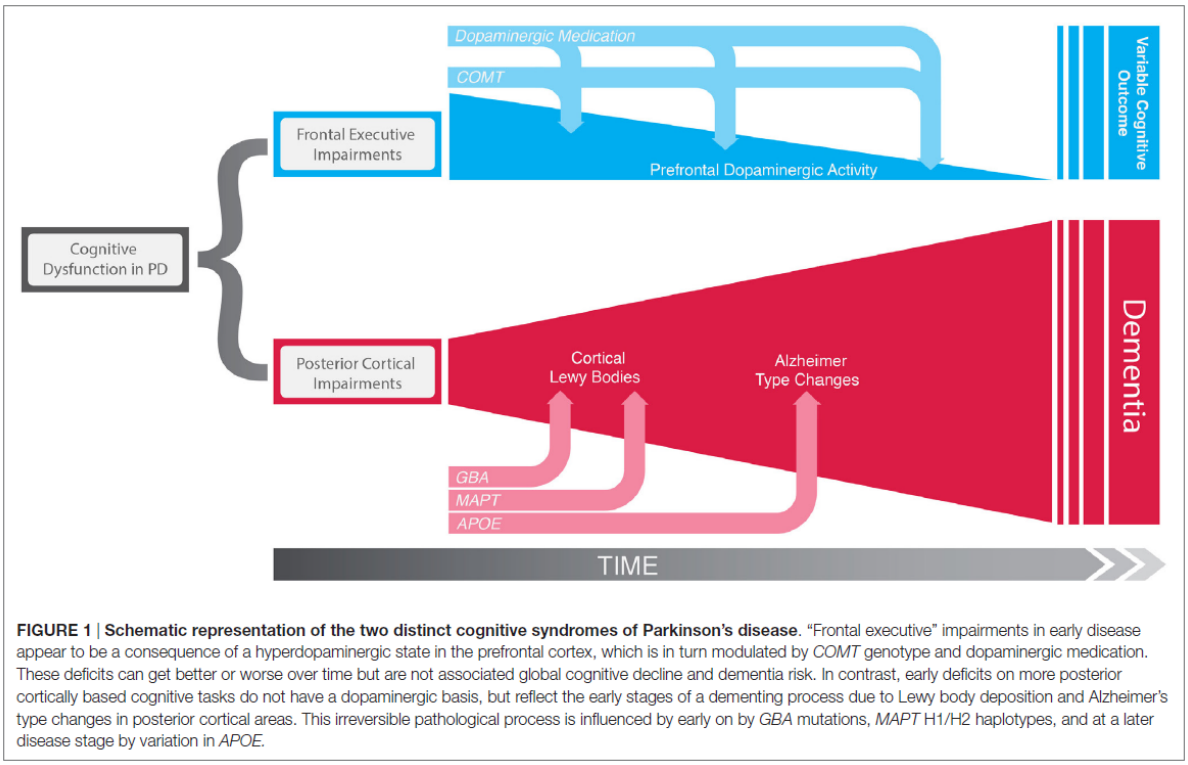


FIGURE 1 | Schematic representation of the two distinct cognitive syndromes of Parkinson's disease. "Frontal executive" impairments in early disease appear to be a consequence of a hyperdopaminergic state in the prefrontal cortex, which is in turn modulated by *COMT* genotype and dopaminergic medication. These deficits can get better or worse over time but are not associated global cognitive decline and dementia risk. In contrast, early deficits on more posterior cortically based cognitive tasks do not have a dopaminergic basis, but reflect the early stages of a dementing process due to Lewy body deposition and Alzheimer's type changes in posterior cortical areas. This irreversible pathological process is influenced by early on by *GBA* mutations, *MAPT* H1/H2 haplotypes, and at a later disease stage by variation in *APOE*.

Figure 8 Schematic representation of Frontal Executive vs Posterior Cortical impairment in PD. Taken from Williams-Gray (2013)

In line with these findings, recent research by Bohnen (2015) demonstrated that cortical cholinergic denervation is very frequent in PwP with greatest cognitive deficits. Importantly however, the authors highlighted that cortical cholinergic denervation occurs mainly in subjects with significant caudate nucleus dopaminergic denervation. This finding indicates deficits of the caudate nucleus dopaminergic and forebrain cholinergic pathways exhibit both independent and interactive contributions to cognitive impairment in PD with dopaminergic denervation inducing compensatory over-activity of cortical cholinergic afferents (Bohnen et al., 2015).

1.2.11.2 Sleep Disorders

1.2.11.2.1.1 Sleep Fragmentation:

Sleep disruption is common in PD, and affects the majority of patients. Although the causes of sleep fragmentation are multifactorial, the pathological degeneration of central sleep regulation centres in the brainstem likely play a causative role (Chaudhuri, Healy, & Schapira, 2006). In addition, other NMS can have an effect on the quality of sleep, such as restless-leg syndrome, which can cause frequent arousal.

1.2.11.2.1.2 REM Sleep Behaviour Disorder (RBD):

REM Sleep Behaviour Disorder (RBD) is characterised by a loss of muscle atonia that is normally experienced during REM sleep. As a result, patients are able to physically enact their dreams, which can involve making vocalisations (shouting, talking) as well as violent, abnormal movements (Muzerengi, Contrafatto, & Chaudhuri, 2007) which can be distressing for patients and their bed partners (Comella, Nardine, Diederich, & Stebbins, 1998). RBD is common in PD, affecting around a third of patients (Olson, Boeve, & Silber, 2000), as well as being a strong predictor of future PD development (Noyce, Lees, & Schrag, 2016); however the pathological cause is not well defined. It has been suggested that RBD occurs due to degeneration of the lower brainstem nuclei, including the pedunculopontine and subcoeruleal nucleus (Chaudhuri et al., 2006).

1.2.11.2.1.3 Excessive Daytime Sleepiness (EDS):

Excessive daytime sleepiness (EDS) is commonly experienced by PwP, affecting up to 50% of patients (Arnulf, 2005). There are several factors that are thought to play a role in the causation of EDS, including the disease process, the effect of disturbed night-time sleep, and the effects of antiparkinsonian medication (Muzerengi et al., 2007). The presence of EDS has also been linked with the development of sudden onset sleep, which has been linked to road traffic accidents in PwP, therefore posing a threat to patient safety (Frucht, Rogers, Greene, Gordon, & Fahn, 1999).

1.2.11.2.2 Autonomic Symptoms:

Autonomic symptoms in PD including orthostatic dizziness, constipation, bladder dysfunction and erectile dysfunction are commonly experienced by PwP, and can have a significant impact on daily living (Magerkurth, Schnitzer, & Braune, 2005). The pathological basis for dysautonomia is thought to involve the degeneration and dysfunction of the dorsal vagal nucleus, nucleus ambiguous, and other centres including the rostral ventrolateral medulla, ventromedial medulla and caudal raphe nuclei (Chaudhuri et al., 2006). In addition, abnormalities of modulatory effects within the peripheral and central autonomic network are thought to occur due to the degeneration of cholinergic and monoaminergic nuclei (Chaudhuri et al., 2006). Some of the autonomic symptoms in PD will be described in more detail below.

1.2.11.2.2.1 Gastrointestinal Dysfunction:

In recent years, there has been increasing evidence to suggest that the gastrointestinal tract may be the site of initiation of PD (Tredici & Braak, 2008). The presence of Lewy bodies in the enteric nervous system (ENS) has led to the suggestion that a-synuclein deposition may originate within the ENS before spreading to the brain (Hill-Burns et al., 2017). However, mixed findings regarding the specificity of enteric α-synuclein has prevented it from becoming an established biomarker for the diagnosis of PD (Visanji, Marras, Hazrati, Liu, & Lang, 2014).

The dysfunction of the gastrointestinal system in PD can lead to a variety of complications, including drooling and swallowing problems, delays in gastric emptying and constipation.

1.2.11.2.2.2 Constipation:

Constipation is the most common gastrointestinal symptom in PD, experienced by 80–90% of patients (Fasano, Visanji, Liu, Lang, & Pfeiffer, 2015). Constipation does not respond well to dopaminergic treatment (Muzerengi et al., 2007) and can impede the absorption of anti-PD medications, leading to Urinary Tract Infections (UTIs), confusion and falls, which are common causes of hospital admission (Muzerengi et al., 2007).

1.2.11.2.2.3 Genitourinary dysfunction:

Genitourinary dysfunction includes several PD NMS including bladder dysfunction (urinary urgency or frequency). The pathological basis for the overactivity of the bladder is thought to be due to an altered dopamine-basal ganglia circuit which normally suppresses the

micturition reflex (Sakakibara, Uchiyama, Yamanishi, & Kishi, 2010). However, some patients may experience an underactive bladder whereby they have difficulty starting urination.

Another symptom that comprises genitounirnary dysfunction is sexual dysfunction (including erectile dyfunction and a decreased libido). Hypothalamic dysfunction is thought to be responsible for sexual dysfunction experienced in PD, via altered dopamine-oxytocin pathways which normally promote sexual function (Sakakibara, Uchiyama, et al., 2010).

In addition, some patients may experience an increased sex drive due to developing Impulse Control Disorder (ICD), which can occur as a result of taking dopamine agonists. Clinicians should be alert to the signs of ICD, and regularly check with their patients for symptoms, so that medications can be adjusted as necessary. In addition to hypersexuality, other impulse control behaviours may include compulsive gambling, binge eating and obsessive shopping (NICE Guidelines, 2017).

1.2.11.2.2.4 Orthostatic Hypotension (OH):

Orthostatic hypotension (OH) occurs in 20-50% of PwP and is a recognised predictor of falls (Farombi et al., 2016). Sympathetic denervation has been suggested as a possible cause for OH in PD, and can be assessed via norepinephrine levels in the blood (Dubow, 2007). Patients experiencing OH have been found to have lower concentrations of norepinephrine than those without OH, and do not experience the same increase in concentration on standing that patients without OH experience (Dubow, 2007).

1.2.11.2.3 Sensory Symptoms:

1.2.11.2.3.1 Pain:

Pain is a common sensory symptom in PD affecting between 40%-85% of patients (Broen, Braaksma, Patijn, & Weber, 2012). There are five types of pain associated with PD. These include:

- Musculoskeletal pain; characterised by a dull aching, primarily confined to joints and experiences with motion and after rest. This pain is typically worse in an 'OFF' medication state.
- Radicular pain; limited to a specific neuronal distribution, this type of pain is experienced as a stabbing, throbbing or shooting sensation.
- Dystonic pain; dystonia causes severe painful and involuntary muscle spasms, which are characterised by twisting or jerking repetitive movements.
- Central neuropathic pain; this pain is constant and not well localised, nor limited to a specific neuronal distribution.
- Akathisia pain: this type of pain is related to dopaminergic deficit and characterised by an intolerance of remaining still, with a constant need to move.

1.2.12 Treatment for NMS

If left untreated, NMS can cause detrimental health complications and are a major cause of institutionalised care (Chaudhuri et al., 2006). It is therefore essential that effective treatment is provided in a timely manner to prevent further complications.

Treatments for NMS in line with NICE recommendations for the management of PD (NICE, 2017), in addition to recommendations from the MDS Evidence-Based Medicine Committee on the treatment of NMS in PD (Seppi et al., 2019) are summarised in Table 2.

In line with NICE guidelines (NICE, 2017), a full medications review should be carried out when treating NMS, to establish whether any existing treatments are contributing towards symptoms. If reducing an existing medication (dosage or frequency), the severity of symptoms and possible withdrawal effects must be considered. If adding a medication to an existing regime, consideration of risks and side effects of the patient's current medication is essential.

Table 2 Treatment guidelines for NMS in PD in line with NICE (2017) and MDS Task Force (2019) recommendations.

Non-motor Symptom	Recommended first line treatment	Recommended second line treatment
Depression	• Low intensity psychosocial interventions (physical activity program, group based peer support, or computerised cognitive behavioural therapy (CCBT))	• Dopamine Agonist Pramipexole • Serotonin and Norepinephrine Reuptake Inhibitor (SNRI) venlafaxine • Individual or group cognitive behavioural therapy (CBT)
Psychotic Symptoms (Visual Hallucinations and Delusions)	• Reduce the dosage of any PD medications that may have triggered the symptoms	• Quetiapine (in PwP without cognitive impairment) • Clozapine if standard treatment is not effective.
Cognitive impairment	• Cholinesterase inhibitor	• Memantine
Sleep Fragmentation	• No formal guidelines	

Non-motor Symptom	Recommended first line treatment	Recommended second line treatment
	• Encourage use of bedsheets and pyjamas that slip easily (Overeem & Reading, 2018) • Suggest that items needed throughout the night (e.g. medication, water) are within easy reach (Overeem & Reading, 2018)	
REM Sleep Behaviour Disorder (RBD)	• Clonazepan • Melatonin	
Excessive Daytime Sleepiness (EDS)	• Adjust medications to reduce the occurrence of EDS	• Modafinil
Constipation	• Lifestyle recommendations (such as increased fibre and fluid intake) • Use of probiotics and prebiotic fibers	• Laxatives
Urinary urgency/frequency	• Advise pt to avoid excessive tea and coffee consumption • Advise pt to stay hydrated	

Non-motor Symptom	Recommended first line treatment	Recommended second line treatment
	• Bladder training exercises • anticholinergics	
Erectile Dysfunction	• Sildenafil	
Orthostatic Hypotension (OH)	• Midodrine	• Fludrocortisone
Pain	• Dopaminergic therapy • Nonsteroidal anti-inflammatory drugs (NSAIDs) • Physiotherapy and exercise programs	

1.2.13 Parkinson's Subtypes:

The clinical manifestations of PD are heterogeneous in nature, and their varied presentation across PwP has led researchers to propose the existence of underlying motor and non-motor subtypes of PD.

In one of the largest natural history studies of PD (the DATATOP trial, 1990), 800 participants with early PD were classified using the Movement Disorders Unified Parkinson's Disease Rating Scale (MDS-UPDRS) (Goetz, Tilley, et al., 2008) (a widely used scale to assess symptom severity in PD), as having either postural instability and gait difficulty-predominant disease (n= 441), tremor-predominant disease (n= 233), or an indeterminate subtype (n= 126) (Jankovic et al., 1990). Interestingly, these groups had differences in their abilities to complete ADL and in their NMS, which led to the conceptualisation of discrete clinical subtypes in PD (Kotagal, 2016).

Over the past decade, there have been various further attempts to provide well-defined criteria for PD phenotypic subgroups based on the presentation of motor and non-motor symptoms (Erro et al., 2013; S. J. G. Lewis et al., 2005; Selikhova et al., 2009).

Most recently, Lawton and colleagues (2018) have suggested 4 possible PD phenotypic subgroups based on a sample of patients with early PD from Tracking Parkinson's (n=1601) and Discovery cohorts (n=944) (Lawton et al., 2018).

The 4 identified phenotypic subgroups with associated levodopa response, non-motor features and motor progression rates are as follows: (1) fast motor progression with

symmetrical motor disease, poor olfaction, cognition and postural hypotension; (2) mild motor and non-motor disease with intermediate motor progression; (3) severe motor disease, poor psychological well-being and poor sleep with an intermediate motor progression; (4) slow motor progression with tremor- dominant, unilateral disease. Figure 9 describes each of the subgroups identified (Lawton et al., 2018).

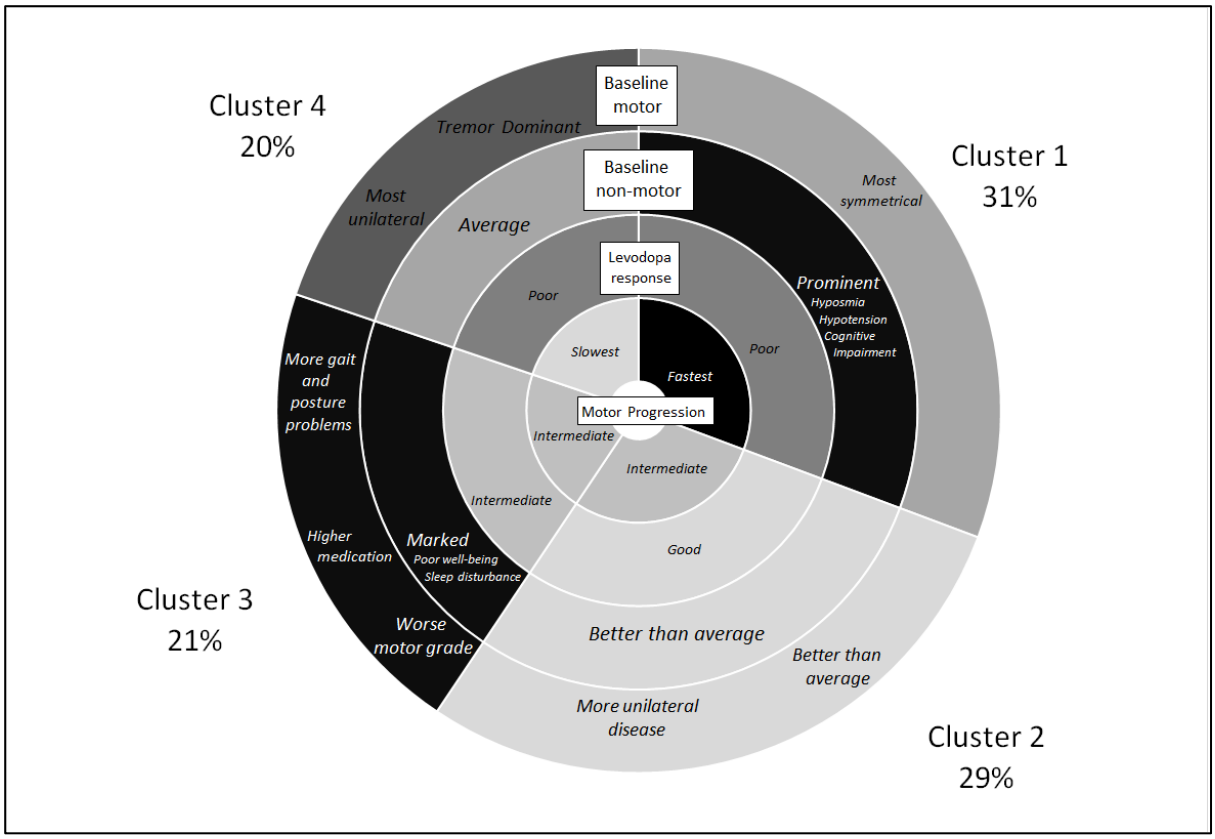


Figure 9 Salient clinical features of the four PD subgroup clusters across the Tracking Parkinson's and Discovery cohorts. Taken from Lawton (2018)

These cohort cluster findings highlight the potential value of identifying different PD phenotypic subgroups, with implications for early access to personalised, preventative treatment, and allowing for patient stratification in future clinical trials.

1.2.14 Diagnosis

As there is no definitive test to confirm the diagnosis of PD, NICE guidelines recommend a patient with suspected PD (patients presenting with tremor, stiffness, slowness, balance problems and/or gait disorders) should be referred quickly and untreated to a specialist with expertise in the differential diagnosis of PD (NICE, 2017). A diagnosis of PD is given following a detailed clinical examination, and in line with the UK Parkinson's Disease Society Brain Bank Clinical Diagnostic Criteria (Gibb et al., 1988), which requires the presence of bradykinesia in addition to at least one other symptom including: rest tremor, rigidity, or postural instability. The UK Brain Bank Diagnostic Criteria are outlined in Table 3.

Table 3 The UK Parkinson's Disease Society Brain Bank Clinical Diagnostic Criteria (Gibb et al., 1988)

Step 1. Diagnosis of Parkinsonian Syndrome
• Bradykinesia
• At least one of the following
▪ Muscular rigidity
▪ 4-6 Hz rest tremor
▪ Postural instability not caused by primary visual, vestibular, cerebellar, or proprioceptive dysfunction
Step 2. Exclusion criteria for Parkinson's disease
• History of repeated strokes with stepwise progression of parkinsonian features
• History of repeated head injury
• History of definite encephalitis
• Oculogyric crises
• Neuroleptic treatment at onset of symptoms
• More than one affected relative
• Sustained remission
• Strictly unilateral features after 3 years
• Supranuclear gaze palsy
• Cerebellar signs
• Early severe autonomic involvement
• Early severe dementia with disturbances of memory, language, and praxis
• Babinski sign
• Presence of cerebral tumor or communication hydrocephalus on imaging study
• Negative response to large doses of levodopa in absence of malabsorption
• MPTP exposure

Step 3. Supportive prospective positive criteria for Parkinson's disease

Three or more required for diagnosis of definite Parkinson's disease in combination with step one

- Unilateral onset
- Rest tremor present
- Progressive disorder
- Persistent asymmetry affecting side of onset most
- Excellent response (70-100%) to levodopa
- Severe levodopa-induced chorea
- Levodopa response for 5 years or more
- Clinical course of ten years or more

In addition to the diagnostic criteria for Prodromal PD described previously (see section 1.2.8) (Berg et al., 2015), the MDS Task Force have also published clinical diagnostic criteria for PD (Postuma et al., 2015). In line with previous versions, the MDS diagnostic criteria detail a two-step process for a PD diagnosis, whereby parkinsonism is firstly identified (as bradykinesia with rest tremor, rigidity or both) and then defined as to whether it is attributable to PD (Postuma et al., 2015). In addition, the updated diagnostic criteria incorporate non-motor manifestations such as sleep dysfunction (sleep fragmentation, excessive daytime somnolence, symptoms of RBD), autonomic dysfunction (constipation, daytime urinary urgency), or psychiatric dysfunction (depression, anxiety, or hallucination).

1.2.15 Parkinson's disease - Treatment

Due to the multifaceted picture of motor and non-motor symptoms and the variable rates of progression experienced, a comprehensive and multidisciplinary approach is required in the treatment of PD. In line with recent NICE Guidance referrals to Physiotherapists, Speech and

Language Therapists, Dieticians, Occupational Health and Palliative Care should be considered throughout the disease course (NICE, 2017). All PwP should have a comprehensive care plan in place, agreed between their PD specialist (consultant neurologist or consultant geriatrician), their families and carers.

Current NICE Guidelines recommend that patients with early PD should be seen at regular intervals of 6-12 months to review their diagnosis, with follow-up review increasing to 2-3 monthly intervals according to clinical need to assess the response to medication, titrate dosage, and re-visit the diagnosis (NICE,2017). In addition, NICE guidelines recommend that people with advanced PD may require review at frequent intervals (every 2–3 months) (NICE,2017).

In practice, different models of care provision are experienced by patients dependent on their local service provision; some patients are reviewed every 3 months; some annually or anywhere in between; and some secondary care services offer no follow-up.

NICE guidelines further recommend that all PwP should have access to a Parkinson's disease Specialist Nurse (PDNS) (NICE,2017). However, differences in capacity across services means there are varied models of care provision experienced by patients (see Table 4). In addition, a geographically large rural caseload, such as in the Plymouth area, adds to PDNS pressures.

Table 4 Differences in PDNS service provision

Model of PDNS Care Provision	Description	Limitations
Emergency only	Some PDNS teams have no capacity for regular review and so rely on patients to contact them when in difficulty.	This model of care does not facilitate anticipatory care and prevention of complications.
Clinic appointments only	A service based almost exclusively on clinic appointments.	This model of care provides no capacity for monitoring changes to medication regime or development of complications, and means it is difficult for the service to be a useful adjunct to consultant care.
Combination	Some services provide a combination of clinic appointments, routine review, supplemented with triggered review (telephone, clinic or home visit), close liaison with the consultant (usually by email) and the ability to triage patients for consultant clinics.	While this model of care allows for delivery of best practice, issues are still apparent. For example, some nurses are able to prescribe and others are not, introducing delay and lack of consistency in some aspects of management.

The differences in provision of care between services highlights the importance of managing patient's expectations of care from the point of diagnosis. By managing patients' expectations as to the regularity with which they will be seen from the outset, frustrations can be minimised and patient education can be promoted. Indeed, the recognition of the patient as an 'active player' in their health care is revolutionising traditional models of care, and encourages patients to take part in shared decision making with their clinician, rather than

assuming a passive role (Van der Eijk, Nijhuis, Faber, & Bloem, 2013). Engagement in healthcare has been found to have improved health outcomes (Bauman, Fardy, & Harris, 2003), and will be discussed in more detail (see section 1.2.27).

1.2.15.1 Pharmacological Treatment

As yet, there is no neuroprotective therapy available in PD, and so management of PD is guided by severity of motor and non-motor symptoms, complications and side effects of pharmacological therapy. The time to initiate pharmacological treatment in PD varies between patients, and largely depends on the interference of symptoms with the patient's ability to carry out ADL whilst remaining independent.

Once the decision to begin pharmacological treatment has been made, there are several first-line treatment of motor symptoms available, as outlined in the NICE guidelines (NICE, 2017). These include: levodopa, dopamine agonists and monoamine oxidase B (MAO-B) inhibitors.

Levodopa:

Initial treatment with levodopa (L-dopa) has well established benefits for patients including better symptom control and improved quality of life (QoL) (Gray et al., 2014), and continues to be considered the gold standard for PD treatment (Mercuri & Bernardi, 2005). Despite initial benefits, more than 50% of patients will go on to experience motor complications (including motor response fluctuations and dyskinesias) between 5-10 years after commencing L-dopa therapy (Davie, 2008). Motor complications pose a major challenge for

patients and clinicians, and negatively impact on QoL (Chapuis, Ouchchane, Metz, Gerbaud, & Durif, 2005).

1.2.16 Motor response fluctuations

1.2.16.1 End-of-dose wearing off

The end-of-dose wearing-off phenomenon refers to the shortened effectiveness of a single dose of L-dopa, with motor symptoms (eg. tremor) as well as NMS (eg. anxiety) remerging towards the end of a treatment interval (Fackrell et al., 2018). The frequency and severity of wearing off is increased with disease progression and duration of drug treatment, and eventually affects the majority of patients (Olanow et al., 2013).

In addition to wearing off, another motor complication frequently experienced by patients is the re-emergence of symptoms in the morning prior to a patient's first dose of L-dopa, known as an 'early-morning off' period. Early morning off periods are common in PD, experienced by up to 80% of patients in a recent survey (n=2205) (Onozawa et al., 2016).

Other types of motor response fluctuations associated with long term treatment of L-dopa are 'delayed-on periods', whereby the beneficial effect of a dose of L-dopa is delayed, and 'dose-failures', whereby the dose of L-dopa fails to achieve the desired 'on state' (Fackrell et al., 2018).

Guidelines on the management of different types of wearing off were recently published by a panel of UK PD specialists (Fackrell et al., 2018). Prior to altering a patient's medication

regime, the panel highlight several modifiable factors that affect wearing off to be considered, including:

- Therapy compliance; influenced by depression, cognitive function and apathy.
- Dietary factors; a large protein meal can delay gastric emptying and competes with the absorption of L-dopa, meaning the quantity and timing of protein intake should be considered.
- Gastrointestinal (GI) absorption; constipation is a common GI symptom of PD and may interfere with L-dopa absorption, worsening motor fluctuations.

1.2.16.2 Dyskinesia:

There are several risk factors identified for the development of L-dopa -induced dyskinesia, including younger age of disease onset (Kumar, Van Gerpen, Bower, & Ahlskog, 2005) and higher L-dopa dose (Thanvi, Lo, & Robinson, 2007). The treatment of L-dopa -induced dyskinesia remains challenging, with reductions in daily dose of L-dopa often rendering patients highly bradykinetic and sometimes immobile (Davie, 2008). This challenge highlights the difficult balancing act for clinicians to control motor symptoms without inducing further motor complications, such as L-dopa-induced dyskinesia.

1.2.16.3 Non-motor fluctuations:

Non-motor fluctuations affect two-thirds of patients receiving long term L-dopa treatment (Quinn, 1998). Non-motor fluctuations are typically experienced as fluctuations in mood, and can present as a combination of depression, anxiety, panic, irritability, or apathy in “off state”

periods. In the “on state”, patients usually experience normal mood, but can occasionally be euphoric, hypersexual, or hypomanic, and sometimes withdrawn (Quinn, 1998).

1.2.17 Treatment of motor fluctuations

Due to the significant adverse motor complications associated with L-dopa use, many clinicians consider the use of drug therapy adjuvants to L-dopa as the disease progresses, including dopamine agonists, Monoamine Oxidase B (MAO-B) Inhibitors, Catechol-O-Methyl Transferase (COMT) Inhibitors, and amantadine (NICE 2017). The different pharmacological treatment options available in PD are outlined in Table 5, adapted from NICE guidance 2017 (NICE 2017).

Table 5 A summary of the different pharmacological treatment options available in PD based on NICE Guidelines (2017)

Drug Class	**Examples**	**Mode of Action**	**Benefits**	**Disadvantages**
Levodopa	co-careldopa (sinemet) co-beneldopa (madopar)	Uptake by remaining dopaminergic neurons, allowing for conversion to dopamine.	Improved motor symptoms and improved ADL, fewer adverse events*, different forms available (eg. controlled release/dispersable)	Development of motor complications, increased risk of dyskinesia, half-life approx. 60 mins
Dopamine agonists (oral/transdermal)	pramipexole - oral (mirapexin) ropinerole - oral (requip) rotigotine - transdermal (neupro) apomorphine	Direct stimulation of dopamine receptors	Improved motor symptoms and improved ADL, more OFF-time reduction, non-oral route (apomorphine)	Intermediate risk of adverse events, greater risk of hallucinations, expensive (apomorphine)

Drug Class	Examples	Mode of Action	Benefits	Disadvantages
Monoamine Oxidase B Inhibitors (MAO-B)	rasagiline (azilect) selegiline (eldepryl)	Inhibits MAO-B and increases available dopamine in synaptic cleft	Improved motor symptoms and improved ADL, fewer adverse events*,OFF-time reduction, lower risk of hallucinations	Comparatively limited symptom control
COMT Inhibitors	entacapone tolcapone opicapone	Inhibits COMT and increases half-life of levodopa	Improved motor symptoms and improved ADL, OFF-time reduction, lower risk of hallucinations	More adverse events
Amantadine	amantadine	A glutamate receptor agonist that increases dopamine release and blocks reuptake	Reduced dyskinesia	Limited evidence of benefit to motor symptom or ADL improvement

* Adverse events refer to an increased risk of impulse control disorder, psychotic symptoms and sudden onset of sleep associated with dopaminergic therapy (Voon et al., 2011). Patients should be regularly warned of the signs so that intervention can be put in place.

1.2.18 Advanced Therapies

For patients experiencing severe motor complications, advanced therapies (AT) can increase the time the patient experiences at their best (reduced OFF time), and can lead to an improved quality of life for the PwP and carer (Lezcano et al., 2004).

1.2.18.1 Apomorphine

Apomorphine is a highly potent dopamine agonist acting at D1 and D2 dopamine receptors (Trenkwalder et al., 2015), and is typically used to manage sudden and unexpected levodopa-induced 'off states' (Deleu, Hanssens, & Northway, 2004). Apomorphine is administered by the subcutaneous route, either intermittently as an injection (pen-injection formulation) or as a continuous infusion (the pump formulation) (Trenkwalder et al., 2015) and has been shown to achieve anti-parkinsonian efficacy comparable to that of orally-administered L-dopa (Deleu et al., 2004).

1.2.18.2 Duodopa

Duodopa (also known as L-dopa /carbidopa intestinal gel (LCIG)) is an aqueous gel comprising a combination of L-dopa and carbidopa in a 4:1 ratio, and can be delivered continuously to the proximal jejunum via a percutaneous gastrojejunostomy tube connected to a portable infusion pump (Olanow et al., 2014). Duodopa has been found to be clinically effective in improving symptoms of advanced PD, and improving overall quality of life in comparison with standard therapy (Fasano, Ricciardi, Lena, Bentivoglio, & Modugno, 2012; Nyholm, 2012). However, maintaining the positioning of the tube can be problematic, and there is a risk of

local infections developing at the site of insertion (Trenkwalder et al., 2015). NHS England has provided strict guidance regarding patient selection and use of Duodopa (NHS England, 2015), and Duodopa is not currently recommended for use by NICE, due to lack of cost-effectiveness (NICE, 2017).

1.2.18.3 Deep Brain Stimulation (DBS)

Deep brain stimulation (DBS) is the administration of high-frequency continuous electrical stimulation to the subthalamic nucleus through a surgically implanted device (Deuschl et al., 2006). DBS has been shown to be very effective for patients who are not well controlled, or who cannot tolerate dopaminergic therapy (Fasano, Daniele, & Albanese, 2012). A five year follow up study found patients had improved motor symptoms, with improved mobility and reductions in dyskinesias observed (Krack et al., 2003). However despite its effectiveness, due to the risks associated with the necessary surgery, DBS is not encouraged in patients of older age.

Due to the surgical risks and costs associated with DBS, there are strict eligibility criteria that candidates must fulfil in order to be offered the treatment (Munhoz et al., 2016). In reality, a very small sub group of PwP meet the clinical eligibility criteria for DBS, ranging from 1% to 10% (of PwP). In 2013, NHS England estimated that the total number of DBS per year would indicate about 300 Parkinson's patients per year receive DBS (plus patients for dystonia and tremor) (NHS England, 2013).

Despite the benefits of AT, access to these therapies is limited, due to their expense, the lack of familiarity of ATs amongst clinicians, and limited time to carry out necessary assessment in clinic (Worth, 2013). Furthermore, selecting patients that are suitable for AT can be challenging, and inappropriate referrals to specialist AT centres cause frustration, and are costly in terms of time and resource (Worth, 2013).

To assist in the identification of patients with advanced disease and those who may be suitable candidates for advanced therapies, several guidelines have been published via consensus from international experts (Antonini et al., 2018; Luquin, Kulisevsky, Martinez-Martin, Mir, & Tolosa, 2017; Worth, 2013).

1.2.19 Service Provision at University Hospitals Plymouth NHS Trust (UHPNT)

1.2.19.1 UHPNT Catchment area

The University Hospitals Plymouth NHS Trust (UHPNT) service catchment area covers three geographical regions comprising West Devon, North East Cornwall and Plymouth. Based on current prevalence figures (NICE, 2017) it is estimated that there are approximately 1,500 PwP living in the UHPNT population footprint.

1.2.19.2 UHPNT Parkinson's Service

All UHPNT neurologists (n=8) manage patients with PD. There are two consultant neurologists specialising in PD (Dr Simon Edwards and Dr Camille Carroll). In addition, there are five specialist PD nurses based in the community (Plymouth n=2; Cornwall n=2; West

Devon n=1), and two hospital specialist PD nurses who provide both an in-patient and out-patient service, supported by an assistant practitioner.

1.2.20 Challenges to UHPNT Parkinson's Service

1.2.20.1 Insufficient capacity to meet service demand

As mentioned previously, national standards of PD care suggest that patients with early mild symptoms of PD should be reviewed by a specialist (PD consultant or PDNS) every 6-12 months to review diagnosis and the need for treatment (NICE, 2017). Once treatment is commenced, follow-up is recommended to be more frequent (2-3 months) to assess response to medication, titrate dosage and re-visit the diagnosis. Within our service, we have recently audited patient experience of PD care, and found that 46% of patients have consultant appointments delayed by more than 6 months, and 60% have not seen the community nurse within the last year. Our current waiting time is 12-24 months for a routine review appointment in the consultant clinic. Table 6 displays the shortfall of clinics in our service required to achieve minimum and standard level of service in accordance with NICE guidelines (NICE, 2017).

Table 6. Number of clinic slots per week needed to achieve minimum and standard levels of PD care, in accordance with NICE guidelines and those currently available at UHPNT

Level of Service	Number of slots required	Number of slots available	Shortfall (%)
Minimum (1 per 12 months)	32	22	10 (31%)
Standard (1 per 6 months)	63	22	40 (63%)

1.2.20.2 Service Threats

Providing sub-optimal care further contributes to staff dissatisfaction, stress and poor retention, which is a cause of significant threat to PD services. Parkinson's UK recently carried out an evaluation of threats to PD services across the UK. Forty-seven active threats were identified, with the majority of these (82%) being from within the PDNS Community. The type of threat identified is summarised in Figure 10. The biggest identified challenge was the number of vacancies due to resignations, which may reflect the high demands on staff and services. Within our service, we have had reduced community PDNS capacity for the last year due to retirement and long-term sick leave. The resulting increased demand on the hospital PDNS team has led to increased delays within the hospital-based care pathways.

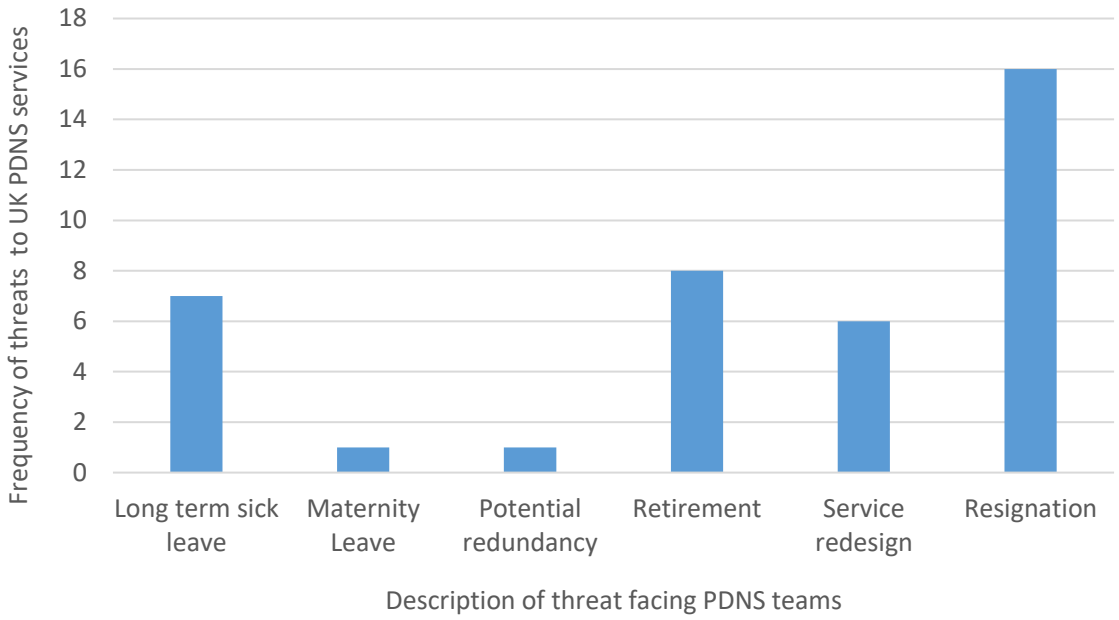


Figure 10 Types of threats facing Parkinson's Disease Nurse (PDNS) Community teams. Taken from personal communications (Parkinson's UK).

1.2.20.3 Increasing prevalence and incidence of PwP in the UHPNT catchment area:

The challenges associated with providing a timely and patient-centred service are expected to increase due to an ageing population and increased life expectancy. Figure 11 and Figure 12 demonstrate the projected prevalence and incidence of PwP in the UHPNT catchment area from 2015 to 2025, based on current prevalence and incidence figures for the UK (Parkinson's UK, 2017).

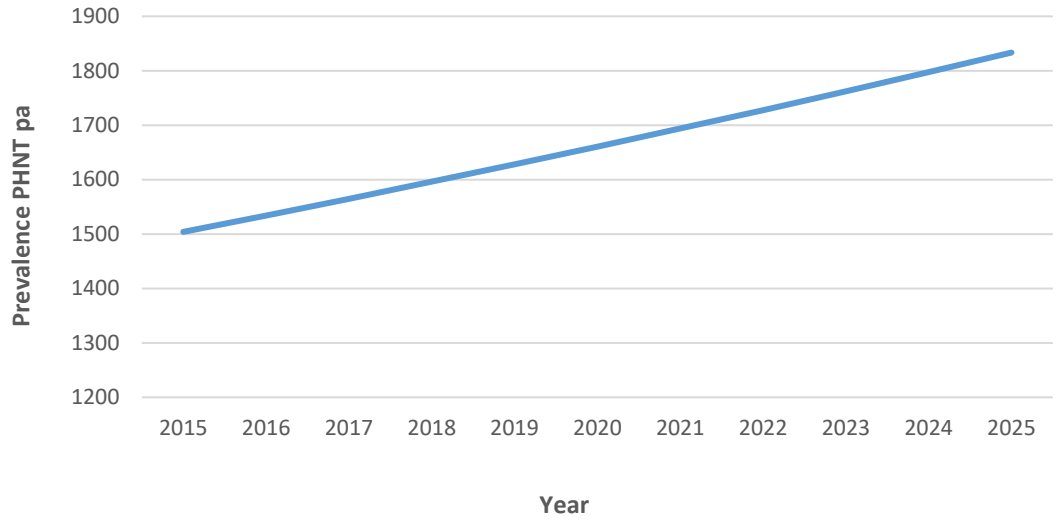


Figure 11 Projected prevalence of PwP living in the UHPNT catchment area per annum (pa)

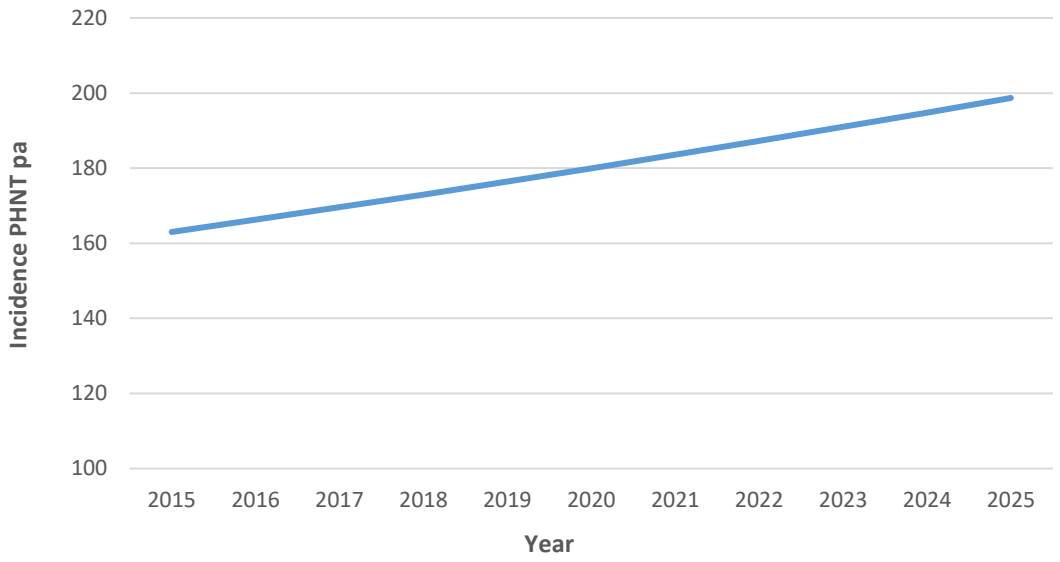


Figure 12 Projected incidence of PwP living in the UHPNT catchment area per annum (pa)

1.2.20.4 Inappropriate method of review:

It has been suggested that time locked clinic review is unable to meet the demands of a condition which progresses at a variable rate and affects individuals in multiple ways (Maetzler, Domingos, Srulijes, Ferreira, & Bloem, 2013). A recent *BMJ* essay written by a 'E-patient' describes the frustration associated with time-locked clinical reviews (Riggare, 2018, p.2):

"*I see my neurologist once or twice a year for about 30 minutes each time. So he observes my symptoms, and assesses the effect of the treatment he prescribes, for one hour a year*."

This extract highlights the limitations of a 30 minute clinic review, whereby the clinician is only provided with a mere snapshot of the patient's condition, on the basis of which treatment decisions are made that will impact on the patient for the rest of that year, or until their next review.

A further challenge of a short clinic review, is that a clinician is unable to carry out a comprehensive assessment of symptoms in this time frame. Treatment decisions are therefore based on a limited amount of information and observations that is obtainable within 30 minutes. In reality, many neurology appointments are less than 30 minutes, sometimes lasting just 15 or 20 minutes.

Other than observations that are made by the clinician within these 30 minutes, evaluation is also dependent on patient recall, the validity of which may be limited due to poor patient awareness of symptoms (Pietracupa, Latorre, Berardelli, & Fabbrini, 2014) or a tendency for

PwP to under or over-estimate symptom severity (Zach, Dirkx, Pasman, Bloem, & Helmich, 2017). Inaccuracies in patient recall can therefore lead to erroneous assessment and inappropriate or inadequate interventions being implemented.

Furthermore, attending clinics can be arduous for both patient and carer, presenting logistical and physical challenges that add to burden and distress. Dorsey et al (2016) outlined several limitations of current care models of PD care (summarised in Table 7) and highlighted how current models of care fail to meet the needs of PwP. These challenges are particularly valid for our service with its rural catchment and poor public transport provision.

Table 7 How current care models fail to meet the need of PwP. Table based on Dorsey et al (2016)

Feature	**PwP**	**Current care models**
Location	Primarily suburban and rural areas	Primarily urban centres
Driving	Impaired ability	Usually requires driving
Mobility	Limited	Generally required to access care
Cognition	Frequently impaired	Often demanding to navigate
Disease Course	Progressive	Least accessible for those with most advanced disease
Caregivers	Burdened	Increases the burden

1.2.21 Current measures of disease

In addition to the issues with current service provision already identified, there are further limitations surrounding the assessment tools used in both clinical and research settings in PD to assess symptom severity and monitor disease progression.

There is no well-established bio-marker (a naturally occurring molecule, gene, or characteristic by which progression of disease can be identified (Strimbu & Tavel, 2010)) of disease progression in PD. Therefore, clinical assessment is the primary means of evaluation in clinic, with rater-dependent clinical scales often the primary endpoints in PD research (Espay et al., 2016).

1.2.21.1 Motor Symptom Measures:

There are a number of measurement instruments and scales to assess the motor symptoms of PD, including posture, gait and balance (see (Bloem et al., 2016) for a review). Some of the most commonly used motor symptoms measures are described in more detail below.

1.2.21.1.1 Movement Disorders Unified Parkinson's Disease Rating Scale (MDS-UPDRS)

The most widely used scale to assess symptom severity in PD is the MDS-UPDRS (Goetz, Tilley, et al., 2008). In addition to use in disease management, the MDS-UPDRS is one of the most widely used efficacy measures to investigate the potential neuroprotective effects of a PD therapy in clinical trials (Athauda & Foltynie, 2016). The MDS-UPDRS requires training to administer, and is divided into four parts (described below). Responses for each item are rated on a 5 point scale; 0 (normal), 1 (slight impairment), 2 (mild impairment), 3 (marked

impairment), 4 (severe impairment). Scores for each item are summed to produce a total score, with higher scores reflecting more severe impairment.

The four parts of the MDS-UPDRS are described below:

Part I: Part I concerns "non-motor experiences of daily living" and comprises 13 items. Seven of these items are in a questionnaire format and designed to be self-completed by the patient, while the remaining items that deal with complex behaviours require the investigator to conduct the interview. Rater involvement time for administering Part I is estimated to require less than 10 minutes (Goetz, Tilley, et al., 2008).

Part II: Part II concerns "motor experiences of daily living" and comprises 13 items, all of which are designed to be self-completed by the patient.

Part III: Part III is the "motor examination". Part III can be used in isolation to assess motor performance and is comprised of 33 scores based on 18 items which the rater asks the patient to perform on their right and left side. The rater observes performance and rates each item on the 4-point scale described previously. Rater involvement time for administering Part III is estimated to require 15 minutes (Goetz, Tilley, et al., 2008).

Part IV: Part IV concerns "motor complications" and comprises 6 items which are asked by the investigator and expected to take 5 minutes to administer.

The total rater involvement time required to administer the MDS-UPDRS is therefore approximately 30 minutes, extending to approximately 45 minutes for the patient (to include the self-completed items).

1.2.21.1.2 The Timed Up & Go (TUG) Test

The Timed Up & Go (TUG) Test is a physical measure, whereby a patient is asked to rise from a seated chair position, walk 3 meters, turn, walk back and sit down. The performance is timed, with longer test times associated with decreased mobility and a higher falls risk (Foreman, Addison, Kim, & Dibble, 2011). The measure requires little equipment, is easy to administer and only takes a few minutes, thereby making it a useful test in an outpatient setting (Nocera et al., 2013).

1.2.21.1.3 The Finger Tapping (FT) Test

The Finger Tapping (FT) Test is a timed test whereby two buttons are attached to a counter 30cm apart. Subjects are asked to alternately tap each button as fast as they can with their left hand for one minute. This procedure is then repeated using their right hand. The sum of the taps is calculated for each hand with an increased number of alternate taps indicating better performance. The FT is used to assess the impact of bradykinesia in the upper extremity, and has been found to have high validity and reliability (Shimoyama, Ninchoji, & Uemura, 1990). Furthermore, the FT has been shown to successfully distinguish PwP from controls (Shimoyama et al., 1990).

1.2.21.2 Non-motor symptom measures

There are a number of clinical scales and screening tools developed for use in PD. Non-motor symptoms scales allow for an assessment of the severity of a NMS to be carried out, whereas NMS screening tools are used to alert clinicians that a patient may be experiencing an NMS.

1.2.21.2.1 Pain

King's Parkinson's disease Pain Scale (KPPS)

The King's Parkinson's Disease Pain Scale (KPPS) is a screening tool for pain, comprising 14 items across 7 domains (musculoskeletal pain (1 item), chronic pain (2 items), fluctuation-related pain (3 items), nocturnal pain (2 items), oro-facial pain (3 items), discoloration (2 items) and radicular pain (1 item)) (Chaudhuri et al., 2015). Each item is scored by severity (0, none to 3, very severe) multiplied by frequency (0, never to 4, all the time) resulting in a subscore of 0 to 12, the sum of which gives the total score with a possible range from 0 to 168. The scale is administered by an investigator and takes approximately 10-15 minutes to complete. The scale has been internationally validated, and found to have excellent inter-rater and test-retest reliability (Chaudhuri et al., 2015).

1.2.21.2.2 Sleep:

There are a number of scales available to measure sleep in PD (see (Kurtis, Balestrino, Rodriguez-Blazquez, Forjaz, & Martinez-Martin, 2018) for a review), including the SCOPA-Sleep scale for the assessment of overnight sleep and Excessive Daytime Sleepiness (EDS) (Marinus, Visser, van Hilten, Lammers, & Stiggelbout, 2003), and the Epworth Sleepiness Scale (ESS), that measures the risk of falling asleep during daily activities (Johns, 1991).

The Parkinson's disease Sleep Scale (PDSS-2)

The Parkinson's disease Sleep Scale (PDSS -2) is a common scale used to assess sleep in PD (Trenkwalder et al., 2011). The scale comprises 15 items evaluating nocturnal sleep

disturbances. Items are scored from 0 (never) to 4 (very frequent). Total scores can range from 0-60, with higher scores indicating more sleep problems.

1.2.21.2.3 Depression

There are several depression scales available in PD (see (Schrag et al., 2007) for a review).

Beck Depression Inventory (BDI)

The Beck Depression Inventory (BDI) is a widely used sale in PD (Beck, Ward, Mendelson, Mock & Erbaugh, 1961), used to both to measure severity of depression and as a screening tool. The BDI is self-completed by patients, and comprises 21 items with each response assigned a score ranging from zero to three, with a higher score indicating greater severity of the symptom. The BDI has been validated for use in PwP and found to have high test-retest reliability (Visser, Leentjens, Marinus, Stiggelbout, & van Hilten, 2006).

1.2.21.2.4 Cognitive impairment:

There are a number of cognitive assessments for use in PD (see (Kulisevsky & Pagonabarraga, 2009) for a review), including the Scales For Outcomes Of Parkinson's Disease—Cognition (SCOPA-COG). Although not specific to PD, the Montreal Cognitive Assessment (MoCA) and the Mini-Mental State Examination (MMSE) are widely used screening instruments for cognitive impairment. Both scales are quick to administer, taking around 10-15 minutes to complete. In recent years, stricter copyright protection has been enforced, meaning the MMSE is no longer freely accessible in the public domain (Newman & Feldman, 2011) .

1.2.21.2.5 Disability:

A number of disability scales are available for use in PD (see Shulman et al (2016) for a review).

Functional Status Questionnaire (FSQ)

The functional status questionnaire (FSQ) is a self-administered questionnaire comprising 36 items across six summary scales: 1) basic and intermediate activities of daily living (ADLs); 2) mental health; 3) social activity; 4) work performance and quality of interactions, plus six single-item scores. Items are rated on scales of 1 to 4 and 1 to 6, with summary scores standardized to 100 based on percentage (Shulman et al., 2016). The FSQ has been validated in a PD cohort (Rubenstein et al., 1998) and was shown to have good internal consistency and content validity.

1.2.21.2.6 Quality of Life (QoL):

There are several quality of life (QoL) scales validated for use in PD (see Martinez-Martin et. al (2011) for a review), however the 39 item Parkinson's Disease Questionnaire (PDQ-39) is the most commonly used (Martinez-Martin et al., 2011).

The Parkinson's Disease Questionnaire (PDQ-39)

The Parkinson's Disease Questionnaire (PDQ-39) is a 39 item disease specific questionnaire, designed to characterise the impact of PD on patients (Jenkinson, Peto, Fitzpatrick,Greenhall & Hyman, 1995). The items cover eight dimensions (mobility, ADL, emotional well-being, stigma, social support, cognitions, communication, and bodily discomfort). Factor analysis

was used to create an overall single index figure (Parkinson's disease summary index (PDSI)) from the eight dimension scores. The PDQ-39 has been extensively validated and is widely used as a patient completed measure of QoL in research (Peto, Jenkinson, & Fitzpatrick, 1998). A shorter form version (PDQ-8) has since been developed and validated (Jenkinson et al., 1997).

Quality of Life Measure for the Carers of People with Parkinson's disease (the PDQ-Carer)

Parkinson's disease can have detrimental effects on quality of life (QoL) not only for the people diagnosed with PD, but also for the informal care givers who provide the majority of support to PwP.

The PDQ-Carer is a 29 item self-completed questionnaire designed to assess the effects of PD on QoL for carers (Jenkinson et al., 2012). Items are spread across four domains including; personal and social activities (12 items), anxiety and depression (6 items), self-care (5 items), and strain (6 items). Response categories for each item include "Never"/"Occasionally"/"Sometimes"/"Often"/"Always".

Responses for each item are transformed to have a range from 0 (best, i.e. no problem at all) through to 100 (worst, i.e. maximum level of problem), with scores >60 suggesting seriously compromised aspects of quality of life (Jenkinson et al., 2012).

A carers quality of life questionnaire has since been developed for Atypical Parkinsonism (PQoL Carers) (Pillas et al., 2016).

1.2.21.2.7 Non-Motor Symptom Burden:

Non-Motor Symptoms Questionnaire (NMS Quest)

In order to enhance the identification of NMS in PD patients and allow for appropriate and timely treatment, a self-rated Non-Motor Symptoms Questionnaire was developed (NMS Quest) (Chaudhuri et al., 2006). This 30-item screening questionnaire allows for a comprehensive assessment of the range of non-motor symptoms that occur in PD (see Table 8), and provides an opportunity for the patient to self-declare any possible problems to their clinician for further investigation. Furthermore, the NMS Quest was designed to be completed by the patient in the waiting room, which provides an economic solution to screen for possible problems prior to clinical consultation (Chaudhuri et al., 2006). The NMS Quest has been internationally validated (Chaudhuri et al., 2006), and is used extensively as part of routine clinical care. The Non Motor Symptom Scale (NMSS) was later developed mainly for use as a research tool, to measure the frequency and severity of symptoms (4). The NMSS was found to highly correlate with the NMS-Quest and measures of Quality of Life (both r=.7) (Chaudhuri et al., 2007).

Table 8 Domains in the NMS-Quest

Domain	Number of items
Gastrointestinal tract	7
Urinary tract	2
Sexual function	2
Cardiovascular	2
Apathy/attention/memory	3
Hallucinations/delusions	2
Depression/anxiety	2
Sleep disorder	5
Miscellaneous (e.g., diplopia, weight loss)	5

1.2.22 Limitations of current measures of Parkinson's disease

There are several limitations surrounding the use of rater-dependent clinical scales as the primary assessment tools in PD care.

As mentioned previously, the MDS-UPDRS is the most widely used and accepted measure to assess motor symptoms in PD in both clinical and research settings (Goetz, Tilley, et al., 2008). The MDS-UPDRS Part III is a subjective measurement, assessed by an independent rater. However, despite objective instructions for use, and a mandatory rater training process, there is evidence of notable intra and inter-rater variability associated with the scale which limits its use as a reliable measure of disease progression (Post, Merkus, de Bie, de Haan, & Speelman, 2005). In addition, the MDS-UPDRS assessment is typically administered during

clinic visits often weeks or months apart, and only provides a 'snap-shot' of a patient's symptoms, which, as identified previously, can be variable from a day to day, or even hour to hour basis (Papapetropoulos, Mitsi, Espay, Kaji, & Colosimo, 2015). In addition, many patients find the requirement to carry out the MDS-UPDRS Part III in the OFF medication state highly burdensome, which can be a barrier to trial participation and retention (Athauda & Foltynie, 2016).

Also, a number of the measures described previously are reliant on patient recall of symptom severity. Self-completed measures including patient diaries have been previously associated with poor compliance, recall bias and diary fatigue which impacts on their usefulness as a reliable indicator of symptom severity (Athauda & Foltynie, 2016.; Papapetropoulos, 2012). This is particularly poignant in patients with cognitive dysfunction, which is commonly experienced in PD (Aarsland et al., 2009). Moreover, patient diaries frequently do not correlate with quantitative measures (Utsumi et al., 2012).

1.2.23 Limitations of Parkinson's disease Clinical Trials

Similar limitations are also pertinent in the field of PD clinical trials, with no pharmacological agent having been shown to slow, halt or reverse the progression of PD, despite many agents showing promise in pre-clinical studies (Athauda & Foltynie, 2016).

Dorsey and colleagues (2017a) suggested that the failure of Phase III trials to replicate earlier successful Phase II results is partly due to the use of artificial and imperfect outcome

measures, which may reduce confidence in the replicability of findings, and can lead to considerable economic costs (Dorsey, Papapetropoulos, Xiong, & Kieburtz, 2017).

Several other challenges facing PD neuroprotective trials have been identified (Athauda & Foltynie, 2016) including selection of inappropriate endpoints, and poor selection of patient cohorts, which do not take into account the heterogeneity of PD.

1.2.24 Summary of challenges facing Parkinson's disease care and research

To summarise, there are a number of limitations surrounding current PD service provision, which does not meet the needs of PwP or carers. As discussed, current issues include; limited clinic capacity, inappropriate time-locked clinic review, the need for patients to travel to clinic, and the use of rater-dependent clinical scales with limited sensitivity.

Moreover, some of these challenges may also be applied to PD research, whereby the selection of inappropriate endpoints and lack of patient stratification in clinical trial design have been identified as potential reasons for the lack of discovery of a neuroprotective agent (Dorsey, Papapetropoulos, et al., 2017a).

There is a clear need to provide patients, clinicians and researchers with the tools and resources to overcome the current issues described, and ultimately improve the standard of PD care and research.

1.2.25 Digital Health Technologies (DHTs)

In recent years, a multitude of Digital Health Technologies (DHTs) for the objective measurement of PD symptoms have emerged, that may provide potential solutions to some of the shortcomings described previously.

The term DHT refers to a broad range of technologies, including wearable devices such as body-worn sensors, and portable systems such as smartphone-based devices. DHTs can therefore be utilised by clinicians in a clinical or research setting to objectively measure specific behaviours, or self-administered by patients to detect and monitor impairments occurring in everyday life (Espay et al., 2016).

1.2.25.1 Non-motor DHTs

The majority of DHTs that have been developed for use in PD are for the assessment of motor symptoms, with few technologies having been developed for the assessment of Parkinson's NMS (Espay et al., 2016). Several existing DHTs are commercially available for use in industry that have potential to be applied to the measurement of Parkinson's NMS. Some of these, in addition to existing non-motor DHTs for use in PD, are explored below.

1.2.25.1.1 Sleep:

Accelerometer technology offers potential for carrying out assessment of sleep quality in PD. The DynaPort MiniMod is a tri-axial accelerometer validated as a measurement device for physical activity during sleep (Bossenbroek et al., 2010). Quantitative analysis of axial nocturnal movements (including mean acceleration of nocturnal movements) obtained using

the DynaPort MiniMod has been used to differentiate PwP from healthy controls (Louter, Maetzler, & Prinzen, 2015). PwP were found to have overall decreased acceleration of movements as well as smaller and shorter and nocturnal axial movements.

Also, home-based polysomnography devices are available for monitoring sleep ("Somnomedics", 2019) which have potential to be used in PD.

1.2.25.1.1 Cognition:

There are a number of online cognitive assessments available for use in research and clinical practice.

The Cats-and-Dogs Test is an online tool designed to identify visuoperceptual deficits in PD (Weil et al., 2017), which is a risk factor for developing PD dementia (Williams-Gray et al., 2013). The tool is accessible online, and requires participants to identify skewed images of cats and dogs (see Figure 13), with poorer identification performance suggesting impaired visuosperceptual ability.

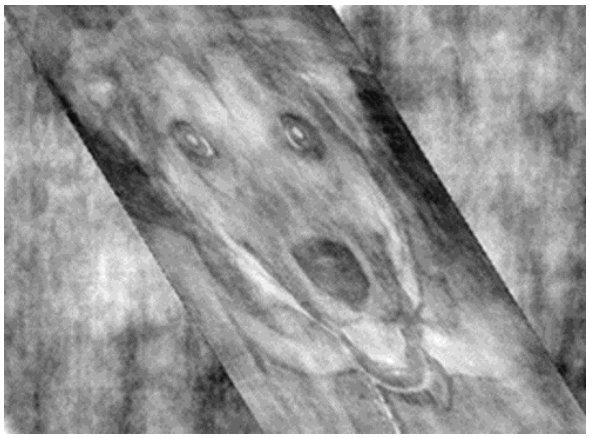


Figure 13 An example of a test image from the Cats-and-Dogs Test (Weil et al., 2017)

1.2.25.1.2 Autonomic Dysfunction:

Several technologies are available to monitor different NMS related to autonomic disturbance. BioWatch is a wrist watch-based system that has been validated to continuously measure blood pressure via ECG electrodes, which may be useful for PwP experiencing orthostatic hypotension (Thomas et al., 2016).

In addition, there are wearable sensors available to measure galvanic skin response for monitoring excessive sweating (Mindfield, 2019) and other causes of physiological arousal such as stress (Picard & Scheirer, 2001).

1.2.25.1.3 Pain:

Digital health technologies designed to measure pain have been developed for use clinically, that may be applicable to PD. The PMD-200™ is a stand-alone monitoring device that quantifies patients' physiological response to pain ("PMD-200™, 2019). The device comprises a non-invasive finger probe and sensors that acquire multiple physiological signals which are analysed using proprietary algorithms to produce a pain index, where 0 represents no pain response and 100 represents extreme pain response. PMD-200™ is commercially available in Europe, Canada, Australia and Israel, and may be useful for monitoring and quantifying levels of PD related pain discussed previously (see section 1.2.11.2.3.1).

1.2.25.2 Motor DHTS

As mentioned previously, the majority of DHTs that have been developed for use in PD are for the assessment of motor symptoms, allowing for the objective measurement of a range

of symptoms (Maetzler et al., 2013). A clear advantage of objective measures is they offer potential to improve the sensitivity, accuracy and reproducibility of assessment in PD motor symptoms over and above traditional clinical scales (Espay et al., 2016), with both clinical and research application.

1.2.25.2.1 Smartphone-based Measures:

A number of studies have investigated the use of smartphones to objectively quantify a range of PD symptoms. For instance, a PD smartphone-based software application, comprising measures of finger tapping, voice, posture, gait and reaction time has been found to differentiate between PwP and controls with high sensitivity (96.2%) and specificity (96.9%) and predicted disease severity, as measured by the MDS-UPDRS (Arora et al., 2015). The smartphone application (developed by the Oxford Parkinson's Disease Centre (OPDC) has since been used in a more extensive study, to identify individuals with RBD from controls and PwP (Arora et al., 2018), which can be indicative of prodromal PD (Noyce, Lees, Schrag, & Schrag, 2016).

Additionally, a number of other studies have investigated the use of smartphones to quantify PD motor symptoms including bradykinesia (Lee et al., 2016), gait (Steins, Sheret, Dawes, Esser, & Collett, 2014) and tremor (Woods, Nowostawski, Franz, & Purvis, 2014). Moreover, the ubiquity and affordability of smartphones make them an appealing platform for DHT development (Trister, Dorsey, & Friend, 2016).

1.2.25.2.2 Wearable Devices:

In recent years, a multitude of wearable technologies for the objective measurement of different PD symptoms have emerged (Maetzler et al., 2013). Wearable devices are able to capture the frequency and intensity of a variety of movements throughout the day, predominantly via inertial sensors (Espay et al., 2016). Movement data collected by these sensors is then processed using proprietary algorithms, to identify PD related symptoms.

In addition to objectively quantifying specific symptoms in a clinical or research setting, wearable devices (including body-worn sensors) offer potential to remotely monitor and assess patients' symptoms from within the home environment, resulting in data that is high in ecological validity (Stamford, Schmidt, & Friedl, 2015).

A recent RAND report on the future of health (Corbett, d'Angelo, Gangitano, & Freeman, 2017) identified wearable technology as an important trend, allowing patients to self-manage long term conditions at home, while reducing the demand on services. Furthermore, wearable devices have the potential to closely monitor individual responses to therapy, and provide tailored information for patients that can be used to optimise treatment (Barker, 2017).

In addition, wearable devices potentially confer specific advantages with respect to PD. The ability to monitor status over a prolonged period of time, as opposed to the snapshot measurements observed in clinic mentioned previously, is likely to be more reflective of true symptom severity (Maetzler et al., 2013) and avoids an over-reliance on patient recall.

Del Din et al (2016) carried out a review on the acceptability and feasibility of wearable technologies to continuously monitor a range of PD symptoms in the home environment, defined as 'free living' (Del Din, Godfrey, Mazzà, Lord, & Rochester, 2016). The review comprised predominantly single-sensor based devices including accelerometers and gyroscopes.

Del-Din and colleagues (2016) included three classifications of validity as part of their review; 1) whether the study demonstrated accurate detection of the clinical feature under investigation, or method of appraisal; 2) criterion validity: the relationship between the outcome obtained via the wearable device and traditional measures (eg. clinical scales) and 3) discriminative validity: the ability of the wearable outcomes to discriminate between groups. Formal testing of utility (e.g. feasibility) of the wearable device was also reported (Del Din, Godfrey, et al., 2016). A number of studies included as part of the review are displayed in Table 9 below.

Table 9 Studies examining free-living monitoring of PD using wearable technology. Based on Del Din (2016) (128)

Study (year), N,	Type of wearable	Placement on body	Clinical feature	Accurate detection of clinical feature	Measures	Criterion Validity	Discriminative Validity	Utility
Das et al (2012) 2 PwP	Accelerometers	Lower back, ankles, wrists	Dyskinesia, tremor	Yes against patient diaries	Acceleration derived features (Mean energy, high frequency energy content, correlation, frequency domain entropy) Acceleration	No	No	No
Griffiths et al (2012) 64 PwP	Parkinson's Kinetigraph (PKG™; Global Kinetics)	Wrist	Bradykinesia, dyskinesia,	Yes, for bradykinesia against dot slide task (spec 88%, sens 95%)	Acceleration derived features: Mean Spectral Power within specific bands, peak, amount of time with no movement	Yes dyskinesia against the AIMS score and both dyskinesia and bradykinesia against UPDRS III and IV	No	No

Study (year), N,	Type of wearable	Placement on body	Clinical feature	Accurate detection of clinical feature	Measures	Criterion Validity	Discriminative Validity	Utility
Mera et al (2012) 10 PwP	Kinesia™	Wrist	Motor tasks, tremor, bradykinesia, motor fluctuations	No	Symptoms severity scale (0-4 points), voluntary movement threshold evaluated with gyro- scope derived features (RMS, peak of power spectrum)	Yes, for tremor and bradykinesia. Yes against videos in lab for symptom severity scale validated against UPDRS.	No	Yes formal testing in subsequent work (Giuffrida, Riley, Maddux, & Heldman, 2009)
Tzallas et al (2014) 12 PwP	ALA-6g (PERFORM)	Lower back, ankles, wrists	Tremor, Bradykinesia, FOG	Yes in the lab and during structured test (eg. for FOG events opening door) against video annotations	Acceleration derived measures (time and frequency domains, range, energy)	Yes, techniques developed in lab and applied in free lving conditions, compared against patient diaries	No	Yes, formal testing

Study (year), N,	Type of wearable	Placement on body	Clinical feature	Accurate detection of clinical feature	Measures	Criterion Validity	Discriminative Validity	Utility
Ferreira et al (2015), 11 PwP,	SENSE-PARK System	Lower back, ankle, wrist	Gait, hypokinesia, dyskinesia, tremor, sleep	NA (feasibility and usability study)	NA (feasibility and usability study)	NA (feasibility and usability study)	NA (feasibility and usability study)	NA (feasibility and usability study)
Hammerla et al (2015) 34 PwP	Axivity AX3	Wrists	Sleeping, ON/OFF state, dyskinesia	Yes in the lab (against video recordings)	Acceleration derived measures (magnitude, jerk)	No	No	Yes formal testing in subsequent work (Fisher, 2016)

The review revealed a number of challenges to clinical adoption of wearable devices. The studies included in the review had small sample sizes, and there were no consistent definitions of clinical features that were being measured (Del Din, Godfrey, et al., 2016). Furthermore, the placement of the wearable device differed between studies, as did the study protocols, making it hard to compare study findings. In addition, the majority of studies were carried out in a controlled, lab environment which does not reflect the unstructured and unpredictable qualities of a real life environment. Finally, the feasibility and usability of devices was not frequently reported across studies, which is necessary to determine before clinical adoption of wearables can take place.

1.2.25.2.3 Wearable measures of gait:

Wearable sensors further provide opportunity to measure complex and multi-dimensional parameters like gait, which are typically difficult to assess in a clinic environment (Del Din, Hickey, et al., 2016). Of importance, gait disturbance has been identified as a potential marker of disease progression (Maetzler, Liepelt, & Berg, 2009), with gait variability having been reported to correlate more strongly than bradykinesia with disease duration (Hausdorff, Balash, & Giladi, 2003). In addition, wearable devices designed to assess gait are able to capture rare incidents such as freezing of gait (FOG) (Delval et al., 2010) and falls (Klenk et al., 2011) which may otherwise go undetected or unreported by patients. Due to the high utility of wearable devices in this field, there is an extensive literature on wearable gait assessments (see (Muro-de-la-Herran et al., 2014) for a review) which is outside the scope of this introduction.

Two of the studies included as part of the Del Din (2016) review described wearable systems that have been extensively validated in subsequent work (The Kinesia™ system (Mera et al., 2012) and The Parkinson's Kinetigraph (PKG™) (Griffiths et al., 2012), which are now commercially available for the assessment of PD symptoms. Details of these systems are described in more detail below.

1.2.25.2.3.1 The Kinesia™ system

The Kinesia™ system, (described in Table 9 above) is a finger-worn motion sensor containing three orthogonal accelerometers and three orthogonal gyroscopes to measure linear accelerations and angular velocities (see Figure 14) (Mera et al., 2012).

The Kinesia™ software (available on a laptop, and more recently an iPad, see Figure 14), guides the patients through a workflow comprising three tremor tasks (measuring rest, postural and kinetic tremor) and three bradykinesia motor tasks (including finger tapping, hand grasping and pronation supnation) based on the MDS-UPDRS motor examination. Proprietary algorithms are used to process the motion data to severity ratings from 0 (symptom absent) to 4 (severe impairment).

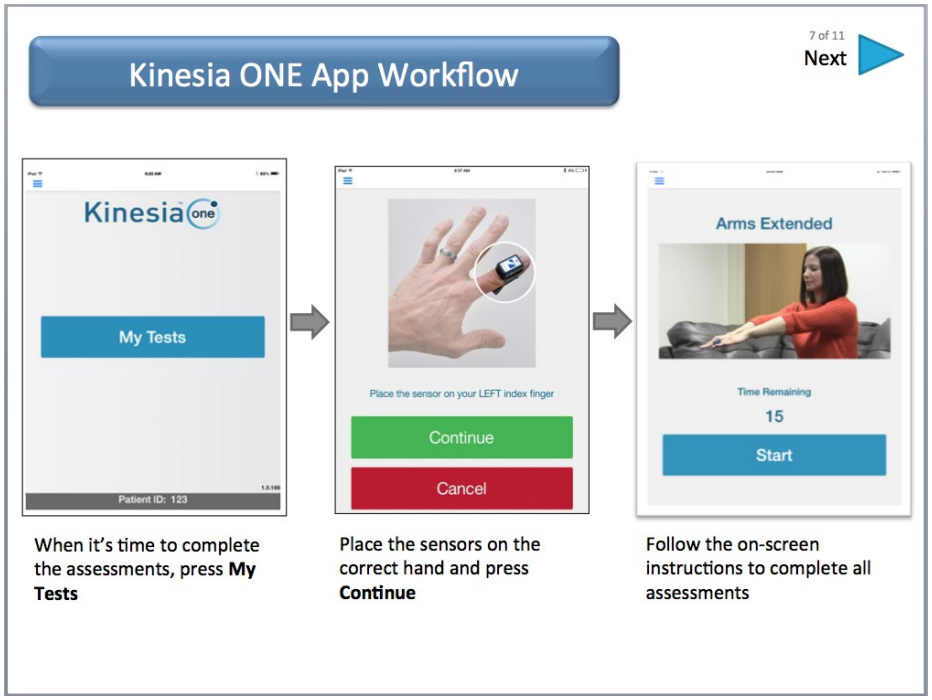


Figure 14 The Kinesia Workflow, from Siteboss (2014)

The Kinesia™ system algorithms have been extensively validated to quantify upper extremity bradykinesia (Heldman et al., 2011), tremor (Giuffrida et al., 2009), and dyskinesia (Mera, Burack, & Giuffrida, 2013). In each of these studies, the algorithms were highly correlated with clinician ratings. Moreover, in a compliance study, participants correctly completed 97% of all motor tasks at home over a 6-day period, which demonstrates the device is feasible and acceptable to patients. In addition, The Kinesia™ system has been identified as clinically useful in identifying patients who may be suitable candidates for AT (Heldman, Giuffrida, & Cubo, 2016) and has been identified as cost-effective in the management of patients with advanced PD (Cubo et al., 2017).

The Kinesia™ system is commercially available, and in 2007 The Kinesia™ system received Food and Drug Administration (FDA) approval for the measurement of bradykinesia, tremor and dyskinesia (Siteboss, 2014).

1.2.25.2.3.2 The Parkinson's Kinetigraph (PKG™)

In addition to wearable systems that require active interaction from the patient (such as the Kinesia™ System), monitoring devices are also commercially available for use in PD that are passively worn by the patient and require little to no interaction. One such device that was included as part of the Del Din review (2016) is the Parkinson's Kinetigraph (PKG™) (Figure 15).

The PKG™ is a wrist worn monitoring device comprising 3-axis accelerometers, and has been validated to detect bradykinesia (Griffiths et al., 2012), dyskinesia (Griffiths et al., 2012) and tremor (Braybrook et al., 2016) as well as several NMS including an immobility summary indicative of excessive day time sleepiness (Kotschet et al., 2014) and potential signs of impulse control disorder (ICD) (Evans et al., 2014).

The PKG™ is commercially available and has also received FDA approval to quantify tremor, bradykinesia and dyskinesia ("Brandon Captial", 2016). I will describe a clinical evaluation of the PKG™ as part of the PD service at UHPNT in Chapter 4.

Figure 15 An image of the PKG™ system (Gen 2)

1.2.26 Remote care

The use of DHTs (including wearable and portable devices such as smartphones) to monitor and assess PD symptoms offers the potential to move PD care to a home setting, which could provide clear benefits to both patients and health care providers (Dorsey et al., 2016). Remote care models can be tailored to meet patients' needs and deliver interventions when required, resulting in targeted and timely management of complications (Kelsey & Cavendish, 2014), thereby reducing disease burden on the patient and caregiver (Papapetropoulos et al., 2015) and reduced use of healthcare resource. People with Parkinson's (PwP) are hospitalised one and a half times more frequently than non-PwP and have generally longer durations of hospital stay, and increased mortality (Gerlach, Winogrodzka, & Weber, 2011). Timely intervention may therefore prevent (and subsequently reduce) PD hospital admission rates. In support of this view, engagement with a remotely deliverable PD education network has

been found to reduce the annual rate of hip fractures and lead to fewer in-patient admissions (Beersen, Marc Berg, Mirte van Galen, Kees Huijsmans, & Niels Hoeksema, 2011).

In addition, remote monitoring technologies may provide a means of dealing with increased capacity requirements within services, given the prevalence of PD in the UK is expected to rise (Parkinson's UK, 2017). For example, recent initiatives have shown that remote contact with patients, such as web-based video conferencing and tele-heath calls, is a feasible and cost effective method for PD care delivery that can produce similar health outcomes as in-person care from a specialist (Dorsey et al., 2013).

With regards to PD research, DHTs offer the potential to carry out daily active tests, and can monitor status continuously over a prolonged period of time in highly naturalistic environments, which would provide a more accurate reflection of the patient's symptom severity and be ideally suited to longitudinal studies (Espay et al., 2019). In addition, the increased test frequency could lead to increased statistical power, allowing for the identification of impairment that may otherwise go undetected using infrequent in-clinic assessments (Dorsey, Papapetropoulos, et al., 2017).

1.2.27 Patient self-management

A further advantage of DHTs is they have been found to increase participants' perceived involvement in their healthcare (Ferreira et al., 2015). As discussed previously, increasing involvement allows patients to identify themselves as 'active players' in their treatment (Van der Eijk et al., 2013), which is in line with the 'participatory' nature of P4 medicine, meaning

medicine that is predictive, personalised, preventative and participatory (Flores, Glusman, Brogaard, Price, & Hood, 2013). Of interest, patient engagement in health care has been found to increase treatment adherence, improve quality of life, and result in better health outcomes (Bauman et al., 2003).

There is a need to empower people living with long term conditions to become better at managing their own health, make informed treatment choices and avoid complications (Hibbard, Stockard, Mahoney, & Tusler, 2004). To help meet this need, NHS England have launched the Patient Activation Tool (PAM) which aims to measure patients' ability to self-manage their condition, and tailor services accordingly to increase patient capacity for self-management (Hibbard et al., 2004).

Advances in DHTs have the potential to play a role in facilitating self-management of long term conditions by providing insight into a patient's condition, helping patients make informed choices, and encouraging engagement in self-care habits (Alpay, Blanson Henkemans, Otten, Ro, & Dumay, 2010).

According to the World Health Organisation (WHO) there is great potential for DHTs to transform existing health services in coming years (*WHO,* 2011). In 2018, The NHS launched an 'Apps Library' in an attempt to signpost patients towards healthcare apps that meet NHS standards for quality, reliability and effectiveness ("NHS Apps Library," 2018). Parkinson's UK (PUK) have taken a similar approach, and developed an 'Apps and Devices Library' ("Apps for Parkinson's", 2018) with the aim to promote apps and devices that have been tried and tested

by a panel of PwP. Only apps and devices that the testing panel find to be genuinely useful, and would recommend to other PwP are included as part of the PUK library.

In addition, there is an increasing number of studies piloting DHT interventions to support the management of long term health conditions (Wang et al., 2014). In PD, 'ParkinsonTV' (launched by the Dutch strategy group 'parkinsonNet' (Bloem et al., 2017) broadcasts monthly programs for people affected by PD, allowing for easily accessible information on a variety of PD related projects. The success of this channel has recently led to episodes being broadcast in English.

Moreover, the MDS Technology Task Force are in the process of developing an e-Diary, with the aim of bringing the traditional PD diary (used primarily to assess fluctuations in symptoms for research purposes) into the 'digital age' (Vizcarra et al., 2019). The e-Diary would be web-based, and would allow for the integration of individualized assessments of motor and non-motor symptoms via a selection of hardware components (such as accelerometers and gyroscopes) as part of the diary itself. The e-Diary is currently under development, and is expected to be delivered over the coming years via a series of 'milestones'.

A recent review of studies using DHTs to manage long term conditions identified several benefits, including improved patient self-management, patient education tailored to patient need, and improved communication between health care professionals (Matthew-Maich et al., 2016). All of these recommendations are in line with the NHS Long Term Plan (The NHS

Long Term Plan, 2019), which promotes the use of 'digitally-enabled' care to provide patients with more control over their health and to facilitate personalised care.

Furthermore, significant reductions in cost have been associated with DHTs in comparison with traditional care (Noel, Vogel, Erdos, Cornwall, & Levin, 2004).

1.2.28 Summary and overall aims

Current PD service provision in the UK faces several challenges including limited clinic capacity, inappropriate time-locked clinic review, the need for patients to travel to clinic, and the use of rater-dependent clinical scales with limited sensitivity.

Moreover, some of these challenges may also be applied to PD research, whereby the selection of inappropriate endpoints and lack of patient stratification in clinical trial design have been identified as potential reasons for the absence of a neuroprotective finding (Dorsey, Papapetropoulos, et al., 2017).

DHTs offer a number of potential improvements to PD care and research. Firstly, DHTs provide potential to objectively quantify PD symptoms with an increased sensitivity than is currently achievable using traditional, rater-dependent clinical scales. In addition, DHTs allow for continual and unobtrusive monitoring in the home environment, allowing for an increased test frequency, reduced patient and carer burden, data that is high in ecological validity, and the opportunity to capture complex symptoms and rare incidents. Finally, there is evidence to suggest that DHTs may help to improve perceived engagement in healthcare, by providing

patients with the tools to self-manage their condition, which has associated improved healthcare outcomes (Ferreira et al., 2015).

However, despite the increase in DHTs that have been developed in recent years, there is no gold standard for the digital assessment of non-motor or motor symptoms in PD (Del Din, Godfrey, et al., 2016), and few technologies have been validated in a clinical setting to show evidence of their impact at the level of the healthcare provider.

Therefore, in this thesis I: 1) explore the potential for a digital objective motor (finger tapping) assessment tool to provide information on potential PD cognitive impairment; 2) develop and evaluate a DHT for the remote monitoring of NMS; 3) evaluate the clinical utility of an existing DHT (the PKG^{TM}) within a NHS clinical service (UHPNT); and 4) explore the potential of DHTs to overcome current challenges in PD neuroprotective trial design.

Chapter 2 Exploring the potential of an automated tapping assessment in Parkinson's disease

2.1 Introduction

Accurate assessment of motor symptoms is clinically important in Parkinson's disease (PD), both for diagnostic purposes, whereby motor symptoms must be present for a diagnosis to be made (Postuma et al., 2015), and throughout the disease course, to assess response to therapy and progression of disease. Accurate monitoring and assessment of motor symptoms is also integral to research, with motor outcomes often used as the primary endpoints in PD clinical trials (Mitchell, Harper, Lau, & Bhalla, 2000).

Currently, the Movement Disease Society Sponsored Revision of the Unified PD Rating Scale (MDS-UPDRS) is the most widely used and accepted measure to assess motor symptoms in PD (Goetz, Tilley, et al., 2008). However, there are a number of recognised limitations surrounding the MDS-UPDRS that limits its functionality, including intra and inter rater reliability and low levels of ecological validity (Palmer et al., 2010) (see section 1.2.22).

In PD, finger tapping is a task frequently used by clinicians to visually assess symptom severity in the upper extremities, characterised by interruptions in rhythm, slowing, and decreased amplitude (Yahalom, Simon, Thorne, Peretz, & Giladi, 2004). Finger tapping can therefore be a useful measure to detect bradykinesia, freezing (akinesia) as well as dysrhythmicity. However, interpretation of finger tapping performance is a subjective judgment which can

vary between raters (Post et al., 2005) and has potential to be improved by implementing a more quantitative, digital approach.

The ubiquity of consumer-grade technology has led to an extensive literature on the objective measurement of finger tapping in PD (Arora et al., 2015; Lee et al., 2016; Stamatakis et al., 2013; Wissel et al., 2018). This rise is due in part to the increasing availability of smartphones and other smart devices which have built in features such as touch screens (Dorsey, Chan, et al., 2017). The development of objective measures using these devices can therefore be carried out at low cost and with relative ease. The portable nature of these devices has further appeal for assessing patients living in remote areas or who are unable to travel due to disease burden, thereby removing geographic barriers to participation in research (Dorsey, Chan, et al., 2017). In addition, digital based devices allow for multiple assessments of motor function to be carried out per day whilst in the home environment, therefore offering the opportunity to capture the impact of ON and OFF state fluctuations.

We have previously described the development of a finger tapping smartphone based software application, named PD-TAP (Dominey et al., 2016). In a pilot investigation, participants (16 people with Parkinson's disease (PwP) and 16 age-matched-controls (AMC)) were required to complete a fast tapping task (Fast-50) whereby participants were asked to tap as fast as they could for 50 taps. The task was carried out using a smartphone device (with taps made on the touch-screen), with the aim to determine the extent to which performance (specifically tapping frequency, variance and overall time) could distinguish PwP from AMC

and correlate with motor impairment as determined by the motor MDS-UPDRS Part III subscore.

Our results demonstrated that the Fast-50 task is able to distinguish PwP from AMC ($t(30)=2.27$, $p = 0.03$), based upon the inter-tap interval (ITI). This is line with previous findings, whereby at higher frequencies of tapping (>4Hz), rhythm generation has been observed to break down in PwP, leading to decreased tapping frequencies (Nagasaki, Nakamura, & Taniguchi, 1978). Moreover, in our previous study, inclusion of inter-tap variance (ITV) in a combined Fast-50 measurement (ITV x ITI) provided a strong correlation with MDS-UPDRS Part III subscores (r =.69, p =.003). Overall, the Fast-50 task, which was completed by patients in <1 minute, demonstrated a strong correlation with patients' MDS-UPDRS Part III subscores, which suggested potential for PD TAP to be used to measure disease progression.

In addition to using quantitative finger tapping measures for diagnostic purposes and to track disease progression (Arora et al., 2015), there is evidence to suggest that finger tapping paradigms that measure motor timing may give insight into cognitive ability, specifically frontal executive function (Pastor, Jahanshahi, et al., 1992).

The study of motor timing has suggested the presence of a hypothetical "internal clock" or "pacemaker" which compares the passage of time with a criterion stored in working memory (Parker, Lamichhane, Caetano, & Narayanan, 2013). Motor timing in the milliseconds and seconds range has been found to be impaired in PwP (O'Boyle, Freeman, & Cody, 1996; Pastor, Jahanshahi, Artieda, & Obeso, 1992) and may contribute towards motor symptoms

such as bradykinesia and akinesia (Jahanshahi et al., 2010). These findings have led to the hypothesis that the basal ganglia and the associated dopaminergic system are involved in temporal processing, and act as the 'internal clock' mentioned previously (Jahanshahi et al., 2010).

Furthermore, dopaminergic medication has been found to improve motor timing deficits in PwP (Pastor, Jahanshahi, et al., 1992), which supports the role of dopamine in temporal processing.

Motor timing is commonly measured using interval timing tasks such as The Paced Finger tapping Task (PFT) (Wing & Kristofferson, 1973). In this task, a participant is required to tap in time with a series of audible tones that are separated by a constant interval, usually in the range of several hundred milliseconds to seconds (Jones et al., 2011). This phase is known as the synchronisation condition. The audible pacing tone is then removed, and the participant is required to continue tapping at the same pace as they had been previously; this is known as the continuation condition (Elsinger et al., 2003). This task elegantly measures timing in two ways; the ability to carry out a motor response to a timed cue (synchronisation phase) and then the ability to maintain the learnt rhythm in the absence of a cue (continuation phase) (Jones et al., 2011).

Performance in this task is generally quantified by analysis of accuracy, meaning how close a response was to its intended target, and this can be explored by using mean absolute error. Variability in performance can also be quantified, by investigating the spread or variance of

the responses from the target, and can be explored using standard measures of variance such as standard deviation (SD) (Jones et al., 2011).

The PFT has been widely used in PD research, with many studies demonstrating PwP have impaired accuracy and increased variability in PFT performance, in comparison with controls (Jones et al., 2011; O'Boyle et al., 1996; Pastor, Jahanshahi, et al., 1992). PwP appear to exhibit difficulty in synchronising their tapping with an external auditory cue (Shimoyama, Ninchoji, & Uemura, 1990), and synchronous finger tapping performance appears to worsen in PwP following removal of an external cue (Yahalom et al., 2004).

Brain imaging studies have allowed for further exploration of the neural correlates of motor timing that underlie performance in the PFT, which may be impaired in PwP.

A PET study of the PFT by Jahanshahi and colleagues (2010) revealed that for the controls, motor timing was associated with increased activation in the left medial prefrontal cortex, right hippocampus, bilateral angular gyrus, left posterior cingulate and left nucleus caudate. For PwP, the same striato-frontal activation was not observed. Instead, PwP demonstrated greater activation in bilateral cerebellum, right thalamus and left midbrain (Jahanshahi et al., 2010). The authors interpreted the over activation of the cerebellum in PwP as a compensatory 'switch', to reliance on alternative neural pathways.

In addition, the continuation phase of the PFT was associated with greater activation in the dorsolateral prefrontal cortex in both the controls and in PwP. The dorsolateral prefrontal cortex is known to play a role in internally generated actions, which have been found to be

impaired in PD relative to controls (Jahanshahi et al., 1995). As mentioned previously, studies investigating the PFT with PwP have found greater levels of relative impairment in the continuation phase than the synchronisation phase (Yahalom et al., 2004), with PwP demonstrating a greater reliance on external cues to maintain rhythm (Elsinger et al., 2003).

Other behavioural research has supported the idea that PwP demonstrate an inability to internally generate strategies to complete a task. Brown and Marsden (1998) demonstrated this in a study whereby PwP showed impairments on a version of the Stroop colour word task when the response was not cued, however these impairments were not apparent when a cue was available. These findings suggest that PwP show deficits in situations when they are not able to rely on external cues for task performance; when internal attentional control is required (Brown & Marsden, 1988).

Abnormalities in pre-frontal dopamine signalling in PD are thought to impair attentional control and other higher order cognitive processes including reasoning, planning, impulsivity and decision making (Miller & Cohen, 2001). These behaviours are referred to as executive processes, and are thought to involve the prefrontal cortex, in particular the orbitofrontal and dorsolateral areas (Bouquet, Bonnaud, & Gil, 2003).

The Supervisory Attentional System (SAS) (Norman, 1980) is a well-known model of executive function (EF) and presents two systems of human action; content scheduling and supervisory attention. Content scheduling is responsible for the execution of routine behaviours that do not require deliberate attention, and allows us to prioritise the order of these behaviours by

selecting from competing schemas (Norman, 1980). The supervisory attentional mechanism is required for action sequences that are novel, or where strong habitual responses have to be inhibited, where planning is required, and where deliberate conscious control (or willed action) is necessary. The difficulty for PwP to generate internally willed actions is thought to provide evidence for reduced resources in the SAS in PD (Brown & Marsden, 1988). Performance in the PFT may therefore be influenced by EF, and I was interested to explore this further by evaluating whether PFT performance may be influenced by executive dysfunction.

2.1.1 Measures of EF

Although there is no gold standard for assessment of EF (Chan, Shum, Toulopoulou, & Chen, 2008), a number of tasks have been designed to test different components of the SAS model, including; planning, monitoring, and inhibition of action responses (Chan et al., 2008). Three frequently used tasks measuring different aspects of EF are described in detail below:

(1) Letter fluency:

Letter fluency tasks require a subject to generate as many words as they can that begin with a certain letter (Delis, Kramer, Kaplan & Holdnack, 2004). This task requires intrinsic generation of new responses, as individuals cannot use external cues or use routine selection of words according to their meaning (Bouquet et al., 2003). In addition, an individual is required to monitor responses and update retrieved items in order to avoid repetitions (Zgaljardic et al., 2006). The process of maintaining word-

list generations over time is considered a frontal function, and has been previously associated with activation in the dorsolateral pre frontal cortex (MacDonald, Cohen, Stenger, & Carter, 2000).

(2) Brixton Spatial Anticipation Test

The Brixton Spatial Anticipation Test is a rule-attainment test, which assesses an individual's ability for rule detection and impulsivity. The test is similar to the Wisconsin Card Sorting Task (Chelune & Baer, 1986), however is less time consuming to complete. An individual is required to detect a rule underlying the placement of blue circles amongst a grid. After several presentations of this pattern, the placement rule changes, and the individual is required to detect the new rule change. Similar tasks involving set-shifting have been previously associated with dorsolateral pre frontal cortex function (Nagahama et al., 1998).

(3) The Stroop Task

The Stroop task is a widely used measure of EF involving conflict, and is thought to require verbal inhibitory processes (Kudlicka, Clare, & Hindle, 2011). The Colour-Word Interference Test measures an individual's ability to suppress a habitual response for a novel one (Zgaljardic et al., 2006), whereby an individual is required to state the incongruent ink colour a word is printed in, and disregard the verbal content. Increased response time in this task is associated with heightened conflict, and performance in this task has been found to correlate with anterior cingulate activation (MacDonald et al., 2000).

The PFT appears to share similar neural circuitry to executive processes, with tasks that load EF having been found to worsen performance on interval timing tasks (Brown, 2006). These findings support the hypothesis that these tasks draw on similar resources. Executive dysfunction experienced in PD may therefore contribute towards patients' impaired interval timing performance. Incorporation of interval timing tasks, such as the PFT task, as part of standard tapping paradigms may therefore be useful clinically, as an indicator of executive dysfunction in PwP.

Executive dysfunction is common in PD (Dirnberger, Frith, & Jahanshahi, 2005), and forms part of the MDS diagnostic criteria for Parkinson's Mild Cognitive Impairment (PD-MCI) (Litvan et al., 2012). Executive dysfunction can have a significant impact on carrying out activities of daily living (ADL). For instance, PwP may initially have difficulty sequencing complex tasks such as cooking or planning the events of a day. These difficulties can therefore have a significant impact on patients' independence and their wellbeing (Kudlicka et al., 2011).

Assessment of EF in PD is therefore important, to allow for personalised intervention and for identifying those at cognitive risk. Indeed, several studies have suggested that PwP with PD-MCI are at a higher risk of developing dementia than those with normal cognition (Aarsland & Kurz, 2010). For instance, Janvin et al (2006) demonstrated that in a cohort of people with advanced PD, more than 60% of people with PD-MCI had developed dementia after 4 years, as opposed to just 20% of people without PD-MCI over the same time frame (Janvin, Larsen, Aarsland, & Hugdahl, 2006).

To investigate the role of EF in the PFT, and which EF processes in particular might be associated with performance in this task, I carried out a computerised version of the PFT task with PwP, and compared performance with three classic EF tests: (1) Letter Fluency (2) The Stroop Test and (3) The Brixton Spatial Anticipation Test.

2.1.2 Hypotheses

My hypotheses for this study were as follows:

1. Performance in the PFT would correlate with performance in the EF tests.
2. Participants with poorer levels of EF would exhibit greater levels of relative impairment in the continuation phase of the PFT than participants with better levels of EF, due to a greater reliance on external cues.

If successful in establishing a correlation between EF and performance in the PFT in PD, there would be grounds to develop an app-based version of the PFT to incorporate as part of the existing PD TAP app or other objective tapping paradigm. This would add value to existing quantitative tapping measures, by providing insight into possible executive dysfunction.

2.2 Methods

This study received approval from the local NHS Research Ethics Committee (ethical approval granted 10/2016, see appendix 1 (section 8.1)) and the Faculty Research Ethics Committee at Plymouth University (ethical approval granted 11/2016, see appendix 2 (section 8.2)). I was responsible for the planning, development, recruitment, data collection and analysis for this study.

2.2.1 Participant Recruitment

Participant recruitment commenced in April 2017. One hundred letters of invitation (see appendix 3 (section 8.3)) and participant information sheets (PIS) (see appendix 4 (section 8.4)) were sent out to PwP that were identified from clinical and research registers including the Livewell Southwest patient register and the Southwest Dementia and Neurodegenerative Diseases Network (PRO-DeNDRON) patient register (patients on these registers had previously consented to be contacted regarding research opportunities). Patients were asked to fill out a reply slip (attached to the PIS) if they were interested in taking part in the study, and send the reply slip back (via freepost envelopes) to the research team. Once the research team had received the reply slip, a follow-up phone call was made to assess the PwP's eligibility for the study (see inclusion/exclusion criteria detailed below) and discuss any questions the participant may have about taking part in the study. If a patient was willing to participate, fulfilled the inclusion criteria and had an absence of exclusion criteria, a study visit at the University was arranged, and the patient was sent a confirmation letter or email outlining the details of the study visit.

2.2.2 Sample Size Calculation

The target recruitment for this study was 128 patients based on a power analysis calculated using G*Power (Faul, Erdfelder, Lang, & Buchner, 2007) for a 2x2 mixed design ANOVA (0.05 alpha and 0.80 power), anticipating a medium effect size (f = .25), interpreted using guidelines provided by Cohen (1988).

2.2.3 Inclusion Criteria

Inclusion criteria for the study were:

- Age greater than 18 years
- Diagnosis of idiopathic Parkinson's disease (IPD)
- Willing and able to give informed consent for participation in the study
- Able and willing to comply with all study requirements

2.2.4 Exclusion Criteria

Exclusion criteria for the study were:

- Inability or unwillingness to comply with study protocol
- Any other significant disease or disorder that is known to affect cognition
- Use of alcohol, benzodiazepines, or other sedating drugs in the 12 hours prior to study visit
- Non-fluent English speaker
- Severe visual impairment
- Inability to use a pen and paper

2.2.5 Study Procedures

Participation involved one study visit at the University of Plymouth. Travel expenses were reimbursed. Participants received no payment for participation in the study. The study visit

lasted approximately 2 hours, which included time for consent, assessments and debrief, as well as breaks where necessary. At the beginning of the session, the investigator read through the information sheet with the participant and answered any questions. If patients were still interested in participating they were asked to sign a consent form (see appendix 5 (section 8.5)).

Each participant was allocated a unique identification number and the date of the study visit was recorded.

2.2.6 Demographic Information

After obtaining informed consent, patient demographics were obtained including; date of birth, gender, dominant hand, ethnicity and years in education. Details about their PD were also recorded including; date of diagnosis, symptoms present at onset, and date of symptom onset.

Once demographic information had been obtained, a pre-testing statement was read to participants by the investigator that outlined the purpose of the assessments, and reminded participants of their right to withdraw or stop at any time.

The following assessments were then carried out by the investigator in the order that they appear below. All participants were tested in an ON state, within an hour of taking Levodopa.

2.2.7 MDS-UPDRS (Part III)

The Movement Disorders Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS) is a validated PD rating scale that is the current gold standard in research for assessing PD symptom severity (Goetz, Tilley, et al., 2008). Please see section 1.2.21.1.1 for a full description of the MDS-UPDRS Part III.

2.2.7.1 Cognitive Measures

2.2.7.2 ACE III

The Addenbrooke's Cognitive Examination (ACE III) is a brief cognitive test, that has been validated for use in a PD population (Reyes et al., 2009). The ACE III takes 15-20 minutes to complete. It comprises six domains (totalling a maximum possible score of 100 points) including orientation (10 points), attention (8 points), memory (35 points), verbal fluency (14 points), language (28 points), and visuo-spatial abilities (5 points).

2.2.7.3 Measures of Executive Function (EF)

All participants completed the measures of EF listed below.

2.2.7.4 The Stroop Test

The Stroop Test comprises a series of trials which are designed to test attention and inhibition (Stroop, 1935). In the first trial, the participant is asked to read aloud a series of colour words, printed in black ink, as quickly as possible. After 30 seconds have passed, the investigator asks the participant to stop reading, and makes a note of how many words were correctly read aloud in the time frame. In the second trial, the participant is asked to look at a series of colour blocks, and to name the colours as quickly as possible. The number of correct responses in 30 seconds is recorded as before. In the third trial, the participant is asked to look at a series of colour words, printed in incongruent ink colours, and name the colour of the ink instead of reading the word (Erdodi et al., 2018). This trial is the key test of inhibition, as the participant is required to recruit additional cognitive resource to inhibit themselves from reading aloud the colour word, and must instead name the incongruent colour (MacLeod & MacDonald, 2000). The number of correct responses is recorded.

2.2.7.5 The Brixton Spatial Anticipation Test

The Brixton Spatial Anticipation test forms part of the larger Hayling and Brixton test battery, and can be administered in isolation (Burgess & Shallice, 1996). The test is a rule attainment task, which requires the participant to monitor feedback from the environment and adjust rules appropriately. The Brixton is comprised of a 56 page stimulus book containing identical 2 × 5 displays of 10 empty circles, one of which is coloured solid blue. With each turn of the page, the location of the solid blue circle changes in line with a particular rule sequence. Participants were read aloud standardized instructions to predict which of the 10 circles will

be blue on the subsequent page. The task requires the patient to learn and apply the current rule in order to predict the location of the next blue circle correctly (Burgess & Shallice, 1996). After completion of the task, the number of errors was counted to produce a total error score. A higher number of errors reflected poorer performance.

2.2.7.6 The DKEFS Verbal Fluency (Letter Verbal Fluency)

The D-KEFS Verbal Fluency Test forms part of the larger D-KEFS test battery (Delis et al., 2004), and can be used in isolation. In the letter fluency trial, the participant is required to name as many words beginning with 'F' in one minute, followed by 'A' and then 'S' one minute trials.

2.2.8 Executive Function Selection Criteria

We were interested to see which measure of EF would correlate most strongly with tapping performance, which was determined using Pearson correlations. Performance on the measure of EF with the strongest relationship with tapping performance was then used to categorise participants into two groups; executive dysfunction (EF_{low}) and executive function (EF_{high}).

Participants were categorised by using a mean standard deviation criterion as opposed to using a median split analysis (MacCallum et al., 2002). It has been discussed previously that it is not appropriate to consider values just above or below the median as meaningfully different from each other (Jaiswal, Tsai, Juan, Liang, & Muggleton, 2018). We therefore adopted a mean ± standard deviation (SD) criteria similar to that used in other studies (eg (Jaiswal, Tsai, Juan, Liang, & Muggleton, 2018).

2.2.9 Paced Finger Tapping Task

2.2.9.1 Materials

Participants were seated comfortably in front of a desktop computer and rested the forearm of their dominant hand (handedness determined by participant) on the surface of the desk.

A bespoke Windows software application was written by the University of Plymouth Psychology Tech Office in C# using Microsoft Visual Studio, and this was run on the desktop computer. This software was connected via an Arduino Uno to a Force Sensing Resistor.

Instructions were displayed on screen throughout, and the investigator was present at all times.

All finger taps were carried out with the index finger of the dominant hand. To make a finger tap, the index finger was raised, whilst keeping all other digits and the palm flat on the surface of the desk. All finger taps were made directly onto a Force Sensing Resistor, which digitally recorded each tap made.

Prior to starting the Paced Finger Tapping Task (PFT), participants were shown the required finger tapping technique, and were given an opportunity to practise. Any errors during the practice trial were corrected by the investigator.

2.2.9.2 PFT Task

The PFT task consisted of a sequence of repetitive auditory cues at a constant inter-stimulus interval (ISI) of either 250ms, 500ms, 1000ms or 2000ms that had been used previously in a similar PFT study (Jones et al., 2011).

Audio cues were delivered via headphones, which participants were required to wear throughout the duration of the task. The presentation order of the ISI was determined using a counterbalanced design. The subject was required to listen to the auditory cues and tap in time with the index finger of their dominant hand (synchronisation phase). After 20 presentations, the auditory stimuli stopped, and the subject had to continue reproducing the rhythm in the absence of any auditory cues for a further 20 taps (continuation phase). Each phase (continuation or synchronization) lasted from 5-40 seconds, depending which ISI was being used for any given particular trial. See Figure 16 for a diagram outlining the task design. Following completion of a trial, participants had a 30 second break before continuing onto the next trial.

The Paced Finger Tapping Task (PFT) design is displayed in Figure 16. Participants are required to tap in time with the auditory stimulus (synchronisation phase). The auditory cues are then removed and participants are required to continue reproducing the rhythm as they had been previously (continuation phase).

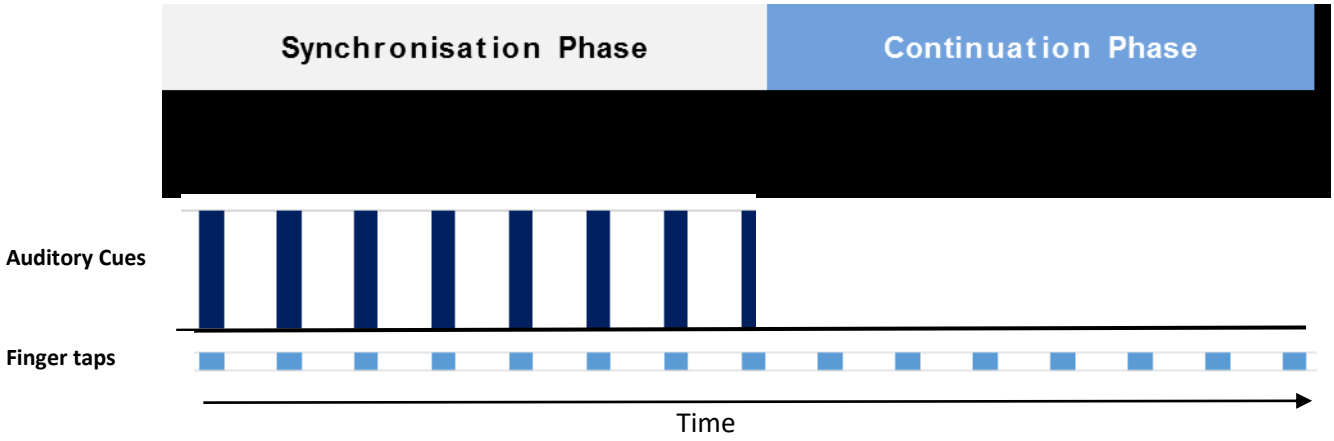


Figure 16: Paced Finger Tapping Task (PFT) design. The dark blue bars represent the audio cues and the light blue bars represent the finger taps made by the participant. After 20 taps (not shown here), the cue is removed and the participant is required to continue tapping in the absence of auditory cues.

2.2.10 Debrief

Following completion of the assessment battery, participants were debriefed and thanked for their involvement in the study.

Participants were made aware that this study was not a clinical assessment and they will not be told the results; however, if participants expressed concern as to their symptoms or test performance, they were advised to discuss their concerns with their GP or consultant. Participants' GPs were contacted to inform them of their patient's participation in the study.

2.2.11 Data Analysis

2.2.11.1 Paced Finger Tapping data

All tapping tasks generated time-series data, whereby the time point of each finger contact was recorded in milliseconds (ms).

From these data, the inter-tap interval (ITI) was calculated by subtracting each time point from the previous time point. An average (mean) percentage error was then calculated for each participant: $(\sqrt{((ITI/ISI)-1)^2})*100$ for each of the four ISIs (250ms, 500ms, 1000ms and 2000ms) in both the synchronisation and continuation conditions. The root mean square (RMS) was calculated, in order to determine the absolute error. This was applied as calculation of mean error in positive and negative values (either side of the target) can artificially minimise error in those with the greatest performance variance.

A similar method to previous PFT studies was used (Jones et al., 2011), whereby erroneous responses were considered to be those where the ITI was 50% longer or shorter than the target ISI. These responses were considered outliers and were excluded from the analysis, although the remainder of the run was kept.

The difference in error values between the two conditions was also calculated, by subtracting the continuation phase error from the synchronisation phase error. This was done for each ISI (250ms, 500ms, 1000ms and 2000ms). These difference values were transformed by calculating the square root of the absolute value to create an adjusted difference measure.

Participants who were unable to complete all four task speeds were excluded from analysis.

2.3 Results

Figure 17 summarises the number of participants recruited to the study, and reasons for exclusion.

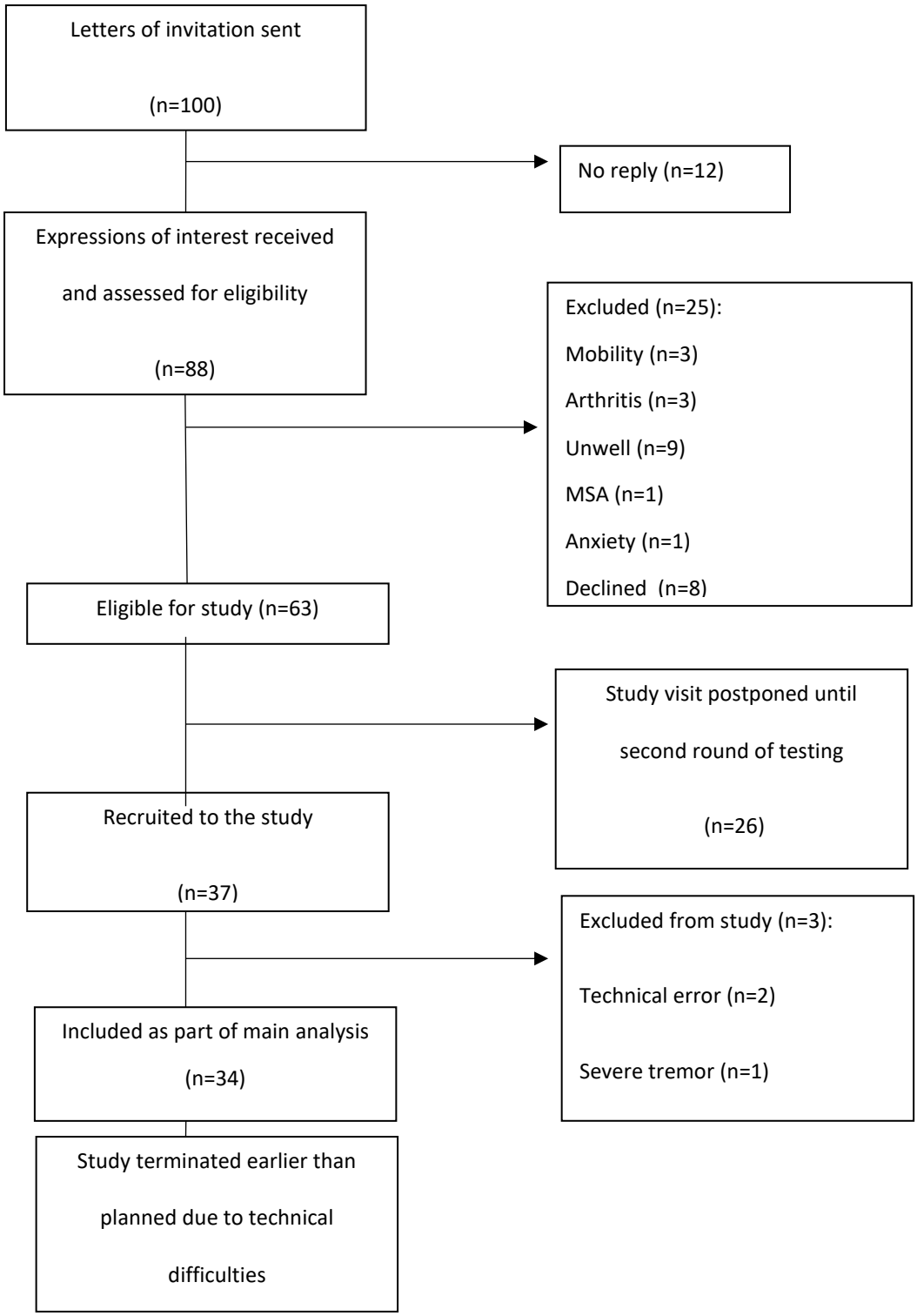


Figure 17 Consort flow diagram detailing the number of participants recruited to the study, and reasons for exclusion

As summarised in Figure 17, 37 people with a diagnosis of idiopathic PD were recruited to the study. Three participants were unable to complete the full finger tapping battery due to technical error (n=2) and severe tremor (n=1). Unfortunately, I had to terminate recruitment after the first 37 participants due to technical difficulties with the equipment, with lack of resource to resolve. Therefore a total of 34 participants were included as part of the analysis.

Participant demographics are presented in Table 10 below. In line with validated ACE III scores for discriminating between different cognitive subtypes in PD (Berankova et al., 2015), four participants were in the Parkinson's disease Dementia (PDD) range (≤82.5), 7 participants were in the Parkinson's disease Mild Cognitive impairment (PD-MCI) range (≤88.5) and 23 were in the normal cognitive range (>88.5).

Table 10 Participant demographic data (n=34) (median, min-max range)

Age (years)	Gender (% male)	Disease duration (years)	Years in education	UPDRS III Score	Ace III Score
70 (49-85)	62%	4yrs (4 m-24 yrs)	13 (12-18)	25 (6-73)	91 (78-100)

2.3.1 Executive Function (EF) Scores

Mean (SD) scores for each of the EF subtests and the normative values for these (stratified by age) are displayed in Table 11. For the letter fluency test and the Stroop Test, a higher

score indicates better performance, whereas for the Brixton Spatial Anticipation Test, a higher score indicates poorer performance.

Table 11 Mean (SD) scores for the EF subtests.

	Letter Fluency	Brixton Spatial Anticipation Test	Stroop (Colour-Word Interference Test)
Normative data*	49.56 (11.57)	20.5 (7)	34 (3)
Study cohort	41.02 (14.8)	24.9 (8.7)	30.1 (9.8)

*based on normative values for a healthy population aged 60-79 for FAS (letter fluency) (Tombaugh, Kozak, & Rees, 1999), The Brixton Test (Van Den Berg et al., 2009a) and The Stroop Test (Scarpina & Tagini, 2017).

Relationships between EF tests were investigated visually using a scatterplot matrix (see Figure 18) and were followed up using Pearson correlations (see Table 12).

Figure 18 Scatterplot matrix of relationships between EF Tests (Letter fluency, Brixton and Stroop)

Table 12 Pearson Correlation (r=) among EF test scores, none of these were found to be significant (p>.05)

	1.Letter Fluency	2.Stroop	3. Brixton
1. Letter Fluency	-	-	-
2. Stroop	.325	-	-
3. Brixton	.017	-.268	-

There were no significant differences detected between measures of EF (see Table 12).

2.3.2 Tapping error at 250ms, 500ms, 1000ms and 2000ms intervals

Figure 19 displays the mean tapping percentage error for each interval (250ms, 500ms, 1000ms and 2000ms) in the synchronisation and continuation conditions. The graph suggests that in general, there was a greater amount of mean tapping percentage error in the continuation condition than the synchronisation condition, apart from at 1000ms, where mean tapping percentage error was less in the continuation condition.

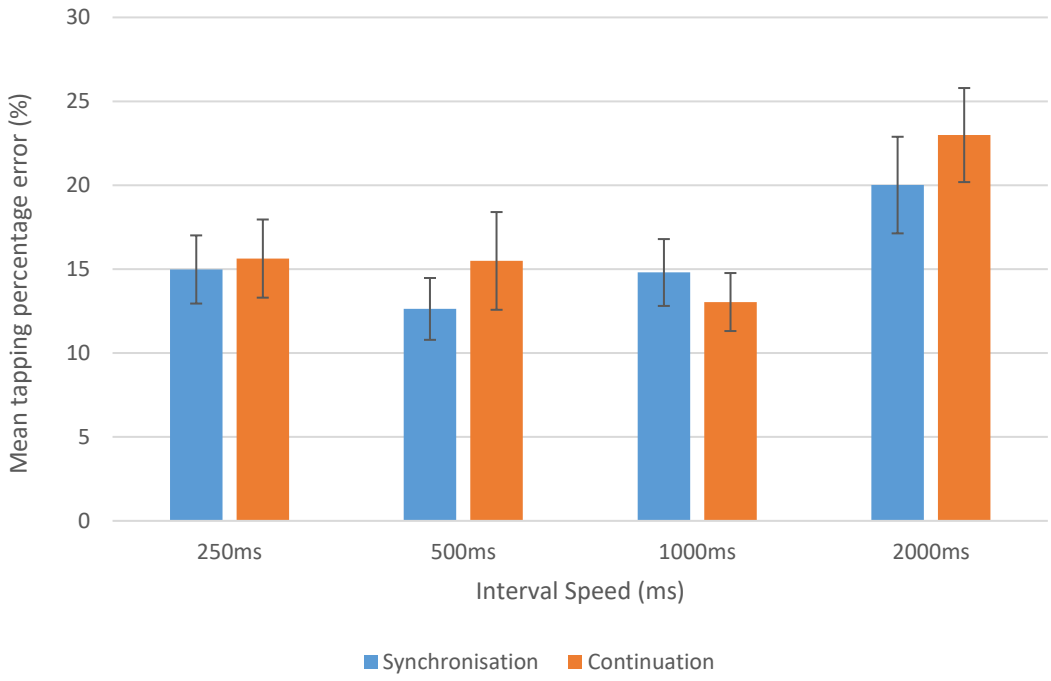


Figure 19 Mean tapping percentage error at each of the four tapping intervals (250ms, 500ms, 1000ms, 2000ms). Error bars represent standard error (SE).

Exploration of the data using histograms revealed mean tapping percentage error was not normally distributed at any of the ISIs (see appendix 6 (section 8.6)), and this was confirmed by a Shapiro-Wilks test for normality (p<.001 for all interval speeds).

The ANOVA technique has been found to be robust despite departures from normality (See Norton (1952) as cited in (Boneau, 1960)) and so was utilised here rather than using less powerful non-parametric alternatives.

A two-way repeated measures ANOVA was conducted that examined the effect of condition (synchronisation vs continuation) and interval speed (250ms, 500ms, 1000ms 2000ms) on mean tapping percentage error. Effect sizes were measured using partial eta squared (η_p^2)

and interpreted using guidelines provided by Cohen (1988). Greenhouse-Geisser corrected values are reported where necessary to correct for violations of sphericity.

There was no main effect of condition detected ($F(1,31)= .39$, $p= .53$, $\eta_p^2 = .01$), with participants performing similarly in the synchronisation condition ($M= 15.36$, $SD= 9.1$) and the continuation condition ($M=16.1$, $SD= 8.48$) overall. However, a main effect of speed (F (3, 93) = 4.65, p =.01, η_p^2 = .13) was revealed. The main effect of speed was investigated using Bonferroni corrected pairwise comparisons (summarised in Table 13). The pairwise comparisons revealed significant differences in mean tapping percentage error between 500ms and 2000ms (p=.04) with participants demonstrating a significantly higher level of percentage error at the 2000ms interval (M=21.53, SD= 15.27) than at the 500ms interval (M=12.69, SD= 11.87). A significant difference was also detected between the 1000ms and 2000ms intervals (p<.001), with participants demonstrating a significantly higher level of error at the 2000ms interval (M=21.53, SD = 11.87) than the 1000ms interval (M=13.64, SD= 9.78).

There were no significant interactions detected between speed and condition (F (3,93) = 1.57, p=.21, η_p^2=.05).

Table 13 Pairwise Comparisons between interval speeds

Interval speed	Comparison	*p*
250ms	500ms	>.99
	1000ms	>.99
	2000ms	.34
500ms	1000ms	>.99
	2000ms	**.04***
1000ms	2000ms	**<.001****

*significant at the .05 level, ***significant at the .001 level

2.3.3 Tapping Percentage Error and Motor Performance

Pearson correlations were used to investigate the relationship between tapping percentage error and motor performance (see Table 14). A weak positive correlation between motor performance and tapping percentage error was detected at 500ms in the continuation condition (*r*=.35*, p*=.04*).* No other statistically significant relationships were detected between MDS-UPDRS part III motor subscores and tapping percentage error in the synchronisation or continuation conditions, at any of the ISI speeds (250ms, 1000ms or 2000ms). Pearson correlation coefficients are summarised in Table 14.

Table 14 Pearson correlation (r=) among motor performance and tapping percentage error in the synchronisation and continuation conditions

	Synchronisation Condition				Continuation Condition			
	250ms	500ms	1000ms	2000ms	250ms	500ms	1000ms	2000ms
UPDRS III	.023	.18	.07	.11	-.02	.35*	.03	-.008

* Correlation is significant at the .05 level.

2.3.4 Tapping Percentage Error and Executive Function

Relationships between tapping percentage error and measures of EF were investigated using Pearson correlations. The relationship between tapping performance in the synchronisation and continuation condition with each measure of EF is described below, and summarised in Table 15 (synchronisation condition) and Table 16 (continuation condition).

2.3.4.1 Synchronisation Condition

2.3.4.1.1 Letter word fluency

In the synchronisation condition, letter word fluency scores were negatively correlated with tapping percentage error at the 500ms interval (r=-.55, p=.001). No other significant correlations were revealed between letter word fluency and tapping percentage error at any of the other interval speeds (see Table 15).

2.3.4.1.2 Brixton Spatial Anticipation Test:

In the synchronisation condition, no significant correlations were observed between Brixton Test scores and tapping percentage error at any of the interval speeds (p>.05) (see Table 15).

2.3.4.1.3 Stroop:

In the synchronisation condition, no significant correlations were observed between The Stroop Test scores and tapping percentage error at any of the interval speeds (p>.05) (see Table 15).

Table 15 Pearson correlations among EF test scores and tapping percentage error in the synchronisation condition

	250ms	500ms	1000ms	2000ms
Letter Fluency	-.24	-.551**	-.063	-.146
Stroop	.061	-.095	-.01	-.12
Brixton	-.28	.015	.03	.08

** Correlation is significant at the .01 level

2.3.4.2 Continuation Condition:

2.3.4.2.1 Letter word fluency:

In the continuation condition, letter word fluency scores were negatively correlated with tapping percentage error at the 500ms interval (r=-.51, p=.002) (see Figure 20). No other significant correlations were revealed between letter word fluency and tapping percentage error at any of the other interval speeds (p>.05) (see Table 16).

2.3.4.2.2 Brixton Spatial Anticipation Test:

In the continuation condition, no significant correlations were revealed between Brixton Test scores and tapping percentage error at any of the other interval speeds (p>.05) (see Table 16).

2.3.4.2.3 Stroop:

In the continuation condition, no significant correlations were revealed between Stroop scores and tapping percentage error at any of the other interval speeds (p>.05) (see Table 16).

Table 16 Pearson correlations among EF test scores and tapping percentage error in the continuation condition

	250ms	500ms	1000ms	2000ms
Letter Fluency	-.309	-.514**	-.183	-.067
Stroop	.198	-.208	-.127	-.069
Brixton	-.378	-.193	-.101	.199

** Correlation is significant at the .01 level

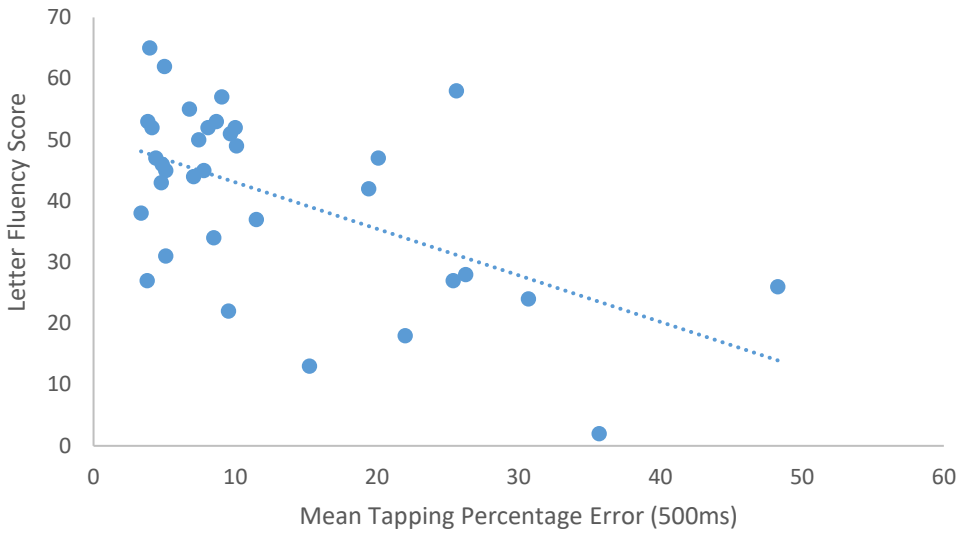


Figure 20 Relationship between Letter fluency scores and tapping percentage error in the continuation condition (r=-.51, p=.002)

2.3.5 Executive Function and tapping performance

As letter fluency was the EF measure found to have the strongest relationship with tapping performance, letter fluency scores were used to categorise participants into the executive function (EF_{high}) and executive dysfunction (EF_{low}) groups (see methods, section 2.2.7.3).

Appendix 6 (section 8.6) displays a histogram of letter fluency scores across the sample.

A mean ± 1 SD criteria was initially used to categorise participants into the two EF groups, however this did not result in a sufficient number of subjects in each group to compare performance (EF_{high} n=5).

The threshold was therefore lowered to a mean ± 0.5 SD criteria, to ensure higher numbers of participants in each group.

The mean letter fluency score for the entire sample was 41 with a SD of 14.81. Therefore participants were selected for the EF_{high} group if their letter fluency scores were greater than or equal to 48 (41 + 0.5 SD). If participants' letter fluency scores were less than or equal to 34 (41 – 0.5 SD), participants were assigned to the EF_{low} group.

This procedure resulted in the following number of participants in each group: EF_{high} group (n=13) and EF_{low} group (n=12).

2.3.5.1 General cognitive function

ACE III scores were found to be normally distributed across the sample (see Appendix 6 (section 8.6)). Differences in ACE III scores between EF_{high} and EF_{low} groups were therefore investigated using an independent samples t-test. The test revealed a significant difference in ACE III scores between groups: $t(23)= 3.92$, $p=.001$. Participants in the EF_{high} group had higher ACE III scores (M=94, SD=3.05) than participants in the EF_{low} group (M=87 SD= 5.88).

2.3.5.2 Tapping performance

Due to the significant relationship between tapping performance and letter fluency at 500ms, performance at this interval was explored in more detail.

Figure 21 displays the mean tapping percentage error in the executive dysfunction group (EF_{low}) and the normal executive function group (EF_{high}) at 500ms in both the synchronisation and continuation conditions. As the graph suggests, in the synchronisation condition, the EF_{low} group had a higher level of mean tapping percentage error (M=19.47, SD= 14.31) than the EF_{high} group (M= 8.63, SD=5.6). This was also observed in the continuation condition,

where the EF_{low} group had a higher level of mean tapping percentage error (*M*=26.93, *SD*= 22.04) than the EF_{high} group (*M*= 10.41, *SD*=9.1).

To investigate this further, a 2x2 mixed design ANOVA was carried out on the effect of condition (synchronisation vs continuation) and EF group (EF_{low} vs EF_{high}) on mean tapping percentage error at the 500ms interval. Effect sizes were measured using partial eta squared (η_p^2) and interpreted using guidelines provided by Cohen (1988).

A significant main effect of EF group on tapping performance was revealed overall $F(1,23)= 7.7$, $p=.01$, $\eta_p^2= .25$, with the EF_{low} group demonstrating a higher percentage of tapping error overall (*M*=23.20, *SD*= 12.30) than the EF_{high} group (*M*=9.5, *SD*= 12.29).

There was no significant main effect of condition (synchronisation vs continuation) on mean tapping performance error overall $F(1,23)=3.07$, $p=.09$, $\eta_p^2=.12$, with participants showing similar mean tapping percentage error in the synchronisation (*M*=14.05, *SD*= 20.9) and continuation (*M*=18.67, *SD*= 13.53) conditions.

There was no significant interaction identified between condition and EF group $F(1,23)=100.29$, $p=.29$, $\eta_p^2= .05$. Descriptive statistics showed that EF_{low} participants had a lower mean tapping percentage error in the synchronisation condition (*M*=19.47, *SD*= 14.31) than the continuation condition (*M*=26.93, *SD*= 22.04) and this was also true for the EF_{high} group (synchronisation condition *M*= 8.63, *SD*=5.6; continuation condition *M*= 10.41, *SD*=9.1).

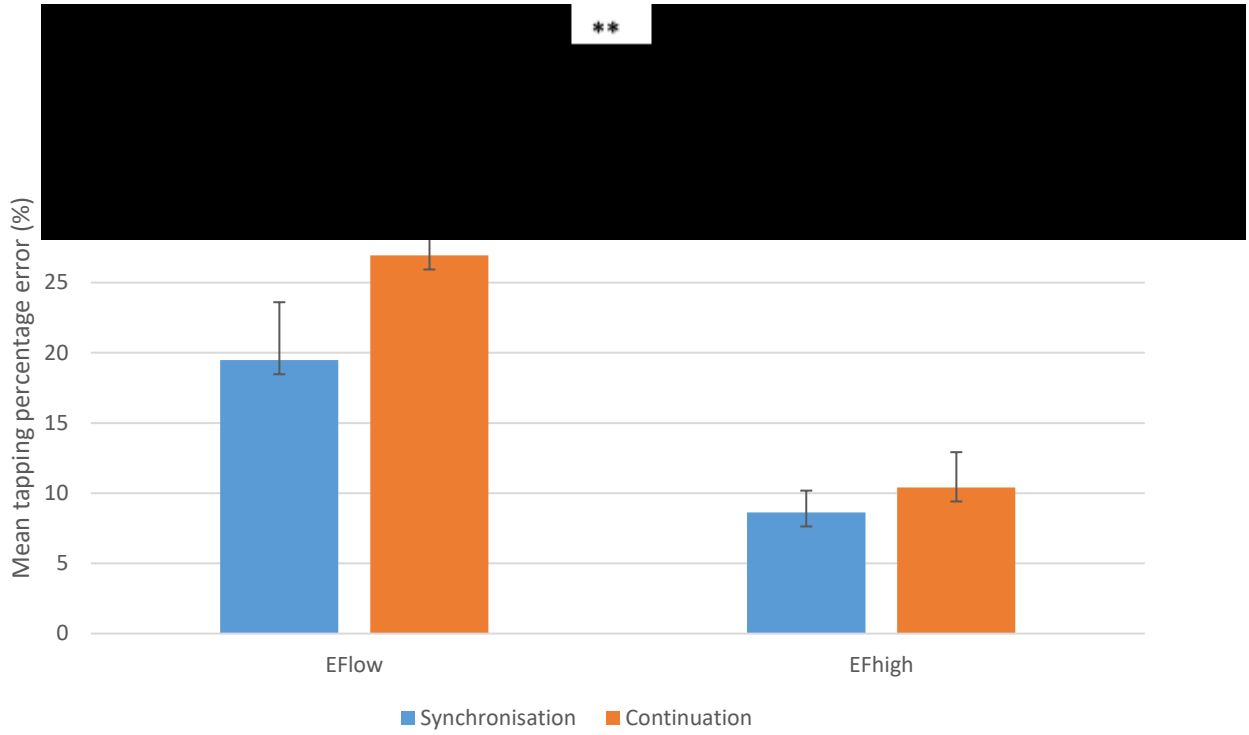


Figure 21 Percentage error at the 500ms interval in the executive dysfunction (EF_{low}) and normal executive function groups (EF_{high}) in the synchronisation and continuation condition. Error bars represent standard error (SE).

As I was particularly interested in exploring the relative difference in tapping performance across conditions between the two groups, the difference in tapping performance between the synchronisation and continuation condition at 500ms was calculated for the two groups by subtracting performance in the synchronisation condition from performance in the continuation condition. As before, the root mean square (RMS) was calculated, in order to determine the absolute error ($\sqrt{\ }$(tapping percentage $error_{continuation}$ - tapping percentage $error_{synchronisation}$)^2).

A Mann Whitney U test revealed a significant difference between groups (U= 32, p=.01), with participants in the EF_{low} group demonstrating a greater difference in performance between the synchronisation and continuation condition (M = 13.76, SD =12.62) than participants in the EF_{high} group (M = 5.06, SD = 4.19).

2.3.6 Main findings

To summarise, the main findings from this study were as follows:

- The letter fluency task was found to correlate significantly with PFT performance at the 500ms ISI in both the synchronisation and continuation conditions.
- A 2x2 mixed ANOVA revealed a main effect of EF group at the 500ms ISI, with participants in the EF_{low} group demonstrating a higher level of tapping percentage error than participants in the EF_{high} group overall.
- However there was no significant main effect of condition (synchronisation/continuation) overall, and no significant interaction between condition and EF group.
- The difference in tapping performance between conditions (synchronisation/continuation) was significantly greater in the EF_{low} group than in the EF_{high} group.

2.4 Discussion

I carried out a study using a computerised version of the Paced Finger Tapping Task (PFT) to evaluate whether tapping performance in PwP was affected by executive function (EF). I hypothesised that performance in the PFT would correlate with performance in the EF tests, and that participants with poorer levels of EF would exhibit greater levels of relative impairment in the continuation phase of the PFT than participants with better levels of EF.

Study findings in relation to each of the hypotheses and limitations of these will be discussed in detail below.

2.4.1 Hypothesis 1: Performance in the PFT would correlate with performance in the EF tests.

In relation to my first hypothesis, the study revealed a significant correlation between tapping performance at the 500ms interval in the PFT and a measure of letter fluency (FAS). This finding provides support for my first hypothesis, and suggests that people with poor letter fluency ability will perform more poorly on the PFT. As mentioned previously, letter fluency is considered a frontally based task, and has been associated with activation in the dorsolateral pre frontal cortex (MacDonald, Cohen, Stenger, & Carter, 2000). Our results support previous suggestions there may be shared neural circuitry between frontally based tasks and performance in interval timing tasks (Brown, 2006).

It is important to note however that letter fluency scores were not found to be associated with the Stroop Test Scores nor with the Brixton Test scores, and these EF measures were also not found to correlate with one another, nor with tapping performance at any of the interval speeds in either the synchronisation or continuation condition. These findings provide support for the idea that measures of EF can be dissociated in PD (Gurd, 1995), and suggests that degeneration in PD may not impact on EF globally. The Stroop Test is a conflict based task, designed to assess an individual's ability to inhibit a habitual response, whereas The Brixton Spatial Anticipation Test assesses an individual's ability to detect a rule, follow a rule and switch to a new rule (Van Den Berg et al., 2009). The lack of a relationship between EF

measures highlights the need for specificity when assessing for impairments of EF clinically (Mckinlay, Grace, Dalrymple-alford, & Roger, 2009).

In addition, performance on the letter fluency task was not found to correlate with tapping performance at any of the interval speeds other than at 500ms, in either the synchronisation or the continuation conditions.

It is of interest as to why significant relationships between tapping performance and EF were only detected at the 500ms interval. Research into motor timing performance at specific intervals in the millisecond to second range has revealed that PwP demonstrate the least amount of variability in tapping at 500ms, indicating a 'preferred' tapping rate (Jones et al., 2011). Our data support this finding, as of all four interval speeds, tapping error and variability were lowest for the 500ms interval in the synchronisation condition. Furthermore, when asked to tap at a 'comfortable pace', PwP have been found to tap at around 600ms (Yahalom et al., 2004). These findings suggest that around 500ms is a tapping rate that PwP find most natural or comfortable.

In addition, previous research has suggested that at cue frequencies higher than 500ms, tremor may pace voluntary repetitive movements to go faster than intended by the patient. At 500ms and lower frequencies however, PwP do not seem as affected by tremor (Logigian, Hefter, Reiners, & Freund, 1991).

These findings suggest that the noise in tapping performance (variability between subjects) at the other interval speeds may have prevented significant correlations between tapping and

fluency being detected, and this may be partly explained by our small sample size. The inclusion of a larger sample size may have helped to overcome this issue.

2.4.2 Hypothesis 2: Participants with poorer levels of EF would exhibit greater levels of relative impairment in the continuation phase of the PFT than participants with better levels of EF, due to a greater reliance on external cues.

In order to investigate my second hypothesis, and due to the significant relationship between performance in the letter fluency task and tapping performance, letter fluency scores were used to stratify patients into two EF groups; EF_{high} and EF_{low}.

The results of the 2x2 mixed ANOVA revealed there was a main effect of EF group on tapping performance, with participants in the EF_{low} group demonstrating a significantly greater level of tapping percentage error than the EF_{high} group overall. While these results provide some support for my hypothesis, suggesting EF impacts on PFT performance overall, there was no main effect of condition (synchronisation or continuation) on tapping performance detected, and no interaction effect found between EF group and condition.

These findings demonstrate that while participants with poorer levels of EF performed worse overall, there was no significant difference between performance in the synchronisation condition in comparison to the continuation condition.

This result is not in line with my second hypothesis, and contradicts previous research which has indicated that people with low levels of EF may have reduced SAS resources (Brown & Marsden, 1988), and so experience difficulty in producing novel responses that are not cued

automatically by the environment (Norman, 1980). In addition, findings from previous research has suggested that impairments in verbal fluency may reflect a failure for PwP to carry out novel responses that are dependent on internal control (Bouquet et al., 2003), rather than due to verbal intelligence or difficulties in word production (Flowers, Robertson & Sheridan, 1995). Due to the absence of external cues in the continuation condition, performance in this condition was entirely reliant on internal action. I therefore expected there to be an interaction between executive functioning and condition, with participants in the EF_{low} group expected to perform significantly worse in the continuation condition (in the absence of external cues) than participants in the EF_{high} group.

The difference in performance between the synchronisation and continuation condition was significantly larger for participants in the executive dysfunction group (EF_{low}) than participants in the normal executive function group (EF_{high}) however, indicating that tapping performance in the low fluency group was less consistent across the two conditions.

This finding therefore may suggest that people with low levels of EF are more reliant on external cues to maintain consistency in tapping performance than people with high levels of EF, and therefore provides some support for my second hypothesis.

Other variables that may have impacted on tapping performance were also considered:

2.4.3 Sample size

As discussed, my power calculation revealed that a sample size of 128 participants was required to reach adequate power (0.8) for this study. Unfortunately, due to difficulties with

the tapping equipment and a lack of resource to resolve, I was unable to continue with recruitment past 37 participants. This study was therefore underpowered, and there were small numbers of participants in each EF group, which may partially explain the lack of a main effect of condition. However, my data did show a trend for poorer performance in the continuation condition, and this difference in performance was found to be significantly greater in the EF_{low} group.

2.4.4 Tapping performance and motor ability

Tapping error percentage was found to weakly correlate with MDS-UPDRS III scores only at the 500ms interval (r=.35, p=.04), which suggests that tapping performance was not strongly associated with motor ability. This was surprising, particularly for performance at the fastest (250ms) interval, as my previous study findings (PDTAP Study) revealed tapping performance at fast speeds was correlated with UPDRS III scores (Dominey et al., 2016). Furthermore, previous research has found impaired reproduction of time intervals to be correlated with disease severity (Pastor, Artieda, Jahanshahi, & Obeso, 1992), which suggests people with more severe PD would have performed more poorly on the PFT than those with milder PD, however I did not find this to be the case.

There are several possible explanations as to why I was unable to replicate these findings. Firstly, as mentioned previously, our sample size was fairly small, which made it difficult to draw out relationships between tapping performance and motor ability. In addition, participants were only tested in the ON medication state. Inclusion of testing in an OFF

medication state may have made relationships between tapping performance and motor ability more clear.

2.4.5 Tapping performance and general cognitive ability

Findings revealed that the EF_{high} group had higher levels of cognitive function (ACE III scores) than participants in the EF_{low} group, which may suggest that differences in tapping performance between these groups may be due to general cognitive ability, as opposed to purely EF. It would be of interest in future studies to explore this further, by stratifying patients by cognitive ability for example. Due to the small number of people in our sample with evidence of Parkinson's disease Dementia (PDD) (n=4) it was not possible to stratify patients' tapping performance based on general cognitive ability. However, recent evidence has suggested that cholinergic deficits that occur in some PwP exacerbate fronto-striatal dysfunction, due to a loss of compensatory fontal cortical executive functions (Bohnen et al., 2015). Cortical cholinergic denervation has been found to be significantly less common in PwP without cognitive impairment, but strongly associated with PwP with the greatest level of cognitive impairment Bohnen et al (2015). It would be of interest to investigate whether there were differences in tapping performance between people with and without cognitive impairment, to see if performance in the PFT task is reliant on intact cholinergic functioning, which is known to help preserve executive functioning in PwP (Bohnen et al., 2015). This could be achieved by implementing more robust inclusion criteria and recruiting participants with a wider range of cognitive abilities, including participants with normal cognition, MCI and PDD, whilst ensuring we had equal numbers of participants in each of these groups.

2.4.6 Application of findings

Our findings demonstrate that a PFT paradigm using intervals of 500ms could be added to existing quantitative tapping measures to provide an indication of possible executive dysfunction, due to the overall poorer PFT performance by participants with low levels of EF.

A number of quantitative tapping measures are being used currently to objectively assess finger tapping performance in PD that may offer a suitable platform for integration of such a test. The Bradykinesia-Akinesia Incoordination Test (BRAIN test) for example is a computer based tapping task, based on an alternating finger tapping paradigm (Giovannoni et al., 1999). The test uses a computer with a standard keyboard as the test device, and the two tapping targets are the "S" and ";" keys, 15cm apart. Subjects are asked to alternately tap the 'S' and the ';' keys as rapidly and as accurately as they can over a 30-second time period (Giovannoni et al., 1999). The program has been validated to assess kinesia (number of key taps in 30 seconds), akinesia (mean dwell time on each key (ms)) and incoordination (variance of travelling time between key presses). These measures have been shown to successfully differentiate PwP and controls, as well as correlating with PD severity measured by MDS-UPDRS total score and motor MDS-UPDRS sub scores (Giovannoni et al., 1999). Furthermore, an online version of the BRAIN test is available, meaning it can be accessed remotely from any computer with an internet connection and a keyboard, thereby making the test widely accessible (Noyce et al., 2014). The BRAIN test has already been implemented as a remote motor assessment in an extensive online Parkinson's risk study (PREDICT-PD (Noyce et al., 2017)), whereby differences in kinesia scores were detected between patients with high and

low risk scores for PD. In addition, the BRAIN test is being used as a secondary outcome measure in a trial of Simvastatin as a neuroprotective agent in Parkinson's (PD-STAT) (Carroll & Wyse, 2017). The BRAIN test has therefore been validated as an objective finger tapping tool to measure motor function in established PwP (Noyce et al., 2014), as well as in in pre-diagnostic cohorts (Noyce et al., 2017).

Another quantitative measure of finger tapping has been developed as part of a smartphone software application to assess motor function. For the finger tapping component, participants were required to tap the screen alternately, keeping a regular rhythm. The screen pixel position (x,y coordinates) and time of finger touch were recorded, and used to quantify: tapping speed, rhythm, inter-tap interval, fatigue, and tremor. The summary measures, which in addition to finger tapping, included voice, posture, gait and reaction time, were found to differentiate between PwP and controls with high sensitivity (96.2%) and specificity (96.9%) and predicted disease severity, as measured by the MDS-UPDRS (Arora et al., 2015).

Both of these finger tapping measures implement a single instruction paradigm and alternating tap locations, on either a computer keyboard or touch screen phone. While these measures have been validated to provide useful information on disease severity (as described above), it might be possible to add further value to these measures by introducing a secondary tapping task that is higher in complexity (such as a paced finger tapping task) which has potential to provide insight on the presence of some executive dysfunction.

As these devices have already been designed and validated to measure finger tapping in PD, it would be hoped the process of adding the PFT to these paradigms would not be too costly or complex.

2.4.7 Study Limitations

There are several limitations to this study that will be discussed.

Firstly, unlike other studies investigating the PFT, we did not include a control condition such as a simple reaction time test (Jahanshahi et al., 2010). This means I was unable to account for aspects of motor function that may contribute towards the findings. This limits the interpretability of the results. The weak positive correlation found between tapping performance at the 500ms interval in the continuation condition and UPDRS-III scores suggests that other aspects of motor function might be influencing PFT performance at this frequency.

Secondly, I did not include an age-matched healthy (non-PD) control group, which meant it was not possible to demonstrate whether our findings revealed impairments in tapping and EF that were unique to PwP. Previous studies have demonstrated that performance between PwP and controls is more similar for the synchronisation phase than the continuation phase for instance, which provides support for the view that PwP experience greater difficulty for internally generated movements. It would be of interest to include a control group to ensure our findings replicated those of previous studies implementing the PFT (Jones et al., 2011).

A further limitation to this study is that I only tested participants in a reported ON medication state. Differences in PFT performance have been reported previously between ON and OFF medication states, with the administration of dopamine found to reliably improve accuracy of tapping performance (Koch et al., 2008) with increased activation in the prefrontal areas when in an ON state (Jahanshahi et al., 2010). In contrast, dopaminergic modulation has been found to both impair and enhance cognitive function in PD, depending on the task demands (Cools, Barker, Sahakian, & Robbins, 2001). It would therefore be of interest to test participants in an ON and OFF state to evaluate dopaminergic influence on performance in EF and tapping measures.

In addition, my study had limited sensitivity due to the software that was used. This study had originally been planned to be carried out as part of a tapping software application on a smartphone, by implementing a similar design to our previous PD-TAP study (Dominey et al., 2016), and would have avoided the need to create an additional computer software program. Unfortunately, the support to write the software in iOS code was not available at the time of planning the study. A new programme was therefore created for this study, utilising Microsoft Visual Studio software to simulate a smartphone experience. Unfortunately a technical error was identified during the study. The refresh rate of the computer program was set as 30ms, which introduced a <60ms window of uncertainty for the precise timing of taps. While this has a relatively minor consequence at lower frequencies, introducing ~0.015Hz variance at 0.5Hz (2000ms) tapping speed, the potential error is amplified at higher speeds, resulting in a ~0.9Hz variance at 4Hz (250ms) tapping speed. This reduction in sensitivity posed a potential

limitation to the application of these data. Due to this and other technical difficulties, it was not possible to continue the study after the 37th participant, which limited the statistical power of the study. This highlights a potential issue when developing software applications for research, as these designs can be resource heavy in terms of coding and ongoing technical support.

Therefore, while there is some evidence of a relationship between measures of EF and performance on the PFT, a greater sample and finger tapping software with increased sensitivity would be needed to explore this in more detail.

2.4.8 Conclusions

Our study has revealed interesting relationships between motor timing in PD (as assessed by finger tapping performance in the PFT) and levels of EF.

In relation to my first hypothesis, tapping performance in the PFT was found to correlate with performance in the letter verbal fluency task at 500ms in both the synchronisation and continuation condition. This finding provides support for my hypothesis, and demonstrates that performance in the PFT task at 500ms may provide some insight into levels of executive functioning.

In relation to my second hypothesis, my findings revealed that although participants with poorer levels of EF performed worse overall, there was no main effect of condition detected, meaning participants in the EF_{high} and EF_{low} groups did not perform significantly differently between the synchronisation and continuation conditions. This finding does not support my

second hypothesis that people with low levels of EF would perfom relatlively worse in the continuation condition due to a greater reliance on extrernal cues, and instead suggests performance is similar across the synchronisation and continuation condition for both EF_{high} and EF_{low} groups.

Our findings suggest a quick and simple measure of paced finger tapping at the 500ms interval has potential to be incorporated as part of an existing quantitative measure of finger tapping, to provide insight into potential deficits of executive function that relate to letter fluency including search strategies, inhibition, self-monitoring and self-initiation of response.

2.4.9 Challenges to the development of Digital Health Technologies (DHTs)

There were a number of challenges related to the development of Digital Health Technologies (DHTs) that I learnt as a result of this study.

Firstly, the development of a computerised version of a pre-existing measure (in this case the PFT) should follow a standardised procedure. There are guidelines that have been published since the computer software was developed for this study, that clearly outline stages of development and necessary considerations that would have ensured our measure was more suitable for intended use (Mhra, 2017; Patient Reported Outcomes-From Paper to ePROs, 2016):

- Involvement with end users:

  As outlined in the MHRA guidance for engineering medical devices (Mhra, 2017), the first stage in the development of a new DHT should be to involve end users.

Involvement from end users throughout the development of a DHT ensures that the technology is usable, and easily accessible for users. As reported previously, one participant was unable to complete the study due to severe tremor, which meant they were unable to accurately press the sensor. In addition, several participants expressed discomfort when adopting the required hand position for finger tapping, which could have led to inaccuracy. Furthermore, several participants made incorrect finger taps (eg. holding down the sensor) which had to be corrected by the researcher. MHRA guidance (Mhra, 2017) further recommends that end users should be involved with the development of the task instructions to ensure these are clear and understandable by users. If there had been greater involvement with patients throughout the development of the computer program and selection of accompanying equipment, these aspects could have been detected much earlier in the design process, and mitigations could have been put in place to overcome these, to ensure the design met user needs.

- Frequent evaluation and iterative design:

  The guidelines further recommend frequent stages of formative evaluation to be carried out prior to the technology being implemented as part of a larger study, which allows for potential risks and design errors to be detected early on, and iterative refinements to be made (Mhra, 2017). As mentioned previously, it was only after the data had been collected that a technical error was detected, whereby the sensitivity of the computer program (the refresh rate) had been set to a lower sensitivity than

expected. This finding highlights the need for extensive pilot testing to be carried out prior to the implementation of a DHT as part of a more extensive study. Guidelines suggest that equivalence testing is also carried out as part of the development process, whereby a novel DHT is assessed against an existing measure to ensure performance does not vary significantly across the two measures (Patient Reported Outcomes-From Paper to ePROs, 2016). In addition, the technical error we experienced demonstrates the need to work closely and collaboratively with IT developers throughout the development process, so that channels of communication are kept open and clear. By implementing these best practises, the chances of detecting a technical error early on, before data collection has taken place, are maximised.

In conclusion, while I have found suggestion that PFT performance might be influenced by EF, the applicability of our findings is limited due to concerns surrounding the sensitivity of the computer software used. The study has highlighted some important considerations when implementing novel DHTs, which I have taken forward as learning for the subsequent studies in my thesis.

Chapter 3 The development and formative evaluation of a smartphone based non-motor symptoms application: "NMS Assist"

3.1 Introduction

Non-motor symptoms (NMS) are a significant cause of morbidity in Parkinson's disease (PD), and have been shown to have a major impact on quality of life (QoL) (GDPS, 2002), as well as being closely associated with increased care partner burden (Schrag et al., 2006). Common NMS include psychiatric problems such as depression and confusion, as well as urinary and gastro-intestinal dysfunction, and sleep disturbances (Martinez-Martin, Rodriguez-Blazquez, Kurtis, & Chaudhuri, 2011.) (see section 1.2.11). NMS are common at first presentation of disease (Todorova, Jenner, & Ray Chaudhuri, 2014), but the frequency of symptoms increases with disease progression, leading to a greater burden of NMS in advanced stages (Muzerengi et al., 2007). Indeed, NMS have been identified as the major cause of disability in patients living with PD for 15 or more years (Hely, Morris, Reid, & Trafficante, 2005). If left untreated, NMS can cause detrimental health complications and are a major cause of institutionalised care (Muzerengi et al., 2007).

Despite the evident importance of recognising and appropriately treating these symptoms in order to improve patient QoL (GDPS, 2002) reduce care partner burden (Schrag et al., 2006) and avoid unplanned hospital admissions (Muzerengi et al., 2007), NMS are frequently not declared by patients in routine clinic appointments, and are not often asked about by clinicians (Chaudhuri et al., 2010). This may be due to limited clinic appointment times, which

prevent clinicians carrying out comprehensive assessments, or due to lack of NMS awareness amongst clinicians (Chaudhuri et al., 2010). In addition, patients may be unaware their symptoms are related to their PD, or they may be too embarrassed to discuss them (Chaudhuri et al., 2010).

In order to enhance the identification of NMS in PD patients and allow for appropriate and timely treatment, a self-rated Non-Motor Symptoms Questionnaire was developed (NMS Quest) (Chaudhuri et al., 2006b) which can be completed by the patient in the waiting room prior to clinical consultation. As described previously (see section 1.2.21.2.7), this 30-item screening questionnaire allows for a comprehensive assessment of the range of NMS that occur in PD, and provides an opportunity for the patient to self-declare any possible problems to their clinician for further investigation. The NMS Quest has been internationally validated (Chaudhuri et al., 2006b), and is used extensively as part of routine clinical care.

3.1.1 Self-management

In addition to identifying NMS, there is a need to educate patients on simple self-management techniques to ameliorate many NMS, facilitate timely medical intervention, and prevent further deterioration (Duncan et al., 2013). Patients with knowledge and skills to manage their own health conditions have been found to experience better health outcomes, and have lower associated costs than patients with poor levels of engagement (Hibbard & Gilburt, 2014). In PD, patient involvement and access to information has been linked to reduced

length of hospital stay, decreased risk of adverse events, and improved QoL (Bauman et al., 2003; Michie, Miles, & Weinman, 2003; van der Eijk et al., 2013).

As outlined in the NHS Long Term Plan (The NHS Long Term Plan, 2019), there is a need to empower people living with long term conditions to become better at managing their own health, make informed treatment choices and avoid complications (Hibbard & Gilburt, 2014). To help meet this need, resources and tools are needed to increase patient capacity for self-management.

3.1.2 mHealth Solutions

Advances in mobile technology have the potential to play a role in facilitating self-management of long term conditions by providing insight into a patient's condition, helping patients make informed choices, and encouraging engagement in self-care habits (Alpay et al., 2010).

The increased accessibility of smartphones has contributed towards the rapid development of mobile health technologies (mHealth) in recent years (Matthew-Maich et al., 2016). Ofcom has recently estimated that 66% of adults in the UK own a smartphone, which has increased by 27 percentage points since 2012 (Ofcom, 2015). Although older adults are less likely than younger age groups to own a smartphone (an estimated 18% of people over the age of 65 have one, compared with 50% of those aged 55-64), smartphone ownership in older adults has more than trebled since 2012, and continues to rise (Ofcom, 2015).

According to the World Health Organisation (WHO) there is great potential for mHealth to transform existing health services in coming years (WHO, 2011). As mentioned previously (see section 1.2.27), The NHS and Parkinson's UK have recently launched an 'Apps Library' in an attempt to signpost patients towards healthcare apps that meet high standards for quality, reliability and effectiveness ("Apps for Parkinson's", 2018; "NHS Apps Library", 2018).

In addition, there are an increasing number of studies piloting mHealth interventions to support the management of long term health conditions (Wang et al., 2014). In PD, telemedicine has been recognised as a feasible way of providing specialist care for patients at home, offering similar clinical benefits to in-person care, and avoiding the need for travel (Dorsey et al., 2013). A recent review of studies using mHealth technology to manage long term conditions identified several benefits, including improved patient self-management, patient education tailored to patient need, and improved communication between health care professionals (Matthew-Maich et al., 2016). Furthermore, significant reductions in cost have been associated with mHealth technology in comparison with traditional care (Noel et al., 2004).

A particular advantage of utilising smartphone technology, is the ability to incorporate educational material in a variety of media, including video. A review on the use of videos within clinical practice found that patients who viewed videos had a better understanding of their treatment options, and were more likely to be active participants in decision making (Krouse, 2001). In PD, 'ParkinsonTV' (launched by the Dutch strategy group 'parkinsonNet' (Bloem et al., 2017) broadcasts monthly programmes for people affected by PD, allowing for

easily accessible information on a variety of PD related projects. The success of this channel has recently led to episodes being broadcast in English. In addition, videos have been found to increase information accessibility for people with poor literacy skills, or those with poor vision (Krouse, 2001). Videos are therefore a potentially feasible method for facilitating self-management of long term conditions.

3.1.3 Challenges associated with mHealth solutions

Despite the potential benefits of mHealth interventions, there are a number of associated challenges that have recently been identified (Baniasadi, Niakan Kalhori, Ayyoubzadeh, Zakerabasali, & Pourmohamadkhan, 2018; Gurupur & Wan, 2017):

1. Usability is a key consideration when designing an mHealth intervention, particularly for a diverse cohort such as older adults, who would be expected to have differing levels of digital literacy (Choi & Dinitto, 2013), as well as cognitive and motor limitations (Kruse, Mileski, & Moreno, 2017). Engagement with end users is therefore a priority to ensure that the app design is acceptable and meets user needs. Successful integration of end users' considerations throughout the development of mHealth solutions has been found to influence engagement with and adoption of mHealth technologies (Matthew-Maich et al., 2016).

2. Compliance and continued use of mHealth solutions is a key issue, with high dropout rates identified among app users. Once downloaded, 26% of apps have been found to be used only once, and 74% of apps are not used more than 10 times (Espay et al.,

2016). Sustained engagement with mHealth solutions is thought to be dependent on several key variables including satisfaction, confirmation of expectation, and perceived usefulness (Bhattacherjee, 2001). These variables should therefore be considered when developing and evaluating an mHealth solution.

3. Infrastructure, including the availability and strength of internet networks to transmit and receive data, particularly in emergency situations (Baniasadi et al., 2018) needs to be considered. If the necessary infrastructure is not in place or not widely available, then it would prevent the use of mHealth solutions.

4. Data security is of particular importance when managing data that contains personal health information (Gurupur & Wan, 2017). Data needs to be stored in a secure location in compliance with relevant guidelines, and only accessible through secure transmission channels.

Additional challenges to implementing mHealth solutions include reliability, meaning the result provided by the technology must be accurate enough to help the patient, and system integration, whereby the design system must be scalable, and allow for integration with other pre-existing clinical and data-management systems (Gurupur & Wan, 2017).

It is therefore important with the design of any new mHealth technology that these challenges are considered and addressed, to ensure the successful implementation of the system, with user safety being the primary focus.

3.1.4 NMS App

Despite the challenges described above, mHealth technologies such as smartphone based applications offer great potential in facilitating patient self-management of long term conditions, and provide the opportunity to monitor patients within the home environment (Matthew-Maich et al., 2016).

With regards to NMS in PD, there is a need for tools to help patients self-manage their NMS, and provide remote monitoring of these symptoms with triggered response, to allow for timely and effective intervention, and to avoid development of complications.

To meet these needs, the Applied Parkinson's disease Research Group (led by Camille Carroll) set up a project group to develop a mobile app version of the NMS Quest (Chaudhuri et al., 2006) in collaboration with its author, Prof. Ray Chaudhuri (Kings College London). The main aims of the app are to provide remote monitoring of NMS and triggered service support for PwP and their care partners, as well as information on self-management of PD NMS. The app will also be used by care partners so that 'carer voice' can be heard, which can provide insight on non-motor issues that might not be recognised or reported by the patient themselves. Discordance in cognitive and neuropsychiatric symptom ratings have previously been found between carers and patients (Janssen, 2013), which demonstrates the importance of obtaining information from care partners to provide the most clinically valid picture of a patient's symptom severity.

The self-help information provided as part of the app has been developed in collaboration with Ron Postuma, (McGill University), author of 'A Guide to the Non-Motor Symptoms of Parkinson's Disease' (Postuma & Galatas, 2012). App development was supported by funding from Plymouth Hospitals NHS Trust Charitable Fund and the Hoover Foundation.

The NMS App project group is an interdisciplinary team made up of clinicians, researchers, mHealth designers and end users (PwP, Caregivers and PD Nurse Specialist (PDNS)). Project group roles of the main project group and external collaborators are described in appendix 7 (section 8.7). All members of the main project group contributed to the iterative design process, and end users were involved at all stages of the app development process to ensure the app design was acceptable and met their needs. I was responsible for co-ordinating the app design process, whilst ensuring the app met user requirements. I was also responsible for leading the design, recruitment, delivery and analysis of the formative evaluation of the app as well as maintaining the Medicines and Health Products Regulatory Agency (MHRA) Site File.

3.1.5 App Development

The process of app development is described in Figure 22. Following identification of app uses and users, the development of the app can be broadly divided into three processes that ran in parallel to one another:

- Development of the app wireframe
- Development of self-help materials

- Development of app build

In addition to the identification of app uses and users, I was involved in the development of the app wireframe, the development of the self-help materials, and the formative evaluation of the app, ensuring that all regulatory requirements were met.

3.1.6 Overall Project Aims

The overall aims of the project were:

1. To design and develop a non-motor symptoms app using a user-centred, iterative design process, in line with MHRA guidance, and with end user engagement throughout.
2. To evaluate whether the app is usable by the intended users.
3. To identify key areas of amendment to the app design prior to a summative evaluation of the app.

3.1.7 Chapter Outline

This chapter will therefore be divided into 3 parts, representative of the app development process:

- Part One relates to the identification of app use and user groups
- Part Two relates to the iterative design process. This chapter will be split into two subsections:
    - Part Two (A) refers to the wireframe development process

- Part Two (B) refers to the self-help materials development process

- Finally, Part Three relates to the formative evaluation of the app

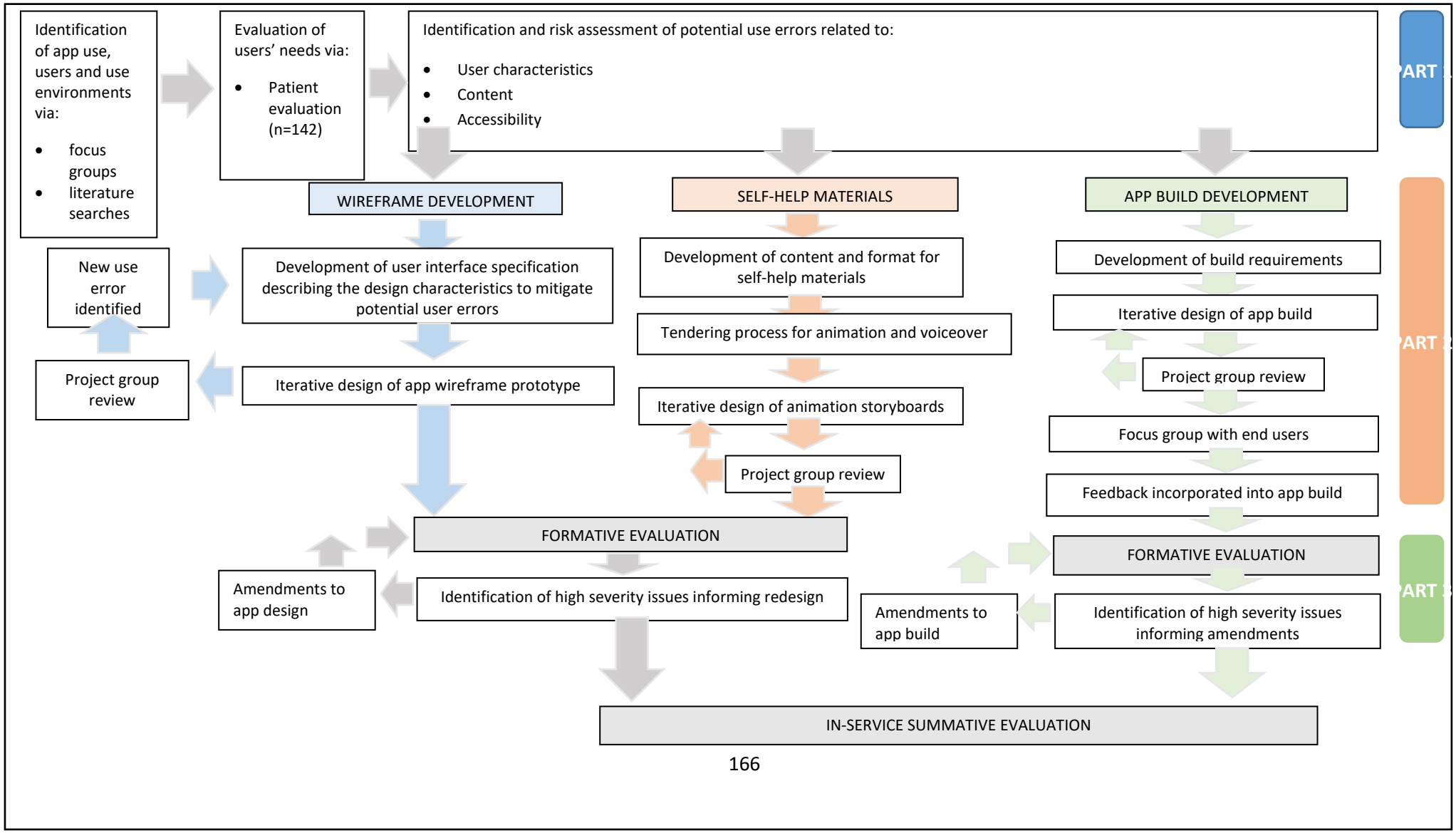


Figure 22 The NMS App development process and corresponding chapter sections. Part 1 details the identification of app use and user groups, Part 2 details the development of the app wireframe and self-help materials, and Part 3 details the formative evaluation of the app.

3.2 Part One: Identification of app use, users and environment

3.2.1 Part One Aims

- To identify app users and their environments via evidence from the literature
- To evaluate patient experience of NMS via a patient questionnaire

3.2.2 Part One Hypothesis

1. There will be a wide range of potential end users identified from the literature, including those with a breadth of demographic variables, disease presentation, NMS burden and prior experience with digital devices.

3.2.3 Identifying Users and Environments

To ensure the app was designed for real world use, it was necessary to identify and understand who the end users were, and the intended environment for use.

We identified two main user groups who will be interacting with the app interface – PwP and their care partners. Each of these user groups will be discussed in turn below.

People with Parkinson's (PwP)

There is known heterogeneity in PwP, including a breadth of age, disease severity, and clinical presentation. Recent figures published by Parkinson's UK (Parkinson's UK, 2017) suggest potential end users with Parkinson's could cover a wide age range, from 20-90+ years, with prevalence increasing with age. In terms of gender, the prevalence of PD is higher for men

than for women, with men accounting for 57.5% of the PD population in the UK. For men aged 50-89, prevalence is 1.5 times higher than for women in the same age-group (Parkinson's UK, 2017).

Disease severity across the PD population is also varied. Studies involving large cohorts of patients have found similar distributions of disease stage (Goetz et al., 2004). In these studies, Hoehn & Yahr Stages 1 (unilateral involvement only) and 5 (wheelchair bound or bedridden unless aided) were found to account for the smallest number of participants, followed by Stage 4 (severe disability; still able to walk or stand unassisted). The majority of participants (52%-77%) were in Stages 2 (bilateral involvement without impairment of balance) and 3 (mild to moderate bilateral disease; some postural instability; physically independent) (Goetz et al., 2004).

The clinical presentation of PD is also varied. As mentioned previously, research from two early PD cohorts (Tracking Parkinson's (n=1601 patients) and Discovery (n=944 patients)) has identified four subgroups, or 'clusters' of PD symptoms that are associated with levodopa response and rates of motor progression (Lawton et al., 2018). These include (1) fast motor progression with symmetrical motor disease, poor olfaction, cognition and postural hypotension; (2) mild motor and non-motor disease with intermediate motor progression; (3) severe motor disease, poor psychological well-being and poor sleep with intermediate progression and (4) slow motor progression with tremor dominant unilateral disease.

These data highlight the complexity of clinical presentation that is apparent in PD, and suggests our end users will likely have a wide range of motor and non-motor symptoms that may affect their interactions with the app. For instance, PwP in the severe motor disease cluster (cluster 3) may experience impaired dexterity and slowness of movement (which for example might limit ability to double-tap), while PwP in the tremor dominant cluster (cluster 4) may have difficulty tapping where desired, or in maintaining uniform pressure on the screen (e.g. to produce a swipe). Furthermore, there is a high level of cognitive impairment in PD (Aarsland et al., 2009) which may impact on users' ability to interact with the app. PwP with poor cognition (cluster 1) may experience impairment in attention and concentration over sustained periods of time (Muzerengi et al., 2007) which could make it difficult for users to successfully complete required tasks.

Care Partners

The majority of care to PwP is provided by informal care partners, often spouses or partners of the PwP (Alonso, Clínico, Carlos, & Catalan, 2014). Although typically aged over 65 years (Mclaughlin, Kernohan, Waldron, & Mclaughlin, 2010), it is important to consider there will be some carers using the app who are well below this age, reflective of the wide age range of PwP, or of care provided by a younger generation (Parkinson's UK, 2017). There will also be differences related to the independence of PwP, where their care partner may not be so intimately involved in providing their care needs; compared with more disabled PwP whereby their care partner will have much greater knowledge of their symptoms.

Carer burden is prevalent in PD, and has been found to increase with increasing disease severity (Schrag et al., 2006). Care partners using the app are likely to have varying levels of carer burden, including depression and stress, as well as impairments in physical health and quality of life (Schrag et al., 2006). As the majority of carers are older adults, some may experience limitations associated with normal ageing including visual and hearing impairments (Lorenz & Oppermann, 2008) as well as cognitive limitations (Roberts et al., 2012). In addition, some care partners may have their own long term health condition that could affect their interactions with the app.

Furthermore, levels of digital literacy amongst PwP and care partners are expected to be variable, due to a reported age-based 'digital divide' (Fox & Connolly, 2018), whereby adoption of technologies is lower amongst older adults than younger populations. As mentioned previously, older adults are less likely than younger age groups to own a smartphone (Ofcom, 2015), and younger smartphone users are likely to have downloaded a greater number of apps than older users (Ofcom, 2015). It is therefore expected that both care partners and PwP will have varying degrees of experience with apps and digital literacy in general, largely dependent on age (Choi & Dinitto, 2013).

Identified Environments

As the app will be available on a smartphone (and therefore portable), it is expected that the primary environment for use will be in patients' homes, particularly as this is the environment where older people spend the majority of their time (Gao & Koronios, 2010). The app may

also be used in a clinic environment with the PDNS as a point of reference when discussing NMS. Some features of the app will require an internet connection. While the patient is able to use other features in the app offline, online features will not be available until an internet connection has been made. The National Office of Statistics reports that in 2018, 90% of homes in the UK had access to the internet ("Office for National Statistics," 2018). While this figure is lower for households with one adult aged 65 years and over (59%), these households had the largest growth in internet access since 2012 (23 percentage points). If the patient does not have internet access at home, this may mean the app is used in other environments (e.g. libraries, cafés or family or friends' houses) in order to access an internet connection.

In line with my first hypothesis, the literature review revealed a wide range of end user characteristics including a breadth of demographic variables, disease presentation and levels of digital literacy. We therefore had some understanding of the characteristics of our expected end users (PwP and care partners), as well as the environments in which we expect the app to be used in.

To survey patient experience of NMS, I developed a patient questionnaire in collaboration with the NMS Project Group.

As this was a survey of patient experience of NMS, ethical approval was not required.

3.2.4 Questionnaire Items

The questionnaire items (n=15) focussed on 4 key areas: NMS burden (6 items), frequency of PD clinical appointments (3 items), self-help behaviours (3 items), and interactions with technologies (4 items). Demographic data was also collected including date of birth, gender and date of diagnosis.

Prior to starting the questionnaire, responders were provided with a brief explanation as to what NMS were, and what kind of symptoms were included within the term.

See appendix 8 (section 8.8) for a copy of the questionnaire in full.

Once the items had been developed, the wording and formatting of the questionnaire were reviewed by patient representatives within the project group to ensure it was understandable. Any necessary changes were made.

3.2.5 Questionnaire dissemination

Once finalised, the questionnaire was made suitable for a web platform, accessible via a link, using the program 'Jisc Online Surveys' which met University standards for General Data Protection Regulation (GDPR) compliance. The questionnaire was then disseminated via the Cure Parkinson's Trust (CPT) monthly newsletter and the link was posted to a local PUK support group forum. All responses were anonymous. In addition, to ensure responses were also collected from people who did not have access to a computer, printed copies of the questionnaire were disseminated at a local PUK Support Group in Cornwall. Responses were collected over a period of 6 weeks.

3.2.6 Questionnaire findings

One hundred and three responders completed the survey. All included responders were from the UK. Fifty-two were male (51%) and 47 were female (47%). Four responders (4%) did not give details of their gender. Responders had a median age of 62 years (39-85 years), and a median disease duration of 5 years (1 month-25 years).

The majority of the questionnaires included as part of the main analysis (n=83, 81%) were completed online via the CPT website, and 20 of the questionnaires (19%) were completed using the paper version and sent via post.

3.2.6.1 Non-motor symptom burden

Eighty-six percent of responders reported finding their non-motor symptoms moderately to extremely troublesome.

3.2.6.2 Length between appointments

Table 17 summarises the reported intervals between appointments with a Parkinson's Nurse and the reported intervals between appointments with a Parkinson's Doctor.

19 UK responders (18%) reported not having a Parkinson's Nurse.

Overall, 86% (n=88) of responders reported an interval of 6 to 12 months between appointments with *either* a Parkinson's Nurse or Doctor.

Table 17 The interval between appointments with respondents' Parkinson's Dr and Parkinson's Nurse

	Parkinson's Dr	Parkinson's Nurse
<6 months	19 (18%)	18 (18%)
6-12 months	53 (52%)	38 (37%)
12-18 months	21 (20%)	10 (10%)
>18 months	9 (9%)	17 (17%)

3.2.6.3 Frequency of GP visits related to PD

Forty-two percent of responders reported never seeing their GP about their PD. Of the remaining responders, responses ranged from seeing their GP about their PD more than twice every six months, to once every 18 months. Responses are summarised in Table 18.

Table 18 The frequency responders reported seeing their GP about their PD

	Frequency of repsonse (%)
More than twice in 6 months	13 (13%)
Once every 6 months	19 (18%)
Once a year	12 (12%)
Once every 18 months	15 (15%)
Never	43 (42%)

3.2.6.4 Frequency with which NMS are discussed in clinic:

Figure 23 summarises the frequency with which responders discussed their NMS in clinic with their GP, their Parkinson's Dr or their Nurse. Just under half of responders reported discussing their NMS symptoms with their Parkinson's Dr (49%) or Parkinson's Nurse (45%) at almost all clinic appointments.

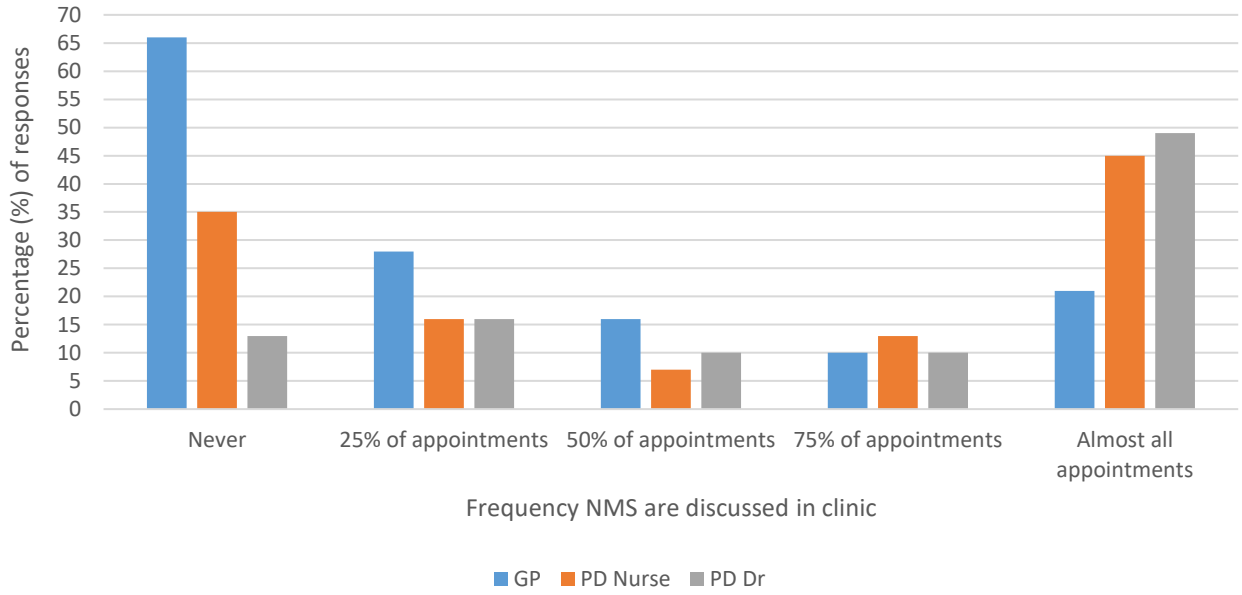


Figure 23 The frequency with which NMS are discussed in clinic with patients' GP, Parkinson's Nurse or Parkinson's Dr

3.2.6.5 Seeking help from healthcare professionals for NMS symptoms:

Half (50%) of responders (n=51) reported seeking help from healthcare professionals about their NMS infrequently or very infrequently. Of the remaining responders, 30% reported seeking help occasionally and 20% frequently or very frequently.

The majority of responders reported seeking help from their Parkinson's Nurse (55%), followed by their GP (40%), their Parkinson's Dr (38%) and 'other' (25%) (no details given). Responders were able to select more than one response for this question.

3.2.6.6 Other self-help behaviour:

The majority of responders reported seeking self-help advice occasionally (40%). Thirty percent of responders reported seeking self-help advice infrequently or very infrequently, and 27% reported seeking self-help advice frequently or very frequently.

Figure 24 summarises the information sources responders reported using to seek self-help advice for their NMS. Responders were able to select more than one response. Websites were the most frequently used format (78%) and included Cure Parkinson's Trust, PUK, Health Unlocked website, Facebook forums and Michael J Fox. Online videos included YouTube, and Michael J Fox webinars. Support groups included PD warrior and local PD drop-in groups.

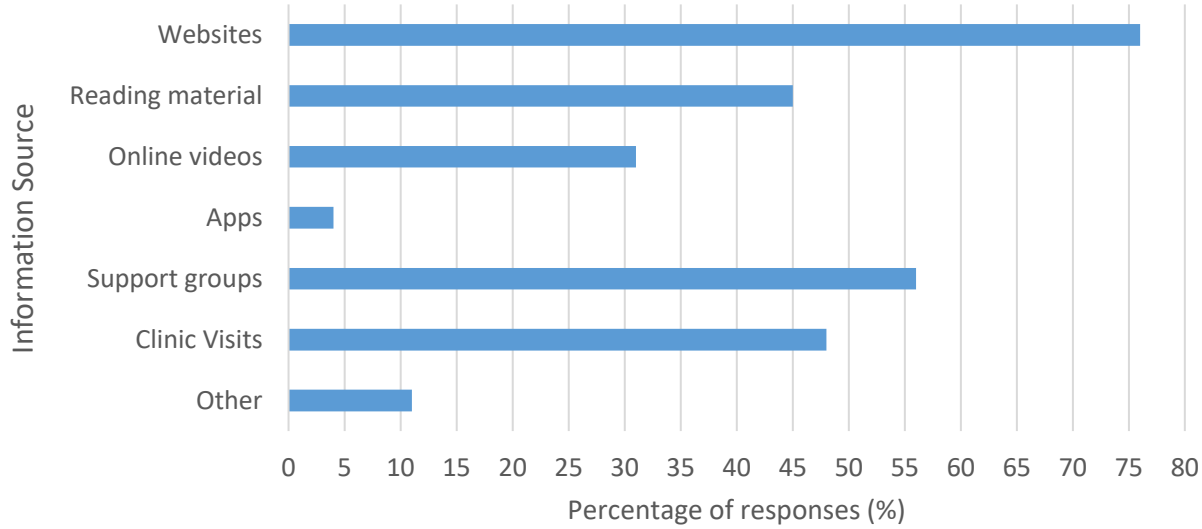


Figure 24 Information sources used by responders to seek self-help advice on non-motor symptoms

3.2.6.7 Preferred format for self-help info:

The majority of responders reported they would prefer to receive self-help information via a video of an expert giving advice (36%) in person (31%) or in a text format (23%).

3.2.6.8 Current Parkinson's disease app use:

Ten percent of responders reported they currently used an app associated with their PD, these included a voice volume app, a mindfulness app, a mobility, speech and dexterity app ('Beats Medical'), and a symptom tracker ('Parkinson's LifeKit').

Seventy-eight percent of responders reported they would consider using an app in the future to gain self-help advice on how to manage their NMS.

3.2.6.9 Access to devices:

Six percent of responders reported not having access to any electronic devices. The remaining responders reported having access to a smartphone (71%) a tablet or iPad (71%) or computer (69%).

3.2.6.10 Environments of use:

The majority of responders reported using these devices in the home environment (92%), in public (35%) and some reported using these in clinic (2%).

3.2.7 Discussion of findings:

I carried out a patient questionnaire to survey patient experience of NMS. Key findings will be discussed below.

3.2.7.1 NMS Burden and current care provision:

The survey revealed a high level of NMS burden amongst responders, with 86% reporting they found their NMS moderately to extremely troublesome. This is also in line with previous research on NMS in PD whereby NMS burden has been found to be high. For example an international study on the prevalence of non-motor symptoms in 545 PwP found on average, and irrespective of cultural background, patients reported experiencing 9-12 different NMS, across all stages of disease (Martinez-Martin et al., 2007). In addition, in an assessment of 265 PwP, a number of NMS including mood, drooling, sleep, pain, as well as bowel and urinary

problems, were ranked as part of patients' top 10 most bothersome PD related symptoms (Politis et al., 2010).

The majority of responders reported waiting between 6-12 months between appointments with either their Parkinson's Nurse or Doctor. Although the average interval observed between appointments is therefore broadly in line with NICE guidelines (NICE, 2017), there may be unmet clinical need in those who reported waiting more than 12 months between consultant and nurse appointments.

In addition, 18% of responders (n=19) reported not having a Parkinson's Nurse, which highlights a lack of important service provision of care for these patients.

The frequency with which NMS are discussed in clinic was greater than expected, with around 45% of responders reporting they discussed their NMS at almost all clinic appointments with their Parkinson's Nurse or Doctor.

This was surprising as previous research has demonstrated lower levels of self-declaration of NMS, although this was dependent on the type of NMS being discussed (Chaudhuri et al., 2010). For instance in an international study of 242 patients, 31.8% of patients reported not declaring diplopia whereas 65.2% reported not declaring delusions. These previous findings suggest certain NMS may have more embarrassment or stigma associated with them than others, or patients may not realise these symptoms are related to their PD (Chaudhuri et al., 2010). Our findings may therefore have been different if we had asked responders about the frequency they discuss specific NMS in clinic (e.g. delusions).

Another potential explanation for our finding may be explained by the attributes of the patient cohort, as patients were recruited to the survey via the Cure Parkinson's Trust mailing list and local PUK support groups. The survey responders may therefore represent a generally more informed patient cohort than other PwP who do not attend or belong to these groups. Our survey responders may therefore already be more aware of the importance of NMS in PD.

Discussion of NMS symptoms with the GP was significantly less however, with 66% of responders reporting they never discussed NMS symptoms with their GP.

Nevertheless, as the majority of patients reported waiting longer than 6 months between appointments, the opportunity to discuss NMS is limited. Furthermore, half of responders (50%) reported actively seeking out help from professionals for their NMS infrequently or very infrequently which may not be enough to meet levels of need, particularly as NMS burden was previously described as moderately to extremely burdensome for the majority of responders. These findings highlight patients have limited opportunity to discuss their NMS, despite experiencing a high NMS burden.

3.2.7.2 Self-help behaviours:

The frequency with which responders reported seeking self-help advice for their NMS was fairly mixed, with the majority of the responders (40%) reporting they did so occasionally. While it is encouraging that patients are already somewhat motivated to engage with self-

help platforms, it would be of interest to explore methods to encourage this, to ensure sustained engagement with self-help tools.

Most of the responders reported using websites to gain self-help information (78%), with well-known PD websites such as PUK and Cure Parkinson's Trust mentioned frequently, in addition to Facebook Forums. This finding suggests the majority of the cohort have access to the internet, and are comfortable using technology to find out information on their NMS. A minority of the cohort (10%) reported using an app that was associated with their PD. These apps ranged from apps for speech, symptom diaries and mindfulness apps. Seventy-eight percent of the responders reported they would use an app in future however, which is encouraging and demonstrates potential feasibility of the app.

The majority of responders (94%) reported having access to smart devices including a smartphone (71%), a tablet or iPad (71%) and a computer (69%) which demonstrates that the app would be accessible to the majority of patients on a range of platforms. It is important to consider however that the majority of survey responses were completed online (81%) and so the high proportion of responders with access to smart devices observed in our sample may not be representative of the general PD population.

The majority of participants reported using these devices in the home environment (92%) while fewer reported using their smart devices in public (35%). This is important when considering the functionality and task demands of the app, for instance users would need an

internet connection to sync their data with the nurse portal, and would require a quiet environment to fill out the symptoms assessments or view the self-help materials.

3.2.7.3 Self-help format:

The most popular formats for preferred self-help information to be received in was a video of an expert giving advice (36%), in person (31%), or in a text format (23%). We will incorporate these preferences in the development of the NMS self-help materials, by providing both text and video versions of the self-help information.

3.2.8 Discussion: Part One

In Part One, I carried out a literature review and patient questionnaire to identify potential app users and their environments, and to survey patient experience of NMS.

I hypothesised there will be a wide range of potential end users identified from the literature, including those with a breadth of demographic variables, disease presentation, NMS burden and prior experience with digital devices.

The results of the literature review carried out in Part One provided support for my hypothesis, revealing a wide range of potential end users, including people with varying levels of digital literacy. Considerations will need to be taken into account when designing the wireframe and self-help materials, to account for the limited dexterity, vision, hearing and cognitive ability that PwP may experience, as well as their carers, who may be of an older age. The results of Part One further confirmed that the app will be mainly accessed in a home environment, although it may be used in public spaces by some users.

Furthermore, the patient questionnaire demonstrated that although the majority of patients experience a high level of NMS burden, 76% of patients are not able to obtain appointments with their PD Nurse or Doctor within 6 months, and 14% patients are not able to obtain appointments within the NICE recommended guidelines of between 6-12 months. We have therefore identified an unmet need that the app may help to address, by offering self-help resources and monitoring of NMS in-between clinic appointments. The evaluation further indicated that the majority of PwP surveyed have access to a digital device, and would be willing to use an NMS app to help monitor their symptoms, which demonstrates feasibility of our app.

3.3 Part Two: Iterative design process

3.3.1 Part Two Aims:

- To design and develop an app wireframe suitable for end users, which prioritises patient safety
- To design and develop suitable and informative self-help content which is delivered in an accessible and engaging format

Part Two will be divided into two subsections:

- Part Two (A) will describe the wireframe development process
- Part Two (B) will describe the self-help materials development process

3.3.2 Part Two (A) Wireframe development process

3.3.2.1 Selection process for the app design and build:

Firstly, a tender process was carried out to select the design and build companies responsible for developing NMS Assist. The three tenders received were reviewed by the IT procurement team at the University of Plymouth, and the leading tender selected. The tender for the wireframe design was awarded to a local app design company (Made with Maturity), and the tender for the app build was awarded to a separate local company (Suvo).

3.3.2.2 Design of the wireframe:

The wireframe was based on an initial design created by CN (see appendix 10 (section 8.10)), following a series of 3 design meetings with CC, JW and SW, during which the user journeys through the app were conceptualised.

The initial wireframe design was then revised in an iterative process led by myself, involving the whole project group (09/18 to 12/18), in association with Made with Maturity, leading to the creation of an initial prototype. The prototype was also iteratively redesigned, with a final prototype being taken forward for the first stage of formative usability testing. Iterations to the design of the wireframe and prototype were based around core app functions.

3.3.2.3 Core Functions:

As a result of the group discussions (see section 3.3.2.2), six core functions of the app were identified including:

1. First time log in
2. Carrying out a full NMS assessment
3. Carrying out a partial NMS assessment
4. Viewing symptom summary
5. Accessing self-help information
6. Requesting contact from the healthcare team

Each of the core functions is described in more detail below (see section 3.3.2.3).

3.3.2.4 Identified issues:

In line with MHRA guidance, potential issues were identified throughout the development of the wireframe and recorded (see Table 19). Issues were grouped into three main areas: those related to user characteristics, those related to content and those related to layout. Solutions to these issues are also detailed in Table 19 (see 'solution' column). These solutions informed key design features the app which are described in relation to each of the core functions described below (see 'relevant core function' column in Table 19).

Table 19 Issues identified and relevant decisions made throughout app development

Issue group	Issue identified	Solution	Relevant core function
Content	Users would not understand the purpose of the app	Include a strapline that clearly describes the purpose of the app	See core function 1
	Users would not understand how to use the app	Include instructions for use that appear during first time log in and accessible at any time	See core function 1
	Users may not give consent for their data to be used	Include a consent page outlining how app data will be used	See core function 1
	Users would need to be reminded to complete regular full symptoms assessments	Send notifications to users to remind them when a next assessment is due	See core function 2
	Users would need to be reminded to complete regular full symptoms assessments	Display the date of upcoming assessment on the home screen	See core function 2

Issue group	Issue identified	Solution	Relevant core function
Content	Users may not want notifications on their device.	Provide users with an option to 'allow' or 'not allow' notifications on first time login	See core function 1
		Allow users to amend notifications in settings	See core function 1
	Users would need to have an option to contact their healthcare team if running into trouble.	Add a 'request contact' button to the main home screen	See core function 6
	Users would need to receive acknowledgement their contact request had been received, and when they will hear back.	Include a 'contact request received' message with relevant details	See core function 6

Issue group	Issue identified	Solution	Relevant core function
Content	The healthcare team will need to distinguish between a care partner assessment and a patient assessment	Include a page that asks the user to identify as either the care partner or the patient	See core function 2
	We wanted to include a QoL measure	Include the PDQ8 as part of the full assessment – PDQ39 too burdensome.	See core function 2
	PDQ8 needs to comply with Oxford University Innovation guidelines	Add a back button and a menu button to all PDQ8 screens	See core function 2
	Users may not understand the purpose of PDQ8	Include a page prior to the PDQ8 that explains the purpose and instructions	See core function 2
	Users will want to know how many questions they have left to answer	Include a progress bar that shows how many questions are left to complete	See core function 2

Issue group	Issue identified	Solution	Relevant core function
Content	We wanted participants to complete a comprehensive assessment of non-motor symptoms	Use the NMSQ	See core function 2
	Users may not understand the purpose of NMSQ	Include a page prior to the NMSQ that explains the purpose and instructions	See core function 2
	ICD not addressed by NMSQ	Add a Q31 that evaluates ICD	See core function 2
	We needed to assess symptom severity	Include a question that asks how much the symptom is troubling the patient	See core function 2
	We wanted to include an opportunity for interim assessment to evaluate response to medication/ other intervention	Include option for partial assessment	See core function 3
	Users may not realise when they have selected a response	Response is highlighted blue if selected	See core function 3

Issue group	Issue identified	Solution	Relevant core function
Content	Users need to be alerted towards worsening symptoms	Include symptom summary	See core function 4
	Users need to be directed towards self-help info for worsening symptoms	Provide a link to self-help information for each symptom in the summary	See core function 4
	Users might not be attracted to app	Use an attractive and consistent colour scheme throughout	See core function 5
	Users may want to logout	Provide a dropdown menu with logout option	See core function 6
User Characteristics	Users may not be able to read text clearly	Provide an option to increase font size	See core function 6
	Users may not be able to hear the voiceover	Provide a text alternative for each of the self-help videos Provide option to adjust volume	See core function 5

Issue group	Issue identified	Solution	Relevant core function
User Characteristics	Users may become fatigued/distracted	Allow for a pause and return function	See core function 2
	Users or their care teams may wish to determine if they are experiencing non-motor fluctuations	Include a question that ascertains if patient experiences fluctuations Include an on/off scale	See core function 2
	Users may struggle to press buttons accurately	Ensure buttons are big and widely spaced apart	See core function 2
Accessibility	Users may be unable to access features of the app without internet	Add an 'online/offline' symbol to the home screen to notify users of their connectivity	See core function 6
	Non-service users may download the app and not have service support	Service users are provided with a token by their healthcare team that is linked with their registration details.	See core function 1

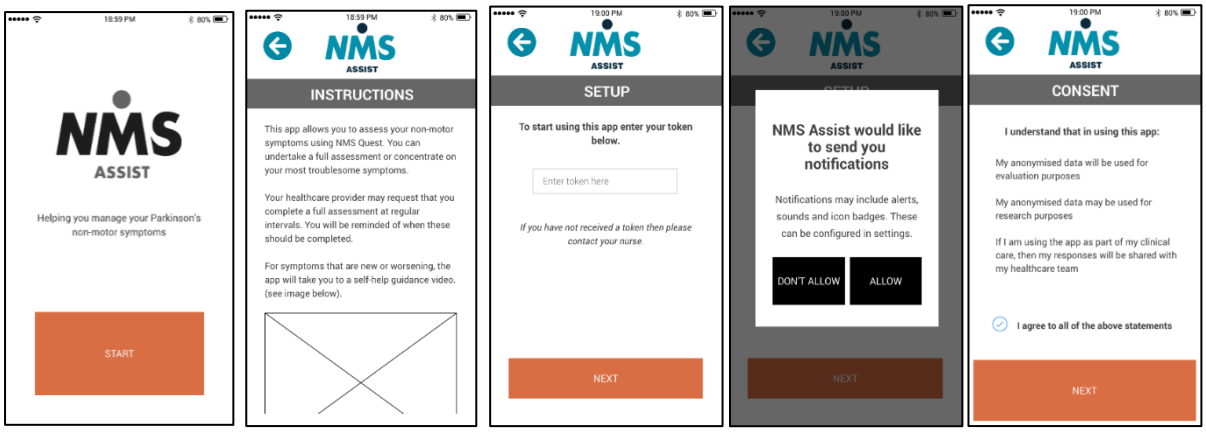
Issue group	Issue identified	Solution	Relevant core function
Layout	The display page for the partial assessment may look overwhelming/too cluttered	Group symptoms into relevant sub domains	See core function 3

3.3.2.5 Wireframe design and core functions:

Details of the core functions of the app are given in each section below.

3.3.2.5.1 Core function 1. First time log in

The first core function of the app was the first time log in. The user journey for Core function 1 is displayed in Figure 25 below (from left to right).



(A) (B) (C) (D) (E)

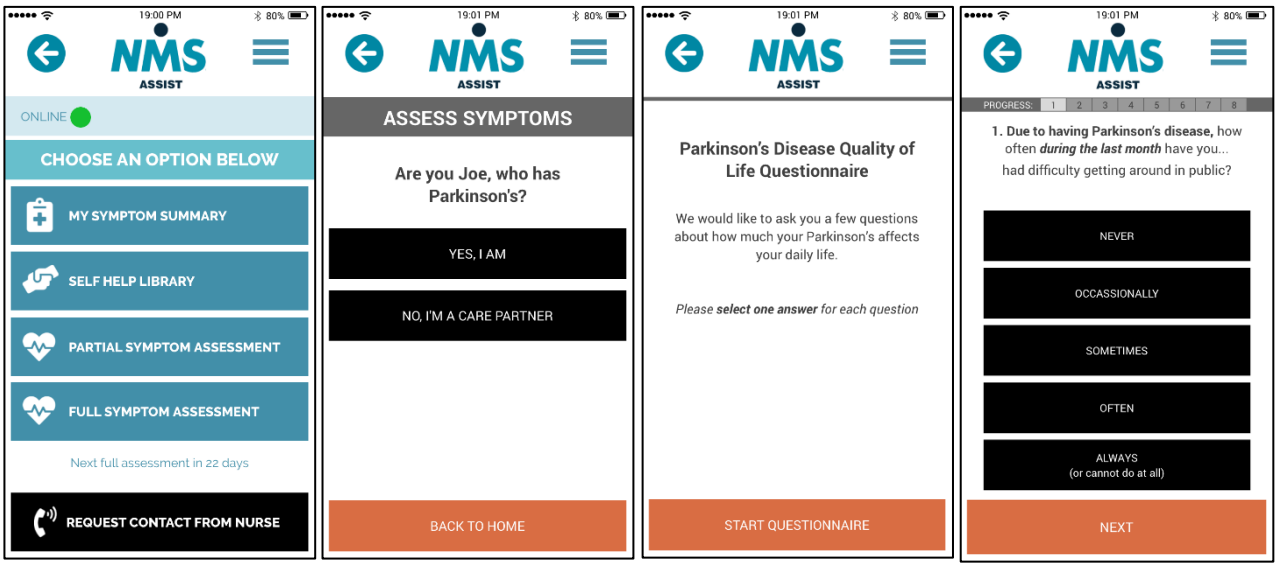
Figure 25 Screen shots of the user journey for Core function 1 (first time log in) from left to right (A-E)

To ensure that first time users would understand the purpose of the app prior to using it, a strapline was added to the first screen (see Figure 25, A). Additionally, an instructions page (see Figure 25, B) was added to ensure participants would understand the various functions associated with the app, and what would be expected of them as users (eg. to fill in regular assessments). To avoid non service users downloading the app without backend service support, a token system was introduced (see Figure 25, C), whereby users will be required to enter a token provided by their healthcare team. In line with MHRA guidelines (Mhra, 2017),

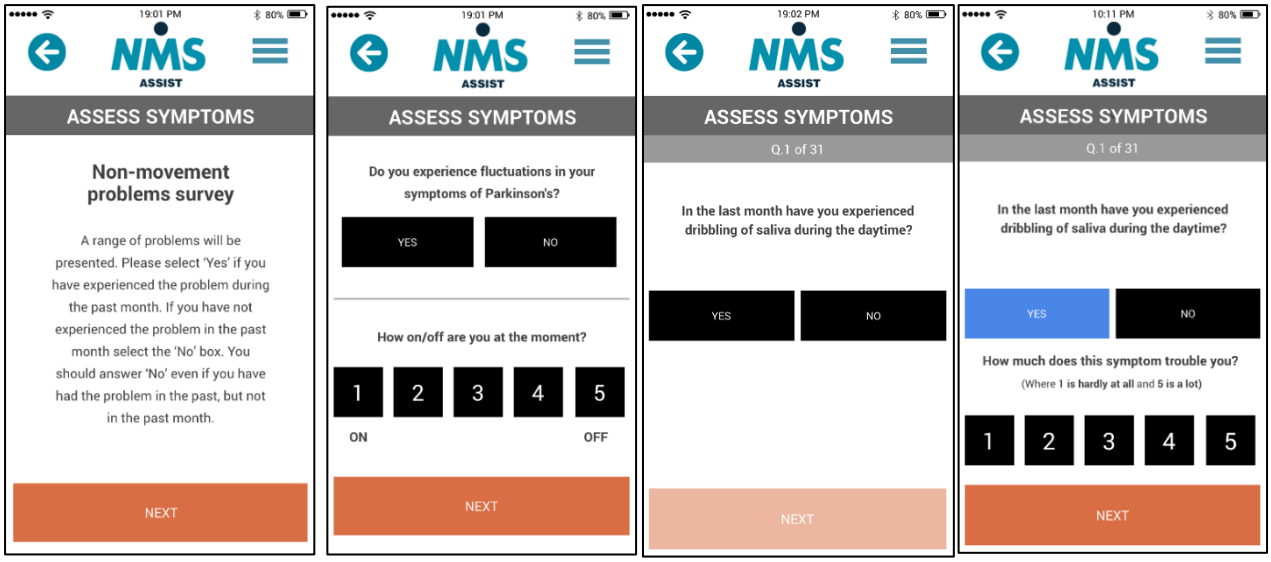
it is necessary to allow users to have the option to 'allow' or 'not allow' the app to send them notifications (e.g. assessment reminders), and so we included the notifications pop up (see Figure 25, D). The consent page (see Figure 25, E) was included to obtain consent from users to use their data for clinical, research and evaluation processes.

3.3.2.5.2 Core function 2. Completing a full NMS assessment

The second core function of the app was completing a full NMS assessment. The user journey for Core function 2 is displayed in Figure 26 below.



(A) **(B)** **(C)** **(D)**



(E) **(F)** **(G)** **(H)**

Figure 26 Screen shots of the user journey for Core function 2 (completing a full NMS assessment) from left to right (A-H)

To provide regular monitoring of NMS, it was agreed that the app would be based on the NMSQ (Chaudhuri et al., 2006). Users would be required to complete a full NMS assessment routinely at intervals determined by the Parkinson's Nurse (or other member of their healthcare team). Users would be provided with notifications to remind them to complete an assessment, in addition to a reminder displayed on the home screen (see Figure 26, A) (date of their next assessment). In addition, we wanted to include a question on Impulse Control Disorder (ICD), which is not currently included as part of the NMSQ. After discussion with its author (Ray Chaudhuri, Kings College London), a 31st question on ICD was added to the full NMS assessment, worded as follows; '*Had an increase in gambling, sexual, buying, or eating behaviours or routinely taken more anti-parkinsonian medications than prescribed*?'

To distinguish between users that were care partners, and users that were PwP, a screen was added asking users to identify themselves (see Figure 26, B).

In order to include a measure of patient QoL, the PDQ8 was included as part of the full NMS assessment, in accordance with licencing stipulations from Oxford University (PDQ8 creators) (Patient Reported Outcomes-From Paper to ePROs, 2016) (see Figure 26, C). The shortened version of the PDQ39 measure was chosen to avoid over-burdening users, and is recommended over the PDQ-39 where a shorter form measure is required (Jenkinson, Fitzpatrick, Peto, Greenhall, & Hyman, 1997). Instructions were included prior to completing the PDQ8, so that users understood the purpose of the questionnaire, and how to complete it.

Due to dexterity limitations and other motor impairments that are prevalent in PD (Jankovic, 2007), it was ensured that response buttons had a large surface area, and were well spaced apart (see Figure 26, D). A progress bar was also included so that users could see how many questions they had left to answer. In order to comply with Oxford University Innovation guidelines, a menu button and back button were added to each screen, meaning users could leave the assessment at any time.

Due to limitations in attention that many PwP experience (Cosgrove et al., 2015) and to avoid user fatigue, a pause and return function was made available, whereby users would be able to pause their assessment and complete it at a later time (within 72 hours).

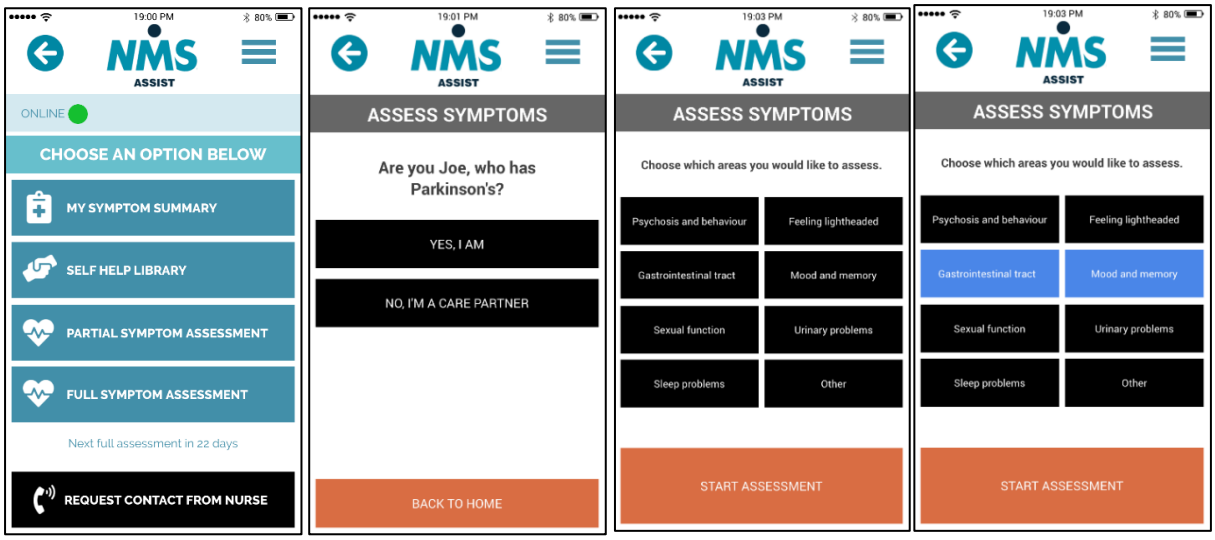
In order to assess the medication state users were in at the time of completion, users were asked to indicate the extent to which they were on/off, using a five point scale (see Figure 26, F).

To capture symptom severity, a second question automatically appeared after a user responded 'yes', asking them to rate how troublesome the symptom was for them. The wording and scale response for this question was decided in collaboration with end users (see Figure 26, G). Patient representatives were asked whether they would prefer a numerical scale, or a visual scale, whereby symptom severity was indicated by pictures of faces displaying a range of emotions from happy to sad (see appendix 11 (see section 8.11)). The majority of patient representatives reported they preferred the numerical scale, and so this was incorporated as part of the app design.

Selected responses were highlighted blue to ensure users would recognise when they had selected an option.

3.3.2.5.3 Core function 3. Completing a partial NMS assessment

The third core function of the app was completing a partial NMS assessment. The user journey for Core function 3 is displayed in Figure 27 below.



(A) **(B)** **(C)** **(D)**

Figure 27 Screen shots of the user journey for Core function 3 (completing a partial NMS assessment) from left to right (A-D)

It was decided that an option for an interim assessment would be made available so that users could assess the effectiveness of a medication or treatment for a particular NMS without having to do a full assessment. Users would therefore be able to select which symptom areas they would like to assess from a number of options (see Figure 27, C). To avoid the page looking too cluttered or overwhelming, individual NMS symptoms were grouped into subdomains (see Figure 27, C).

3.3.2.5.4 Core function 4. Viewing the symptom summary

The fourth core function of the app was viewing the symptom summary. The user journey for Core function 4 is displayed in Figure 28 below.

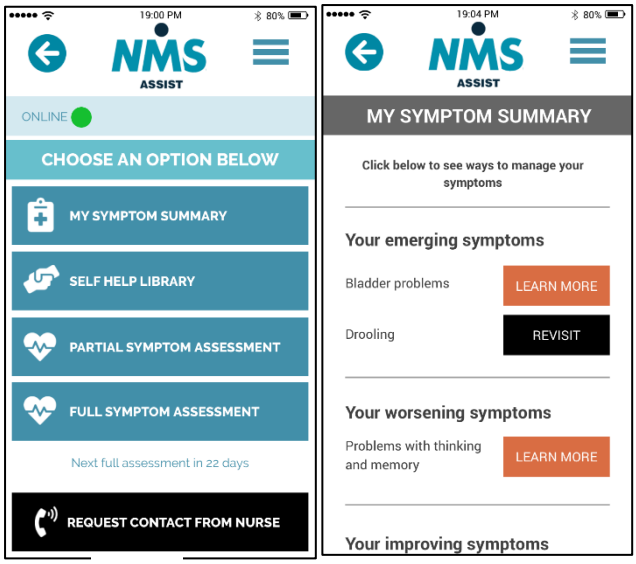
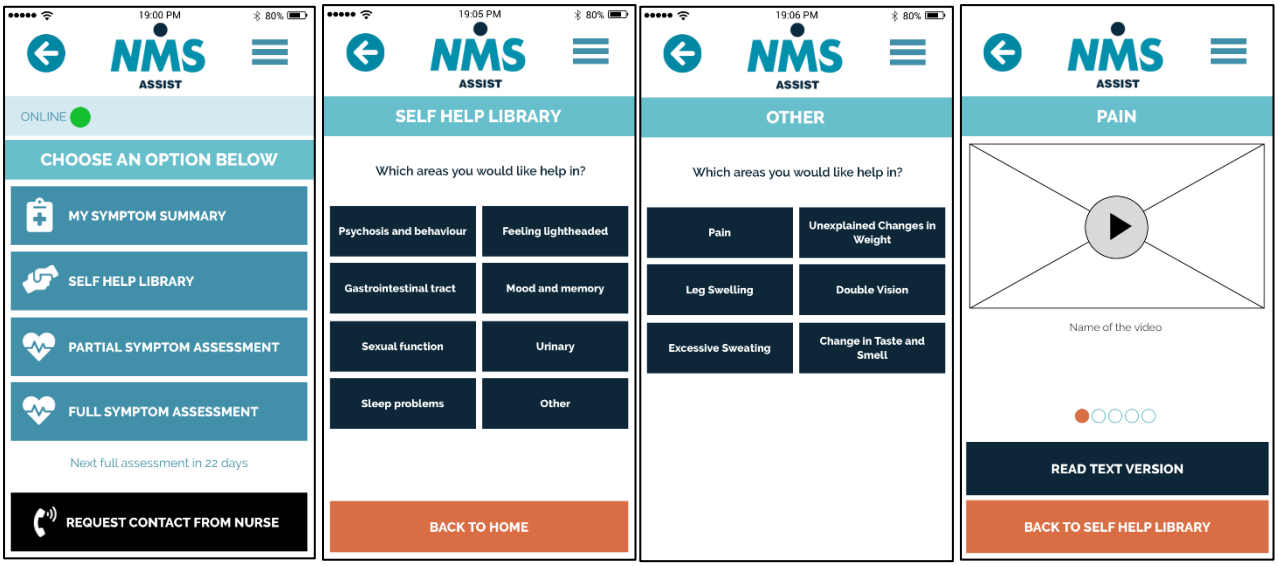


Figure 28 Screen shots of the user journey for Core function 4 (viewing the symptom summary) from left to right (A-B)

It was essential that users would be able to clearly review a summary of their symptoms, particularly those symptoms that were emerging or worsening since their last review. To meet this need, we developed a symptom summary that categorised symptoms as emerging/ worsening/ improving or symptoms that had been suggested by their care partner, based on patient and care partner app data (see Figure 28, B). An option to access self-help information for these symptoms was also provided on this page (see below) to help facilitate users to self-manage symptoms.

3.3.2.5.5 Core function 5. Accessing self-help information

The fifth core function of the app was accessing self-help information. The user journey for Core function 5 is displayed in Figure 29 below.



(A) **(B)** **(C)** **(D)**

Figure 29 Screen shots of the user journey for Core function 5 (Accessing self-help information) from left to right (A-D)

A full methodology for the development of the self-help materials is described in Part Two Section B.

Self-help information could be accessed via the self-help library. As in the partial assessment, to avoid the page looking too cluttered or overwhelming, the NMS symptoms were grouped into subdomains (see Figure 29, B).

In order to cater for users who may have impaired hearing or other impairments that may affect their ability to watch the video, facility was incorporated for users to be able to adjust

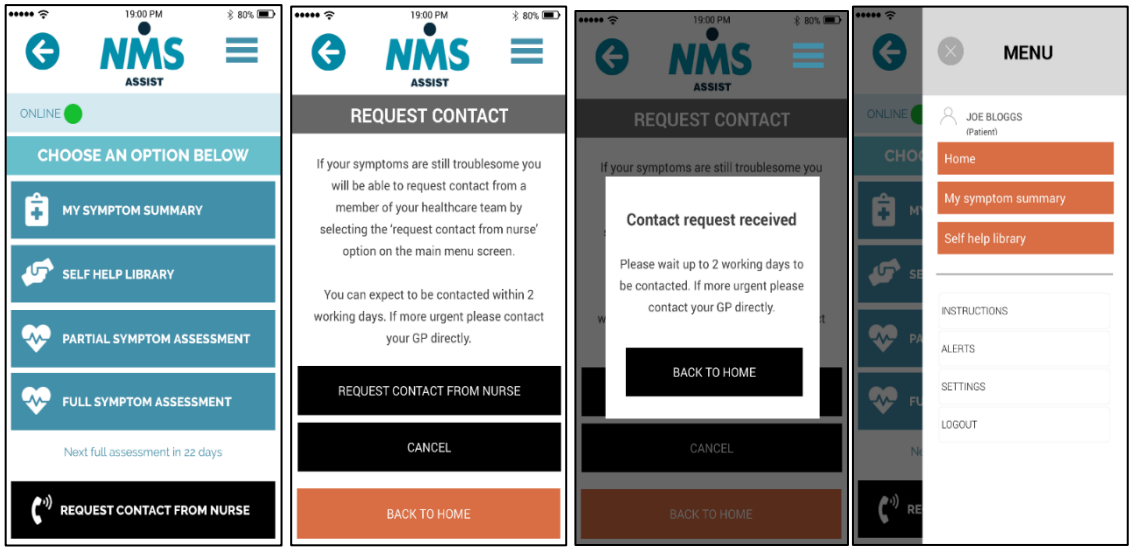
the self-help videos' volume, and a text version was also made available (see Figure 29, D). Users would be able to pause, stop and rewind the video as they desired.

To ensure users would be engaged with the app, a bright and aesthetically pleasing colour scheme was used throughout. Images (A),(B),(C) and (D) in Figure 29 above are displayed using the core colours of the app that will appear in the final version. The core colours had not yet been applied to all screens prior to usability testing.

Please see Part Two section B for more information on the development of the self-help materials.

3.3.2.5.6 Core function 6. Requesting contact from the healthcare team

The sixth core function of the app was requesting contact from the healthcare team. The user journey for Core function 6 is displayed in Figure 30 below.



(A) **(B)** **(C)** **(D)**

Figure 30 Screen shots of the user journey for Core function 6 (requesting contact) from left to right (A-D)

Patient safety is an absolute priority within digital solutions (Black et al., 2011). Different mechanisms by which patient safety could be achieved were discussed, and it was decided that a 'request contact' button (see Figure 30, A) would be most appropriate, whereby a patient could request contact from their healthcare team if they were to run into difficulty from a NMS perspective. Through discussion with EE, our PDNS representative, we developed a Standard Operating Procedure (SOP) for responding to a call request that would be achievable, acceptable for patients, and prevent duplication of current procedures. Users will be provided with a message to acknowledge receipt of their contact request (see Figure 30, C) and reminded they would be contacted within 2 working days.

To ensure users with visual impairments would be able to access the app, font size was made adjustable in the 'settings' section of the drop down menu, which could be accessed from all screens (see Figure 30, D).

An expert in PD visual perception problems (Dr. Rimona Weil, University College London) also reviewed the written text that appeared within the app and gave feedback in terms of appropriate font size, contrast and style of text that should be used.

The drop down menu also provided users with the option to quickly access other areas of the app, change alerts settings, and logout.

To ensure users would be aware of their internet connectivity status, an offline/online status symbol was added to the home screen.

3.3.2.5.7 Healthcare team portal:

It was decided that an online portal would facilitate monitoring of patients' NMS symptom burden. The Parkinson's Nurse would be able to log in and be notified of any contact requests that had been made by service users so that they could respond accordingly. It was a priority that the portal was simple to use, as ease of use has been previously identified by clinicians as barriers to using apps as part of their clinical care (Jebraeily, Fazlollahi, & Rahimi, 2017). To meet this need, it was ensured the Parkinson's Nurse would be able to rapidly evaluate patients' NMS scores via a coloured chart that would indicate if a patient is progressively worsening or improving between each routine assessment (see appendix 12 (section 8.12). The portal also includes a log of treatment decisions that have been made for each patient, with the option to add new entries.

A focus group was held in February 2019 with 3 healthcare professionals, including 2 PDNS and 1 clinical administrator, as well as project group members SM, IM and EE (PDNS) to discuss potential design changes to the portal. Formal usability testing is planned for July 2019.

3.4 Part Two (B): Development of the self-help materials

3.4.1 Aims

- To create accessible content that would support patients in self-managing their NMS.

3.4.2 Script development

The content of the script for the self-help videos was based on the publication 'A Guide to the Non-Motor Symptoms of Parkinson's Disease' (Postuma & Galatas, 2012) which maps onto the NMSQ (Chaudhuri et al., 2006). CC met with RC to reword the guide for a UK audience, and in line with current clinical practice. Following this, PPI members of the project group helped to reduce the script to 45 seconds in length for each non-motor symptom, whilst ensuring the content remained clear and understandable by end users.

The section of script for each NMS was consistent throughout, with subsections entitled; "What is it?";"Why is it important in PD?"; "What can I do?".

The script for the NMS symptom orthostatic hypotension is displayed in Figure 31. For the full symptom script, please see appendix 13 (section 8.13).

Feeling Lightheaded on Standing

What is it?

Feeling lightheaded on standing is due to a drop in blood pressure. Headache and shoulder or neck pain can also occur. If this is severe, you could black out and fall.

Why is this important in Parkinson's disease?

This blood pressure drop can be due to Parkinson's itself, and can be made worse by Parkinson's medications and possibly other blood pressure tablets.

What can I do?

If you have this problem avoid standing up quickly; try counting to 10 before you move off. Increasing salt intake can help. Drink at least 2 litres of water per day and avoid caffeinated drinks. Full length compression stockings may be helpful. Specialist treatments are available.

Figure 31 The symptom script for the NMS orthostatic hypotension.

3.4.3 Animation storyboard development

The results of our patient questionnaire (see section 3.2.6.10) revealed that the majority of responders would prefer delivery of self-help information via a video of an expert giving advice. It was therefore proposed that the self-help videos should be created in a 'talking heads' format, whereby PD 'experts' would be filmed reading aloud the script. However, in order to meet MHRA requirements and maximise accessibility of the app, it was decided the videos should be made available in multiple languages.

In order to achieve this, it was decided that the educational videos would be made in an animation format, rather than talking heads. This change would facilitate the recording of the voice-over in different languages, whilst ensuring the animations would stay the same (regardless of language). It was decided that text would appear onscreen summarising the key points from each video, which could easily be replaced by text in an alternative language. Similarly, text that appeared as subtitles could be changed as necessary.

I was responsible for coordinating the tendering process for the animations (see appendix 9 (section 8.9) for creative brief). Tender submissions were judged by the project group based on the animation style, representability of the characters, overall feel of the animation, and clarity of the information being provided.

Following review of the submissions, the tender for the animations was awarded to a local animation company, which was also the company that was awarded the design tender (Made with Maturity (MwM)). The script was received by the company, and storyboards were drafted for each of the non-motor symptoms. Figure 32 and Figure 33 display an example of one of the 29 storyboards that were reviewed during the animation development process. The draft storyboards were regularly reviewed by the project group in terms of accessibility for PD patients, representativeness, and style; comments were fed back to MwM for further iterations to be made (see feedback forms appendix 14 (section 8.14)). In total, there were 7 cycles of review, feedback and iteration to the storyboard design over a period of 4 months (from November 2018 to February 2019). Once the project group were satisfied with the storyboard designs, they were signed off by CC for development.

3.4.4 Voiceover selection process

The voiceover to read aloud the script was selected by group consensus following review of a number of audio samples available (https://www.voiceboxagency.co.uk). It was a priority that the voiceover was easy to understand, friendly and relatable.

Once the voiceover had been selected by the project group, end users (n=12) were shown a mock-up of the animation for the NMS constipation (see Figure 32 and Figure 33 for the constipation animation storyboard) with the accompanying voiceover recording.

Users were asked for their views on various aspects of the animation including the style of the voiceover, the clarity, and the voiceover speed. Two users reported they felt the speed of the voiceover was too quick, however the remaining users (n=10) felt the speed and tone of the voiceover were appropriate and easy to understand. User responses were sent as feedback to the voiceover artist.

Once the feedback had been received, the voiceovers were recorded by the selected voiceover artist using the finalised version of the script (see appendix 13 (section 8.13)). Members of the project group including PPI members and the PDNS listened to a selection of the voiceover recordings live, and gave real time feedback to the artist, who then incorporated the feedback into the subsequent recordings.

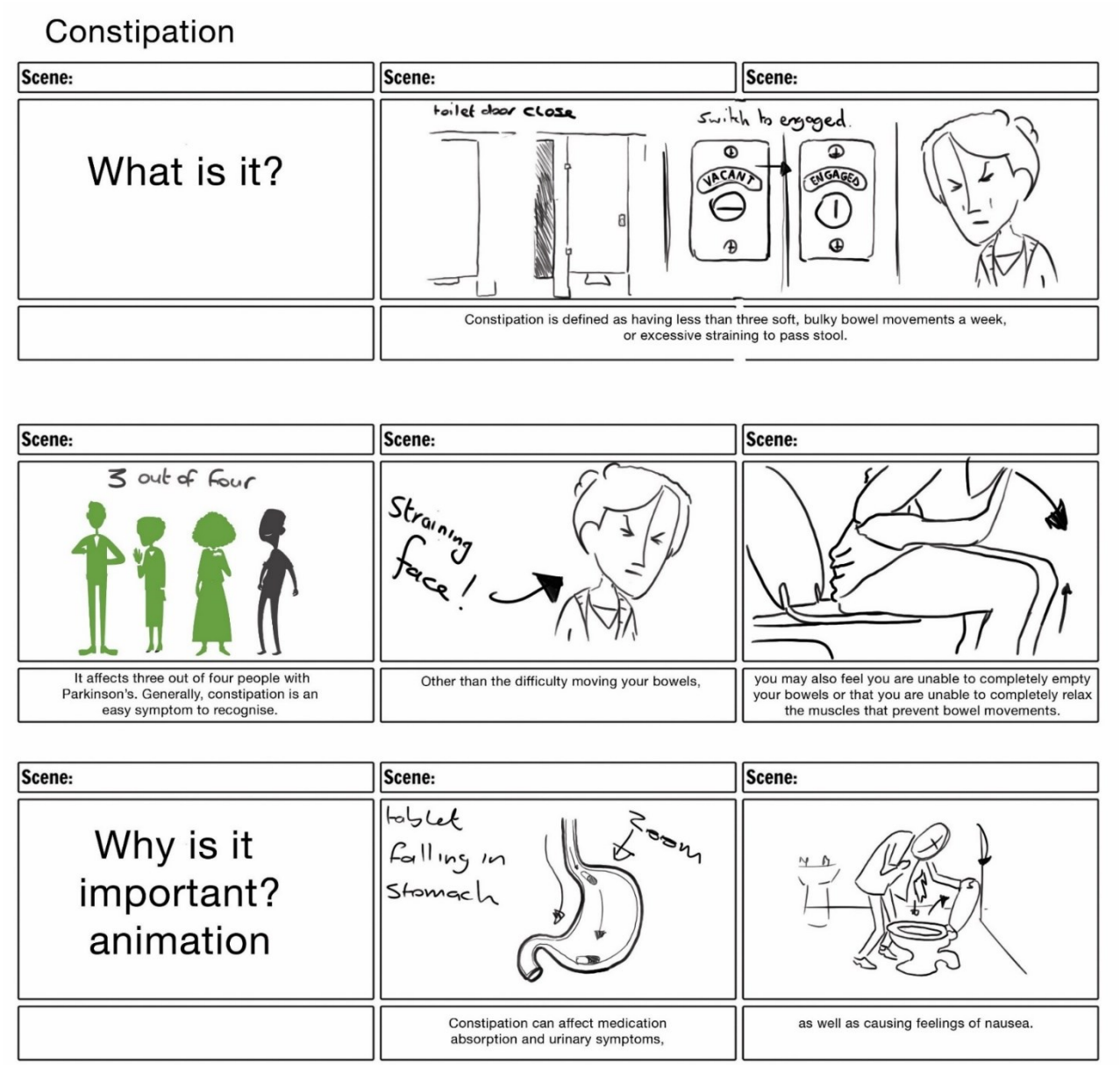


Figure 32 Storyboard for the constipation animation (part 1 of 2)

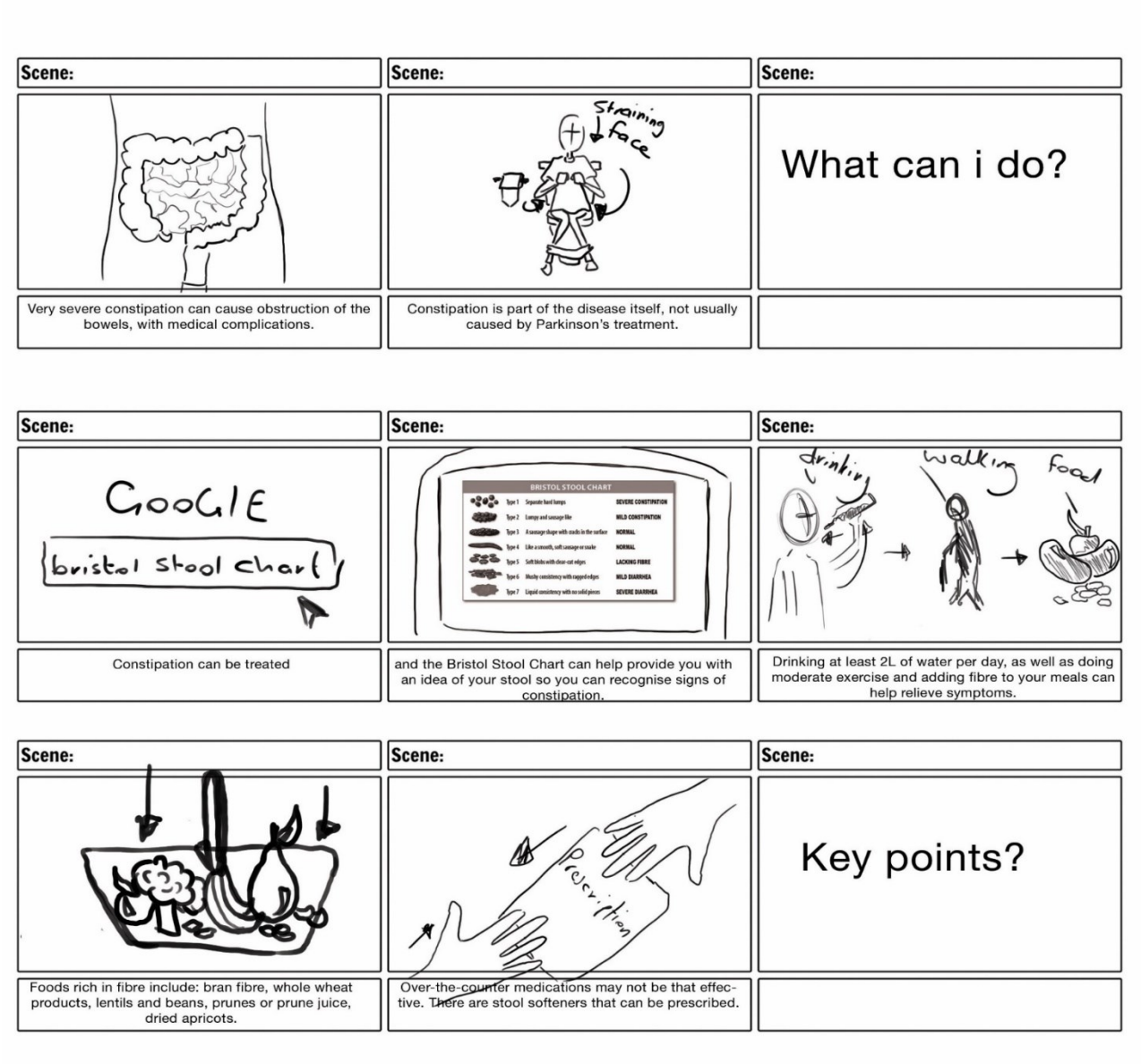


Figure 33 Storyboard for the constipation animation (part 2 of 2)

3.4.5 Discussion: Part Two

The results of Part Two led to the creation of the prototype wireframe for NMS Assist, and the self-help materials, with input from end users, and informed by issues identified throughout the development process.

A formative evaluation of the prototype wireframe was the essential next step to highlight key issues with the existing design and comply with MHRA guidance (Mhra, 2017).

3.5 Part Three: Formative Evaluation

3.5.1 Part Three Aims

- To ensure that the device was usable by the intended user, quantified by effectiveness (error free completion rate) and satisfaction measures (including the Single Ease Question (SEQ) (Sauro, 2016) and the System Usability Scale (SUS) (Brooke, 2013).
- To identify key areas of amendment for future design.

3.5.2 Part Three Hypotheses

I hypothesised:

1. There would be no statistically significant difference in measures of effectiveness or satisfaction between experienced and non-experienced smartphone users (due to the iterative, user centred design process applied in Part Two).
2. The think aloud method would reveal key areas of amendment for future design.

3.5.3 Methods

This study received approval from the Faculty Research Ethics Committee at the University of Plymouth (ethical approval granted (07/2018, see appendix 15 (section 8.15)).

3.5.3.1 Recruitment

Two user groups were recruited to the study; a group consisting of PwP (PD group, n=10) and a group consisting of people who cared for a person with PD, referred to as Care Partners (CP group, n=5). Usability testing guidelines for sample size were followed that recommend the use of 5-15 test participants for an iterative usability testing process (Nielsen & Landauer, 1993).

In order to ensure the final app would be usable by a broad range of users, it was important to recruit a sample that were representative of the demographic of the intended users. I therefore aimed to recruit participants with a range of ages, disease duration, cognitive ability, and varying experience with smartphones and smartphone-based apps.

Potential participants were identified via the local PUK Support Group Networks in Cornwall, Tavistock and Plymouth. A patient information sheet was provided to those who expressed an interest in taking part, which provided information on the study (see appendix 16 (section 8.16). All individuals were given at least 72 hours to consider the study information, prior to being contacted by telephone, when they had the opportunity to ask any outstanding questions. During this phone call, participants were screened for inclusion and exclusion criteria, and demographic information (including self-described experience with smartphone

apps) was collected. Attendance to the usability study was arranged. Participants were reimbursed for any travel costs.

3.5.3.2 Inclusion Criteria

- Aged ≥40 (to recruit a sample with a wide age range)
- Diagnosis of PD (PD group only) or Care Partner for a PwP (CP group only)
- Willing and able to give informed consent for participation in the study
- Willing and able to comply with study requirements

3.5.3.3 Exclusion Criteria

- Inability to comply with study protocol
- Any other significant disease or disorder that is known to affect motor function or cognition
- Use of alcohol, benzodiazepines, or other sedating drugs in the 12 hours prior to study visit
- Non-fluent English speaker

3.5.3.4 Usability testing environment:

Usability testing was performed at Plymouth Science Park (PSP), in a large meeting room. Figure 34 illustrates the experimental set-up for usability testing. Participants accessed the app using an iPhone 6s (IOS operating system) which was placed flat on the table. Usability

testing was carried out on a wireframe prototype of NMS Assist. Video recordings of participants' interactions with the app and audio recordings of participants' comments were recorded using Mr Tappy Software (www.mrtappy.com). The researcher was seated a reasonable distance away from the participant, and live video footage was displayed in real time on the researcher's laptop via ManyCam screen recording software (https://manycam.com/), allowing the researcher to record observations about the participant's interaction with the app in real time.

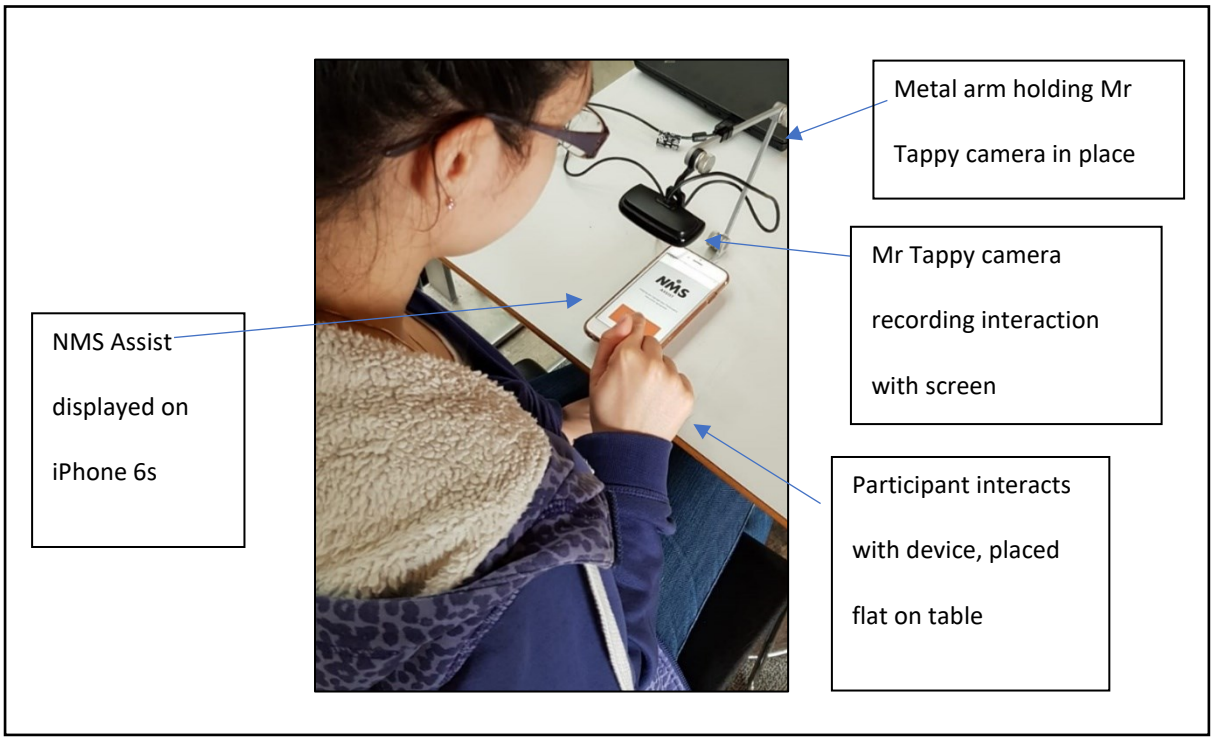


Figure 34 An example of the experimental set up for the usability testing procedure

3.5.3.5 Usability test procedure

On arrival to PSP, participants were given a copy of the information sheet and there was an opportunity for participants to ask any outstanding questions. Informed consent was then obtained via signing of the consent form (see appendix 17 (section 8.17)). After written consent had been obtained, participants were asked to complete the following assessments:

3.5.3.6 Cognitive ability

- Montreal Cognitive Assessment (MoCA) (Nasreddine et al., 2005)

  The MoCA is a brief screening tool that takes 10 minutes to administer. The MoCA is scored out of 30, with a cut off of <26 indicating mild cognitive impairment. The MoCA is made up of questions from different themes including; visuospatial/executive function, naming, memory, attention, language, abstraction, delayed recall and orientation.

3.5.3.7 Non-motor symptom burden (PD group only)

- Non Motor Symptoms Questionnaire (NMS Quest) (Chaudhuri et al., 2006) (see section 1.2.21.2.7 for description).

3.5.3.8 Disease Severity (PD group only)

- Hoehn & Yahr Scale (Hoehn & Yahr, 1967). The Hoehn and Yahr Scale describes five stages of PD progression, and is completed by an experienced rater.

Completion of the above assessments took around 30 minutes. Following this, each participant was provided with a scripted verbal introduction to the usability study by the

researcher. Participants were reminded several times that there were no right or wrong answers. Participants were given the opportunity to ask any questions. There were no scheduled breaks, however participants were reminded they were able to request a break at any time. Medication state (ON/OFF) for PwP was not recorded.

3.5.3.9 User Tasks

Prior to usability testing, a discussion guide was created (see appendix 18 (section 8.18)) with input from RD, an experienced usability testing researcher. The guide included verbal instructions for each of the usability testing tasks to be read aloud by the researcher, as well as space for the researcher to make notes in real time while the participant completed the relevant tasks.

Following a short warm up (see think aloud method below) participants were given verbal instructions for 1 of 6 tasks to carry out (see Table 20 below). A paper version of the task instructions was placed in front of the participant as a reminder throughout the task. The selected tasks were developed with input from the NMS App project group and were representative of the core functions of the app (as described in Part Two, see section 3.3.2.3), thus providing good coverage of real-world use. Tasks are described in Table 20 below.

Table 20 Task descriptions and verbal instructions given to participants

Task Number	Task Description	Verbal instruction
Task One	Requesting contact from the nurse	"Please show me how you would request contact from the nurse"
Task Two	Carrying out a full NMS assessment	"Please show me how you would carry out a full symptoms assessment"
Task Three	Carrying out a partial NMS assessment	"Please show me how you would carry out a partial symptoms assessment for the symptoms thinking and memory and constipation"
Task Four	Viewing the symptom summary and accessing self-help information for "improving symptoms"	"Please show me how you would access a summary of your symptoms" "Please show me how you would access self-help info for your improving symptoms"
Task Five	Accessing self-help information for "pain" and "hallucinations"	"Please show me how you would access self-help for the symptoms "pain" and "hallucinations"
Task Six	Turning off the notifications	"Please show me how you would turn off the alerts function"

3.5.3.10 Task Order

All participants completed Task One (requesting contact from nurse) first, so that they had an opportunity to read the app instructions and enter their login token. To control for order effects, the order of the remaining 5 tasks was randomised using a random sequence

generator (“random.org”, 2019). This also ensured a range of tasks were completed across participants. The time it took to complete each task was not predefined and was expected to vary in length across participants. Participants were asked to complete as many of the six tasks as possible within the session time (75 minutes, in addition to the first 30 minutes of clinical assessment).

After the participant completed a task, they were asked some questions about their experience (see data collection below).

The participant was then given instructions for the next task. A debrief was performed at the end of the study session (see appendix 19 (section 8.19)) and participants were thanked for their time.

3.5.3.11 Data collection and analysis

3.5.3.11.1 Qualitative and observational data

Qualitative and observational data were collected via the ‘think aloud method’ (Jaspers, Steen, Van Den Bos, & Geenen, 2004), whereby participants were asked to verbalise their thoughts during interaction with the app, and think aloud whilst completing all tasks. A short warm up was carried out to help participants get used to this methodology (see appendix 18 (section 8.18)). During the think aloud procedure, the researcher played a neutral role. When asked for help by participants, the researcher firstly asked participants to continue as if the researcher was not present, and if asked for help a second time, the researcher would prompt participants to consider alternative options to complete the task. When necessary, the

researcher would ask a participant to elaborate on a comment. If the participant failed to 'think aloud', the researcher would prompt the participant by asking "What do you think of this page?" or "What are you thinking here?".

The researcher took observation notes throughout, and when an error or issue occurred, the location (screen) and the task the user was engaging with at the time was logged by the researcher.

Following usability testing, the video recordings were watched by the researcher to detect any further issues that may have been missed at the time of testing, and to cross check the observation notes. Emerging categories of usability issues were identified, and logged in a database (see Table 25) including when the issue occurred, and a brief description.

It was necessary to prioritise usability issues in terms of their risk to patient safety. The method for prioritisation of issues was similar to those used previously (Sauro, 2016). In order to do this, a severity of harm rating was assigned to each usability issue, which was influenced by the following factors:

1. Task Criticality: Rated in terms of impact on patient safety if the task was not accomplished (rated 1 (low) to 5 (high)).
2. Frequency: The frequency that the issue occurred. Issue frequency was calculated by dividing the number of occurrences by the total number of participants that completed the task. This was calculated across all participants, in addition to PwP and carers separately.

3. Impact: Rated in terms of impact on the user trying to accomplish the task. Impact was rated using the following scale:

   1= Suggestion: the issue is a suggestion from the participant

   2= Minor: the issue has a minor effect on task performance

   3= Major: the issue causes frustration and/or delay

   4 = Blocker: the issue prevents the user from accomplishing the task

Once all of the issues had been assigned ratings for criticality, frequency and impact, these ratings were multiplied to create a severity of harm score for each issue (severity of harm = task criticality x impact x frequency).

This process for harm rating was repeated independently by a second researcher (CC), and any discrepancies in ratings were addressed, and resolved via discussion with the NMS App project group. If there was variation in whether group members thought the issue had a minor or major impact on performance across participants (score of 2 or 3), the issue was rated as having a major impact (score of 3), to ensure ratings reflected the worst case scenario experienced.

Usability issues were then ranked in order of highest to lowest severity of harm for participants overall, as well as for PwP and Carers separately. A low (≤2), medium (>2 ≤4) and high (>4) severity of harm rating was assigned to each issue.

Once severity of harm ratings had been assigned to each of the usability issues, they were prioritised for amendment accordingly. This was achieved by a colour coded system whereby

red indicated high severity issues, orange indicated medium severity issues, and yellow indicated low severity issues. In addition, elements of the app design that worked well were rated green. Ratings with high severity of harm ratings were prioritised for amendment over issues with less high ratings.

The researcher suggested potential solutions for each of the issues that were identified, and these were commented on by the project group before being incorporated as part of a usability testing report (see appendix 20 (section 8.20). Once finalised, the usability testing report was sent to the app developer for review and incorporation into the app design.

3.5.3.11.2 Quantitative measures

In line with the ISO/IEC 9126-4 standard (ISO, 2016), usability metrics for effectiveness and satisfaction were included as part of the study protocol, as described below. Unfortunately, it was not possible to include metrics for efficiency in this round of usability testing (as explained below, section 3.4.2.10.4).

3.5.3.11.3 Metrics for effectiveness

Error free completion rate

A task was considered successfully completed if the user carried out the required task without making a critical error (an error that results in the participant not being able to successfully complete the task or results in incorrect information). Effectiveness (error free completion rate) was measured by the following equation:

$$\text{Error free completion rate} = \left(\frac{\text{number of tasks completed without critical error}}{\text{total number of tasks undertaken}}\right)^{*100}$$

The results of this equation provided an error free completion rate (%) for each task and for task completion overall (median, min-max range).

3.5.3.11.4 Metrics for Efficiency

Metrics for efficiency include measures such as the number of clicks made by the participant to successfully complete as task, or the time taken to complete a task. It was not possible to use number of clicks as a metric for efficiency in this round of testing due to participants carrying out exploratory clicks whilst 'thinking aloud', which affected the number of clicks made during each task. Additionally, we chose not to use time taken to complete a task as a metric of efficiency due to confounding symptoms of PD such as slowness of movement and problems with attention, and again due to implementation of the think-aloud methodology, which affected the time taken to complete tasks.

3.5.3.11.5 Metrics for Satisfaction

Task-level satisfaction

User satisfaction was measured following completion of each task (irrespective of whether the participant successfully completed the task or not) via 'The Single Ease Question' (SEQ) (Sauro, 2016). Participants were asked: "Overall, how difficult or easy was the task complete?" Responses were given on a 7 point scale (1= very difficult and 7= very easy).

Test-level satisfaction

User satisfaction at test level was measured at the end of the testing session to measure users' impression of overall ease of use. For this purpose, the 10 item System Usability Scale was used (Brooke, 2013). The SUS is a validated usability tool that uses a 5-point Likert scale to provide a quantitative measure of the usability of a system. An overall value was calculated from the raw score to provide a score between 0 and 100.

3.5.3.11.6 Statistical Analysis

I planned to evaluate differences between experienced (frequent smartphone users) and inexperienced (never users) groups.

Due to unequal group size, differences between user groups (Experienced vs Inexperienced Users) were investigated using non-parametric measures (Mann-Whiney U). Bivariate Pearsons correlations were used to investigate relationships between continuous variables. A *p* value of <.05 was used throughout. A Bonferroni correction was applied for multiple comparisons.

3.5.4 Results

Two participants (1 PD and 1 CP) were unable to attend the study visit due to illness, therefore a total of 13 participants took part in usability testing (9 PD and 4 CP). None of the 13 participants had used NMS Assist before. Of the total sample, 7 (54%) were frequent smartphone users (everyday use), 2 (15%) were occasional users (> once a month use). Due to a small number of occasional users (n=2), frequent users (n=7) and occasional users (n=2)

were combined to form the 'experienced users' group (n=9) for the purposes of the analysis. Four participants (31%) were inexperienced users (never used a smartphone before), forming the inexperienced group (n=4). Demographic data for participants is displayed in Table 21. Almost all participants scored above the MoCA cut-off for cognitive impairment (>26), however one participant in the CP group scored 21, which is in the range of mild cognitive impairment (MCI) (Nasreddine et al., 2005).

Table 21 Demographic data (median, min-max range)

	PwP (n=9)	Care Partners (n=4)	All participants (n=13)
Age	68 (44-82)	75 (69-80)	69 (44-82)
% Male	89	50	77
MoCA	28 (26-30)	28 (21-30)	28 (21-30)
Disease duration (yrs)	10 (1-17)	NA	NA
H &Y	2 (1-3)	NA	NA
NMSQ	17 (3-22)	NA	NA
Smartphone Experience			
Frequent	4	3	7
Occasional	1	1	2
Never	3	1	4

3.5.4.1 Effectiveness

Effectiveness of the app was measured using participants' error free completion rate (see methods, section 3.5.3.11.3).

Error free completion rate

The proportions of users participating in, and successfully completing each task (without critical error) are displayed in Table 22.

Table 22 The proportions of users participating in, and successfully completing each task without critical error (error free completion rate) for all participants, as well as by experience (experienced vs inexperienced users).

	Request contact	**Full NMSQ**	**Partial NMSQ**	**View Symptom Summary**	**View self-help info**	**Turn off notifications**
All participants						
Number of participants	13	12	8	9	10	10
Number completed (error free completion rate %)	7/13 (54%)	4/12 (33%)	5/8 (63%)	8/9 (89%)	9/10 (90%)	6/10 (60%)
Experienced Users						
Number of participants	9	9	6	6	7	7
Number completed (error free completion rate %)	6/9 (67%)	5/9 (56%)	5/6 (83%)	6/6 (100%)	7/7 (100%)	6/7 (86%)
Inexperienced Users						
Number of participants	4	3	2	3	3	3
Number completed (error free completion rate %)	1/4 (25%)	0/3 (0%)	0/2 (0%)	2/3 (66%)	2/3 (66%)	0/3 (0%)

Across all tasks, the overall median error free completion rate was 67% (0-100) (% of tasks successfully completed without critical error). It is important to note that one participant in the inexperienced users group (CP03) was the only participant to not successfully complete any of the six tasks without critical error (0% error free completion rate). This participant had a MoCA score of 21, in the range of MCI.

As outlined in Table 22, the tasks associated with the biggest discrepancy in error free completion rate between the inexperienced users and the experienced users were completing a partial NMSQ assessment and turning off notifications, with 83% and 86% respectively of experienced users completing these tasks without critical error, in comparison to the inexperienced users, whereby none of the participants were able to complete these tasks without critical error.

Potential relationships between overall error free completion rate, age and cognition (MoCA) were investigated using Pearson correlations (Table 23). For PwP, it was also of interest to see whether disease related variables such as disease duration and NMS burden (NMSQ score) had an impact on error free completion rate.

Table 23 Pearson correlations between age, cognition, disease duration and NMS burden with error free completion rate

	(*r*)	*p value*
Age* completion rate	-.5	.09
MoCA * completion rate	.47	.10
Disease duration * completion rate	-.33	.38
NMSQ * completion rate	-.43	-.24

As summarised in Table 23 above, none of these relationships were found to be significant and were not followed up with further analysis.

Relationships between error free completion rate and smartphone experience were investigated using non-parametric t-tests. There was a significant difference in overall error free completion rate between experienced and inexperienced users, with experienced users achieving a significantly higher error free completion rate than inexperienced users *U= 2*, *p*= .01. A post-hoc analysis of power was carried out on this t-test to see if our study was adequately powered. The test revealed our power was 0.98 (98%), which was above the level of 0.8 (80%), often considered adequate (Cohen, 1992).

Median error free completion rate between these two groups is displayed in Figure 35.

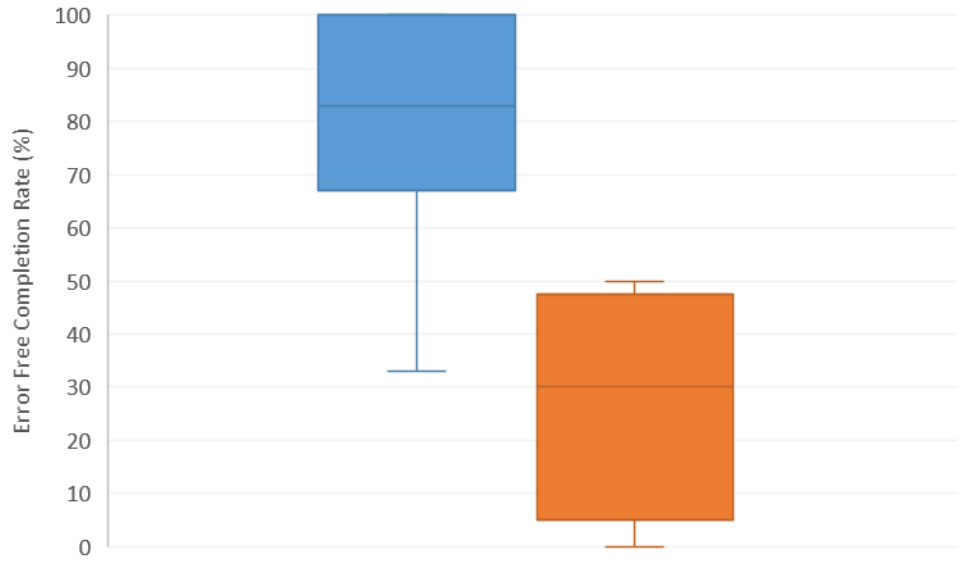


Figure 35 The boxplot shows the lower quartile (Q1), the median, and the upper quartile (Q3) of error free completion rate (%) in the experienced (n=9) and inexperienced (n=4) user groups.

3.5.4.2 Satisfaction

SEQ Scores

A breakdown of SEQ scores across tasks by smartphone experience is presented in Figure 36 (whereby 1= very difficult, 7= very easy).

On average, completing the partial NMS was rated as the most difficult task to complete. Inexperienced users generally rated all tasks harder or the same as experienced users to complete (with the exception of viewing the symptom summary, which was rated easier to complete by inexperienced users than experienced users).

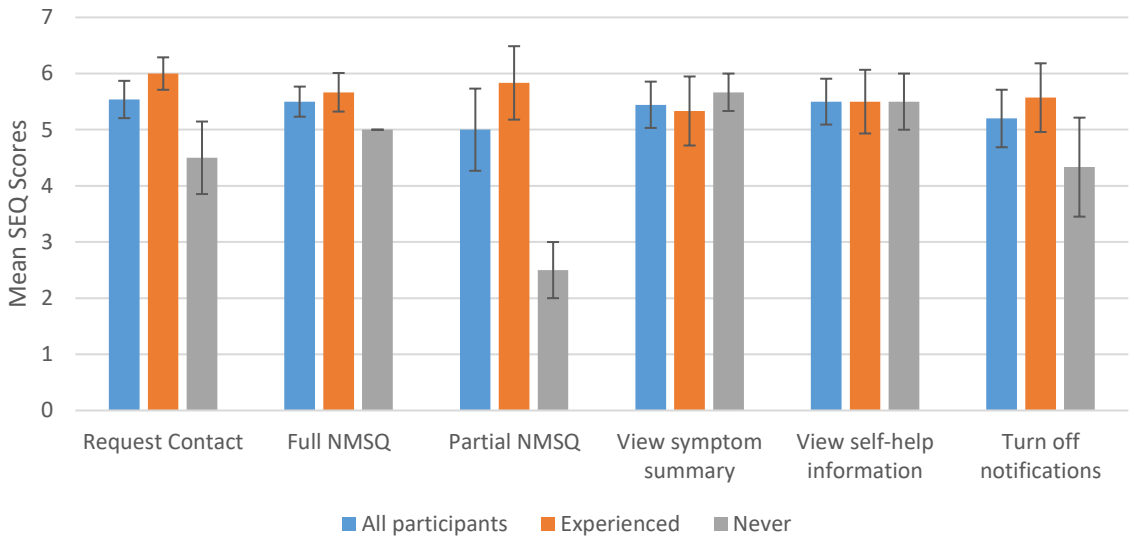


Figure 36 Mean SEQ scores across all participants and by smartphone experience. Error bars represent standard error (SE).

Non parametric t-tests were carried out to investigate if any of the differences in SEQ scores between experienced and never users were significant. None of the differences between user groups were significant however. Results are summarised in Table 24.

Table 24 Differences in SEQ ratings between experienced and inexperienced user groups.

Task	***U***	***p***
Request contact	5.5	.06
Full NMSQ	7.5	.28
Partial NMSQ	.5	.07
View symptom summary	10	>.99
View self-help info	10	>.99
Turn off notifications	5.5	.26

SUS Scores

The SUS measure was carried out following completion of all tasks to provide a measure of overall satisfaction with the app. Based on previous research comparing SUS scores across 500 studies (Sauro, 2016), an SUS score above 68 points (50th percentile) is considered to be an 'above average' score. The median SUS score of our participants overall was 80 out of 100 points (44-95), meaning our results were well above the average SUS score found in previous studies, (Sauro, 2016). Experienced users had higher SUS scores than inexperienced users, although this difference was not significant (U= 13, p= .50) (Figure 37).

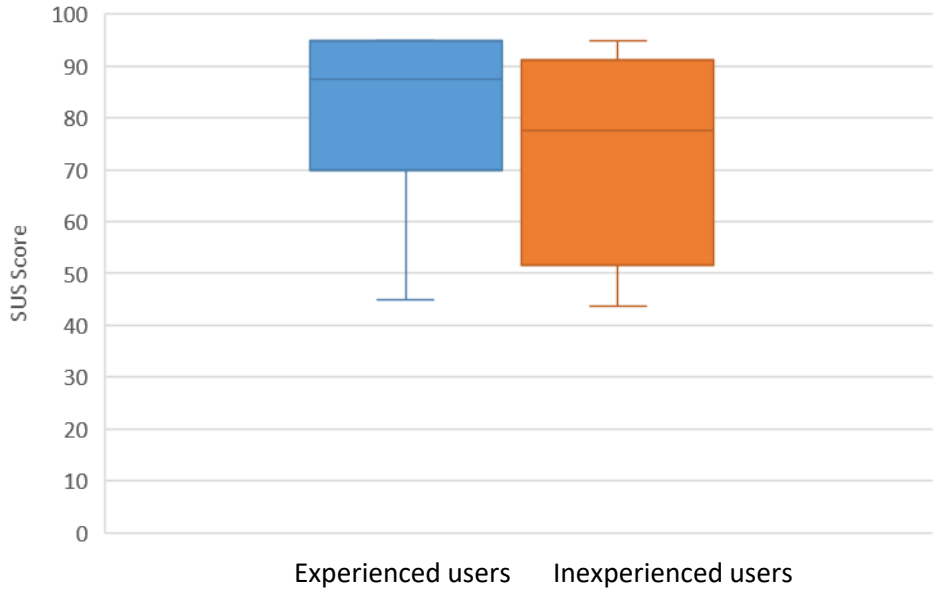


Figure 37 The boxplot shows the lower quartile (Q1), the median, and the upper quartile (Q3) of SUS scores in the experienced (n=9) and inexperienced (n=4) user groups.

Relationship between Satisfaction and Effectiveness

Satisfaction ratings (SUS score) were correlated with effectiveness (error free completion

rate) to investigate a relationship between these variables. No significant relationship between satisfaction and effectiveness was found however (r=.20, p=.51).

3.5.4.3 Usability Issues

Forty-six usability issues were identified via the think aloud method, captured by observation notes and video/audio recordings. Thirty-nine of these issues were task specific, and 7 were general, pertaining to all screens.

A severity of harm rating was assigned for each of the usability issues using the methodology described previously (see methods, section 3.5.3.11.1). Table 25 outlines the usability task and task criticality rating, the description of the issue that occurred during usability testing, the impact score, the frequency with which the issue occurred, and the resultant severity of harm score and the severity of harm rating. Severity of harm ratings were calculated for the PwP and care partner groups separately as well as overall.

Table 25 A description the usability issues experienced and associated severity of harm ratings (severity of harm = task criticality x impact x frequency).

	ID	Task	Criticality (1-5)	Location	Description of issue	Impact (1-4)	Frequency Overall	Severity Overall	Severity Rating
Task one	1	Requesting contact from healthcare team	5	Home Screen	At first, user could not find the 'request contact' button	3	0.23	3.46	M
	2		5	Request Contact	Expected it to initiate an immediate phone call because of telephone icon	2	0.08	0.77	L
	3		5	Contact Request received	Confusion surrounding meaning of contact request received. Expected to give details of problem (verbal/written)	2	0.15	1.54	L
	4		5	Request Contact	Confusion over the word 'still' troublesome	2	0.08	0.77	L

	5	Pressing 'next' on the instruction page	5	Instruction Page	User did not know how to scroll down (required to access 'next')	4	0.15	3.08	M
	6	Entering token	5	Token Page	User entered token incorrectly	4	0.46	9.23	H
	7	Allowing notifications	5	Notification pop up	Confusion as to what was meant by notifications	4	0.23	4.62	H
	8	Reading instructions	5	Instruction Page	Thought there was too much text to read through	2	0.23	2.31	M
	9		5	Instruction Page	Thought the instructions did not make sense from a carer's perspective	2	0.08	0.77	L
	10		5	Instruction Page	Users attempted to click on image, expecting it to take them somewhere else	2	0.23	2.31	M

Task Two	11	Completing PDQ8	5	PDQ8 questions	After pressing next, user did not notice that the question page had changed	4	0.42	8.33	H
	12		5	PDQ8 questions	Had not noticed progress bar	1	0.50	2.50	M
	13		5	PDQ8 questions	Confusion whether answering from own perspective or PwP perspective	4	0.33	6.67	H
	14	Reading the PDQ8 intro page	5	PDQ8 intro page	User skipped past this page without reading it.	2	0.08	0.83	L
	15	Reading the NMSQ intro page	5	NMSQ intro page	User skipped past this page without reading it.	2	0.08	0.83	L
	16		5	NMSQ intro page	Wanted acknowledgement the PDQ8 had finished and were moving onto something new.	2	0.50	5.00	H

	17	Completing 'how troublesome' scale in NMSQ	5	NMSQ Questions	Misinterpreting scale (eg. interpreted as how much saliva)	2	0.33	3.33	M
	18		5	NMSQ Questions	Did not notice scale	4	0.08	1.67	L
	19	Completing NMSQ	5	NMSQ questions	Misunderstanding as to what non-motor symptoms were.	4	0.25	5.00	H
	20		5	NMSQ Questions	Daunted by 31 questions	3	0.25	3.75	M
	21	Completing fluctuations question	5	NMSQ page	Confusion regarding the fluctuations question	2	0.17	1.67	L
	22	Completing ON/OFF scale	5	NMSQ page	Thought would make more sense OFF = 0 and ON = 5	1	0.25	1.25	L
	23		5	NMSQ page	Misinterpretation of ON/OFF scale	2	0.33	3.33	M

Task Three	24	Selecting symptoms for partial assessment	4	Partial assessment	Users did not realise they could select more than one option	3	0.63	7.50	H
	25		4	Partial assessment	Users were unsure which symptoms were under which domain	3	0.75	9.00	H
	26	Starting the partial assessment	4	Partial assessment	Expected assessment to start automatically once had selected symptom.	2	0.25	2.00	L
	27	Selecting symptoms for partial assessment	4	Partial assessment	Users did not like the term psychosis	1	0.13	0.50	L
	28	Carrying out a partial assessment	4	Partial assessment	Could not find the Partial assessment button on home screen	4	0.13	2.00	L
	29		4	Partial assessment	Confusion on meaning/purpose of partial assessment	2	0.63	5.00	H

Task Four A	30	Accessing symptom summary	3	Symptom summary	Took two attempts to find the symptom summary	2	0.11	0.67	L
	31	Viewing symptom summary	3	Symptom summary	Did not meet expectations	1	0.22	0.67	L
Task Four B	32	Viewing improving symptoms	5	Symptom summary	Difficulty finding improving symptoms (scrolling)	2	0.22	2.22	M
Task Five	33	Selecting symptoms for self-help info	5	Self-help library	Users expected to be able to select more than one option at a time	2	0.20	2.00	L
	34		5	Self-help library	User unsure of correct domain to select	3	0.60	9.00	H
	35	Reading the text version of self-help info	5	Self-help library	User attempted to swipe across/tap dots for next page (due to dots)	2	0.40	4.00	M

Task Six	36	Turning off alerts	2	Burger Menu	Could not find the alerts button within the menu	3	0.30	1.80	L
	37	Accessing burger menu	2	Burger Menu	Could not find the burger menu	3	0.60	3.60	M
	38	Turning off alerts	2	Alerts page	Should change to 'notifications off' when pressed	1	0.10	0.20	L
	39		2	Alerts page	Needs to be consistency between word alert/notification	1	0.10	0.20	L
General comments	40	Reading text	5	General	Found white text on light blue background hard to read	3	0.08	1.15	L
	41		5	General	Found white text on dark background cumbersome	2	0.15	1.54	L
	42		5	General	Text could be bigger	2	0.38	3.85	M
	43	Manipulation of buttons	5	General	Difficulty selecting buttons	3	0.23	3.46	M
	44	Wording	3	General	Does not like term 'disease'	1	0.15	0.46	L

	45	Recognising home screen	3	General	Home page not recognisable as home page	2	0.15	0.92	L
	46	Going back home	3	NMSQ Questions	Attempted to press 'NMS Assist' button to go home	2	0.23	1.38	L

A report outlining the usability issues prioritised by their associated severity of harm rating was sent to Made with Maturity to inform future amendments (see appendix 20 (section 8.20)).

Table 26 details the rating system that was used throughout the report to indicate high/medium/low severity of harm ratings for each of the issues described.

Table 26 Severity of harm ratings for the identified usability issues

Severity of harm rating	Descriptive Rating	Colour Rating
>4	High Severity	
<2 ≤4	Med Severity	
≤2	Low severity	
N/A	Positive comment	

Figure 38 displays an extract from the report. Each page of the report includes a screenshot of the screen where issues occurred, details of the issues as well as any positive comments made by participants. Severity of harm ratings for the group overall, and for the PwP and Care Partner group are presented for each of the usability issues, as well as potential solutions suggested by the group. Please see appendix 20 (section 8.20) for the report in full.

Usability Issue	All pps	PD	CP	Suggested solutions (group)
1. Some users struggled to scroll down (had to be shown how to do this) although they knew there was more information on the page				• Provide a tutorial video called 'getting started' or similar which is easy to access for those who need it but easy for proficient users to skip past • Provide a floating down arrow in the centre bottom of the screen. • Also provide a 'back to top' arrow on long pages.
2.Users commented on the font size being too small.				• Ensure users are shown how to increase text size as part of instruction vid
3. Users commented there was too much text to read, and they did not want to have to remember these instructions throughout.				• Reword in bullet points with catchy subheadings
4. Users commented the content did not make sense from a carer's perspective.				• Reword to make relevant for patients and carers
5. Users attempted to click on the image, expecting it to take them somewhere else.				• Consider leaving the image out – it may be too much for users to remember and can be explained as part of tutorial vid

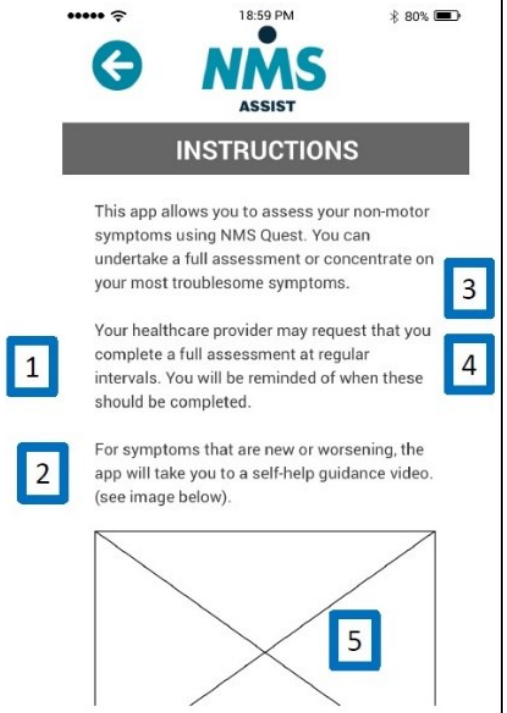


Figure 38 An extract from the report sent to Made with Maturity following usability testing, outlining usability issues, their associated severity of harm rating, and suggested solutions made by the project group.

Overall, eleven high severity issues were found, from which 3 central themes were identified: Navigation, content and accessibility. Table 27 displays the high severity usability issues with representative participant quotes, and suggested solutions by the project group following discussion.

Table 27 Description of high severity usability issues with representative quotes from participants and suggested changes.

Central Theme	Issue description and representative quotes	Suggested Change
Navigation	Users were unable to access all of the instructions, as they did not know how to scroll down the page. "*Either I'm doing it wrong or it doesn't work…there's an arrow at the top of the page (back arrow)...I could try this button (home button)...I think there's more information [on this page] but I'm not sure how to get to it."*	Provide a training video that explains basic functions of app and how to use it. Also, provide a floating down arrow in the centre bottom of the screen to indicate to users there is more information available.
Navigation	Users pressed next and did not notice that the question had changed. *"I didn't notice it [the page] change...I thought oh I haven't pressed the button or it had died on me or something."*	Make transition between questions more noticeable.
Navigation	Users struggled to find the 'burger' menu. *"I would look in the actual app itself…what about the middle one [home screen] would that do it? I don't know."*	The location and purpose of this menu would be explained as part of the training video.

Central Theme	Issue description and representative quotes	Suggested Change
Navigation	Users wanted acknowledgement that they had finished the PDQ8. *"I kind of want something else to tell me I'm in a different place."*	Add another screen following completion of the PDQ8 that thanked participants and indicated they were to move on the full symptoms assessment (NMSQ).
Navigation	Users did not realise they could select more than one symptom to assess. *"I would push the symptom I wanted and then press start assessment."*	Add the sentence: "You can select more than one symptom to assess" to the text.
Navigation	Users entered their token incorrectly. *"I've pressed an 'F' instead of 'P'."*	Do not let user progress unless enter valid token. Make all tokens lower or upper case to avoid case sensitive errors. Consider increasing keyboard size.
Content	Users expressed confusion at what was meant by 'allow notifications'. *"How do I know that's not a scam or something that's coming in…somehow there needs to be some reassurance to the person using it...there should be some sort of security".*	Clarify what notifications and alerts are, the difference between them, and give 1 or 2 examples for what they will receive them for.

Central Theme	Issue description and representative quotes	Suggested Change
Content	Care partners expressed confusion about whose perspective they were answering the questions from (theirs or the person they care for). *"Some of these questions do need to have the precursor 'for the person you're caring for'".*	A sentence will be included as part of the instructions that explicitly asks them to provide their opinion of the symptoms shown by the person they care for.
Content	Users expressed confusion surrounding the ON/OFF scale. *"I've never understood the ON/OFF...I know it's a phrase that's used worldwide in Parkinson's, but I've never really understood it…maybe it's because I've never experienced 'off'."*	Provide a glossary of PD related terms, or change the wording of the scale to PD medications working well' and 'PD medications not working'.
Content	Users expressed confusion surrounding which symptoms would come under which domain.*"…[Gastrointestinal tract] that's what I'd guess for constipation, I would click on that hoping it would give me a clue…it would give me an explanation of what Gastrointestinal tract means."*	Provide an information button on each domain that shows which symptoms come under each domain.

Central Theme	Issue description and representative quotes	Suggested Change
Accessibility	Users commented on the font size being too small. *"Text is a bit small is all I'd say."*	Include demonstration of how to enlarge text size as part of training video.

3.5.5 Discussion: Part Three

The purpose of this formative study was to evaluate the usability of a wireframe prototype of NMS Assist, a smartphone app for the remote monitoring and self-management of PD NMS.

My hypotheses for the study were as follows:

1. There would be no statistically significant difference in measures of effectiveness or satisfaction between experienced and non-experienced smartphone users.
2. The think aloud method would reveal key areas of amendment for future design.

In line with my first hypothesis, there were no significant differences in usability (SUS) scores between experienced and inexperienced users (p=.5), meaning that perceived usability of the app was not dependent on prior smartphone experience. This is a particularly important finding in relation to our intended user group, who are expected to have varying degrees of digital literacy (Lorenz & Oppermann, 2008). The overall SUS scores were above average (80/100 points) and demonstrates that overall, all participants (PwP and CP) found the app highly usable.

The lowest scoring participant (SUS score of 44 points) was an inexperienced user in the CP group, and was the only participant that did not complete any of the tasks attempted without critical error. Of interest, this participant had a MoCA score in the Mild Cognitive Impairment (MCI) range (Hoops et al., 2009). This finding suggests that the app may not be perceived to be usable by users with MCI who have little experience with smartphones, and these users may be less able to successfully complete tasks than users with normal cognitive function.

MCI has been previously recognised as a barrier to older adults using technology to manage long term conditions (Archer, Keshavjee, Demers, & Lee, 2014). As levels of cognitive impairment are high in older adults (Roberts et al., 2012), and even greater in a PD population (Aarsland et al., 2009), it would be necessary to include mitigations as part of the app design to help compensate for cognitive impairment. Previous suggestions to enable people with cognitive decline to use mHealth technologies include: making the content less comprehensive, minimising demands on memory, and providing tools that can aid the user, such as search tools (Czaja et al., 2012). As outlined in the recommendations made previously (see results Table 27), in the next iteration of the app we hope to include several tools that may aid users with low levels of cognition, including a training video, a glossary of technical terminology, and information buttons to explain different symptom domains.

In future testing, it would be essential to include a greater number of participants with MCI, with varying levels of app experience (including experienced and inexperienced users), to investigate whether the mitigations put in place enable users with cognitive impairment to successfully use the app. If unsuccessful, this may mean normal cognitive functioning is a requirement to using NMS Assist, and potential users (both PwP and CP) would need to be screened for cognitive impairment prior to use.

Despite no difference in users' ratings of usability (SUS scores), the experienced group were found to have a significantly higher error free completion rate than inexperienced users (p=.01). This highlights the SUS only measures *perceived* usability and does not reflect actual effectiveness (Brooke, 2013). This was further demonstrated by the non-significant relationship between SUS scores (user satisfaction) with error free completion rate

(effectiveness) (p=.51). Previous studies have similarly suggested that effectiveness and satisfaction do not appear to be related, and should instead be considered as independent aspects of usability (Frekjmr, 2000).

The poorer performance by the inexperienced user group is an important finding because, as mentioned previously, our intended users will likely have varying degrees of digital literacy (Lorenz & Oppermann, 2008). This finding also does not support my first hypothesis, and demonstrates usability of the app is somewhat dependent on prior smartphone experience. It is essential that the design is further amended to fully compensate for users with little prior experience with apps. Matthew-Maich and Colleagues (2016) carried out a review of mHealth technologies, and made a number of recommendations for developers to support older adults using mHealth technologies, including minimising the number of navigation screens and minimising complexity (Matthew-Maich et al., 2016). The recommendations made previously for the high severity issues (see results, Table 27) aim to assist users with lower levels of digital literacy, for example, the inclusion of a training video on how to use the app, and clear definitions of technical vocabulary such as 'notifications'. These recommendations will therefore be incorporated as part of future design iterations of the app to ensure the app is usable by older adults with a wide range of digital literacy.

Furthermore, experienced users rated all tasks as easier to complete than the inexperienced user group (with the exception of 'viewing the symptom summary' which inexperienced users found easier to complete). Although these differences in SEQ ratings were not significant between groups (thereby providing support for my first hypothesis), they indicate prior experience with a smartphone increases perceived ease of use. Ease of use has been

identified as a critical factor in determining future adoption of an mHealth solution (Matthew-Maich et al., 2016). The review by Matthew-Maich and Colleagues (2016) revealed that if a solution was considered too time-consuming or burdensome, it can be perceived by users as not being worth the effort, and will ultimately lead to low levels of user adoption (Matthew-Maich et al., 2016). As part of our recommendations outlined in Table 27 (see results) we aim to provide clear instructions and guidance throughout the app (including inclusion of a training video) to make interaction with the app as easy as possible, and to ensure high levels of adoption and user engagement. SEQ measures will be repeated in future testing to see if scores have improved.

In line with my second hypothesis, the think aloud methodology identified several high severity issues which informed necessary amendment in three key areas of design: navigation, content and accessibility.

Regarding navigation, inexperienced users were unable to access some of the information on the instruction page because they had no prior knowledge of how to scroll down the page. One way in which this could be overcome is by matching the length of message to the screen size where possible, which has been found to improve digestibility and readability (Nielsen & Mathiassen, 2013) and would eliminate the need to scroll down. Inexperienced users also struggled to access the settings, as they did not recognise the menu icon. It was suggested by the project group that a training video and prompts such as arrows could be put in place to educate users with low levels of digital literacy on these navigation features. Training that has been tailored to meet the needs of the end-user is highly valuable, and can improve user

attitudes towards and acceptance of the use of technology (Stroulia, Nikolaidisa, Liua, King, & Lessard, 2012).

Another issue users encountered was entering the token. Some of these errors were due to dexterity issues, particularly in the PD group. To improve the usability of the app on a smartphone platform, an increased keyboard size will be considered, and the keyboard for the token will be automatically in upper case, so that no additional keyboard navigation is required (see results, Table 27). Additionally, the app will eventually be developed for use on multiple platforms, including web-based and tablet versions, which may preferable for some users. Indeed, it has been suggested that tablets with touchscreens may be preferable to smartphones for users with limited dexterity, due to their bigger surface area (Huang & Hsu, 2014).

Regarding content, there was confusion surrounding certain terminology and wording. This highlights the importance of ensuring all content is comprehensible by end users. Past research has demonstrated that choosing appropriate wording and language is critical when developing a digital health intervention, and can have a significant impact on future adherence (Ludden, van Rompay, Kelders, & van Gemert-Pijnen, 2015). To ensure this is incorporated, a glossary will be made available for PD related terms used throughout the app (as outlined in the recommendations made previously, see results, Table 27).

Regarding accessibility, some users commented that the font size was too small. Visual aids such as large text and the use of bold colours have previously been identified as key requirements of smartphone apps for older adults (Gao & Koronios, 2010). Lorenz and Opperman (2008) recommend using font sizes between 36pt and 48pt for elderly users. We

are in the process of developing a feature that will allow users to increase the interface font size, however this feature was not available at the time of testing.

3.5.5.1 Increasing motivation to use the app:

Following usability testing, an expert in digital healthcare (Professor Jackie Andrade, University of Plymouth) was contacted to ask for advice on how to motivate users to engage with the app long term. Professor Andrade (University of Plymouth) advised that reminders to carry out a behaviour (such as completing an assessment) were most effective when the user can choose at what time of day they will receive the reminder (Solbrig et al., 2017). This ensures that the reminder notification will arrive at a time of day when the user can actually respond e.g. for the app to remind them first thing in morning when they are alert, or in the evening when they are relaxed, rather than in middle of day when the user is at work or out shopping.

In addition, positive imagery combined with task reminders has been found to be very effective in motivating behaviour (Solbrig et al., 2019). It may be useful therefore for us to accompany reminder notifications with some positive imagery such as a cup of tea or other image users would find relaxing.

As a result, we will ensure to include questions regarding a personalised reminder schedule as part of the next round of formative evaluation, in order to gauge users' thoughts on this feature.

It was also suggested that we consider the narrative behind the app. Previous research has demonstrated that people are more likely to be motivated to use the app if they are

intrinsically motivated to perform a behaviour (e.g. to gain health benefits), rather than when they are extrinsically motivated (e.g. advised to do so by Dr) (Solbrig et al., 2017). In order to try and intrinsically motivate users to engage with the app, it was suggested that we promote the perspective of 'self-care' to the patient. For example, reminders could be accompanied by the text, 'Check-up in the comfort of your own home,' or 'Do you have 5 minutes to look after yourself?'.

In addition, previous research has found it is necessary to repeat a new behaviour frequently over a period of 6 weeks in order for it to become habitual (Breslin, Sobell, Sobell, Buchan, & Cunningham, 1997). In order to ensure that users adopt using the app on a regular basis (possibly once every 3-6 months to complete full NMS symptoms assessment) we may ask users to complete tasks using the app more regularly after first downloading it. For instance, users could receive reminders once a week for the first six weeks asking them to complete a task, such as watching a symptom video or completing a partial assessment.

3.5.5.2 Limitations:

As discussed previously, a limitation of our study was that we did not include participants with a range of cognitive abilities. Due to the difficulties the participant with MCI experienced completing the tasks, and the high levels of cognitive impairment experienced by older adults and PwP (Aarsland et al., 2009; Roberts et al., 2012), it will be a priority in future studies to include participants with a wider range of cognitive impairment, to ensure our sample are representative of the end user population.

Another limitation of the study was that no observers were present during testing, due to the last minute unavailability of a second researcher (RD), who it was intended would observe

the testing. This may mean that evaluation bias occurred when analysing and interpreting usability issues. To overcome this in future rounds of testing, we have expanded the project team to ensure that a second researcher is available to act as an observer.

Furthermore, due to implementation of the think aloud methodology, it was not possible to provide a measure of efficiency. This is a limitation of the study, as we were not able to provide an overall picture of usability (Brooke, 2013). In the second usability study, we plan to carry out a retrospective think aloud methodology, whereby following task completion, we will show the participant video footage of them carrying out the task, and ask them to comment on what they were thinking at the time. This will allow us to include an efficiency measure, by timing how long it takes participants to complete each of the tasks (without also having to think aloud).

Considerations for the design of the second usability study that have been influenced by the limitations of our current study design are outlined in Table 28, and will be incorporated as part of the second usability study.

Table 28 Description of current study design limitations, and considerations for second usability study design to overcome these

Current study design limitations	Considerations for second usability study design
• Limited range of cognitive abilities were represented	• We will recruit a bigger sample including participants with a range of prior digital experience and cognitive ability (including users with MCI)
• There were no observers present during usability testing	• We will expand the project team to ensure there will be an observer present during all usability testing sessions

• There were no measures of efficiency	• We will include measures of efficiency as part of the study design, such as task completion time.

3.5.5.3 Conclusions

This initial formative evaluation was carried out to evaluate the usability of NMS Assist for end users with and without previous smartphone experience.

In line with my first hypothesis, there were no differences in perceived usability between experienced and inexperienced users, suggesting that perceived uability is not dependent on prior smartphone experience. However, differences in measures of effectiveness between groups revealed the app needs further refinement in order to meet the needs of end-users with low levels of digital literacy and poor cognition.

In line with my second hypothesis, the think aloud method revleaed key areas of amendment related to navigation, content and accessibility.

The findings from this evaluation have therefore informed necessary and appropriate solutions for future app development (see results, Table 27), as well as important study design considerations for the next usability study, to overcome the limitations of our current study design (see Table 28).

It is hoped the amendments to app will increase overall usability, and these will be measured by efficiency, effectiveness and satisfaction measures in the second round of usability testing.

3.6 Overall chapter discussion

In order to ensure NMS Assist is safe, usable, and successfully meets users' needs, we employed an app development process guided by the MHRA Human Factors and Usability Engineering guidance for medical devices (Mhra, 2017). In addition to the MHRA guidance, the Department of Health and Social Care more recently (September 2018) published a set of principles in the code of conduct for data-driven health and care technology (DHSC, 2018). These principles complement the MHRA guidance, and are aligned with the digital design principles published by the NHS (NHS Digital, 2018).

Our phases of app development (to date) include; (Part 1) identification of app use, users and environment, (Part 2) development of wireframe design and self-help materials, and (Part 3) a formative evaluation of the app. Each of these phases will be discussed in turn.

3.6.1 Part 1: Identification of use and users

A key principle outlined in the code of conduct (DHSC, 2018) that has been implemented as part of the app development process was to understand users, their needs and the context. A literature review and patient questionnaire were carried out in Part 1 to gain valuable insight into our users and their needs.

In line with my hypothesis, the literature review revealed a wide range of user characteristics which could have an impact on users' interaction with the app such as limited dexterity, vision and prior experience with smartphones. The patient questionnaire of patient experience of NMS provided insight into the clinical needs of end users, such as the generally high NMS burden of PwP, and the infrequency with which these are currently reviewed or monitored.

The patient questionnaire further provided insight into practical user needs, such as access to technology, current use of digital health technologies (DHT), and willingness to use a DHT in the future.

Our findings from Part 1 were instrumental in understanding our user needs so that we could develop a suitable app. Services and products that are designed around users and their needs are more likely to be used, and will cost less in the long term by avoiding costly revisions further down the line (DHSC, 2018).The results of our literature search and patient questionnaire were therefore taken forward and incorporated as part of the next phase of app development.

3.6.2 Part 2: Iterative design process

Patient representatives continued to be closely involved during the development of the app wireframe and the self-help materials in Part 2. As mentioned previously, engagement with end users throughout the development of DHTs has been found to positively influence future engagement with and adoption of DHTs and so it was a priority for us to include patient representatives at every stage of the development process.

Our patient representatives were key to identifying potential risks to patient safety so that relevant mitigations could be included as part of the app wireframe design. For example, a patient representative was concerned that users may not understand the purpose of a full NMS assessment. To mitigate for this risk, a screen was included prior to the full NMS assessment that explained the purpose and task instructions. Furthermore, during the development of the self-help materials, patient representatives were closely involved in the development of the scripts to be read aloud by the animation voiceovers, and the

development of the animations. Their involvement was integral to ensuring we selected terminology that was accessible to readers and easily understood, as well as being conveyed in an appropriate tone.

Another key principle incorporated as part of the app development process was an iterative development process, meaning that we iteratively refined the design of the app to ensure all identified potential issues and risks to patient safety were addressed. An iterative development process is a key factor in the design of DHTs, and allows for prototype versions to be regularly tested and refined (MHRA, 2017). In order to achieve this, we required regular engagement with all members of the project group throughout all phases of development, to review and provide feedback on each aspect.

Although valuable and necessary, this process required a central person to coordinate the feedback schedule (this role was carried out by myself). This included; sending the project group initial invites for feedback, chasing delayed replies, collating group feedback, and reporting the collated feedback to the project group as a whole, as well as to the app developers. Although worthwhile, this process was timely, and we required additional resource to carry out the changes made as a result of the feedback, as these exceeded the number of rounds of amendment that were originally quoted to us by the app designers. Furthermore, absence of project group members (due to holidays or sick leave) induced delays to the development process, particularly to the app wireframe design and the development of self-help materials, whereby the creators could not progress with the next iteration until they had received feedback from all members of the project group. A stricter schedule for feedback, and tools to assist with the oversight of this (such as project

management software) may help to improve this process as we move forwards, and reduce delays to project delivery.

3.6.3 Part 3: Formative evaluation

A further key principle outlined as part of the code of conduct is to generate evidence of effectiveness for the DHT's intended use (DHSC, 2018). NICE has recently developed an evidence standards framework for DHTs (published in Dec 2018) that has been designed to complement the code of conduct principles (NICE, 2019). The framework aims to inform technology developers and evaluators about the types of evidence needed to show the effectiveness of a DHT. The framework further aims to provide standardised criteria against which DHTs can be assessed, dependent on the function of the DHT.

The formative evaluation that we have carried out in Phase 3 provides some of evidence on the effectiveness of the device in line with that required by the framework, including an evaluation of user satisfaction and involvement of intended users in the development of the DHT.

In line with my first hypothesis, there were no differences in perceived usability between experienced and inexperienced users, suggesting that perceived uability is not dependent on prior smartphone experience. However, differences in measures of effectiveness between groups revealed the app needs further refinement in order to meet the needs of end-users with low levels of digital literacy and poor cognition.

In line with my second hypothesis, the think aloud method revleaed key areas of amendment related to navigation, content and accessibility that will be incorporated as part of the app

refinement process. The refined version of the app will then be evaluated as part of our next round of formative evaluation (planned for July 2019). In addition, limitations to study methodology identified as a result of our initial formative evaluation will also be addressed, such as the inclusion of an observer, measures of efficiency and participants with a wide range of cognitive abilities and digital literacy. It is hoped these amendments will increase the robustness of the second formative evaluations' findings and inform the finalisation of the app design.

A strength of this development process is that evaluations of usability were carried out at an early stage of development in a laboratory setting. A review of health information technology usability methodologies found that the majority of evaluation studies take place at a later development stage, once the product is in use. These studies identified by the review reported several barriers to adoption of DHTs, including usefulness and ease of use (Yen & Bakken, 2010). The authors conclude that some of these barriers may have been avoided by carrying out evaluation of the technology at an earlier stage in the app development process.

However, in order to fully provide evidence of effectiveness in line with the framework, and to meet similar requirements outlined by the MHRA, further, more rigorous testing is needed. Following finalisation of design and minimisation of risks identified through formative testing, a summative evaluation of the finished app design will be carried out.

The purpose of a summative evaluation will be to carry out testing of the app in the intended environment for use, and (as identified via the patient questionnaire, see section 3.2.6.10), this will primarily be in patients' homes. We therefore plan to carry out an in-service summative evaluation, whereby patients and carers will be required to use NMS Assist at

home over the course of 12 weeks. Participants will receive app training, before being asked to complete a full NMS assessment at pre-specified time points over the course of 12 weeks, and a number of other tasks in-between these intervals that reflect the range of app functions; these will include accessing the self-help information; re-assessing troublesome symptoms and requesting a healthcare contact. At the end of the 12 weeks, user evaluations will be carried out to capture perception of change over the study duration, as well as a focus group to obtain more detailed insights into user experiences, perceptions, and satisfaction.

A key element of the summative evaluation is ensuring that app training is tailored to user skills and knowledge, the acceptability of the training provided (in terms of timing, content, delivery and duration), and whether the training is effective. Training acceptability will be evaluated by questionnaire administered by telephone interview within 3 days of baseline visit. Training effectiveness will be evaluated by logging app use and user journey completion.

3.6.4 Development of the app build

The development of the app build was not included as part of this chapter, but is an ongoing part of the app development (led by SM). The app build process includes the development of the web portal element, whereby the clinical team will be able to view patients' interactions with the app as well as view patient and carer NMS assessments. The web portal will therefore facilitate support and communication with patients and their carers as required. As outlined in Figure 22, the app build followed a similar process of design as the wireframe and self-help materials, and will similarly be evaluated using a formative and then summative evaluation process in due course.

3.6.5 Further considerations

There are further key principles outlined in the code of conduct that pertain to the app build and design, which will be considered throughout our ongoing app development process:

3.6.5.1 Data protection

The use of data will need to adhere to the recently updated Data Protection Act (2018). A key consideration will be that the minimum personal data necessary will be used to achieve the desired outcomes. In addition, the code of conduct outlines that developers should be fair, transparent and accountable about what data is being used. Data-sharing agreements with users must be implemented and adhered to (DHSC, 2018).

3.6.5.2 Data security

A core element of design and development will be to ensure security methodology has been incorporated. As part of the code of conduct, it is recommended that when developing an application, it is necessary to ensure the app meets the OWASP Application Security Verification Standard (OWASP, 2018) , which is used to determine a level of confidence in the security of applications. Furthermore, NHS digital provides information and resources relevant to securing medical devices as part of the 'NHS Digital Data Security Knowledge Library' ("NHS Digital", 2019). It will be a priority to ensure these resources and guidelines are implemented and adhered to as part of the app build and development.

3.6.5.3 Economic impact

A key principle that pertains to all aspects of app development is providing evidence of the economic impact of the app. Section B of the NICE Evidence Standards Framework provides

the economic analysis that should be carried out for DHTs that present differing levels of economic risk. Risks are defined as any harm associated with the expected cost and system impact of commissioning a DHT. It is essential that the framework is adhered to in order to calculate the level of economic risk and subsequent economic impact that NMS Assist may present.

3.6.6 Conclusions

As a result of the first three phases of this ongoing app development process, we have:

- Identified our user charactersitics and needs, and incorporated these throughout the design process.
- Iteratively refined the app's content, functionality and interface, with consideration of user needs and engagement from end users at all stages.
- Carried out a formative evaluation in the laboratory setting, which revealed that while the app was rated as highly usable by our end-users, further refinement is needed to increase usability for inexperienced users.
- Identified key areas of additional amendment to future app design including those related to navigation, content and accessibility.

Findings from our formative evaluation will inform the next iteration of the app design, and important methodological considerations will be put in place to improve the robustness of this study design. Following finalisation of the app design (via the next round of formative testing), we plan to carry out an in-service summative evaluation to test NMS Assist in the environment of intended use, and in line with relevant guidelines and procedures for the development of digital health technologies (DHSC, 2018; Mhra, 2017).

Chapter 4 Evaluating the clinical utility of objective measurement in the remote management of people with Parkinson's disease

4.1 Introduction

In recent years, a multitude of wearable technologies for the objective measurement of Parkinson's disease (PD) symptoms have emerged (see (Del Din, Godfrey, et al., 2016; Maetzler et al., 2013) for recent review). As discussed previously (see section 1.2.25.2.2), incorporating wearable devices as part of PD management may help to overcome some of the current challenges surrounding care provision and assessing symptom severity. For example, wearable devices allow for continual assessment of patients' symptoms from within the home environment, resulting in data that is high in ecological validity, without the need for the patient to travel to clinic (Stamford et al., 2015). Furthermore, wearable devices have the potential to provide tailored information on a patient's response to a therapeutic intervention, which can be used to further optimise treatment and identify areas of unmet need (Barker, 2017).

Although other wearable devices are commercially available for the assessment of PD symptoms (e.g. (Mera, Heldman, Espay, Payne, & Giuffrida, 2012) see section 1.2.25.2.3.1), the Parkinson's KinetiGraph (PKG™) is unique in that it offers continuous monitoring over a 6-day period, and requires little interaction from the user (see section 1.2.25.2.3.2).

In this chapter, I present a clinical evaluation on the use of the PKG™ as part of routine management of people with Parkinson's disease (PwP) as well as the results of a patient evaluation investigating the feasibility and acceptability of the PKG™ for patients.

4.1.1 The PKG™ System:

The Parkinson's Kinetigraph (PKG™; Global Kinetics Corporation (GKC)) is a U.S. Food and Drug Administration (FDA) approved wrist worn device that provides continuous, objective and ambulatory assessment of PD symptoms. The PKG™ comprises 3-axis accelerometers and sufficient memory for 10 days of continuous recording (see Figure 39).

Figure 39 The PKG™ System (Generation 1) (pictured left) used by patients in this clinical evaluation. An updated version has since been released (Generation 2) (pictured right).

The PKG™ is worn by patients on the wrist of the most affected side for 6-10 days, after which data is downloaded from the device and analysed by proprietary cloud-based algorithms, to calculate a bradykinesia score (BKS) (Griffiths et al., 2012) and a dyskinesia score (DKS) (Griffiths et al., 2012). In addition, the percentage of time that tremor was present (PTT score) is available (Braybrook et al., 2016), as well the percentage of time immobile (PTI score), indicative of excessive day time sleepiness (Kotschet et al., 2014). Median PKG™ symptom scores (BKS, DKS, PTT and PTI scores) from throughout the waking day (9am-6pm), are used to represent overall severity.

The PKG™ device (logger) is programmed with patient L-dopa medication times, and patients are required to acknowledge intake of medication by placement of a digit on the device (Generation 1) or swiping across the screen (Generation 2). This feature of the PKG™ has been used as a means to assess for impulse control disorder (ICD) (Evans et al., 2014).

All propriety algorithms used as part of the PKG™ system have been previously validated, and are described in detail below.

4.1.2 Validation of the PKG™ Propriety Algorithms

4.1.2.1 Bradykinesia (BKS Scores)

In the PKG™ algorithm, bradykinesia is recognised as epochs containing movements of lower acceleration and amplitude and with longer intervals between them (Griffiths et al., 2012). The specific details of this algorithm are proprietary, and are not available in the public domain.

Griffiths et al (2012) carried out a validation study of the algorithm for BKS scores with data from PwP (n=34) and age matched controls (AMC) (n=10) after having worn the PKG™ for a duration of 10 days. The aim of their study was to validate the use of this algorithm against traditional clinical rating methods for bradykinesia.

A dot slide task (an example of an alternating movements task used to measure bradykinesia in PD) correlated well with the BKS algorithm (p<.001) with a specificity of 88% and sensitivity of 95%. Additionally, the BKS score was found to correlate well with the Movement Disorders Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS) motor subscale (Part III) scores

(r=.64, p<.00005), with 1 MDS-UPDRS Part III unit calculated to equate to 1.3 BKS units (Griffiths et al., 2012).

In addition, the distribution of the BKS was found to differ from controls. For instance, the BKS of a PwP with bradykinesia was greater than the 50th percentile of controls for almost 90% of the time.

The authors concluded that the close correlation between the BKS scores with existing established clinical measures, and the differentiation in scores from an age-matched control population helps to validate the PKG™ as a reliable measure of bradykinesia in PwP (Griffiths et al., 2012).

4.1.2.2 Dyskinesia (DKS Scores)

In the PKG™ algorithm, dyskinesia is recognised as epochs containing movements of normal amplitude and acceleration but with shorter intervals between them. As before, the specific details of this algorithm are proprietary, and therefore not available in the public domain.

Griffiths et al (2012) carried out a validation of the algorithm for DKS scores as part of the same validation study for the BKS scores. The aim of their study was to validate the use of the DKS algorithm against traditional clinical rating methods for dyskinesia.

The correlation between the DKS score and the Abnormal Involuntary Movement Scale (AIMS) (a task used to measure dyskinesia in PD) was highly significant (r=.8, p<.0001). Furthermore, the DKS score achieved a smaller margin of error to a neurologist scoring the AIMS (Griffiths et al., 2012).

In addition, the distribution of the DKS was found to differ from controls. For instance, the DKS of a patient with dyskinesia was greater than the 50th percentile of controls almost all of the time.

As with the algorithm for BKS, the authors concluded the close correlation between the DKS scores with existing established clinical measures, and the differentiation in scores from an age-matched control population helps to validate the PKG™ as a reliable measure of dyskinesia in PwP.

4.1.2.2.1 Bradykinesia and Dyskinesia Summary Output

Figure 40 displays an example of a bradykinesia and dyskinesia summary graph that the clinician receives after the patient has worn the PKG™ for the required duration (6 days). The thick lines represent median bradykinesia (blue lines) and median dyskinesia (green lines) from over the 6 days the PKG™ is worn, and the thin lines represent the interquartile range (IQR).

The severity of BKS and DKS is based on the average 50th, 75th and 90th percentiles of the distribution of BKS and DKS from control subjects recordings (see (Griffiths et al., 2012)). These have been used to define four levels of severity for bradykinesia and dyskinesia; Level I: <50th percentile of controls, Level II: 50–75th percentile of controls, Level III: 75th −90th percentile of controls and Level IV: >90th percentile of controls.

The red lines represent the pre-programmed prescribed L-dopa times, and the red diamonds indicate times when the patient registered taking their L-dopa.

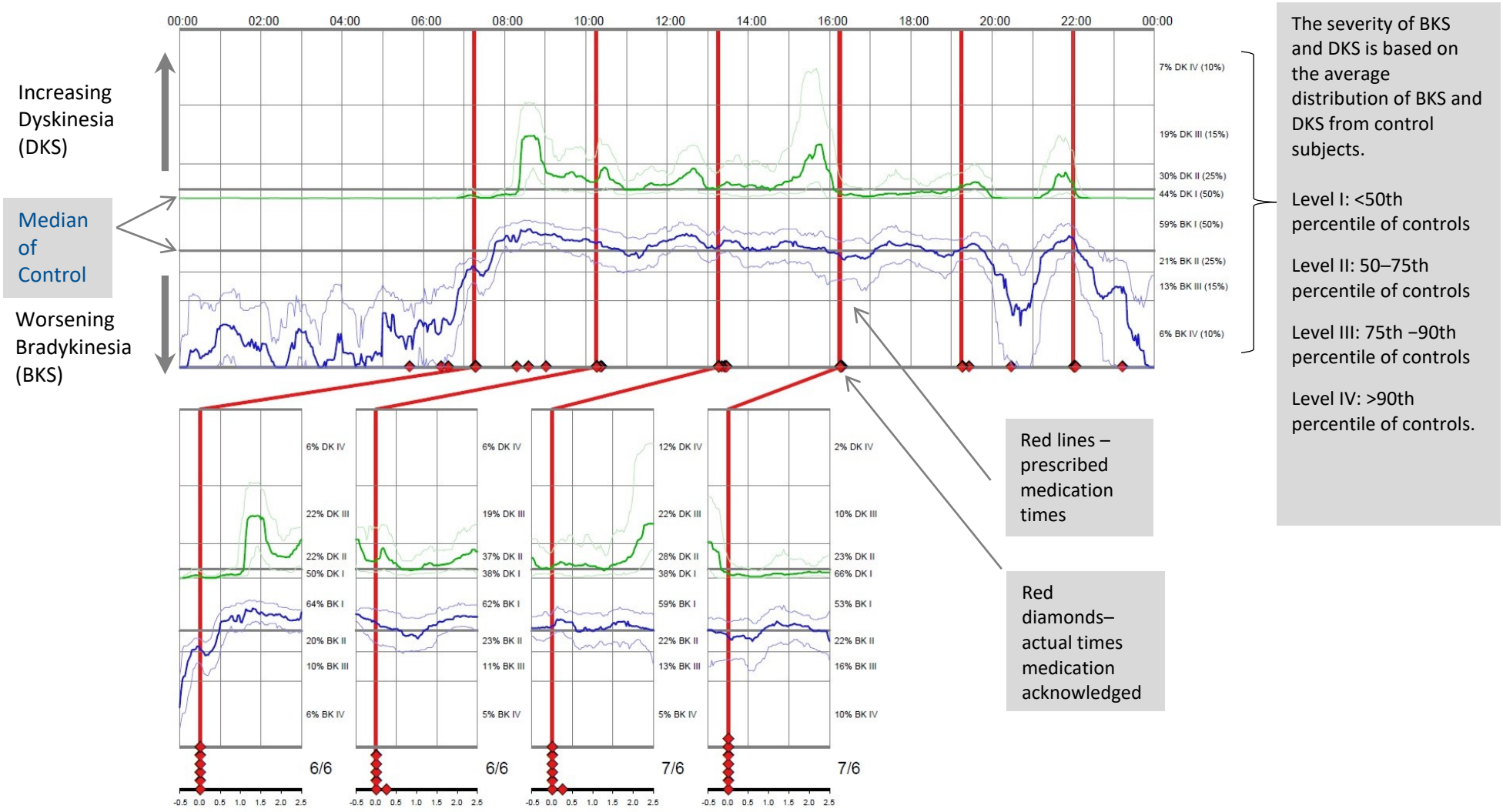


Figure 40 An example of a PKG™ bradykinesia and dyskinesia summary graph. The thick lines represent median bradykinesia (blue lines) and dyskinesia (green lines) from over the duration the PKG™ was worn, and the thin lines represent the interquartile range (IQR). The red lines represent the pre-programmed prescribed L-dopa times, and the red diamonds indicate times when the patient registered taking their L-dopa.

4.1.2.3 Motor Fluctuations (FDS Score)

Motor fluctuations refer to the presence of dyskinesia or the re-emergence of bradykinesia prior to the next dose of L-dopa (see section 1.2.16). An examination of the variation of bradykinesia and dyskinesia over the course of a dose of L-dopa may therefore reflect the severity of fluctuations a patient is experiencing.

Horne (2015) used PKG™ data to investigate fluctuations by examining the combined variations in the BKS and DKS.

The authors examined the IQR of BKS and DKS in 527 PwP who had worn a PKG™ over a period of 6 days. The IQR for each score was summed to produce a combined IQR.

The median combined IQR was able to distinguish between populations of known fluctuators (patients on waiting list for Deep Brain Stimulation (DBS)) and non-fluctuators (disease duration ≤3 years) (p<.001). The area under the receiver operating characteristic (ROC) curve (AUC) for combined IQR was 0.98, and provided a sensitivity of 97.1% and a selectivity of 87.5% (at combined IQR of 22.5).

An algorithm was then developed to express the combined IQR as a formula for the PKG™ Fluctuation Score (FDS) (see Horne et al., 2015).

The authors concluded that the combined IQR of BKS and DKS (FDS) provides a useful tool for identifying patients experiencing motor fluctuations, allowing for timely and effective intervention.

4.1.2.4 Tremor (PTT score)

In the PKG™ algorithm, the accelerometry data from the 6 day recording period is sampled at 50 Hz and processed through a 250 sample sliding window in steps of 1 second (s). Tremor is identified when the accelerometery data meets certain frequency criteria including:

- The peak spectral power in each 1 second step is larger than the spectral median between 1 Hz and 10 Hz.
- The frequency of the spectral peak in each step is between 2.8 Hz and 10 Hz.
- The frequency of the spectral peak within a step differ from the frequency of the spectral peak in the two immediately adjacent steps by no more than 0.4 Hz/s.

The percentage of time that tremor is present (PTT) is then calculated for the duration of the waking day (9am-6pm). For full details of the tremor algorithm, see Braybrook (2016).

Braybrook and colleagues (2016) were interested in exploring the potential of the PKG™ tremor algorithm to identify the presence of clinically diagnosed tremor, and to correlate its appearance with bradykinesia and dyskinesia (Braybrook et al., 2016).

People with Parkinson's were recruited to the study (n=194) who were either previously known to have had tremor (T+) or did not have tremor (T-). Data from PwP and 28 control subjects wore the PKG™ for 6 days on the most severely affected wrist. Following recording, the data was downloaded and analysed.

A ROC curve was generated and performed to find the PTT score that discriminated between T(+) and T (-) with the greatest sensitivity and selectivity.

In the T(-) cohort, a PTT 0.8% had a selectivity and sensitivity of 92.5% and 92.9% respectively (AUC =0.92).

In the T(+) cohort, a PTT of 0.8% again provided the best selectivity and sensitivity (90.3 and 92.7 respectively: AUC=0.96).

In relation to BKS and DKS scores, the authors found tremor to be present more frequently when the BKS is high than when it is low. There was little relationship between tremor and high DKS.

4.1.2.4.1 Tremor Summary Output

Figure 41 displays an example of a tremor summary plot that the clinician receives after the patient has worn the PKG™ for the required duration (6 days).

Each 2-minute epoch in which tremor is present is plotted in the tremor summary as black markings on the corresponding days and times. The red lines on the summary represent the patient's pre-programmed prescribed L-dopa times.

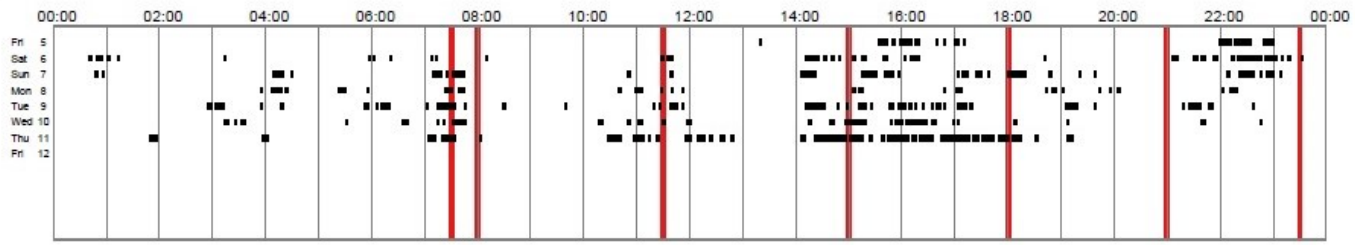


Figure 41 An example of a PKG™ tremor summary. Each 2-minute epoch in which tremor is present is plotted in the tremor summary as black markings on the corresponding days and times. The red lines represent pre-programmed prescribed L-dopa times. In this example, tremor is seen to cluster around medication times, suggesting dopa-responsiveness.

4.1.2.5 Immobility (PTI Scores)

In the PKG™ algorithm, periods of immobility are identified as 2 minutes or greater in length, with the BKS being at or below the threshold of 80 BKS. The amount of time spent immobile is then calculated as a proportion of the waking day (Percentage Time Immobile, PTI (%)).

Kotschet et al (2014) investigated PKG™ recordings from 68 PwP and 30 controls over a period of 10 consecutive days (Kotschet et al., 2014) to explore the potential of using the PKG™ PTI as a marker of daytime sleepiness. The PTI was compared against two widely accepted markers of Excessive Daytime Sleepiness (EDS), which were the Ambulatory daytime polysomnography (PSG) and the Epworth Sleepiness Scale (ESS) (Johns, 1991).

Daytime ambulatory PSG was recorded simultaneously alongside the PKG™ recording, and the presence (+) or absence (-) of immobility (PTI Score) and sleep (PSG score) for each subject was explored. The Kappa statistic for the concordance of the two methods was high at 0.63, with the sensitivity at 0.83 and the selectivity at 0.89.

When compared to the ESS, patients with an ESS ≥10 (considered 'high') had significantly higher PTI scores than subjects with a low ESS (p=.001).

Furthermore, patients with a high PTI had higher BKS than those with low PTI (p<.0001). In contrast, dyskinesia as measured by the DKS was higher in patients with a low PTI than a high PTI (p<.0001).

Due to the high levels of concordance between the PTI and established measures of EDS, the authors concluded that the PTI could be used as a useful surrogate marker of EDS (Kotschet et al., 2014).

4.1.2.5.1 Immobility Summary Output

Figure 42 displays an example of an immobility summary plot that the clinician receives after the patient has worn the PKG™ for the required duration (6 days). Each 2-minute epoch in which immobility is present is plotted in the immobility summary as black markings on the corresponding days and times. Although there is no algorithm available for overnight sleep, it is possible to use the immobility summary to make a visual qualitative assessment of overnight sleep quality, by evaluating the duration and continuity of immobility during night time hours.

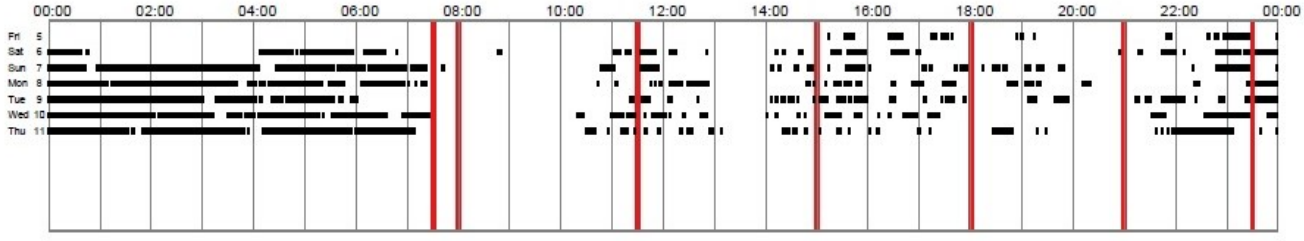


Figure 42 An example of a PKG™ immobility summary. Each 2-minute epoch in which immobility is present is plotted in the immobility summary as black markings on the corresponding days and times. The red lines represent pre-programmed prescribed L-dopa times. In this example, the patient has good sleep overnight, but evidence of immobility throughout the day, suggestive of daytime somnolence.

4.1.3 Clinical utility of the PKG™

There is evidence to support the use of the PKG™ to enhance clinical decision making in PD care. A recent survey study of movement disorder specialists using the PKG ™ as part of routine PD care revealed that the PKG™ provided novel additional information (beyond that routinely captured) in 41% of 112 visits, and resulted in an adjustment to a patient's therapeutic management plan almost a third of the time overall (Santiago et al., 2019).

The results demonstrated that the PKG™ most commonly provided new information in relation to daily OFF time, which highlights an area where the PKG™ can provide value to

clinicians. Furthermore, the survey indicated the PKG™ was found to be most useful when given to new patients to the service after their first patient visit, to establish a baseline assessment of symptoms and determine what next steps in medical management were needed.

A Parkinson's UK (PUK) evaluation on the clinical utility of the PKG™ involving information from 209 patients from seven centres across the UK (including University Hospitals Plymouth NHS Trust (UHPNT)) revealed similar findings (Carroll, Kobylecki, Silverdale, Thomas et al, 2019). The PUK evaluation demonstrated information from the PKG™ provided additional information to inform clinical decision making in 45.5% cases. Changes in decision making included ten cases where the PKG™ results prompted a change to treatment when clinical assessment alone suggested no adjustments were needed. These findings further demonstrate potential for the PKG™ to add value to clinical decision making, and facilitate management of PwP.

In addition, the PKG™ has been recently recommended for use by two expert panels of internationally recognized movement disorder specialists (Odin et al., 2018; Pahwa et al., 2018). The groups promoted the utilisation of PKG™ measurements to improve the clinical management of PD. Furthermore, the panels discussed that while the PKG™ should be used by all clinicians, the least experienced may find it the most value, provided they were supported by guidance from experts.

4.1.4 Indicative Thresholds

The use of indicative thresholds when utilising objective measurement in the clinical management of PwP has been identified as a key aspect of their implementation (Odin et al., 2018).

Indicative thresholds based on PKG™ normal target ranges for BKS and DKS scores have been developed to separate “treated” from “undertreated” symptoms, to allow for subsequent therapeutic intervention with the aim of moving a patient’s PKG™ scores to ‘within target’ of the desired BKS or DKS range (Farzanehfar et al., 2018; Odin et al., 2018) (see Table 29).

Previously published PKG™ indicative thresholds are summarised in Table 29. The slight differences in the thresholds displayed in Table 29 demonstrates these are still under evolution, and are expected to be refined further as the PKG™ is used more extensively on larger cohorts of patients.

Table 29 Previously published indicative thresholds for treated and undertreated bradykinesia and dyskinesia using the PKG™.

	Odin et. al, 2018		**Farzanehfar et. al, 2018b**		**GKS Parameters (Personal Communication from GKC personnel)**	
BKS Treatment Range	BKS	FDS	BKS	FDS	BKS	FDS
Optimally controlled	<23	Not specified	<23	>8	<23	>8
Acceptable control	≥23 and ≤25	No fluctuations	>23 <26	Not specified	>23<26	And/or >7.5
Uncontrolled	>25	Not specified	>26	Or <7.5	>26	And/or <7.5
DKS Treatment Range	DKS	FDS	DKS	FDS	BKS	
Optimally controlled	<7	And FDS <10.8	<9	Not specified	<9	And <10.8
Acceptable control	7-9	And FDS <13 and no fluctuations	Not specified	Not specified	>7<9	And <13
Uncontrolled	>9	Not specified	7-9	And >13	>7<9	And >13

Farzanehfar (2018) carried out a recent investigation of the PKG™ in an Australian PD cohort and demonstrated benefit from treating PD symptoms against indicative thresholds outlined in Table 29 (under column 2, Farzanehfar et. al, (2018)). Patients in the treated range (within target) had better motor (UPDRS III), non-motor (NMS, UPDRS total) and quality of life (PDQ-39) scores than those in the undertreated range (Farzanehfar et al., 2018). These findings demonstrate the potential benefit of treating patients in line with predefined thresholds.

4.1.5 Implementation of the PKG™ at University Hospitals Plymouth NHS Trust (UHPNT)

As discussed previously, national standards of PD care suggest that PwP with early PD should be seen at regular intervals of 6-12 months to review their diagnosis, with follow-up review increasing to 2-3 monthly intervals (according to clinical need) to assess the response to medication, titrate dosage and re-visit the diagnosis. In addition, NICE guidelines recommend that people with advanced PD may require review at frequent intervals (every 2–3 months) (NICE, 2017). Within our service, we have recently found that 46% of patients have consultant appointments delayed by more than 6 months, and 60% have not seen the community nurse within the last year. Our current waiting time is 12-24 months for a routine review appointment in the consultant clinic (see section 1.2.19).

Due to the long wait between appointments in our service, we expect there will be a high number of patients with an unmet treatment need experienced between clinic appointments. Past research has demonstrated patients who do not have regular review by a PD specialist have a higher risk of an adverse outcome including falls, nursing home placement and death (Willis, Schootman, Evanoff, Perlmutter, & Racette, 2011).

New patients in our service follow the New Patient (NP) Pathway (see Figure 43). Within this pathway, patients are seen regularly at 2-3 month intervals over the first 18 months following diagnosis, with opportunities for titration of medication to optimise treatment at each clinic visit, as well as receiving education, treatment and advice about non-motor symptoms. Patients progress from this pathway at around 18 months (or once on a stable medication regime) onto the Follow Up (FU) pathway.

In an attempt to address service pressures and to facilitate the remote monitoring of patients during long waits between clinic appointments, the PKG™ was implemented (since 2015) as part of routine PD care in almost 600 patients at University Hospitals Plymouth NHS Trust (UHPNT) in both FU and NP pathways.

4.1.6 Research Question

I undertook an evaluation of the utility of the PKG™ to identify patients experiencing unmet treatment needs inbetween clinic appointments. In addition, I undertook an evaluation of patient acceptability of the PKG™.

4.1.7 Hypothesis

Due to the long wait between appointments in our service, I hypothesised the PKG™ would identify a high number of patients experiencing an unmet treatment need between clinic appointments.

4.1.8 Chapter Outline

This chapter will be divided into two parts.

Part One will describe a clinical service evaluation of the the utility of the PKG™ to identify patients experiencing unmet treatment needs inbetween clinic appointments.

Part Two will describe an evaluation of patient acceptability of the PKG™.

Following Part One and Part Two, there will be an overall chapter discussion and conclusion.

4.2 Part One

4.2.1 Methods

This was a clinical service evaluation of PKG™ use within routine clinical care pathways for PwP at University Hospitals Plymouth (UHPNT); as such ethical approval was not required.

4.2.1.1 Participant Inclusion

All PKG™ recordings included as part of the evaluation (n=217) were performed as part of routine care in either the Follow Up (FU) Pathway or the New Patient (NP) Pathway at UHPNT between July 2015 and January 2018, prior to the introduction of a web portal system (January 2018).

4.2.1.2 The Follow Up (FU) Pathway

Patients in the FU pathway (n=88) have progressed beyond their first year of care. The PKG™ was implemented to identify areas of unmet need between clinic visits. The PKG™ was arranged for patients for whom it was felt treatment changes were likely to be required prior to the next clinic appointment.

4.2.1.3 The New Patient (NP) Pathway

Patients in the NP pathway (n=78) follow a nurse-led care pathway that encompasses the first year of care post diagnosis (summarised in Figure 43). The clinic appointments allow for detailed evaluation (as outlined below).

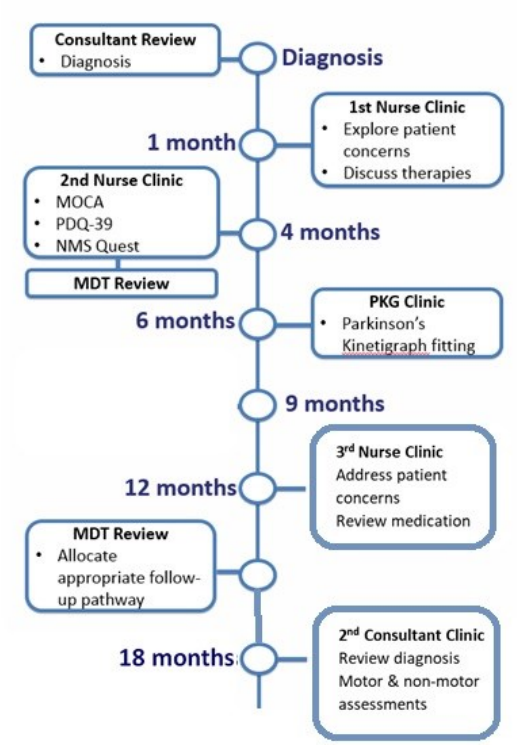


Figure 43 The New Patient (NP) pathway at UHPNT. Prior to receiving the PKG™, measures of cognition, quality of life and NMS-burden are administered.

4.2.1.4 The PKG™ Process

The PKG™ process is outlined in Figure 44. The PKG™ was applied in clinic and worn by patients for up to 6 days. During the clinic visit, the device was programmed with the patient's medication regime and activated. The patient was then shown how to take the device on and

off and acknowledge medication reminders. Patients were provided with an information leaflet about the device as well as contact information should there be difficulties.

All other processes, including reporting PKG™ findings and discussing with the patient any changes to treatment based on PKG™ findings, were carried out remotely (see Figure 44). After 6 days, patients returned the device by post, and the device was then connected to a tablet device which allowed upload of the data to the cloud. A PKG™ graph was emailed back to the clinician within a few minutes for interpretation and reporting. The graph included the graphical representation described previously (see section 4.1.2.2.1) as well as numerical values for BKS, DKS, FDS, PTT and PTI.

Not all of these parameters were available in 2015; PTT was only available on later graphs. Following preparation of the report, the results were shared with the patient, community nurse and GP by letter, and copy of report and graph. The patient was then telephoned by a member of the hospital team to discuss the report; any treatment suggestions were discussed, and implemented if agreed. A copy of the reporting template is in appendix 21 (section 8.21).

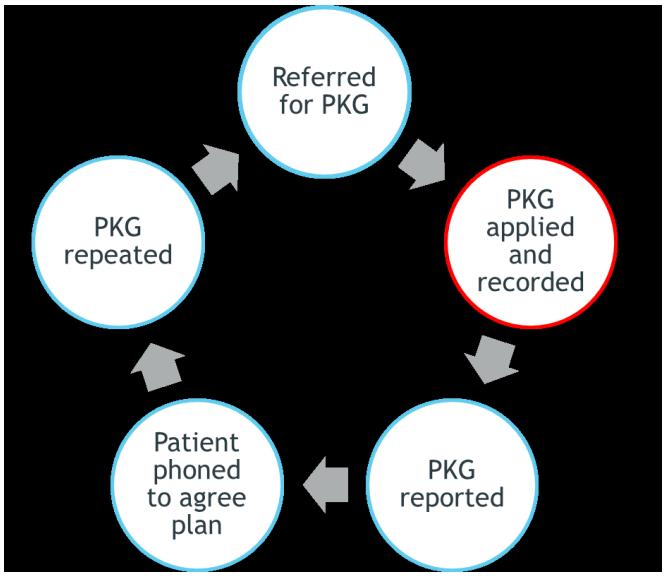


Figure 44 The PKG™ process at UHPNT. The blue circles represent processes that were remote, and the red circles represent the processes that took place in clinic.

4.2.1.5 PKG™ Reporting

A consultant neurologist and two Parkinson's Disease Nurse Specialists (PDNS) were trained in PKG™ reporting, which required completing an online assessment and attending advanced reporting training. The neurologist oversaw the reporting of each of the PDNS until reporting was standardised.

4.2.1.6 PKG^{TM} database

I developed the PKG^{TM} database, in collaboration with the clinical team, to capture key information related to PKG^{TM} recordings including; relevant PKG^{TM} scores, patient demographics (age, sex, disease duration, LEDD), available clinical scores (e.g. prognosis score), reason for PKG^{TM} request, clinical interpretation of PKG^{TM} findings and treatment recommendations. Where available, I investigated follow up patient clinic letters to obtain

information on reported outcomes following a PKG™, to see whether recommendations were adhered to.

The PKG™ database was completed by the relevant member of the PD clinical team following completion of a PKG™ report (see appendix 22 (section 8.22).

4.2.1.7 Standardisation of responses

In order to standardise database entries and quantify responses for analysis, dropdown multiple choice options were available for each variable of the database (see Table 30). These options were designed in collaboration with the PD clinical team to best reflect clinical practice. If more than one of the multiple choice options applied per patient, the team member was able to select multiple options for each of the variables.

Table 30 The multiple choice dropdown options available in the PKG™ database

Purpose of PKG™	PKG™ Finding	Recommendation
Baseline Assessment	Delayed on	Add another agent (constipation)
Evaluate Bradykinesia	Device failure	Add another agent (mood)
Evaluate Dyskinesia	Dyskinesia	Add another agent (other)
Medication response	Early morning off	Add another agent (pain)
Sleepiness/ Sleep cycle	Excessive daytime sleepiness	Add another agent (postural hypotension)
Tremor extent	Good quality sleep	Add another agent (sleep)
Wearing off	No clear drug response	Add another agent (motor control) amantadine
Other	Patient error	Add another agent (motor control) oral DA
	Poor drug adherence	Add another agent (motor control) oral ldopa
	Prevalent tremor	Add another agent (motor control) MAOI
	Sleep fragmentation	Add another agent (motor control) COMT I
	High BKS	Add another agent (motor control) DA patch
	Varied drug response	Add another agent (motor control) disp regime
	Wearing off	Address sleep hygiene
	Well managed	Advise exercise
	Improved	Alter dose timings
	Other	Increase dose of existing agent
		Increase frequency of existing agent
		Reduce an agent
		Switch agents
		Withdraw an agent
		Consider advanced therapy
		Bowel management advice
		Diet management advice
		No change

4.2.1.8 Statistical Analysis

In order to evaluate the clinical utility of the PKG™ and the associated indicative thresholds to identify patients experiencing unmet treatment needs, I carried out a sensitivity and specificity analysis. Specifically, I was interested in comparing the patients identified as undertreated by the PKG™ indicative thresholds in comparison with the patients identified as undertreated by clinican interpretation of the PKG™.

To achieve this, the database was searched for patients who met the indicative threshold requirements for treated or undertreated bradykinesia or dyskinesia (see Table 29, column 1 (Odin, 2018)). These parameters for identifying patients in the treated or undertreated range were used for analysis as they were published most recently, and were recommended by a panel of 11 internationally recognised movement disorder specialists as part of guidance on the incorporation of objective measurement into the management of PD (Odin et al., 2018).

Patients that had been identified by clinican interpretation of the PKG™ report and graph as undertreated were also identified by highlighting any database entries that included the findings “early morning off”, “no clear drug response”, “varied drug response”, “wearing off”, “high BKS” and “dyskinesia”.

4.2.2 Results

4.2.2.1 Clinical Evaluation

217 PKG™ recordings were carried out as part of routine PD care at UHPNT from July 2015 – January 2018.

Of the 217 recordings identified, 7 had incomplete data available, 4 experienced a device failure, and 4 were affected by patient error (eg. off wrist for long periods of recording), thus 202 PKG™ recordings were available for analysis.

Of the 202 complete and correct PKG™ recordings, 36 were repeat PKG™s. Due to the small number of repeat data available, repeat data was not included as part of the main analysis.

One hundreded and sixty-six complete baseline PKG™ recordings were therefore included as part of the clinical evaluation. All patients included as part of the evaluation belonged to one of two PD management pathways as described previously (see section 4.2.1.1) (FU (n=88) and NP (n=78) pathways).

4.2.2.2 Patient Demographics and PKG^{TM} data

Patient demographics and PKG^{TM} data for the FU and NP pathways are summarised in Table 31.

Table 31 Patient demographics and PKG data in the FU and NP pathways, median (min-max range)

	FU (n=88)	NP (n=78)
Age (years)	71 (46-85)	69 (39-87)
Disease Duration	6yrs (4m- 23yrs)	1yr (2m-13yrs)
LEDD (mg)	750 (0-2674)	375 (0-1000)
BKS	27.2 (6.9-55.9)	29.6 (15.9-40.5)

DKS	1.9 (.10-60.4)	1 (.1-11.2)
FDS	7.6 (3.8-31.4)	6.9 (4-17)
PTT	1.35 (0-50.1)	3.1 (.1-40.2)
PTI	5.4 (.1-48.9)	9.4 (.3-35.4)

4.2.3 Utility of the PKG™ indicative thresholds to identify patients experiencing unmet treatment needs

Table 32 displays the frequency of patients (in the FU and NP pathways combined) identified by the PKG™ parameters (see Table 29 column 1 (Odin, 2018)) as undertreated from a motor perspective (undertreated bradykinesia and dyskinesia), the frequency of patients identified by clinican interpretation of the PKG™ report and graph as undertreated from a motor perspective, and the frequency of patients identified by both the PKG™ parameters and clinician interpretation of the PKG™ as undertreated.

The median (min-max range) age, LEDD, disease duration and FDS scores for patients that were identified as undertreated by either the PKG™ parameters, the clinical team, or both, are also summarised in Table 32.

Table 32 Demographic information for patients identified as undertreated from a motor perspective by the PKG™ parameters, by the clinical teams or by both the PKG™ parameters and the clinical teams. Median (min-max range) values are presented.

Undertreated Bradykinesia	**PKG™ Parameters only** **n= 10 (6%)**	**Clinical team only** **n= 18 (11%)**	**Identified by both** **n=106 (64%)**
Age (years)	70.5 (54-85)	73 (51-80)	70 (48-87)
LEDD	462.5 (53-750)	1100 (6-2674)	475 (0-2000)
Disease duration (months)	29 (9-113)	78 (9-234)	38.5 (2-281)
BKS Score	30.3 (25.1-40.9)	22.1 (16.9-25)	31.25 (25.2-55.9)
FDS Score	7.15 (5.7-9.8)	9.55 (6.1-14.1)	6.8 (3.8-10.9)
Undertreated Dyskinesia	**PKG™ Parameters only** **n=4 (2%)**	**Clinical team only** **n= 10 (6%)**	**Identified by both** **n=9 (5%)**
Age (years)	66.5 (55-76)	70.5 (48-80)	65 (49-78)
LEDD	400.5 (100-850)	1000 (325-2139)	1171 (225-1255)
Disease duration (years)	46 (27-60)	131 (40-195)	105 (59-270)
DKS Score	11.6 (9.5-13.8)	3.8 (.3-7.9)	16.7 (10.3-60.4)
FDS Score	13.7 (12.2-17)	9.25 (6-14.2)	15.7 (11-31.40)

The data in Table 32 demonstrates that an additional 28 patients were identified by clinician interpretation of the PKG™ report as undertreated from a motor perspective that were not identified using the PKG™ indicative thresholds alone.

4.2.3.1.1 Undertreated Bradykinesia

The sensitivity and specificity of the indicative thresholds to correctly identify patients as undertreated from a bradykinesia perspective was calculated, as these were the patients with the greatest care need.

The sensitivity of the BKS parameter was 0.85 (106/(106+18)), meaning the PKG™ indicative thresholds for undertreated BKS (BKS >25) (as defined by Odin and colleagues (2018)) will correctly identify 85% of patients who are undertreated from a bradykinesia perspective.

The specificity of the BKS parameters was 0.76 (30/(30+9)), meaning the PKG™ indicative thresholds for undertreated BKS (BKS >25) (as defined by Odin and colleagues (2018)) will correctly identify 76% who are not undertreated from a bradykinesia perspective.

It was of interest to investigate the reasons why either the clinical team or the PKG™ did not identify certain patients as undertreated from a motor perspective, and this will be explored below.

Patients identified as undertreated from a bradykinesia perspective by the PKG™ parameter only (n=10):

Clinic letters for three of the patients in this group were not available at the time of analysis. For two of the patients identified as undertreated by the PKG™ parameter only, they had high levels of immobility which limited the validity of the bradykinesia recording. Three of the

reports queried whether the reading was representative of true symptom severity, due to the PKG™ being carried out over the Christmas break.

However, for two patients the main finding reported by the clinical team was prevalent tremor, which might have diverted attention away from their bradykinesia.

Patients identified as having undertreated bradykinesia by the clinical team only (n=18):

This group of patients showed signs of wearing off throughout the day, but had an optimal response on average, and so failed to be identified as undertreated using the PKG™ parameter. Some patients in this group also had no clear medication response, or delayed responses to medication (delayed on).

Figure 45 and Figure 46 display a PKG™ graph and tremor summary plot respectively, for one of the patients in this group. The graph demonstrates this patient (from the NP pathway) was identified as having some wearing off and peri-dose tremor. The medications for this patient at the time of recording were Ropinirole XL 6mg a day at 13:00. Although the medication reminders should only be used for short acting dopa preparations, in this case they have been used as a dopamine agonist (DA) reminder.

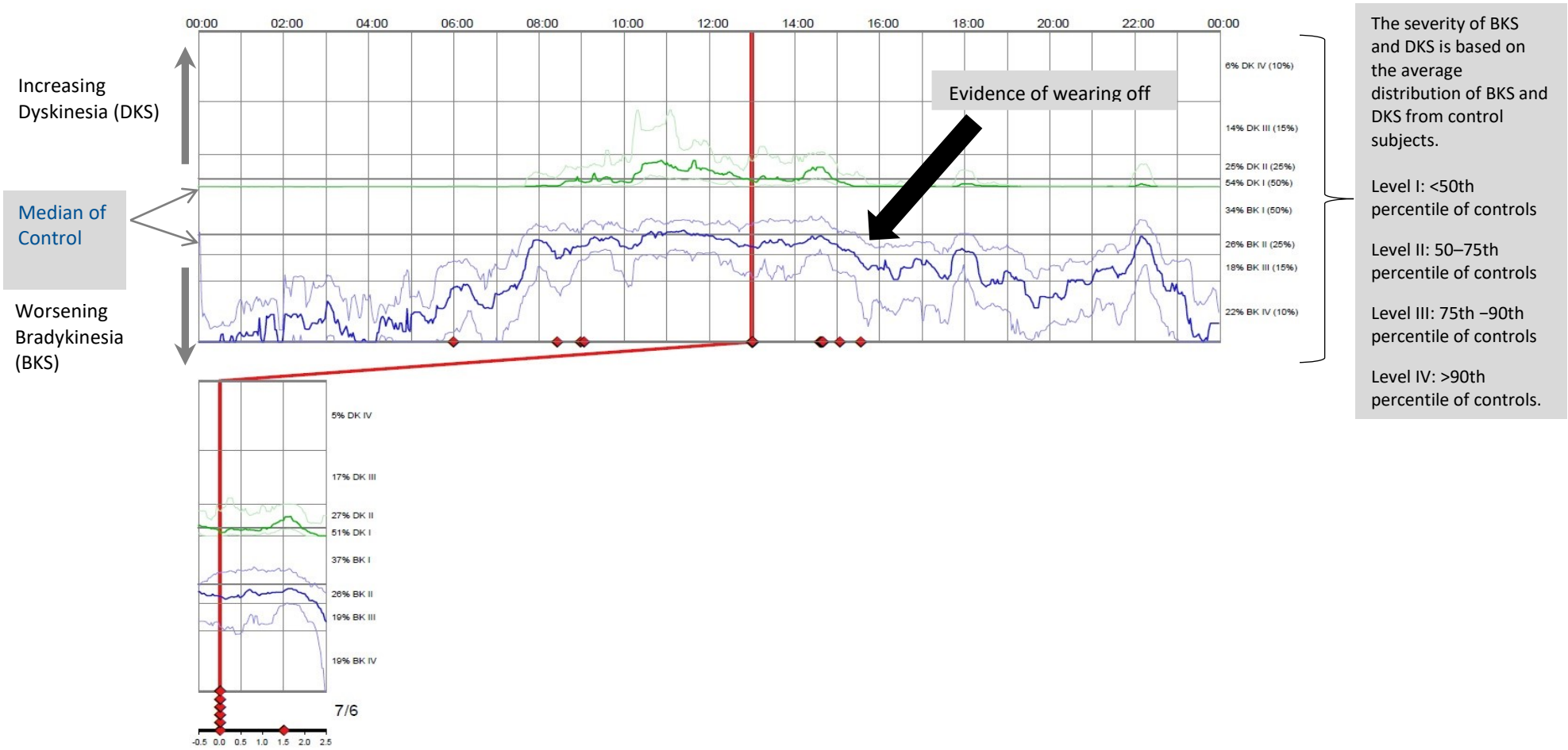


Figure 45 PKG™ graph for a patient that was not identified by PKG™ parameter as undertreated from a bradykinesia perspective, despite demonstrating some wearing off. The thick lines represent median bradykinesia (blue lines) and dyskinesia (green lines) from over the duration the PKG™ was worn, and the thin lines represent the interquartile range (IQR). The red lines represent the pre-programmed prescribed L-dopa times, and the red diamonds indicate times when the patient registered taking their L-dopa.

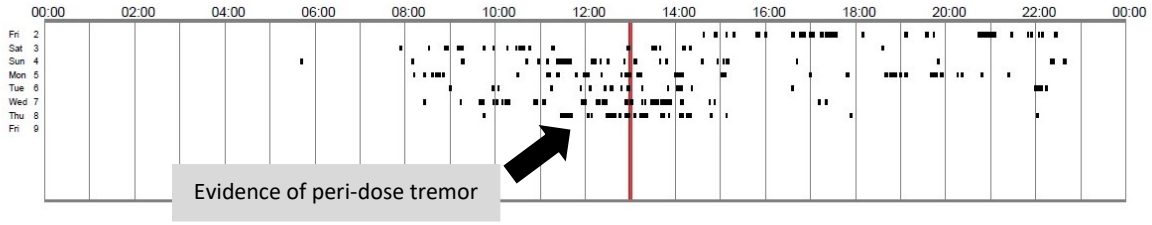


Figure 46 Tremor Summary for a patient that was not identified by PKG™ parameter as undertreated from a bradykinesia perspective, despite demonstrating reoccurrence of peri-dose tremor. Each black mark on summary plot represent every 2min epoch where tremor is. The red lines represent the pre-programmed prescribed L-dopa time.

The tremor score (PTT) for this patient was 3.8% which is above the suggested cut-off for acceptable level of tremor (1%) (Braybrook et al., 2016). Despite this finding, this patient was not identified as undertreated from a bradykinesia perspective in line with published indicative thresholds (this patient had a BKS score of 23).

To ensure the PKG™ graph represented clinically meaningful information, I reviewed the follow up clinic letter for this patient. Wearing off in the afternoon was confirmed by the patient, although they reported they were managing well. It was agreed that the Ropinirole would be moved to an earlier time in the day to give the patient additional support when they are most active (this patient attended the gym most mornings). The clinician also discussed commencing levodopa medication with the patient.

4.2.3.1.2 Undertreated Dyskinesia

The sensitivity and specificity of the PKG™ indicative thresholds to correctly identify patients as undertreated from a dyskinesia perspective were calculated.

The sensitivity of the PKG™ parameter was .47 (9/(9+10) = .47), meaning the PKG™ indicative thresholds for undertreated DKS (DKS >9) (as defined by Odin and colleagues (2018)) will correctly identify 47% of patients who are undertreated from a dyskinesia perspective.

The specificity of the PKG™ parameter was .97 (156/(156+4)= .97) meaning the PKG™ indicative thresholds for undertreated DKS (DKS >9) (as defined by Odin and colleagues (2018)) will correctly identify 97% who are not undertreated from a dyskinesia perspective.

It was of interest to investigate the reasons why either the clinical team or the PKG™ did not identify certain patients as undertreated from a dyskinesia perspective, and this will be explored below.

Patients identified as undertreated from a dyskinesia perspective by the PKG™ parameter only (n=4):

Three of the patients identified as undertreated by the PKG^{TM} parameter were reported by the clinical team as having a good overall level of function. One patient was reported as having a striking dopa-responsive tremor with wearing off, and this was the overriding issue picked up on by the clinical team. The PKG^{TM} graph and tremor summary for this patient is displayed in Figure 47 below.

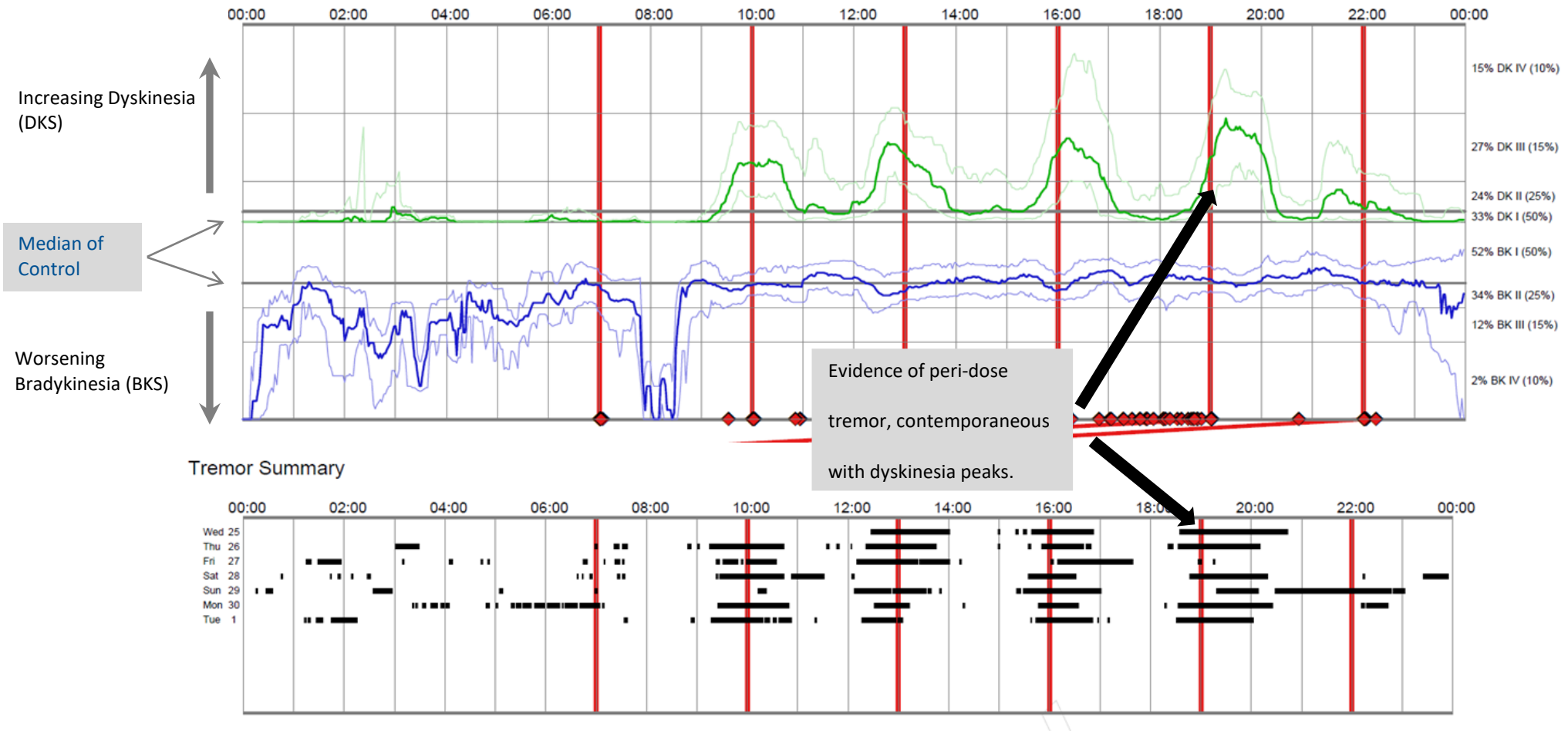


Figure 47 PKG™ graph (above) for a patient that was identified by PKG™ parameter only as undertreated from a dyskinesia perspective, but was not identified by the clinical team. The thick lines represent median bradykinesia (blue lines) and dyskinesia (green lines) from over the duration the PKG™ was worn, and the thin lines represent the interquartile range (IQR). The red lines represent the pre-programmed prescribed L-dopa times, and the red diamonds indicate times when the patient registered taking their L-dopa. The tremor summary (below) demonstrates evidence of dopa-responsive tremor. Black marks on the summary plot represent every 2min epoch where tremor is. The red lines represent the pre-programmed prescribed L-dopa time.

The DKS trace (green line) and the tremor trace below (tremor summary) demonstrate that tremor can mimic DKS if it is of low frequency and large enough amplitude, and this is referred to as 'tremor bleed through'.

Patients identified as having undertreated dyskinesia by the clinical team only (n=10):

Patients in this group were typically described as having mild-moderate peak dose dyskinesia, but had acceptable levels of dyskinesia overall, and so were not identified by the PKG™ parameter as having undertreated dyskinesia.

Figure 48 is an example of a PKG™ graph that demonstrates some peak dose dyskinesia despite having acceptable levels of dyskinesia overall (DKS <9).

The medications for this patient at the time of recording were as follows: Madopar 250mg 3 times a day at 06:00, 11:30, 16:30, Madopar CR 250mg a day at 21:00 and Rotigotine 4mg a day at 08:00. As before, the red lines only indicate doses of L-dopa.

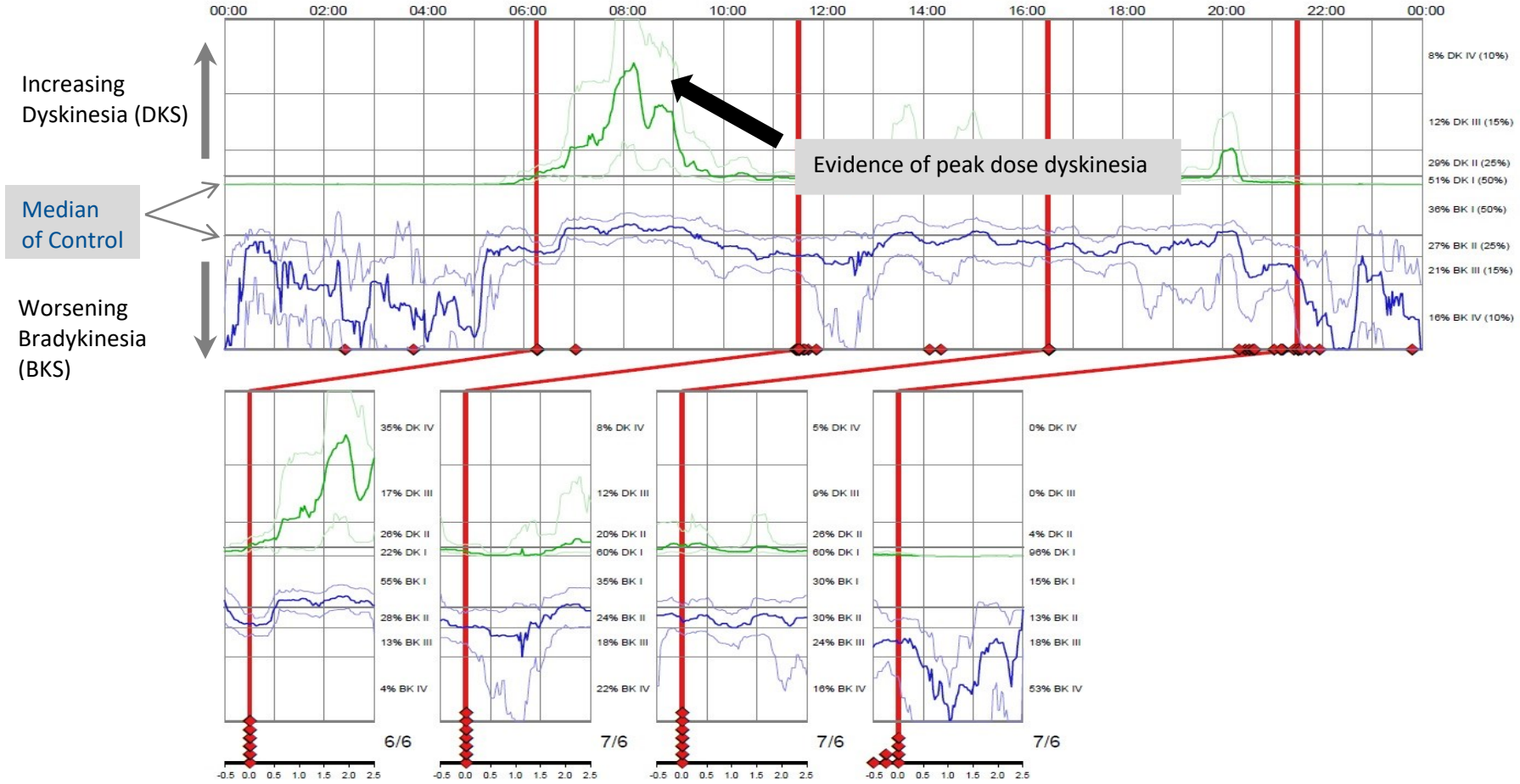


Figure 48 PKG™ graph for a patient that was not identified by PKG™ parameter as undertreated from a dyskinesia perspective despite demonstrating peak dose dyskinesia. The thick lines represent median bradykinesia (blue lines) and dyskinesia (green lines) from over the duration the PKG™ was worn, and the thin lines represent the interquartile range (IQR). The red lines represent the pre-programmed prescribed L-dopa times, and the red diamonds indicate times when the patient registered taking their L-dopa.

To ensure the PKG™ graph represented clinically meaningful information, the follow up clinic letter was reviewed. The clinician noted that the patient was mildly dyskinetic, but wearing off was the overriding symptom discussed in clinic, and was treated by an increase of Madopar to 250mg four times a day, in addition to the Madopar CR 250g dose at night, with a plan to review after a couple of weeks on this regime.

4.3 Part Two

To evaluate patient acceptability of the PKG™, I carried out a patient evaluation. As this was a clinical service evaluation, ethical approval was not required.

4.3.1 Method

4.3.1.1 Item development

A PKG™ project group comprising 4 patients who had expressed an interest in research areas that involved the use of technology in PD were contacted regularly via email and telephone to discuss the design of the patient evaluation and accompanying documentation (e.g. the cover letter), in collaboration with the PD clinical team. Once the patient evaluation items had been developed, the wording and formatting of the questionnaire were reviewed by the patient group to ensure it was understandable by patients, and necessary amendments were made.

4.3.1.2 Evaluation Items

The patient evaluation items (n=20) focussed on 5 key areas: (1) Usability of the device (4 items) (2) PKG™ Results Communication (5 items) (3) Impact on Care (3 items) (4) Overall

satisfaction (5 items) and (5) Areas of concern (3 items). Appendix 23 (section 8.23) details the patient evaluation in full.

All items concerning satisfaction were rated on a five point scale from 1, strongly unfavourable to 5, strongly favourable, or were YES/NO answers from which satisfaction could be inferred. A score >3 was considered favourable for five-point items and a score of >1 was considered favourable for 2 point items. The total satisfaction score was obtained by summing the score of all satisfaction items (maximum possible score of 84 in total).

Once finalised, 100 questionnaires were sent via post (Feb 2018) to the most recent PD patients to have received a PKG™ at UHPNT. Patients were provided with a freepost envelope to return their completed questionnaire within 28 days.

4.3.1.3 Statistical Analysis:

The median values for each of the satisfaction items was given as a value of central tendency. The reliability of the questionnaire was examined by Cronbach's alpha (Cronbach, 1951).

4.3.2 Part Two: Results

61 patients (median age 71 years (39-87), median disease duration 2.5 years (11 months- 17 years)) completed and returned their patient evaluation (61% return rate). As all evaluations were anonymised, it was not possible to identify which pathway responders belonged to (FU or NP).

4.3.2.1 Items Scores

In Table 33 the median scale scores are grouped in the five areas of the evaluation (described above). The percentage of favourable answers (scores >3 for five-point items and >1 for 2

point items) are also given. The mean total score was 48 (*SD*=11) out of a possible maximum total of 84.

4.3.2.2 Evaluation Reliability

To examine the internal consistency of evaluation items relating to satisfaction, the Cronbach's alpha was calculated. The questionnaire reliability was found to have a Cronbach's alpha of .94.

Table 33 Median scale score and percentage of favourable answers for each satisfaction item of the Patient Evaluation

Area of Evaluation	Max Score	Median response	% favourable
PKG™ Usability			
Before you received the PKG™, what was your level of understanding about the purpose of the device?	5	4	54
How helpful was the information provided to you when you first received the PKG™ in explaining about the device?	5	4	80
How comfortable did you find wearing the device?	5	4	82
How did you find the process of returning the device?	5	5	98
PKG™ Results			
If applicable how useful did you find the letter?	5	3	46
If applicable how useful did you find the telephone?	5	3.5	50
If applicable how useful did you find the graph?	5	2.5	27
If applicable how useful did you find the report?	5	3.5	50
Did you feel that these results were reflective of your lived experience during the time the PKG™ was worn?	5	4	56
Impact on Care			
How useful were the medication reminders in assisting you with taking your medication on time?	5	4	100

Area of Evaluation	Max Score	Median response	% favourable
If applicable, how useful was the PKG™ data in assisting with explaining your symptoms to your Doctor or Nurse?	5	3	34
How valuable was the PKG™ in providing data to your Doctor or Nurse about your symptoms that you could not have provided?	5	4	63
Overall Satisfaction			
What level of involvement do you feel you have had in your treatment as a result of receiving the PKG™?	5	4	53
What level of involvement do you feel your consultant has had in your treatment as a result of receiving the PKG™?	5	3	45
What level of involvement do you feel your Parkinson's Nurse has had in your treatment as a result of receiving the PKG™?	5	4	77
Would you be happy not to travel to your appointments?	2	2	81
Would you use the PKG™ in future?	2	2	98

Overall, the device was rated highly usable, with 80% finding the introductory information helpful and 98% finding the process of returning the device simple. All patients valued the medication reminders to assist compliance. Only around half of responders reported finding any form of the reporting process useful in explaining the PKG™ results to them. In keeping with this, only 56% reported finding the PKG™ results were reflective of lived experience. For example, five patients reported concerns the data did not represent a 'typical' week, with one patient expressing concern that the recording had been performed over a particularly sedentary week.

However, 63% of patients reported the PKG™ was valuable in providing data to their PD clinical team about their symptoms that they otherwise could not have provided.

As a result of receiving the PKG™, 77% of patients perceived the PD nurses to have a high level of involvement in their treatment; 45% felt their consultant had a high level of involvement in their treatment; and 53% of patients felt that they had a high level of involvement in their own treatment.

Eighty-one percent of patients reported they were satisfied with not having had to travel to clinic for an appointment and 98% of patients reported being willing to continue using the PKG™ as part of their PD management.

4.4 Chapter Discussion

I carried out a clinical service evaluation to evaluate the utility of an objective monitoring device, the PKG™, and associated indicative thresholds to identify patients experiencing unmet treatment needs in between clinic appointmentments. In addition, I evaluated patient acceptability of the PKG™.

I hypothesised that the PKG™ would identify a high number of patients experiencing unmet treatment need experienced between clinic appointments.

In line with my hypothesis, the evaluation revealed the use of the PKG™ indicative thresholds and clinican interpretation of the PKG™ report identified a high number of patients experiencing an unmet treatment need between clinic appointments.

However, my sensitivity and specificity analysis revealed the PKG™ BKS parameter is slightly more effective at identifying patients who are undertreated from a bradykinesia perspective than identifying patients who are not undertreated. Whereas the PKG™ DKS parameter was more effective at identifying patients who are not undertreated from a dyskinesia perspective than detecting patients who are undertreated.

These findings are important, as they demonstrate that the PKG™ indicative thresholds are not able to identify all patients with unmet treatment needs (undertreated patients) particularly for patients with undertreated dyskinesia. These findings suggest that it may not be clinically viable to use the PKG™ parameters in isolation to identify undertreated patients, as there is potential for patients who are not fully optimised to be overlooked. Furthermore, because the PKG™ scores are based on data recorded during the 'waking day' (0900-1800), wearing off later in the day or early morning off may not necessarily be captured by the PKG™ scores. Instead, these findings highlight the necessity for qualitative as well as quantitative interpretations. For example, my findings revealed that some patients may show an optimal response overall, but on closer inspection of the PKG™ graphs, some of the patients show delayed responses to medication, or pre-dose wearing off.

In addition, a patient in the new patient pathway was not identified by PKG™ indicative thresholds as undertreated from a motor perspective, despite demonstrating peri-dose tremor. Although tremor is often resistant to therapy (Haeri, Sarbaz, & Gharibzadeh, 2005),

there are examples where this is not the case, such as for this patient, whereby tremor appears related to treatment. Moreover, the overall PTT score for this patient was 3.8% which is above the recommended cut-off for acceptable level of tremor (1%) (Braybrook et al., 2016). Tremor is one of the more noticeable symptoms of PD socially, and is rated as highly burdensome by patients (Heusinkveld, Hacker, Turchan, Davis, & Charles, 2018). My findings highlight that the PKG™ parameters for identifying patients as undertreated from a motor perspective do not take into account the patients' tremor score, and this finding may have gone unnoticed without a qualitative and more detailed evaluation of their PKG™ graph.

The authors of a recent qualitative evaluation of the PKG™ in a PD clinic suggest that the PKG™ may be of use in non-speciality care centres, for use by clinicians with varying levels of experience with continuous objective measurement (Santiago et al., 2019). My findings challenge this idea, as they demonstrate that it is not feasible to rely on the quantitative analysis provided by the PKG™ alone; expert clinical interpretation of PKG™ data is needed to successfully identify reports where there are other indicators of under treatment (such as tremor, wearing off or dose failures), identify confounders (such as tremor bleed through) and take account of patient mitigation (such as an unusually sedentary week).

Within our service, all clinicians and nurses carrying out PKG™ reporting are required to undergo PKG™ reporting training, which involves an online assessment and attending advanced training. In addition, an experienced neurologist oversees the reporting of each of the PDNS until reporting is standardised. These measures ensure that the clinical team within our service have a high standard of expertise in interpreting the PKG™ data and identifying

patients who may be undertreated, which helps to overcome some of the insensitivity of the PKG™ parameters found in this evaluation.

My findings therefore suggest high quality clinical interpretation in combination with the PKG™ quantitative data offers a potentially more sensitive measure to identify patients who may be undertreated, as opposed to using the PKG™ data in isolation. As a result of my findings, I would recommend high standards of training are provided for clinicians in other centres using the PKG™, to ensure accurate clinical interpretation of findings. Within our own service, we plan to triangulate information obtained via the expert clinician PKG™ report and the patient perception of symptoms, with patient reported outcomes (PROs) (such as measures of QoL). This will allow us to more fully determine the value and validity of the PKG™ findings.

Part Two explored the patient acceptability of the PKG™ , via a patient evaluation. Overall, the evaluation revealed high usability and acceptability of the device and the PKG™ process. However, a high percentage of patients reported finding the results difficult to interpret, which likely limited patients' appreciation of their relevance. As part of our upcoming service re-design, we plan to discuss with PwP how our patient-facing reports could be improved to increase the accessibility of PKG™ findings. This finding also highlights the importance of discussing the results with the patient and their carer in addition to their receiving a printed copy.

Importantly, and in line with previous reported benefits of continual objective monitoring (Odin et. al, 2018), the evaluation revealed over half of patients found the device useful in providing data to their healthcare team that they otherwise could not have provided,

thereby offering information that would have otherwise gone undetected and therefore untreated.

Furthermore, 81% of patients reported they would be satisfied with not having to travel to clinic for an appointment, which supports the feasibility of remotely monitoring PwP.

Finally, almost all patients (98%) reported willingness to continue using the PKG™ as part of their PD management, which suggests an overall high level of satisfaction with the device.

4.5 Conclusions

In this evaluation, I aimed to evaluate the clinical utility of the PKG™ and associated indicative thresholds to identify patients with undertreated bradykinesia and dyskinesia. I further aimed to evaluate the patient acceptability of the PKG™.

I hypothesised that the PKG™ would identify a high number of patients with an unmet treatment need experienced between clinic appointments.

In line with my hypothesis, the evaluation revealed the PKG™ identified a high number of patients experiencing unmet treatment need between clinic appointments, however the sensitivity and specificity analysis demonstrated there is potential for patients who are not fully optimised to be overlooked when using the PKG™ indicative thresholds in isolation.

My findings therefore highlight the importance of including expert qualitative evaluation of the PKG™ graph and report by an experienced clinician, to ensure all PKG™ findings are identified and interpreted correctly.

The patient evaluation revealed that while patients are largely satisfied with the PKG™ service, there are key areas of service improvements required, including initiatives to help improve patient understanding of results, and increase perceived involvement in care.

Overall, the clinical evaluation has demonstrated we were able to use the PKG™ to identify patients experiencing unmet treatment need between clinic appointments. Next, we would like to investigate whether acting on identified unmet need results in improved patient outcomes.

To achieve a robust evaluation of response to treatment intervention, we would like to evaluate outcome data with repeated patient centred outcome measures, including QoL. In addition, we would like to evaluate patient outcomes following the use of the PKG™ compared with standard care. It is hoped that a pilot study of a homebased care pathway at UHPNT utilising the PKG™ to facilitate remote care will help to better quantify the benefit to using the PKG™ as part of routine clinical service.

If successful, the remote management pathway will help deliver home-based care, thereby replacing the need for current time-locked clinical review, and overcoming some of the issues discussed previously, including reduced pressure on consultant follow up clinics and nurses time, in addition to providing timely care to patients.

4.5.1 Challenges surrounding the use of the PKG™

While the benefits of continuous objective measurement are internationally recognised (Odin et al., 2018), there are several known limitations to the PKG™ device that should be considered.

The PKG™ is worn on the wrist of the most affected upper limb, and therefore does not provide information on axial symptoms including falls or freezing of gait. These symptoms have well established associated physical and psychosocial consequences, and often have a negative impact on patients' quality of life (Bloem, Hausdorff, Visser, & Giladi, 2004). When using the PKG™ to monitor symptom severity, it is therefore important that the clinician is able to gain information from the patient on their experiences of axial symptoms in addition to the PKG™ data.

Furthermore, apart from issues with sleep, the PKG™ does not capture data on NMS such as depression, anxiety or pain. As discussed previously, the impact of NMS on patient well-being is significant (Martinez-Martin et al., 2011), and are the main cause of institutional care (Muzerengi et al., 2007). It is therefore important that clinicians take into account the impact of NMS when making treatment decisions in combination with the available PKG™ data. For this reason, we now routinely send self-report measures of NMS burden and QoL (NMSQ and PDQ8 respectively) with all PKG™ devices to capture contemporaneous NMS information. We hope to use these data, in combination with the PKG™ data, to help identify patients who are struggling from a NMS perspective and facilitate timely intervention. In addition, we are developing a mobile application (NMS Assist) to provide remote monitoring of NMS and triggered service support for PwP and their carers, as well as information on self-management of PD NMS (see Chapter 3).

There were several PKG™ reports that we were not able to include as part of the evaluation due to patient error (n=4) and device failure (n=4). It is a priority that the functionality of the PKG™ is well explained to patients to avoid errors such as large amounts of off wrist time.

Furthermore, an expert panel have recommended that patients' level of cognitive functioning is taken into consideration when administering a PKG™, suggesting that objective monitoring may not be suitable for people with limited cognition (Odin et al., 2018).

Resource and data management requirements also impact the implementation of the PKG™ within routine clinical service.

At the time of the evaluation, the annual licence for the PKG™ was £19,500, however there are additional costs associated with the PKG™, including the nurse time required to arrange the PKG™, time to report the PKG™, MDT discussion time and phoning the patient with the result.

The initial costs associated with objective monitoring technologies have been identified as a challenge to their integration as part of PD care, with healthcare providers reluctant to adopt technologies due to concerns surrounding costs, despite their apparent benefits (Espay et al., 2016). There is a subsequent need for compelling cost-effectiveness studies to demonstrate the feasibility of these devices and support business cases for their use in routine care.

In addition, the time required to report PKG™s has been a challenging issue within our clinical team, and for staff that are new to the process, reporting requires further assistance and time. To address this issue, reporting templates (see appendix 21 (section 8.21)) were implemented to make the PKG™ reporting as simple and quick as possible. However time available to produce reports is still limited, and additional resource such as administrative support is required to ease these pressures.

Finally, the data extraction and analysis of the PKG™ findings was challenging, and highlighted the need for improved documentation of all aspects of the PKG™ process. The management and documentation of large datasets, which are typical in the use of objective monitoring devices, is a recognised challenge associated with objective monitoring in healthcare (Lee & Yoon, 2017). Technical expertise is required to reap the most from the large amount of data that is produced. Advanced techniques including machine learning show promise in the analysis of disease-relevant information (Espay et al., 2016) , however increased support and resource is required in order for services to successfully implement these techniques.

In future, we aspire to patients having access to their own healthcare data, including objective measurements, with potential to titrate their own medications within agreed parameters. The Patient Knows Best Portal ("Patients Know Best Patient Portal",2019) is an example of an electronic personal health record which provides patients with an online platform to help better manage their healthcare, including opportunities for online consultation and sharing data with health professionals and family members. The portal gives patients control of their own medical records, and is approved for use by the NHS.

While promising, it is expected this new era of patient access will bring further data management and resource challenges to busy services (Armstrong, 2017). Concerns have been previously raised surrounding increases in clinicians' time required to address patient concerns (Walker, Meltsner, & Delbanco, 2015), and security challenges with regards to accessibility of patient data (Esch et al., 2015). These challenges will need to be addressed if we are to deliver safe and effective healthcare in line with the new era of personalised medicine.

Chapter 5 An evaluation of Parkinson's disease neuroprotective trial design spanning the last 10 years

5.1 Introduction

In this chapter, I am going to explore the use of technology in clinical trial delivery, with a particular focus on neuroprotective studies.

While the digital health technologies (DHTs) I have discussed in previous chapters have been presented as clinical measures, these technologies also have potential to be used as endpoints in clinical studies. For example, DHTs can be used to perform active protocols (such as finger tapping) to objectively measure specific symptoms, or to perform passive protocols (such as monitoring movement), to detect and monitor impairments occurring in everyday life (Espay et al., 2016; Lipsmeier et al., 2018). Additionally, there are potentially greater uses of DHTs than to measure the outcome of clinical tests or for monitoring purposes. For example, DHTs have potential to aid clinical trial delivery including recruitment and patient stratification, as well as facilitating communication with participants (Espay et al., 2016).

As discussed previously, DHTs include a broad range of mobile health technologies, including wearable devices such as body-worn sensors and portable systems that can be utilised by the patient in clinic, and in the home environment (Espay et al., 2019).

DHTs that use a smartphone interface provide an opportunity to collect a number of clinically important parameters via brief interaction from the patient with the device (Espay et al., 2016). For example, a smartphone application developed by the Oxford Parkinson's Disease Centre (OPDC) mentioned previously, has been validated to detect and monitor Parkinson's disease (PD) symptoms and predict disease severity, demonstrating potential for the

application to be used to monitor disease progression (Arora et al., 2015). The OPDC smartphone application has since been used in a larger scale study to successfully distinguish participants with REM Sleep Behaviour Disorder (RBD) from controls (Arora et al., 2018) and from other PwP, which is an established risk factor associated with developing PD (Noyce, Lees, & Schrag, 2016).

DHTs are also collected via computerised versions of pre-existing pen and paper tests, particularly for the administration of cognitive assessments, thereby providing a potential solution to problems with inconsistent administration and scoring of test data, which have been widely recognised (Luciana, 2003; Lukin, Dowd, Plake, & Kraft, 1985).

DHTs therefore offer a number of potential advantages over current assessments used in clinical studies, as outlined by Lipsmeier and colleagues (2018). Firstly, DHTs offer the potential to quantify symptom severity with increased sensitivity and objectivity than is achievable using rater-dependent clinical scales. Secondly, DHTs allow for increased testing frequency, allowing for assessments of motor symptoms at both a single time point (e.g. at baseline) and change over an interval (Mera, Heldman, Espay, Payne, & Giuffrida, 2017). Thirdly, DHTs allow for assessments to be carried out in the home environment, which produces data that is high in ecological validity, and provides an opportunity to capture rare incidents such as falls that take place outside of the clinic environment (Espay et al., 2016), as well as complex multi-dimensional parameters like gait (Del Din, Hickey, et al., 2016).

Fourthly, DHTs allow the measurement of other parameters within constructs, which would not be measurable in the traditional version of the test (Del Din, Hickey, et al., 2016).

5.1.1 Potential use of DHTs in PD clinical studies

There is growing evidence to support that inclusion of DHTs in clinical studies may help to overcome some of the current issues surrounding neuroprotective trial design (Artusi et al., 2018; Dorsey, Papapetropoulos, Xiong, & Kieburtz, 2017). Inadequacies of current neuroprotective trial design have been discussed in several recent reviews as possible reasons why no pharmacological agent has been shown to slow, halt or reverse the progression of PD, despite many agents showing promise in pre-clinical studies (Athauda & Foltynie, 2016; Dorsey, Papapetropoulos, et al., 2017; McGhee, Ritchie, Zajicek, & Counsell, 2016).

McGhee and colleagues (2016) carried out a review of clinical trial designs used to detect a disease modifying effect of drug therapy in PD (McGhee, Ritchie, Zajicek, & Counsell, 2016). The authors concluded that the best available clinical trial design to demonstrate disease modification was a long term follow up trial which analyses for sustained divergence in outcome measures between treatment arms over time. The authors went on to recommend the use of a primary outcome that was simple and easy to collect, such as death, which can be collected from routine data (e.g. national death registries).

While this may be the best available design for truly determining if a drug has neuroprotective potential, it raises the following challenges; long-term follow up studies are time consuming, and expensive to carry out. Furthermore, long duration studies run the risk of unacceptably high rates of attrition (McGhee et al., 2016). This is particularly challenging currently, when

new compounds and potential therapeutics are being developed more rapidly due to *in silico* drug discovery and repurposing strategies (Wu & Chiang, 2018).

Therefore another solution would be to (a) enrich the study population with those more likely to derive benefit (eg LRRK2 mutation carriers for a mitochondrial drug) (b) enrich the study population with those more likely to progress (eg RBD, prognostic high risk) and (c) develop more sensitive outcome measures to facilitate studies with either reduced sample size requirements or of shorter duration, which is a need that might most easily be met by new technologies.

The potential advantages of DHTs have also been described in a more recent review by Athauda and Foltynie (2016), who discussed several limitations of current neuroprotective trial design, including selection of inappropriate endpoints, and poor selection of patient cohorts, which do not take into account the heterogeneity of PD.

The authors made several recommendations for future trial design, including using disease prognosis models to stratify patients to more homogeneous cohorts, and selecting suitable endpoints to measure disease progression (Athauda & Foltynie, 2016). The authors highlighted that the use of technology based devices to remotely collect objective data has potential to reduce variability in assessments and improve patient compliance, by reducing the need for clinic visits.

In another review, Dorsey and colleagues (2017) suggested that the failure of Phase III studies to replicate earlier successful Phase II results was partly due to the use of artificial and imperfect outcome measures. Dorsey (2017) highlighted that the inter and intra variability of rater-dependent clinical assessments that are administered infrequently and in artificial

environments, reduces confidence in the replicability of findings, which can lead to considerable economic costs and deter future investments for clinical studies (Dorsey, Papapetropoulos, et al., 2017).

Although DHTs have not been utilised extensively in neurodegenerative clinical studies, there is evidence of technologies beginning to emerge as secondary or exploratory outcome measures.

A quantitative motor assessment of finger tapping and other hand movement tasks ("Q-Motor"), was one of the first DHTs to be used in clinical studies of Huntington's disease (HD) (Sampaio, Borowsky, & Reilmann, 2014). In comparison with traditional rater-based assessment of motor symptoms in HD (e.g. The Unified Huntington's Disease Rating Sale Total Motor Score (UHDRS-TMS)), the Q-motor tasks did not appear to exhibit placebo effects (Reilmann et al., 2015). This finding highlights placebo effects may be rater-dependent, and there may be potential to greatly reduce these by the inclusion of DHTs as clinical trial endpoints. The "Q-Motor" tasks have since been used in a PD cohort to differentiate finger tapping performance between PwP and controls, as well as demonstrate associations with The Unified Parkinson's disease Rating Scale (MDS-UPDRS) motor score (Maetzler et al., 2015).

In addition, a smartphone-based measure developed by Roche was recently deployed as an exploratory outcome measure in a 6-month Phase I PD clinical trial (Lipsmeier et al., 2018). The smartphone-based application comprised six active tests including finger tapping, sustained phonation (making continuous 'ahh' sounds) and a balance task, that were designed to assess PD motor symptoms including tremor, bradykinesia, and postural

instability. In addition, the smartphone-based measure carried out passive monitoring of symptoms via smartphone sensors, which required participants to carry the phone in their pocket. Participants were asked to complete the active tasks once daily, and carry the phone with them throughout the day.

The results demonstrated that all active and passive tasks significantly differentiated PwP from controls, and correlated with MDS-UPDRS motor scores (Lipsmeier et al., 2018). In addition, passive tasks revealed significantly reduced mobility in PwP in comparison with controls. Moreover, the active tests detected significant abnormalities in PwP who were rated as having no evidence of abnormalities in the corresponding motor symptoms of the clinical assessment. This finding suggests the smartphone-based measure may have increased sensitivity in comparison to rater-based assessments. In addition, participant adherence with the device was found to be acceptable, with an average compliance of 61% over the 6 months. The authors describe this to be a similar overall adherence to the OPDC smartphone based application described previously (69% adherence) (Arora et al., 2015; Bot et al., 2016). This study demonstrates that the use of a smartphone based outcome measure in clinical studies is feasible, and can provide reliable and clinical meaningful outcome data that has been collected remotely, from the home environment.

A recent review has further examined the existing use of DHTs as primary, secondary, or exploratory outcomes in ongoing and published clinical studies of neurodegenerative

disorders including PD (Artusi et al., 2018). The reviewers did not apply limits on the type of intervention used.

Of the ongoing neurodegenerative clinical studies identified as part of the review (n=1529), 42 studies (2.7%) were found to use DHTs as primary, secondary or exploratory outcomes. Of these, 23 (54.8%) were PD studies. The review revealed that sensor-based DHTs were the most frequently used technology-based outcome measure used in PD studies (n=20 studies, 87%) and gait was the most assessed domain using DHTs (n=10 studies, 43%).

Although the results of this review suggest that the use of DHTs in neurodegenerative clinical studies is limited, there was evidence of an increased trend in the number of published clinical studies integrating DHTs over the years studied (from 1985 to 2015) (Artusi et al., 2018). Furthermore, in a survey carried out by the review authors, 85% of surveyed pharmaceutical companies (total surveyed n=12) stated they were considering integrating DHTs in future neurodegenerative clinical studies within the next five years (Artusi et al., 2018). These findings demonstrate the potential rise in the use DHTs in future clinical research.

In order to explore the potential for DHTs to add value to current PD neuroprotective trial delivery, I undertook an evaluation of key elements of trial design in recent and current PD neuroprotective studies.

5.1.2 Research Aims

The aims of this evaluation were to assess whether there was an established methodology for (1) measuring disease progression, and (2) for stratifying patients for trial entry. If there was

no evidence of an established methodology in these areas, then I aimed to determine the areas of uncertainty where DHTs may add value.

5.1.3 Hypotheses

In light of previous suggestions that inadequacies of current PD neuroprotective trial design may be possible reasons why no pharmacological agent has been shown to slow, halt or reverse the progression of PD, I hypothesised:

1. There would be little evidence of an established methodology for measuring disease progression.
2. There would be little evidence of stratifying patients for trial entry.

To investigate these hypotheses, I undertook a methodological systematic review mapping the research design and characteristics of Phase II and Phase III PD neuroprotective clinical studies, registered or published over the last 10 years (2008-2018).

5.2 Methods:

This review was conducted according to Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines (Moher, Liberati, Tetzlaff, Altman, & PRISMA Group, 2009).

The review was carried out in collaboration with patient representatives who acted as secondary independent reviewers. Role descriptions for each of the reviewers are outlined in Table 34.

Table 34 Description of group roles

Reviewer	Role	Description of role
Thea Dominey (TD)	Main reviewer, Researcher	TD was responsible for carrying out the study search, carrying out initial assessment of studies for inclusion against the study eligibility criteria, the data extraction and the data analysis.
Karen Raphael (KR)	Secondary reviewer, Professor of Oral and Maxillofacial Pathology and Psychiatry*, and patient representative	KR was responsible for independently assessing the studies for inclusion against the study eligibility criteria.
Sue Buff (SB)	Secondary reviewer, patient advocate and co-author of 'PD Trial Tracker' ("PDTrialTracker.info," 2019)	SB was responsible for independently carrying out data extraction for the included studies.
Camille Carroll (CC)	Secondary Reviewer, Associate Professor and Honorary Consultant Neurologist	CC was responsible for assisting the group to reach consensus when discrepancies

Reviewer	Role	Description of role
		in study eligibility or data extraction arose.

* *Professor in Oral Medicine at the New York University College of Dentistry, and in Psychiatry at the New York University School of Medicine, New York, NY.*

5.2.1 Study eligibility criteria

The study eligibility criteria were developed using the PICOS (Population, Intervention, Comparator, Outcome and Study design) formula (Liberati et al., 2009), as exemplified in Table 35.

Table 35 Study eligibility criteria for the systematic review

Criterion	Inclusion Criteria	Exclusion Criteria
***P**opulation*	- Studies in patients with a confirmed diagnosis of PD at any stage of the disease	- Studies in patients without a diagnosis of PD
***I**ntervention*	- Studies involving a potentially neuroprotective agent	- Studies involving all other interventions (eg. symptomatic) - Studies involving no interventions (eg. observational studies)
***C**omparator*	- A comparator, including an existing treatment, no treatment, or placebo was an essential requirement for inclusion	- Studies with no comparator
***O**utcome*	- Studies specifying a well-defined primary outcome	- No well-defined primary outcome specified
***S**tudy design*	- Phase II and Phase III interventional, neurodegenerative randomised controlled studies (RCTs) - Single blind, double blind or open label - Published, or (if still ongoing) first registered from 2008 to 2018	- Phase I RCTs - Phase II and Phase III RCTs outside the time frame of the search - Phase II and Phase III single group studies (no comparator) - Phase II and Phase III non-randomised controlled studies

5.2.2 Principles of the search strategy

The search methods used in this review are listed below, and were used to ensure the greatest number of relevant studies were retrieved, while reducing the number of irrelevant papers.

Search methods included in this review:

- Electronic database search / Clinical trial register search
- Reference list scanning
- Contacting authors of included studies
- Google search

5.2.3 Selecting the databases

Three electronic databases were selected: MEDLINE (MEDLINE, 2019), Clinical Studies.gov (Clinical Studies.gov, 2019) and PD Trial Tracker (PDTrialTracker, 2019).

5.2.4 Search strategy

The following search terms were incorporated as part of the final search strategy:

- Interventional Studies
- Parkinson's disease
- Phase II
- Phase III
- 2008-2018

5.2.5 Supplementary searches:

Reference lists of relevant review papers were searched to identify additional records. Authors were contacted to gain additional information that was not listed, or to gain access to articles. Google was used to search for press releases related to unpublished studies. The last search was performed on 27/06/2018.

5.2.6 Study selection

Studies retrieved from database searches were screened by evaluating records first by title, then abstract, then at full text level, against pre-specified study eligibility criteria (see Table 35). Duplicated reports were excluded at title and abstract level. Eligibility assessments were performed independently by two reviewers (TD and KR) and discrepancies between reviewers were resolved by consensus, via discussion with CC. The study selection process is summarised in Figure 49.

5.2.7 Risk of bias

As the aim of the review was to map research design and characteristics of Phase II and Phase III PD neuroprotective clinical studies, we did not assess the risk of bias of individual studies.

5.2.8 Data extraction

The data extraction form (appendix 24 (section 8.24)) was created in Microsoft Excel and piloted by TD and SB. Piloting led to adaptations to improve its usability (e.g. inclusion of dropdown items).

5.2.9 Extracting the data

Data extraction was performed independently by TD and SB; TD performed a check for accuracy and completeness. Any highlighted discrepancies were resolved by discussion between the group members and CC.

5.2.10 Data Items

Data were extracted from each study relating to:

1) Study phase and (where appropriate) year of publication / year registered
2) Intervention being investigated
3) Number and location of study sites
4) Number of site visits required
5) Details of study design including:
    - masking (double blind, single blind or open label)
    - trial design (e.g. placebo controlled)
6) Details of the inclusion/exclusion criteria for enrolment including:
    - disease stage
    - disease duration
    - H&Y stage
    - cognitive tests and relevant cut offs for inclusion
    - if drug naivety was required
    - genetic criteria
7) Study outcomes including:
    - details of the primary outcome domain and measures used

- secondary outcome measures used, including whether these were mechanistic outcomes

8) Details of patient reported outcomes used (only measures that were completed by patients (i.e. self-administered) were included as a PRO).

5.2.11 Data synthesis

Synthesis involved the combination and collation of the design choices of individual studies included in the review.

5.2.12 Narrative synthesis

Heterogeneity in the status of studies included as part of the review (eg. published or unpublished), in addition to heterogeneity in study design and outcome data precluded the use of a meta-analysis. A narrative synthesis was therefore used to summarise the results of included studies.

5.2.13 Strength of evidence assessment

As only RCT studies were included as part of the review, which are considered to be the gold standard of clinical trial design (Bhide, Shah, & Acharya, 2018), we did not include a GRADE approach as part of our review (Moher, Liberati, Tetzlaff, Altman, & PRISMA Group, 2009).

5.3 Results

5.3.1 Study selection

Database searches identified 1098 records. 5 additional records were identified through supplementary searches. After adjusting for duplicates, 565 records remained. Of these, 312

studies were excluded at title level in line with the study eligibility criteria as outlined in Table 35. Of the remaining 253 records evaluated at full text level, 203 were excluded for the reasons outlined in Figure 49 and in line with the study eligibility criteria as outlined in Table 35 leaving a total of 50 studies included in the final analysis. Figure 49 summarises the study selection process.

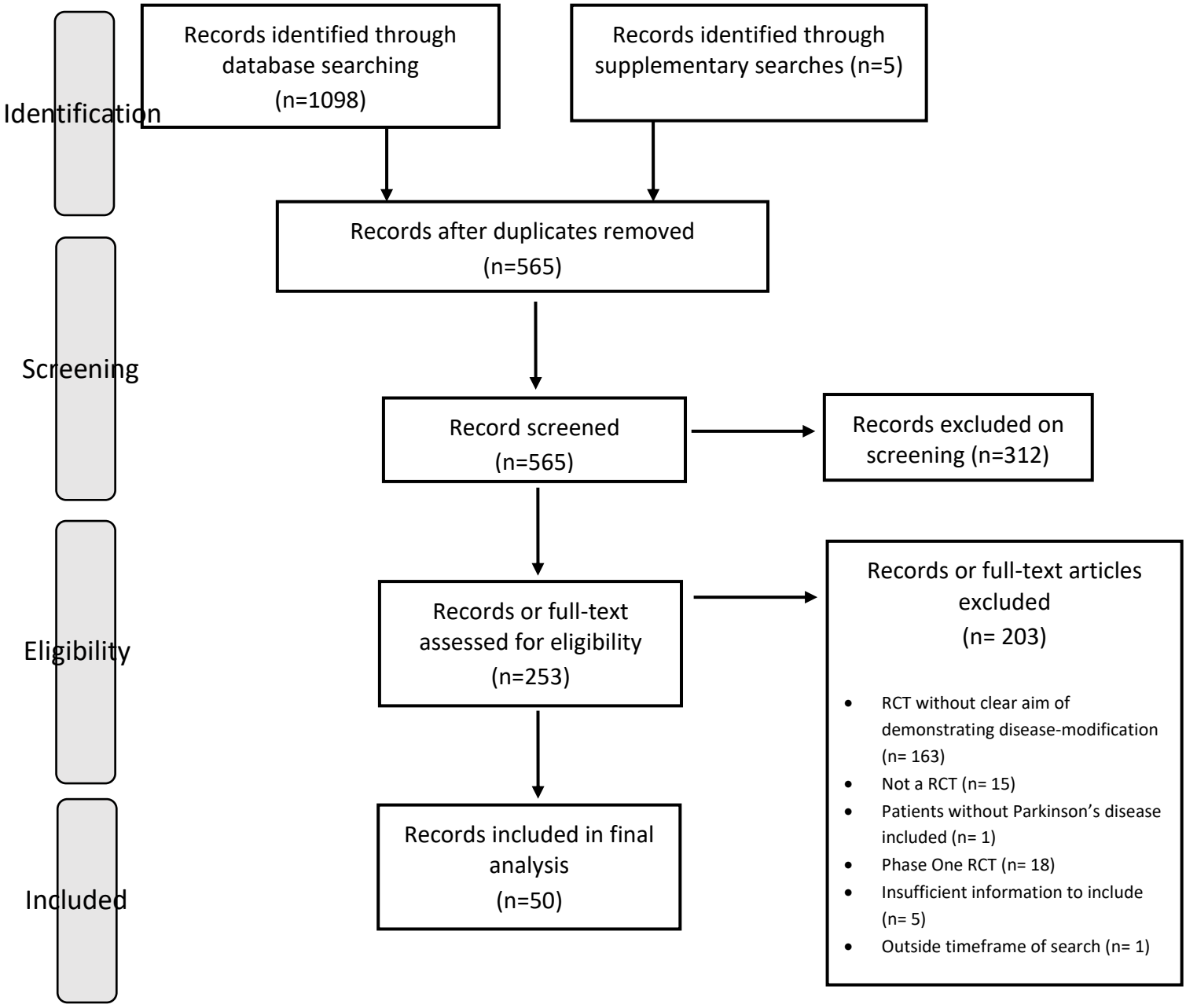


Figure 49 PRISMA flow chart illustrating the study selection process.

5.3.2 Study demographics:

Fifty studies (n=50) met the criteria for inclusion, with the lead site for each study representing 11 countries from four continents: Europe (n=12), North America (n= 28), Asia (n=8) and Oceania (n=2). For published studies, the year of publication is summarised in Figure 50 and for ongoing studies, the year of registration is summarised.

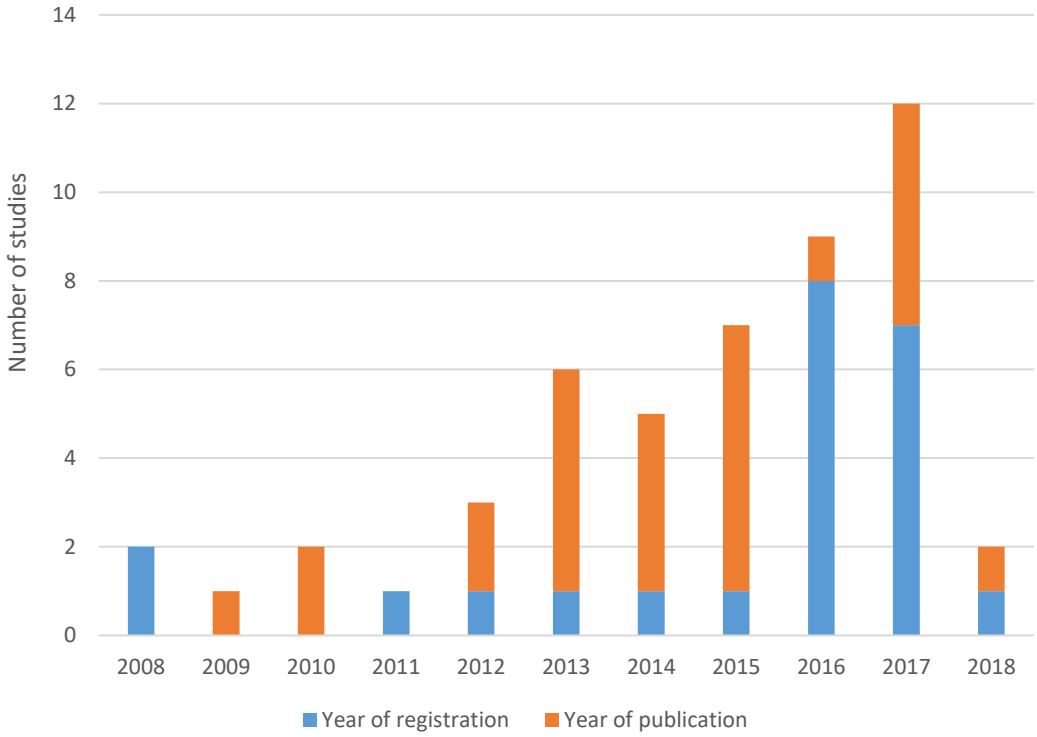


Figure 50 Number of studies registered (ongoing studies n= 23) or published (published studies n=28) per year (2008-18)

Forty-three studies were Phase II and 7 studies were Phase III. Results will be presented separately for Phase II and Phase III studies throughout.

5.3.3 Status

The status and key design features of the Phase II and Phase III studies are summarised in Appendix 25 (section 8.25) and Appendix 26 (section 8.26) respectively.

Of the Phase II studies, 22 (51%) were completed and reported, of which 15 studies (68%) successfully met their primary endpoint.

Of the Phase III studies, 6 (86%) were completed and reported, of which 2 studies (29%) successfully met their primary endpoint.

Figure 51 summarises the status of the included studies.

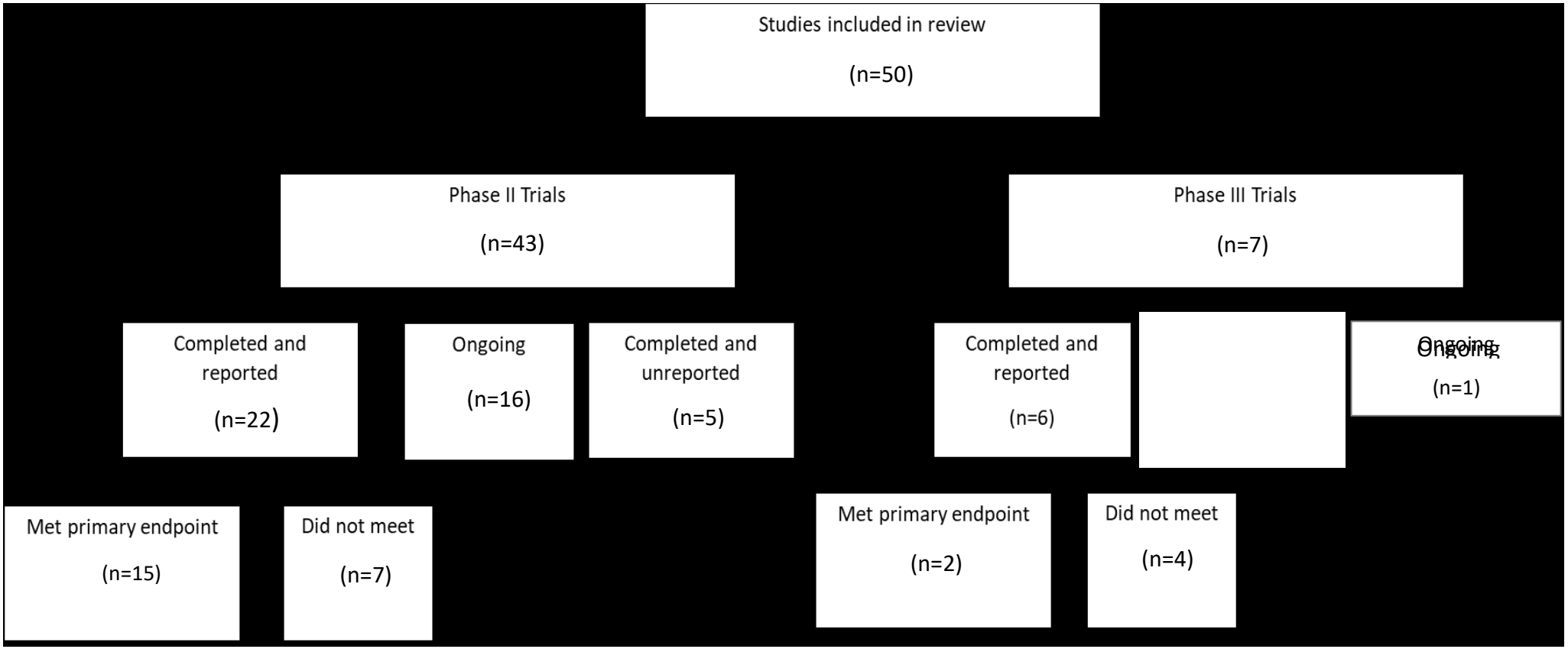


Figure 51 Flow chart illustrating the status of the included studies.

5.3.4 Study design

The majority of Phase II studies used a double blind, placebo controlled design (n=39, 91%). Similarly, the majority of the Phase III studies also used a double blind, placebo controlled design (n=6, 86%).

Details of the study designs used for included studies are described in Figure 52.

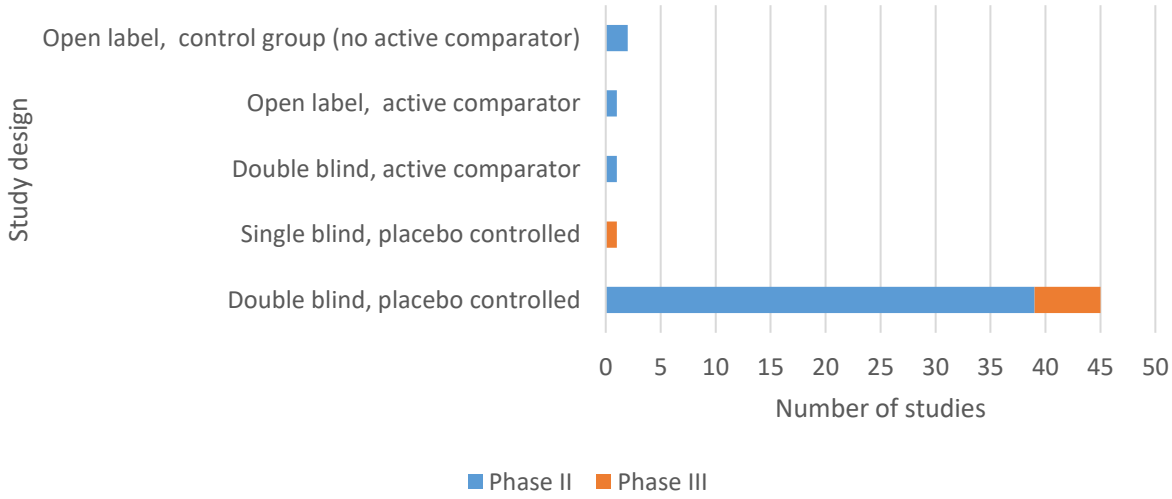


Figure 52 Study design for included Phase II (n=43) and Phase III (n=7) studies

5.3.5 Number of site visits required:

Of the Phase II studies with available data (n=30), the median number of site visits required as part of the study was 7 (2-104 visits).

Of the Phase III studies with available data (n=7), the median number of site visits required as part of the study was 10 (4-38 visits).

5.3.6 Measuring disease progression:

Details of the outcome measures used in the Phase II and Phase III studies are summarised in Appendix 27 (section 8.27) and Appendix 28 (section 8.28) respectively.

5.3.7 Primary Outcomes

The primary outcome domains used in the Phase II and Phase III studies, and the number of measures used to assess these are summarised in Table 36. Across studies, there was disparity in the outcome measures chosen to assess each of the primary outcome domains, with a total of 31 different outcome measures being used to assess 10 domains.

In addition, eight Phase II studies (19%) included more than one primary outcome. None of the Phase III studies included more than one primary outcome.

Table 36 Summary of the number of studies using different primary outcome domains, and the number of outcome measures used to assess these.

	Phase II		Phase III	
Outcome domain	Number of studies	Number of measures	Number of studies	Number of measures
Motor	26	3	6	2
Safety	10	12	0	0
Target engagement	1	1	0	0
Site of action penetration	1	1	0	0
Mechanism of action	3	1	0	0
Cognition	2	3	0	0
Tolerability/Adherence	6	7	0	0
Non-motor	1	1	0	0
Time to start Levodopa	2	1	0	0
Combined	0	0	1	1

The different primary outcome measures used by Phase II and Phase III studies will be discussed in turn.

5.3.8 Primary outcome measures used in Phase II studies

5.3.8.1 Phase II Motor Outcomes

The majority of the Phase II studies included a motor primary outcome (n=26, 60%). All of these studies used the MDS-UPDRS to assess motor impairment, however there was variation in the MDS-UPDRS sub-scale used. Of the studies using the MDS-UPDRS, 14 studies (54%) used the Part III motor sub-score, 11 studies (42%) used the MDS-UPDRS I-III total score, and 1 study (4%) used Part II (motor experiences of daily living) and Part III (motor sub-score).

The medication state that the MDS-UPDRS was carried out in (ON or OFF state) is summarised in

Table 37. A number of studies (n= 5) did not specify which medication state the MDS-UPDRS assessment was carried out in.

Some studies were recruiting patients yet to start dopamine-replacement therapy; for the purposes of this evaluation, these were included in the OFF state assessment category.

The majority of studies completed the MDS-UPDRS assessment in the OFF medication state. Only one study provided justification for carrying out the MDS-UPDRS assessments in the ON state, stating that:

"*We did not evaluate "OFF" phase MDS-UPDRS as the primary endpoint, because the waiting time in the out-patient clinic might have been insufficient to evaluate the symptoms of 'OFF' phase."* (Yoritaka et al, 2015, p. 912).

Table 37 The number of studies stating the medication state in which the MDS-UPDRS assessment was to be carried out in (ON or OFF state)

	ON	OFF*	Not specified
MDS-UPDRS Part III	1	12	1
MDS-UPDRS I-III Total Score	1	6	4
MDS-UPDRS Part II and III	1	-	-

5.3.8.2 Phase II Safety Outcomes

Twenty-three percent of Phase II studies (n=10) included a safety primary outcome. As summarised in Table 38, safety was measured across 10 studies by 11 different definitions, or was not defined. The various definitions of safety used across studies is outlined in Table 38.

Table 38 The definitions used to measure safety across Phase II studies (n=10)

Definitions of Safety	Number of studies
Number of participants with abnormal lab values/adverse events/serious adverse events	1
Number of treatment-related serious adverse events	2
Number and severity of any adverse event (AE)	2
Percentage of participants with AEs and SAEs	1
Absence of serious adverse eperiences (SAEs)	1
Exercise-related adverse events (e.g., strains/sprains, cardiovascular events).	1
Falls and fall injuries in and out of boot camp	1
Change in neuro and physical examination findings	2
Change in ECGs	1
Change in Suicidality Score – CSSRS	1
Blood test	1
Not specified	1

5.3.8.3 Tolerability/adherence Outcomes

Fourteen percent of Phase II studies (n=6) used a tolerability/adherence primary outcome. Various definitions (n =6) were used to measure tolerability/adherence or were not defined, as outlined in Table 39.

Table 39 The definitions used to measure tolerability across Phase II studies (n=6)

Definitions of tolerability/adherence	Number of studies
Proportion of subjects who complete study or to the time of initiation of dopaminergic therapy	1
Number of participants that attend a minimum number of sessions per week	3
Ability to complete study on assigned dose	2
Change in clin lab test data	1
Maximum heart rate	1
Drop-out rate	1
Not Specified	1

5.3.9 Primary outcome measures used in Phase III studies

All 7 of the Phase III studies (100%) used an efficacy outcome as their primary outcome. None of the Phase III studies included a safety or tolerability/adherence outcome as their primary outcome.

5.3.9.1 Phase III Motor Outcomes

Eighty-six percent of the Phase III studies (n=6) used a motor primary outcome. Of these studies, 5 (71%) used the MDS-UPDRS I-III total score (all completed in the OFF state), and 1 study (14%) used the MDS-UPDRS Part III (completed in the OFF state).

One study out of the included Phase III studies did not use a motor primary outcome (Kieburtz et al., 2015). This study used a global statistical test (comprising the Modified Schwab and England Activities of Daily Living Scale, 39-Item Parkinson's Disease Questionnaire (PDQ-39) Summary Index (PDSI), ambulatory capacity (the sum of 5 questions from the Unified

Parkinson Disease Rating Scale [UPDRS]), Symbol Digit Modalities Test, and the modified Rankin Scale) to measure function, activities of daily living, ambulation, cognition, and quality of life. The study authors cite that these measures were chosen because they are generally thought to be relatively resistant to dopaminergic therapy and were the hallmarks of worsening Parkinson disease (Kieburtz et al., 2015).

5.3.10 Mechanistic secondary outcome measures

Seventeen Phase II studies (40%) and 2 Phase III studies (29%) listed a mechanistic outcome measure as a secondary outcome measure. Mechanistic secondary outcomes were most commonly used to show penetration to site of action, target engagement or mechanism of action.

The modality of secondary mechanistic outcome used in the included Phase II and Phase III studies is summarised in Table 40.

Table 40 The frequency of mechanistic secondary outcome measures used across studies

Measure	Phase II (n=17)	Phase III (n=2)
Blood Test	6	1
CSF	2	0
DaTSCAN	4	0
MRI	4	0
PET	0	0
SPECT	1	1
Brain imaging (not specified)	1	0
Urine	0	0
Not listed	0	0

5.3.11 Patient Reported Outcomes

Of the Phase II studies, 8 studies (19%) used a patient reported outcome (PRO) as part of their primary or secondary study outcomes.

Of the Phase III studies, 5 studies (71%) used a PRO as part of their primary or secondary study outcomes.

Table 41 summarises the PROs that were used as primary or secondary outcomes in the included studies (n=50). Some studies used more than one PRO.

Table 41 The frequency and type of Patient Reported Outcomes used in Phase II and Phase III studies as primary or secondary outcomes

	Phase II (n=8)		Phase III (n=5)	
	Primary Outcome measures	Secondary Outcome measures	Primary Outcome measures	Secondary Outcome measures
NMSQ*	0	2	1	0
EQ5D	0	1	0	3
PDSS	0	1	0	0
PDQ39	0	2	1	4
PDQLQ	0	1	0	0
IMI	1	0	0	0
NeuroQoL	0	0	0	2
Schwab and England Scale	0	0	1	2
SCOPA Sleep Scale	0	0	0	1
RBDSQ	0	0	0	1
EQ VAS	0	0	0	1
BDI	0	0	0	2
PD FSQ	0	0	1	0
PFS-16	0	0	1	0

*Non Motor Symptoms Questionnaire (NMSQ), EuroQol (EQ5D), Parkinson's Disease Sleep Scale (PDSS), Parkinson's Disease Questionnaire (PDQ39), Parkinson's Disease Quality of Life Questionnaire (PDQLQ), Intrinsic Motivation Inventory (IMI), Quality of Life in Neurological Disorders (NeuroQoL), Schwab and England Scale, SCOPA Sleep Scale, REM Sleep Behaviour Disorder Screening Questionnaire (RBDSQ), EuroQol-Visual Analogue Scale (EQ VAS), Beck's Depression Inventory (BDI), PD Functional Status Questionnaire (PD FSQ), PD Fatigue Scale (PFS-16).

5.3.12 Stratifying patients for trial entry

The inclusion criteria for the included Phase II and Phase III studies were reviewed to assess whether any methods of stratification were used. Details of the inclusion criteria in the Phase II and Phase III studies are summarised in Appendix 29 (section 8.29) and Appendix 30 (section 8.30) respectively.

5.3.12.1 Genetic criteria

Of the Phase II studies, one study (MOVES PD) (2%) used a selective method of recruitment based on possible mechanism of action, by specifically recruiting patients with mutations of the glucocerebrosidase (GBA) gene to assess the safety of Ambroxol.

No other Phase II or Phase III studies specified genetic criteria for inclusion.

5.3.13 Disease duration

A wide range of disease durations were specified as part of the included studies' inclusion criteria from <1 month of symptoms to <15years since diagnosis. Table 42 details the disease durations listed as part of the inclusion criteria for the included Phase II and Phase III studies. Nineteen Phase II studies (44%) and 1 Phase III study (14%) did not specify disease duration of participants as part of their inclusion criteria.

Table 42 The frequency of disease durations specified for inclusion criteria for the included Phase II and Phase III studies (n=50)

	Phase II (n=43)		Phase III (n=7)	
	Frequency	Percentage (%)	Frequency	Percentage (%)
Not Specified	19	44	1	14
<1 month of symptoms	1	2	0	0
>2 years of symptoms	2	5	0	0
6 months - 8 years since diagnosis	0	0	0	0
PD diagnosis 1 year prior to dementia	1	2	0	0
Within 18 months of diagnosis	2	5	1	14
Within 2 years of diagnosis	1	2	1	14
Within 3 years of diagnosis	5	12	2	29
Within 5 years of diagnosis	4	9	2	29
≥ 3 years of diagnosis	1	2	0	0
≥ 5 years since diagnosis	5	12	0	0
<10 years since diagnosis	1	2	0	0
<15 years since diagnosis	1	2	0	0

5.3.14 Disease severity

Twenty Phase II studies (47%) did not specify a required disease stage as part of their inclusion criteria. Of the studies that did specify disease stage, 'Early PD' was the most frequently specified (n=15, 35%).

Two Phase III studies (29%) did not specify a required disease stage as part of their inclusion criteria. Of the remaining studies that did specify disease stage, 'Early PD' was the most frequently specified (n=5, 71%).

Figure 53 summarises the disease stages specified as part of the included studies' inclusion criteria.

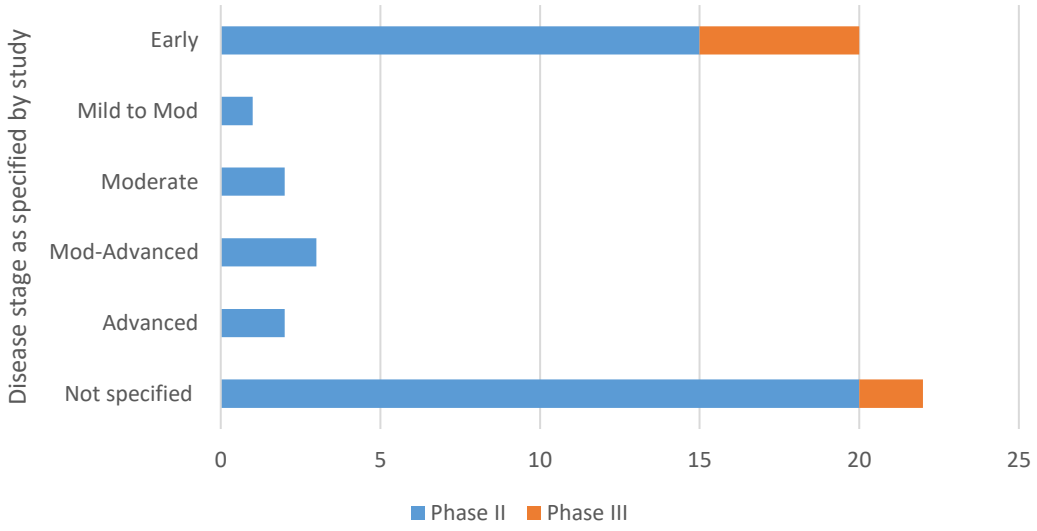


Figure 53 Disease stage as specified by study inclusion criteria for the included Phase II (n=43) and Phase III (n=7) studies.

5.3.15 H & Y Scores

Corresponding H&Y scores were extracted for the studies' inclusion criteria that specified 'Early PD' (Phase II n=15, Phase III n=5). Figure 54 summarises the H&Y scores that were specified by the studies requiring patients with 'Early PD'.

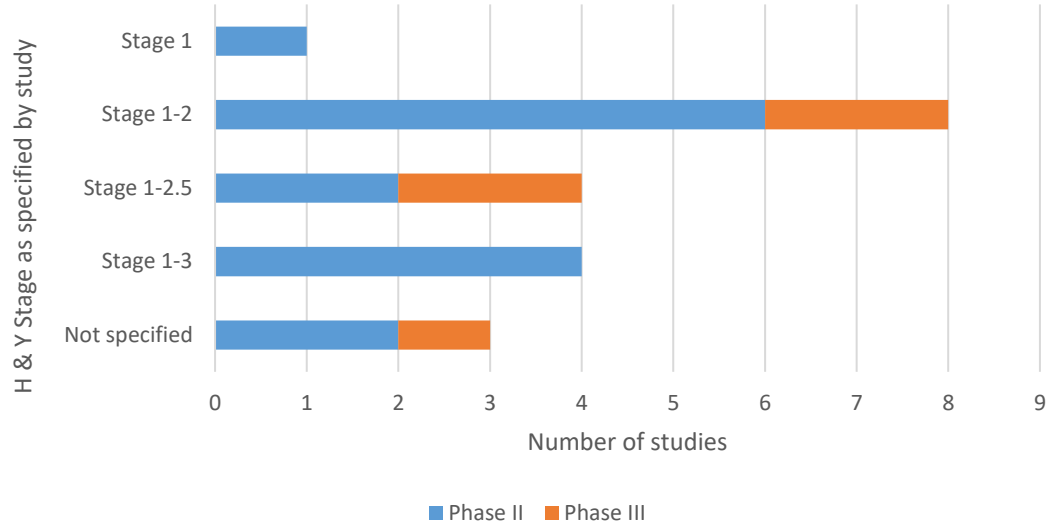


Figure 54 The number of 'Early PD' studies and corresponding H&Y stage specified as part of their inclusion criteria

5.3.16 Drug Naivety

Two of the included Phase II studies (5%) specified that participants had to have not yet started any anti-Parkinson's medication (drug naïve) as part of their inclusion criteria.

Two Phase II studies (5%) specified that participants must have stopped taking their anti-Parkinson's medication 1 month prior to baseline.

Four of the included Phase II studies (10%) specified that participants had to have not yet started dopaminergic medication, but other anti-Parkinson's medication such as MAO-B inhibitors were allowed.

None of the Phase III studies (n=0) specified that participants had to have not yet started anti-Parkinson's medication (drug naïve) as part of their inclusion criteria.

One of the Phase III studies (14%) specified that participants had to have not yet started dopaminergic medication, but MAO-B inhibitors were allowed.

5.3.17 Cognition

For Phase II studies, the most frequently cited cognitive assessments included as part of cognition inclusion criteria were the MMSE (n=13, 30%) and the MOCA (n=11, 26%). Two studies (5%) used the MDRS, and 1 (2%) study used the Folstein Mini Mental Examination. 16 Phase II studies (37%) did not specify using any cognitive assessments as part of their inclusion criteria.

For Phase III studies, the most frequently cited cognitive assessments included as part of cognition inclusion criteria for the included studies was the MMSE (n=3, 43%) and one study specified using the MOCA (14%). Three studies (43%) did not specify using any cognitive assessments as part of their inclusion criteria.

There was disparity across the cut-offs used for each of the cognitive assessments. In Phase II studies, MMSE cut-off scores ranged from 16/30 – 26/30, and MOCA cut-off scores ranged from 20/30 - 26/30. In Phase III studies, MMSE cut-off scores ranged from and 25/30 - 26/30.

5.4 Discussion

I carried out a review of Phase II and Phase III PD neuroprotective trial design spanning the last 10 years. My hypotheses were:

1. There would be little evidence of an established methodology for measuring disease progression.
2. There would be little evidence of stratifying patients for trial entry.

Results of the review are discussed below in relation to each of these hypotheses, with recommendations for how DHTs may add value to each of these areas.

5.4.1 Hypothesis One: There would be little evidence of an established methodology for measuring disease progression.

The review revealed that a wide range of primary outcome measures is used across Phase II and Phase III studies, therefore providing support for my first hypothesis. In total, 31 different outcome measures were used to assess 10 different domains, including motor, safety and tolerability as well as mechanistic outcomes.

Of the Phase II studies, the most frequently assessed domain was motor, with 60% of studies including a motor primary outcome. While all of the Phase II studies used the MDS-UPDRS to assess motor function, there was variation in the sub-score used. Some studies used the MDS-UPDRS total score (parts I-III), which takes into account motor and non-motor experiences of daily living and motor ability, while other studies used the motor sub-score (part III) in isolation. There was also variation in whether the MDS-UPDRS was carried out while patients were in the ON or OFF medication state.

Of the Phase III studies with a motor primary endpoint (86%), all of the studies chose the MDS-UPDRS as their primary motor outcome. As with the Phase II studies, there was variation in the sub-score used (total score or Part III), as well as whether these were carried out in the ON or OFF medication state.

In addition, there was large variation observed in the definition of safety used in Phase II studies, with 11 different definitions used across 10 studies. Similarly, tolerability outcomes lacked consensus in their definitions, with 6 definitions of tolerability being used across 6 Phase II studies.

The variation in primary efficacy endpoints being used in PD neuroprotective studies illustrates the lack of an established methodology for measuring disease progression. Despite the MDS-UPDRS Part III OFF state having been widely accepted as the best available assessment of disease

progression (Ramaker, Marinus, Stiggelbout, & van Hilten, 2002), my review has highlighted that this measure is not always chosen as the primary efficacy outcome in Phase II and even Phase III neuroprotective studies. This may be due to several limitations of the scale.

As discussed previously, the MDS-UPDRS Part III is a subjective measurement, generally assessed by an independent rater. Despite objective instructions for use, and a mandatory rater training process, there is evidence of notable intra and inter-rater variability associated with the scale (Post et al., 2005), which limits its use as a reliable measure of disease progression.

DHTs may offer a potential solution to this issue, as they can provide rater-independent, objective appraisal of symptoms, and so are not susceptible to rater bias or differences in rater experience or expertise (Dorsey, Papapetropoulos, et al., 2017). DHTs further have potential to provide an automated scoring system, which would save time for clinicians or researchers, and reduce the chance of scoring errors (Heldman, Espay, Lewitt, & Giuffrida, 2014).

In addition, the MDS-UPDRS assessment is typically administered during study visits often weeks or months apart, and only provides a 'snap-shot' of a patient's symptoms, which can be variable from a day to day, or even hour to hour basis (Papapetropoulos et al., 2015). In contrast, DHTs such as wearable sensors offer the potential to carry out daily active tests or passive measurement, and can monitor status continuously over a prolonged period of time in highly naturalistic environments, which would provide a more accurate reflection of the patient's symptom severity and would be ideally suited to longitudinal studies (Espay et al., 2019). In addition, the increased test frequency could lead to increased statistical power, allowing for the identification of impairment that may otherwise go undetected using infrequent in-clinic assessments (Dorsey, Papapetropoulos, et al., 2017).

Furthermore, as discussed previously, DHTs offer potential to capture rare incidents such as freezing or falls, that do not frequently occur in clinic (Espay et al., 2016) but which may be valuable indicators of disease progression (Maetzler et al., 2009). Indeed, gait disturbance has been identified as a potential prognostic marker in PD (Lord, Baker, Nieuwboer, Burn, & Rochester, 2011), as well as a possible marker of disease progression (Maetzler et al., 2009), with gait variability having been reported to correlate more strongly than bradykinesia with disease duration (Hausdorff et al., 2003). DHTs that have the ability to quantitatively record these symptoms therefore have the potential to capture more complex data than would be achievable by using clinical rating scales, which are limited by the type of symptoms they can effectively capture. Currently, rare events such as falls are documented via patient diaries, however these can be burdensome for patients to complete, and their reliability is often limited due to recall bias and diary fatigue, particularly in patients with cognitive impairment which is common in PD (Papapetropoulos, 2012). DHTs therefore have the potential to provide a greater complexity of symptom information, which may give insight into prognosis and disease progression.

In addition, many patients find the requirement to attend study visits in the OFF medication state for determination of the OFF-state MDS-UPDRS Part III the highly burdensome, which can be a barrier to trial participation and retention (Athauda & Foltynie, 2016). Indeed, one of the Phase II studies listed the time required to carry out the MDS-UPDRS assessment in the 'OFF' state as a barrier to including an OFF state assessment as part of their study protocol (Yoritaka et al., 2015). Alternative markers for disease progression such as temporal gait parameters (including stride and swing duration) appear independent from dopaminergic medication (Blin, Ferrandez, Pailhous, & Serratrice, 1991), and so by implementing DHTs that have been designed to assess these (Del Din, Hickey, et al., 2016), the need for a patient to be assessed in an OFF medication state may be avoided.

As mentioned previously, objective quantitative assessments that have been introduced as clinical trial endpoints in other neurodegenerative disease areas (Huntington's disease (HD)), have been found to exhibit no apparent placebo-response effect, whereas for traditional clinical rating scales, placebo-response effects were observed (Reilmann et al., 2015). This finding demonstrates placebo-response effects may be rater-dependent, and suggests there may be potential to greatly reduce these by using quantitative measures. In PD studies, positive clinical responses during placebo intervention can obscure identification of potential neuroprotective effects of active treatments in clinical studies (Goetz, Wuu, et al., 2008). In a previous PD randomised placebo-controlled trial (DATATOP-Study), placebo responses were detected in rater-based assessments without substantial changes reported in patient-based ratings (Goetz, Leurgans, Raman, & Parkinson Study Group, 2002), which provides support for the idea that rater bias may be an important consideration of placebo-related improvement (Goetz, Wuu, et al., 2008) and may be overcome via the inclusion of independent and objective measures.

5.4.2 Hypothesis Two: There would be little evidence of stratifying patients for trial entry.

Of the studies included as part of the review, only one study (MOVES PD) stratified patients for trial entry, thereby providing support for my second hypothesis that there would be little evidence of stratifying patients. In the MOVES PD study, the authors used a selective method of recruitment based on possible mechanism of action, by specifically recruiting patients with mutations of the GBA gene to assess the safety of Ambroxol.

For the remaining studies (n=49), recruitment strategies did not take into account the heterogeneity of clinical features, treatment responses or prognostic indicators of their sample.

DHTs may be useful in facilitating the application of different methods of patient stratification to future clinical trial design, and these will be discussed in turn below:

5.4.3 Using PD subtypes as a method of stratification

Recently, new attempts to provide defined criteria for different PD subtypes have been made, and it is thought implementation of these may aid patient stratification for clinical studies. As mentioned previously, Lawton and colleagues (2018) have identified 4 possible PD phenotypic subgroups with associated levodopa response, non-motor features and motor progression rates (Lawton, 2018). The authors highlighted that the mean difference in MDS-UPDRS motor scores between the fastest and slowest motor progression subtypes of their sample (n=1601) was 2.6 points, which was equivalent to the primary endpoint of the ADAGIO study (Rascol et al., 2011). While the efforts to identify PD subtypes are still ongoing, these findings demonstrate the potential value of introducing methods for stratification based on patients' phenotypic subtype, to allow for inclusion of patients to more homogeneous cohorts.

DHTs may offer an opportunity to support stratification of patients into relevant PD subtypes. For instance, in line with the PD subtypes mentioned previously (Lawton, 2018), DHTs that are able to detect participants with tremor dominant symptoms (Braybrook et al., 2016) may indicate a poor levodopa response and slow motor progression, whereas DHTs that detect early cognitive impairment (Dwolatzky et al., 2003) may indicate patients with a poor levodopa response but faster motor progression.

Wearable technologies allow for longitudinal data to be collected in the home environment, thereby providing large amounts of ecologically valid information on the prevalence and severity of symptoms that can be used to stratify patients to relevant disease subgroups (Camicioli et al., 2018). While it is likely that capturing digital data will allow some overlap with the clusters defined by traditional clinical measures (as outlined above), DHTs may also facilitate the identification of novel clusters, which may prove useful in future stratification of patients for clinical studies.

By reducing existing levels of heterogeneity in patient populations, the statistical power of studies is expected to increase, which will result in more efficient data collection, and lower costs (Athauda & Foltynie, 2016).

5.4.4 Early disease detection

The majority of Phase II studies included as part of the review specified that participants were diagnosed within 5 years, and of the studies that specified disease stage, the majority of these requested patients with 'early' PD. Neuroprotective studies commonly recruit patients with early PD to maximise the potential of any neuroprotective effect (Athauda & Foltynie, 2016). However, in line with Braak's (2013) prominent staging theory, neurodegeneration may have already begun outside of the substantia nigra in Stages 1 and 2, but not progressed to the point of a formal diagnosis of PD, which is dependent on the presence of motor symptoms. This phase (whereby symptoms and signs are present but not yet sufficient to meet diagnostic criteria for classical PD) is known as prodromal PD (Postuma et al., 2015).

Being able to detect individuals in the PD prodromal phase is useful in PD research, as this cohort stand to gain the most benefit from a neuroprotective therapy, which could delay or prevent the onset of disease (Athauda & Foltynie, 2016). As described previously, the MDS has published diagnostic criteria for prodromal PD (Berg et al., 2015) based on a variety of non-motor manifestations including REM Sleep Behaviour Disorder (RBD), olfactory dysfunction, constipation, excessive daytime sleepiness (EDS), symptomatic hypotension, erectile dysfunction, urinary dysfunction and depression (see section 1.2.8).

DHTs may prove useful in assisting with the identification of individuals in this prodromal phase. As mentioned previously, the OPCD smartphone application comprising evaluations of voice, balance, gait, finger tapping, reaction time, rest tremor and postural tremor, was found to

successfully distinguish participants with RBD not only from controls (mean sensitivity 89.5% (SD 3.5%) and mean specificity 85.3% (SD 3.7%)), but from other PwP (mean sensitivity 83.4% (SD 3.5%) and mean specificity 87.5% (SD 2.8%)) (Arora et al., 2018). RBD is an established risk factor associated with developing PD, and is included as part of the MDS diagnostic criteria for prodromal PD described previously (Berg et al., 2015). This study therefore highlights the potential use of a DHT to identify individuals in the prodromal stage, via completion of a smartphone based assessment that takes participants no more than 7 minutes to complete.

In addition to using DHTs to identify patients with prodromal disease (Arora et al., 2018) online methodologies have also been used to identify people at a high risk of developing PD.

Predict PD (Noyce et al., 2017) is an example of an internet based pre-diagnostic cohort study. Participants aged between 60 to 80 years without pre-existing PD or other movement or neurological disorder were required to visit the study website on a yearly basis to complete a series of online tests of early features and factors associated with increased risk of PD. The results of these tests were used to create a risk score using the PREDICT PD algorithm (Noyce et al., 2017). In order to gain information on established factors associated with high risk of PD (intermediate markers) against which the risk score could be compared, participants were required to carry out several further online tests. These included; the RBD Screening Questionnaire (RBDSQ) (Stiasny-Kolster et al., 2007) which is a validated questionnaire designed to assess for RBD, and the 'Bradykinesia Akinesia Incoordination test' (BRAIN test (Noyce et al., 2014)) which is an objective measure validated to assess upper limb motor function in Parkinson's (specifically slow finger tapping). The University of Pennsylvania Smell Identification Test (UPSIT) (Doty, Shaman, & Dann, 1984), which has been validated to assess olfactory disturbance in Parkinson's, was sent to participants via post.

Risk scores calculated from online data at baseline and during each year of follow-up were significantly associated with intermediate markers of PD (olfactory disturbance, RBD and slow finger tapping) at follow up (Noyce et al., 2017). These findings suggest that Internet-based approaches could be used to identify individuals at risk of developing PD from the general population (Noyce et al., 2017), and while no risk predictor will be 100% sensitive and specific; this approach may allow for enrichment of study cohorts in neuroprotective studies.

Rapsodi ("Rapsodi" 2018) is another web-based study that aims to recruit GBA gene carriers without a diagnosis of PD. The study uses online measures (similar to those used in PREDICT PD) to collect data linked to genotype. The study is a further example of using internet-based methodologies to recruit a large sample of participants for screening at low cost, and using low levels of resource. The study investigators hope to use Rapsodi as a platform for the targeting of bespoke genetic therapies.

An additional tool to help identify individuals with prodromal PD, is a risk model that has recently been developed to help identify individuals at an increased risk of Parkinson's within 5 years (Schrag, Anastasiou, Ambler, Noyce, & Walters, 2019). In this study, a large primary care database was searched to identify individuals with a diagnosis of PD (n=8,166) and controls (n=46,755). First presentations of symptoms 5 years prior to the diagnosis of PD were included as part of the analysis. Multivariate logistic regression analysis was used to create an algorithm for the risk of diagnosis of PD within 5 years of first presentation of symptoms.

The final model was found to have high predictive accuracy; the area under the curve (AUC) was 0.8 (95% confidence interval (CI) 0.78-0.81). The authors applied a threshold of 5% to split patients into high-risk and low-risk groups based on their predictive risk. At a threshold of 5%, the model had high negative predictive value. Ninety-nine percent of those who were not classified as high

risk did not go on to receive a diagnosis of PD. The model had a slightly lower positive predictive value, with 37% of those classified as high risk receiving a diagnosis of PD within 5 years.

Using routinely collected data, this risk model could be used by primary care services to help identify individuals with possible prodromal Parkinson's from their caseload, allowing for early referral, as well as timely and effective treatment. Furthermore, the model could be used to identify individuals for inclusion into studies, allowing for investigation of individuals in the prodromal phase.

5.4.5 Prognostic indicators

In the review, no studies were found to stratify recruitment according to prognostic risk. Several prognosis predictors have become available that may be useful in this area, which require automated calculations to compute. For example, a prognostic score, which is a composite score comprising age, MDS- UPDRS motor examination axial score and animal fluency score has been validated to indicate the risk of an adverse outcome at 5 years, comprising falls, dementia and death (Velseboer et al., 2016). It is feasible this score could be included as part of clinical trial stratification to recruit those with the highest risk of progression in order to be able to demonstrate a meaningful difference in progression rate within a reasonable time frame (12-18 months). To make this prognostic score clinically viable however, it would be necessary to use a computerised tool which has the embedded algorithm (such as an excel spreadsheet or similar) to automatically compute prognostic scores with maximal ease and efficiency.

In addition, a separate cohort study aimed to identify clinical variables that were predictive of cognitive impairment in early PD, which has implications for clinical prognosis (Schrag, Siddiqui, Anastasiou, Weintraub, & Schott, 2017). Predictive values of baseline clinical variables were calculated using univariate and multivariate linear analyses, with change in MoCA scores at 2 years

as the dependent variable. After age (which was the strongest clinical predictor of cognitive impairment) the strongest clinical predictors of cognitive decline were reduced sense of smell (measured by the UPSIT), RBD (measured by the RBDSQ), depression (measured by the 15 item Geriatric Depression Scale (GDS), and motor impairment (measured by the MDS-UPDRS motor score). This study therefore highlighted the possibility to identify patients early on in the disease course at risk of developing cognitive impairment using clinical characteristics. Similar to the prognostic tool mentioned previously (Velseboer et al., 2016), it may be possible to use this predictive model to create an algorithm for risk of cognitive impairment, which could be calculated automatically using a computerised calculation tool. This automated tool could be used to help stratify patients for clinical studies.

5.4.6 Facilitating trial delivery

The review highlighted the median number of site visits required for the Phase II and Phase III studies was 7 and 10 visits respectively. However for many patients, particularly those living in rural areas, attending this many episodic site visits may be challenging. Indeed, concerns regarding expenses incurred as a result of participating in a trial has been identified as a barrier to PwP participating in clinical studies (Mathur, Dewitte, Robledo, Isaacs, & Stamford, 2015).

DHTs offer opportunities to collect symptom data remotely from the home environment, as well as facilitating the delivery of 'virtual research visits' via teleconferencing (Dorsey et al., 2015). These methods reduce the need for in-person assessments carried out at a research centre (Athauda & Foltynie, 2016), which in turn can reduce participation burden and may improve acceptability for patients who find travel challenging (Dorsey et al., 2016). This may subsequently improve patient compliance and adherence, which could lead to decreased patient dropout.

5.4.7 Challenges and Limitations

Despite the potential value DHTs might add to PD neuroprotective studies, there are several recognised barriers to their implementation.

5.4.7.1 Added value

Firstly, there is a need to demonstrate the additional measurement accuracy that is provided by DHTs, other than simply generating objective based versions of previously validated subjective scales (Artusi et al., 2018). For instance, movement data collected by a sensory based finger tapping task has been used to detect different patterns of change in amplitude, frequency and velocity in PwP compared with controls, which would be difficult to achieve through visual inspection alone (Lones et al., 2014). As mentioned previously, gait is another feature of PD that has been shown to be a useful marker of disease progression and medication response (Del Din, Hickey, et al., 2016) and is traditionally assessed by timing how long it takes patients to walk a short distance, as well as carrying out visual observations. Wearable sensors offer great potential in the assessment of gait, over and above what is possible by visual inspection, by offering precise quantification of clinically relevant spatio-temporal gait features (such as step time, step length and swing time) from which pace, rhythm, variability, asymmetry and postural control can be derived (Del Din, Hickey, et al., 2016).

Furthermore, DHTs have demonstrated the potential to provide increased sensitivity or specificity than that achievable by existing measures, such as the Q-Motor HD measure described previously (Reilmann et al., 2015) and the Roche smartphone-based application in PD (Lipsmeier et al., 2018). Both of these DHTs detected significant motor abnormalities in patients who were not found to perform abnormally in corresponding assessments of motor symptoms using rater-dependent

clinical scales. These findings provide further support for DHTs to potentially provide increased sensitivity in comparison with existing measures.

5.4.7.2 Validity

Despite the potential for added value, further refinement to the algorithms that govern data processing of DHTs is needed, to ensure the reliable detection and measurement of specific motor and non-motor symptoms. It is expected that the reliability of these algorithms will be ascertained through future validation studies (Odin et al., 2018). The MDS Task Force on Technology discuss the need for improved compatibility amongst DHTs, as it remains difficult to combine data gathered by DHTs developed by different developers (Espay et al., 2016).

Furthermore, it is a priority that DHTs are validated in their intended environment for use. For instance, DHTs that are designed to remotely collect data from the home environment will need to be highly robust, to account for extraneous variables that cannot be controlled for outside of a laboratory setting. Previous research of wearable accelerometers in HD however, has demonstrated that although there was increased variability in measures of gait assessed at home compared to those assessed in clinic, this variability was offset by the increased frequency of assessments achieved in the home environment (20 assessments of gait performed in clinic vs 14,000 assessments of gait captured in 1 week outside of clinic) (Andrzejewski et al., 2016). This finding therefore supports the use of DHTs in naturalistic environments.

5.4.7.3 Additional Challenges

There are additional challenges surrounding the implementation of DHTs as part of PD neuroprotective studies, including:

- Long term adherence of participants to comply with the requirements of the DHT measure (e.g. continual wearing of a sensor-based device).
- The usability and acceptability of DHTs for both participants and clinical research teams, so as not to cause burden or increase workload.
- The development and provision of suitable data management systems in line with relevant policies (e.g. General Data Protection Regulations (GDPR)).
- Funds to provide technical support and assistance to participants as well as research teams.

Many of these challenges also pertain to the use of DHTs as part of routine clinical service provision, and so will be discussed in more detail as part of the overall thesis discussion (See Chapter 6).

5.4.8 Limitations of the evaluation

My systematic evaluation of PD neuroprotective studies has several limitations which should be considered. Firstly, I only included interventional clinical studies, which means I did not evaluate observational studies. Second, I only included randomised controlled studies (RCTs), meaning that nonrandomised studies were not included as part of the evaluation. Thirdly, I did not include Phase I studies, which may mean I missed other types of outcome measure that are not applied in Phase II and Phase III studies. In addition, I did not carry out a formal analysis of the study quality due to the wide range of study variables under measurement.

5.4.9 Conclusions

The results of the review have provided support for my hypotheses, by identifying variability in the choice of primary endpoint used across published and ongoing Phase II and Phase III PD neuroprotective studies, as well as a lack of a well-defined patient stratification process. These

findings illustrate the lack of consensus in designing both Phase II and Phase III neuroprotective studies. The review demonstrates that current trial design methodologies are crude in their attempts to recruit a broadly homogeneous population, which together with insensitive outcome measures may be partly responsible for the lack of positive outcome (Athauda & Foltynie, 2016).

As discussed, DHTs hold promise in several domains, including providing an opportunity to remotely collect continuous objective data that may be used to measure disease progression, in addition to helping to stratify patients to more homogeneous cohorts, thereby reducing heterogeneity of samples. DHTs may also have potential to improve patient adherence and compliance, by reducing the need for in-person assessments.

Increased inclusion of DHTs as exploratory or secondary outcomes in clinical studies is needed however, so that the feasibility and reliability of these measures can be ascertained and relevant refinements made to overcome some of the current limitations surrounding DHTs (Dorsey, Papapetropoulos, et al., 2017). These steps are necessary prior to approval applications and the more extensive use of DHTs as primary endpoints in Phase II and Phase III neuroprotective clinical studies.

Chapter 6 Overall thesis discussion

In this thesis, I have described a series of studies and evaluations of Digital Health Technologies (DHTs) for use in Parkinson's disease (PD).

6.1 Main findings

In Chapter 2, I presented a computerised paced finger tapping task (PFT) that was found to correlate with a measure of letter fluency, suggesting there may be potential to implement the PFT as part of a wider finger tapping battery to be used as a screening tool for executive dysfunction in PD.

In Chapter 3, I presented the development and formative evaluation of a DHT (NMS Assist) to enable regular assessment of non-motor symptoms (NMS) and provide self-help information for PwP and carers. NMS Assist was designed using an iterative design process in line with MHRA guidance, and with end user engagement throughout. The app was found to be highly usable (average SUS score = 80), and key areas of amendment were identified related to content, navigation and accessibility. These findings have informed the next round of formative evaluation which will lead to an in-service summative evaluation of the finalised product.

In Chapter 4, I reported the findings from a clinical service evaluation of the Parkinson's Kinetigraph (PKG^{TM}), a remote monitoring device for use in PD. The findings revealed the PKG^{TM} is useful for identifying patients with unmet treatment need even in newly diagnosed PwP who experience more frequent clinic review. These findings highlight the importance of continual monitoring in PD to allow for effective therapy optimisation. In addition, my findings demonstrated high quality clinical interpretation in combination with the PKG™ quantitative data offers a potentially more sensitive measure to identify patients who may be undertreated, as opposed to using the PKG™

data in isolation. These findings challenge those reported previously, whereby the PKG™ has been recommended for use for inexperienced clinicians. Finally, the patient evaluation revealed the PKG™ was acceptable for patients, and deemed valuable in providing information to their clinician that would otherwise have not been available. This clinical service evaluation of the PKG™ will inform a funding application for a randomised controlled trial (RCT) to investigate the impact of the PKG™ on patient-reported outcomes and quality of life (QoL).

Finally, in Chapter 5, the results of my systematic review of neuroprotective trials in PD revealed a lack of consensus among primary outcome measures used across Phase II and Phase III trials, which illustrates the lack of an established methodology for measuring disease progression in PD. In addition, there was little evidence of patient stratification, meaning studies did not take into account the heterogeneity of clinical features, treatment responses or prognostic indicators of their sample. The findings highlighted the potential for DHTs to improve the sensitivity of outcome measures and facilitate patient stratification, as well as improve clinical trial delivery.

While I have presented evidence that supports the use of DHTs to a) quickly and easily identify potential areas of cognitive impairment b) provide regular assessment of NMS and self-help information for PwP and carers c) identify areas of unmet treatment need and d) improve the sensitivity of clinical trial endpoints and facilitate trial delivery, there are a number of associated challenges surrounding the use of DHTs that have been highlighted within my thesis and in the wider literature that must be considered.

6.2 Challenges

6.2.1 Long term adherence

A major challenge to the implementation of DHTs is the behaviour change that is required by patients, clinicians and researchers to ensure the long-term adoption and use of DHTs in healthcare.

Although our patient evaluation of the PKG™ demonstrated that the majority of PwP found the PKG™ acceptable, with most patients reporting they would be willing to use the PKG™ as part of their PD management in the future, we are not yet able to report long-term compliance with the PKG™, and this will only be available over time.

Similarly, in relation to NMS Assist, we are not yet able to report long-term compliance with completing regular NMS assessments or engaging with self-help materials. To evaluate long-term compliance, feasibility studies will be carried out following the planned summative evaluation.

In the wider literature, there is evidence to suggest that there is a lack of patient motivation to use DHTs on a long-term basis, with a recent study showing 32% of users stopped using wearables after 6 months (Ledger & McCaffrey, 2014). In addition, in March 2015, the mPower app was launched with Apple's Research Kit platform (Apple Inc.) (Bot et al., 2016) comprising surveys and tasks that were developed as part of the smartphone-based app described previously (Arora et al., 2015). Whilst over 1,000 PwP and over 5,000 controls completed at least one active test, adherence dropped considerably following download, with just 898 individuals contributing more than 5 days' data over the first 6 months post-download (Lipsmeier et al., 2018).

In order to maximise adherence, further research is needed to design systems that are acceptable to patients for long-term monitoring of symptoms (Espay et al., 2016). Consideration of end-user

characteristics is imperative when designing DHTs, and has been found to improve adoption rates, and reduce user frustration (Fisk, 2009). As mentioned previously, we considered recommendations for the design of technologies for the older adult population when designing NMS Assist, including: increased button size (to account for diminished fine motor control), modifiable text size (to account for visual acuity), customisable volume (to account for hearing impairments) and minimizing the steps required to complete a given action (to account for executive dysfunction and memory decline) (Lewis & Neider, 2017).

Consideration will also be needed with regards to previous experience with digital technologies. Our formative evaluation of NMS Assist demonstrated that there were differences in app performance between experienced and inexperienced app users. This demonstrates that DHTs will need to be designed so that they are usable by people with little or no previous experience with digital technology, and that help or support is available for those that need it.

A recent study investigating the feasibility of wearable sensors in PD (via a smart watch and smartphone) found that the provision of a personalised support centre (whereby scheduled calls were carried out to participants showing low adherence) improved compliance, by quickly resolving technology-related issues (Silva de Lima et al., 2017). This will be an important consideration in the ongoing development of NMS Assist. Currently, technical support for NMS Assist is to be provided by the app builders, however it has not yet been decided whether they have capacity or resource to provide a 'support centre' feature.

Consideration of user characteristics and experiences as part of the design process should therefore help to create effective and safe technologies that will appeal to the end user, and can lead to sustained use and engagement (Lewis & Neider, 2017). Our findings from the formative evaluation of NMS Assist demonstrated this, as our iterative design process with end user

engagement throughout led to end-users rating the app as highly usable in the formative evaluation.

In addition to ensuring DHTs are usable by patient populations, consideration is also needed as to the usability of these devices by clinical teams. Training for staff will need to be easily disseminated, and simple to understand, so as not to over-burden teams or deter investigators from implementing DHTs as part of their study protocols in a research setting.

As mentioned previously, the training and the time required to report PKG^{TM}s has been a challenging issue within our clinical team, and additional administrative support is required to ease this pressure. The impact of NMS Assist on a clinical team's work load is yet to be determined, and will be evaluated as part of our summative evaluation. Some features to help minimise staff burden have already been incorporated however, such as a user-friendly web portal interface, whereby problem areas will be easily identifiable visually through the use of colour (see appendix 12 (section 8.12)). Furthermore, by including PD specialists (Parkinson's nurses and Parkinson's Drs) as part of the project team, we hope to address potential risks to staff burden early on.

6.2.2 Data Management and Analysis

While DHTs are able to collect large amounts of data over a prolonged time frame, the ability to analyse this data to produce clinically relevant information remains limited (Espay et al., 2016). Advances in data analysis techniques such as machine learning hold promise in this regard (Lones et al., 2014), however further expertise is needed for clinicians to be able to confidently apply these techniques to the data obtained by DHTs. In addition, clinical centres and research sites need to be supported in developing suitable and secure data management systems for the storage of large amounts of data that are provided by DHTs. As mentioned previously, producing an effective and error-free data management system has been an ongoing challenge with the implementation of

the PKG™, and was one of the areas identified by the service evaluation as requiring extra resource.

In addition, measures including password protection and dual factor authentication will need to be implemented to ensure the data collected by DHTs is held securely, and in line with General Data Protection Regulations (GDPR, 2018). In relation to NMS Assist, identification is currently obtained via the use of a personalised token that is linked with users' hospital details. The compatibility of this design with data protection regulations will be investigated as part of our ongoing design process.

6.2.3 Infrastructure

Challenges to infrastructure are another potential barrier to the implementation of DHTs, particularly for devices that require a wireless internet connection for reliable and efficient data transmission. As our patient evaluation revealed, the majority of patients use their smart devices in the home environment. Internet connectivity may not be available for patients residing in rural areas or in hospitals, where Wi-Fi connectivity can be temperamental.

In addition, ongoing maintenance and support will need to be provided to research centres, clinical teams and patients, to allow for effective and quick solutions to any technical issues that may arise. At UHPNT, we have experienced several device failures (including with the PKG™) that have led to missing data points and the need for patients to repeat assessments. The functionality of DHTs is therefore an important consideration, particularly with regards to remote monitoring, whereby errors may not be obvious until after the patient has worn the device. This will lead to frustration for both the clinician and patient, and could potentially increase the burden for patients, who would be required to wear the device for a second time.

6.2.4 Device Functionality

Device functionality is a key issue surrounding DHTs that can impact on trust and long-term use (Karvonen & Kristiina, 2000).

As discussed in Chapter 2, the sensitivity of the computerised paced finger tapping task (PFT) was compromised due to technical difficulties with the equipment, and we did not have the required resource to resolve these issues. This experience highlighted the development of DHTs requires ongoing expertise from researchers, clinicians, end-users and developers to ensure the DHT is working as it should. Additionally, regular validation is required, to ensure the DHT is working accurately and as sensitively as possible, and so that iterative changes can be made prior to use more widely.

In addition, evaluating the performance of algorithms underlying DHTs is a complex issue. The MDS-Task force on technology discuss the difficulty of attempting to validate DHTs with "gold standard" clinical scales, due to the possibility that the DHT may outperform subjective clinical scales, which could lead to imperfect correlations (Espay et al., 2019). Nevertheless, the task force recommend that DHTs are validated with regards to accuracy (achieved via laboratory based validity tests), reliability (achieved via test-retest within and between sensors), sensitivity, and establishing minimal clinically significant differences for endpoints of interest. This can be achieved by testing the DHT against a robust measure of clinical meaningfulness (the MDS task force give an example of a pull test to compare a new DHT for balance) (Espay et al., 2019).

6.2.5 Cost

There are a number of costs associated with DHT's including the development of the algorithms, maintaining technical support, the costs associated with data analysis, and the reporting costs.

Currently, all of these sit outside of current healthcare pathways and by extension, outside of existing contractual agreements.

High quality research studies are therefore needed to demonstrate the cost-effectiveness of DHTs so these can be incorporated as part of healthcare pathways. For instance, studies that demonstrate improved patient health or a reduced number of unplanned hospitalisations would demonstrate how initial costs may be offset (Espay et al., 2019). One study has demonstrated the cost-effectiveness of the Kinesia™ system via improved functional status (UPDRS II, III; IV subscale score) over a one year follow up, in comparison to standard care (Cubo et al., 2017). As discussed previously, we are currently planning a randomised control trial (RCT) of the PKG™ to help better quantify the benefit of using the PKG™ (including potential cost savings, and improved QoL) as part of routine clinical service.

6.2.6 Regulatory Approval

A major challenge to the integration of DHTs as part of clinical trials and in healthcare is the acceptability of a DHT by the regulatory authorities, such as the Food and Drug Administration (FDA). The FDA has currently approved some DHTs for use ("Brandon Capital", 2016), where sufficient evidence of value has been provided (Griffiths et al., 2012), but until recently, there has been no defined process for the development and regulation of technology based objective measures (Espay et al., 2016).

As discussed previously, NHS guidelines have recently emerged that aim to aid developers, clinicians, and researchers to enable the development of DHTs that are safe, ethical and effective (DHSC, 2018). In addition, the NICE Evidence Standards Framework for DHTs *(Evidence Standards Framework,* 2019) provides clear standards for evidence for effectiveness that must be met prior to the implementation of a DHT as part of a clinical service.

The planned RCT of the PKG™ may provide evidence of its effectiveness in line with the Evidence Standards Framework (2019) including repeat patient quality of life data following a therapeutic intervention guided by the PKG™ data. In addition, as mentioned previously, following the finalisation of NMS Assist, we will carry out a high quality in service summative evaluation, which has been designed in line with the Evidence Standard Framework (2019), and will include patient reported outcomes (PROs) as well as user satisfaction measures.

The increased availability of guidelines like these in recent months demonstrates the rise in DHTs being developed for use. The MDS Task Force for Technology have recently published a 'roadmap' for implementation of DHTs, with the aim of developing a framework for accessibility and long-term adherence of DHTs to enhance care and research objectives related to PD (Espay et al., 2019).

To address the increasing number of DHTs becoming available for use in PD, the MDS Task Force recommend the formation of a centralized, open-source, web-based structure where mobile health technologies can be integrated. This would help clinicians to gain a 'global picture' of a patient's symptoms rather than capturing separate constructs of interest. For example, such a platform could allow for a patient's PKG™ data to be presented along with their NMS assessments from NMS Assist, allowing for the clinician to consider both motor and non-motor symptoms, and helping to overcome the limited amount of non-motor information that is obtainable by using the PKG™ in isolation. As mentioned previously, the MDS Task Force on Technology is developing an e-Diary for PD which will act as an early, proof-of-concept integration platform for DHTs (Vizcarra et al., 2019). The findings from this initiative will inform the feasibility and effectiveness of such a platform.

Therefore, despite the potential benefit of DHTs to improve the sensitivity and accuracy of symptom assessment, reduce demands on services, and promote self-management of symptoms,

there are a number of challenges to be resolved as we begin to implement DHTs as part of routine PD care and research. This will be an ongoing process over coming years as PD care moves into a new era of 'digital healthcare', and will involve input from researchers, clinicians, developers, and regulatory bodies to be achieved (Health Education England, 2018).

Chapter 7 Conclusion

To conclude, in this thesis I have presented a series of studies and evaluations of digital health technologies (DHTs) to demonstrate how these may help to overcome current limitations of Parkinson's disease (PD) service provision and clinical research.

The findings from my own development of a computerised DHT demonstrated the potential for an automated paced finger tapping task to provide insight into executive function in PwP, while highlighting the associated challenges with developing a DHT for clinical use.

I further identified key areas of amendment to the design of a novel DHT for the evaluation and monitoring of PD non-motor symptoms (NMS), designed using a user-centred iterative design process.

My findings have further demonstrated the potential for an existing DHT (The Parkinson's Kinetigraph (PKG^{TM})) to provide remote monitoring and identification of unmet treatment needs in PwP, while highlighting the importance of qualitative, expert evaluation alongside quantitative approaches.

Additionally, my systematic evaluation of PD neuroprotective clinical trial design demonstrated the potential for DHTs to add value in this field, by increasing the sensitivity of trial endpoints, allowing for patient stratification and improving methods of recruitment.

A number of challenges associated with the use of DHTs were also identified throughout. As a result of the research undertaken as part of this thesis, I am planning two studies to address the associated challenges surrounding the use of DHTs. A randomised control trial (RCT) of the PKG^{TM} will allow for better quantification of the cost and patient benefit of using the PKG^{TM} as part of our PD service, and a summative evaluation of NMS Assist will allow for an evaluation of the device in

its intended environment of use (patient homes). It is hoped the results of these studies will support the use of DHTs in our routine PD service at University Hospitals Plymouth NHS Trust (UHPNT), allowing for the delivery of a remote, home-based care pathway.

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8 Appendices

8.1 Appendix 1 – Ethics approval from the local NHS Research Ethics Committee

NHS
Health Research Authority

South West - Cornwall & Plymouth Research Ethics Committee

21 October 2016

Dr Rupert Noad

Department of Neuropsychology,

Level 9 Derriford Hospital

Plymouth

PL6 8AH

Dear Dr Noad,

Study title:	**Computerised cognitive assessments in neurodegenerative disorders**
REC reference:	**12/SW/0227**
Amendment number:	**6**
Amendment date:	**02 October 2016**
IRAS project ID:	**108254**

The above amendment was reviewed by the Sub-Committee in correspondence.

Ethical opinion

The members of the Committee taking part in the review gave a favourable ethical opinion of the amendment on the basis described in the notice of amendment form and supporting documentation.

The Sub-Committee reviewed the following amendment:

1. Throughout the protocol improvements have been made to presentation.

2. Addition of Dr Craig Newman as Principle Investigator and Dr Camille Caroll, Mr Donnchadh Murphy and Ms Thea Dominey as Co-Investigators.

3. Addition of participants from non-clinical normative groups into the descriptions of cohorts of patients.

4. Removal of the word ‘Hospital’ specialist clinics.

5. Addition of option to collect additional data from non-clinical populations.

6. Addition of option to recruit from non-NHS specialist clinics.

7. Addition of option to recruit from Joint Dementia Research (JDR) database.

8. Clarification/changes to recruitment section.

9. Addition of sites.

10. Additional of seeking consent for video recording of specific assessments.

Approved documents The documents reviewed and approved at the meeting were:

Document	*Version*	*Date*
Covering letter on headed paper [CoCoA Study, Ethical Ammendment, Covering letter, 02.10.2016]		17 October 2016
Letters of invitation to participant [Letter of invitation v2 02.10.2016, CoCoA-AD2]	2	02 October 2016
Letters of invitation to participant [Letter of Invitation, v2, tracked changes, 02.10.2016, CoCoA-AD2]	2	02 October 2016
Letters of invitation to participant [Letter of Invitation, v3, 02.10.2016, CoCoA-PD2]	3	02 October 2016
Letters of invitation to participant [Letter of Invitation, v3, tracked changes, 02.10.2016, CoCoA-PD2]	3	02 October 2016
Notice of Substantial Amendment (non-CTIMP) [CoCoA Substantial Ammendment form]	6	02 October 2016
Participant consent form [Consent Form patient, v4, 02.10.2016, CoCoA-AD2]	4	02 October 2016

Participant consent form [Consent Form patient, v4, tracked changes version, 02.10.2016 CoCoA-AD2]	4	02 October 2016
Participant consent form [Consent Form patient, v5, 02.10.2016, CoCoA-PD2]	5	02 October 2016
Participant consent form [Consent Form patient, v5, tracked changes version, 02.10.2016, CoCoA-PD2]	5	02 October 2016
Research protocol or project proposal [CoCoA Study Protocol v11 clean version, 2.10.2016]	11	02 October 2016
Research protocol or project proposal [CoCoA Study Protocol v11, 2.10.2016, Changes highlighted Version]	11	02 October 2016
Research protocol or project proposal [CoCoA Protocol amendment summary document, v11, 02.010.2016]	11	02 October 2016

Membership of the Committee

The members of the Committee who took part in the review are listed on the attached sheet.

R&D approval

All investigators and research collaborators in the NHS should notify the R&D office for the relevant NHS care organisation of this amendment and check whether it affects R&D approval of the research.

Statement of compliance

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

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

12/SW/0227: **Please quote this number on all correspondence**

Yours sincerely

L Roberts.

pp.

A Research Ethics Committee established by the Health Research Authority

Canon Ian Ainsworth-Smith

Chair

E-mail: nrescommittee.southwest-cornwall-plymouth@nhs.net

8.2 Appendix 2 - Faculty Research Ethics Committee Approval

10th November 2016

Dear Thea

Application for Approval by Faculty Research Ethics Committee

Reference Number: 16/17-674

Application Title: **Validation of a computerised measure of Executive Functioning- a pilot study**.

I am pleased to inform you that the Committee has granted approval to you to conduct this research.

Please note that this approval is for three years, after which you will be required to seek extension of existing approval.

Please note that should any MAJOR changes to your research design occur which effect the ethics of procedures involved you must inform the Committee. Please contact Sarah Jones (email sarah.c.jones@plymouth.ac.uk).

Yours sincerely

Judy Edworthy PhD FAcSS

Professor of Applied Psychology

Chair, Faculty Psychology Ethics Committee

8.3 Appendix 3 - Letter of invitation

CoCoA (Computerised Cognitive Assessments in Neurodegenerative Disorders)

Contact details for Chief Investigator:

Dr. Rupert Noad, Consultant Neuropsychologist, NeuroCoRe, Clinical Neurology Research Group, N13, ITTC Building, Plymouth Science Park, PL6 8BX, Tel. 01752 315264

Dear

Computerised Cognitive Assessments in Neurodegenerative Disorders (CoCoA study)

We are writing to you as you have previously expressed an interest in being contacted about participating in research. We are writing to let you know about a study we are currently running.

We are organising a study here at the Plymouth University Peninsula Schools of Medicine and Dentistry, looking at new ways of measuring movement and thinking problems. We are particularly interested in the kinds of problems that people experience in Parkinson's disease.

We want to include people [aged 18 years or older] who have a diagnosis of Parkinson's Disease.

The study involves one visit which would be arranged at Plymouth University. The study takes about 2 hours and involves completing some tests of your thinking and memory using both paper and pencil and a computer tablet. You do not need to have had any previous experience of using a computer or a computer tablet to be able to participate in the study.

We have enclosed an information sheet which explains the study in more detail and a reply slip with a pre-paid envelope. Please return this to the study team to let us know whether or not you are

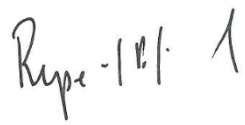
interested in taking part in the study, or whether you would like to find out more about the study. If you have any other questions or would like to talk to the research team please contact:

Thea Dominey: Clinical Neurology Group

Tel : 07792119415

Email : thea.dominey@plymouth.ac.uk

Yours sincerely



Dr Rupert Noad

Consultant Neuropsycholgist, Derriford Hospital, Plymouth, UK

Computerised Cognitive Assessments in Neurodegenerative Disorders

Reply Slip:

Please complete and return this reply slip in the prepaid envelope to:

Thea Dominey, Clinical Neurology Research Group, School of Psychology, Plymouth University,

Drakes Circus, Plymouth, PL4 8AA

Name .....

Address .....

.....

.....

Home phone number .....

Mobile number .....

Preferred contact time: daytime / evenings / weekends / anytime

I have read the information in the subject information sheet and:

(please tick one box)

I **would like** to participate in the study. ☐

I would like to **be contacted** by a member of the research team so that I can get more information before I decide whether or not to take part. ☐

I **do not** wish to participate in the study. ☐

If you **do not** wish to participate it would be very helpful if you could let us know why not:

Thank you for reading the information provided and replying.

8.4 Appendix 4 – Participant information sheet

Computerised Cognitive Assessments in Neurodegenerative Disorders

Contact details for principal investigator:

Dr. Rupert Noad, Consultant Neuropsychologist

NeuroCoRe

Clinical Neurology Research Group

N13, ITTC Building

Tamar Science Park PL6 8BX

Tel. 01752 439779

Contact details for research group:

Clinical Neurology Research Group,

Thea Dominey,

School of Psychology,

B223 Portland Square,

Plymouth University,

Plymouth,

PL4 8AA

Tel: 07792119415

Email: thea.dominey@plymouth.ac.uk

Invitation for Research Participation

Thank you for taking the time to consider participating in our research study.

Please read the attached information sheet before deciding whether to take part.

If you are interested in participating, please complete the reply slip attached to the invitation letter.

The study is voluntary and deciding not to participate will not affect your treatment in any way.

Participant information sheet for patients

Investigating computerised cognitive assessments in neurodegenerative disorders

We would like to invite you to participate in a research project. Before you decide whether you want to take part, it is important for you to understand why the research is being conducted and what your participation will involve. Please take time to read the following information carefully and discuss it with others if you wish. Ask us if there is anything that is not clear or if you would like more information.

What is the study about?

Neurodegenerative diseases, such as Parkinson's disease, Alzheimer's disease or Huntington's disease affect a large number of people in the UK, the majority of patients developing disease in middle to later life. As the population as a whole ages, these diseases will become more common. Neurodegenerative diseases can cause problems with thinking and memory, and also problems with movement. We want to learn more about the way that thinking and memory problems can be assessed in these diseases, and whether using a computer might give more accurate information and make it easier for patients to complete the tests.

Why have you been asked to take part?

You have been invited to take part in this study as you are someone with a neurodegenerative condition.

Do I have to take part?

No. Participation in this study is entirely voluntary and it is up to you to decide whether or not to take part. If you do decide to take part you will be asked to sign a consent form, but you are still free to withdraw at any time in the future without giving a reason. You will be given a copy of this information sheet to keep and you will also keep a copy of your signed consent form. If you decide not to take part, or you withdraw from the study at any point, your usual medical care will not be affected in any way.

Is this a medical assessment?

This is a research project not a medical assessment. You will not be told the scores of your assessments. All data collected during the study will be anonymous. If you feel that you are developing problems with your thinking/memory please contact your GP to discuss this further. We will send a letter to your GP informing them of your participation, but we will not send them any details of the assessments.

What will I have to do?

If you are interested in taking part in the study, you can contact us, either by completing the reply slip (attached to the invitation letter) or by telephoning the study team on 07792119415 . We will then contact you by telephone to discuss the study with you, ask you a couple of questions and see if you want to take part. If you are happy to take part we will arrange a time to do the assessment, in a study clinic at Plymouth University. During the assessment we will ask you for some brief details about yourself. You will then be asked to complete a series of tests of memory and thinking. Some of these tests will involve you being asked questions by the researcher. Some tests will be paper and pencil based. Some tests will be using a computer which the researcher will bring with them. You will then be asked for some feedback on how you found the computer-based tests. The assessment will take around 2 hours in total including a 15 minute break. You can ask for a break at any point during the assessment. You will also be asked whether you would be willing to complete another assessment in the future, looking at a different computer-based test or the same test in more detail.

Will the information collected during the study be kept confidential?

The study will be conducted in accordance with the Data Protection Act (1998). All information collected about you during the study will remain strictly confidential.

Your personal details will be stored securely on a computer in the Peninsula Medical School in Plymouth, accessible only by members of the study team. Your name and address will not appear on any study forms or questionnaires so that you cannot be recognised from them. All other information collected about you during this study will be entered onto a separate, secure database and will only be identifiable by a study number and initials. Only members of the study team will have direct access to these data.

If you consent to take part in the study, your medical records may be inspected by the doctors looking after you.

If you agree to take part we will inform your general practitioner, unless you specifically ask us not to.

What are the benefits to me of taking part in this study?

There are no direct benefits to you from taking part in this study. By completing the study you are helping us design tests that will help in future studies of these symptoms.

What are the risks to me?

You should not experience any adverse effects from taking part in the study. Some people may find some of the questions difficult or upsetting, for example questions about thinking and memory. However, the data collected will be held anonymously as the forms will have only your study number (not your name or date of birth), and you are free to withdraw from the study at any point. If you would like to discuss any aspect of the study then please call a member of the study team on: 07792119415

Will I have to pay for travel?

If your assessment is taking place at a study clinic, then your travel expenses will be reimbursed.

What if I have more questions or do not understand something?

If you have further questions please contact the study team on 07792119415 who will try to answer your queries.

What happens now if I decide to take part?

If you are happy to take part in the study, please complete the reply slip attached to the letter of invitation and return to us in the freepost envelope provided. A member of the study team will be in touch to arrange a time for your assessment.

What happens if I do not wish to take part?

Your participation in this study is entirely voluntary. You do not have to take part, or give a reason if you choose not to. If you do not wish to take part it will not affect your future treatment or care.

What will happen if I don’t want to carry on with the study?

You are free to withdraw from the study at any time. You do not have to give a reason. If you do not wish to continue in the study it will not affect your future treatment or care.

What to do if something goes wrong?

We do not expect any harm to come to you as a result of taking part, thus special compensation arrangements do not arise. If you have any concerns about the way that you have been approached or treated during this study, you are free to follow the usual NHS complaints procedure.

If you are harmed due to someone's negligence then you may have grounds for legal action but you may have to pay for this yourself. Your right to claim for compensation for injury where you can prove negligence is not affected. If you do have any complaints about your experiences with us, please address them to PALS Plymouth: **08451558121**

What will happen to the results of the study?

We intend to publish the study results in a medical journal within a year of completion of the study and also to present the results at medical and scientific meetings. Each participant will receive a summary of the results at the time of publication. We will also publish the results of the study in patient newsletters.

Contact for further information

If you require any further information about this project, or have any questions please contact the research team on 07792119415 during office hours and a member of the project team will be able to help you.

Who is organising and funding the study?

The project is being organised by the Neuropsychology and Clinical Neurology Research teams at the Peninsula Medical School in Plymouth. It is being led by Dr Rupert Noad and coordinated by Thea Dominey.

8.5 Appendix 5 – Consent form

Participant ID | | | | |

Computerised Cognitive Assessments in Neurodegenerative Disorders.

PARTICIPANT CONSENT FORM

Please initial Boxes

1. I confirm I have read the patient information sheet (v2 25/07/12). ☐

2. I confirm that I have had the opportunity to discuss the study. I do not have any further questions regarding the project. ☐

3. I understand that information collected about me and my health during this project will remain strictly confidential and accessible only to appropriate individuals. ☐

4. I give permission for my GP to be informed that I am taking part in this study (optional). ☐

5. I understand that sections of my medical records, including possibly my GP records, relating to my participation in this project may be inspected by members of the research team. ☐

6. I understand that I am free to withdraw from the study at any time, without having to give a reason. ☐

7. I understand that I will not receive a medical assessment; therefore I will not receive feedback about my individual performance.

8. I consent to allowing the research team to make a video recording of my performance on the TULIA assessment and for this to be scored by other members of the CoCoA research team at a later date (optional). ☐ ☐

9. I agree to take part in this study.

Participant's Name (BLOCK CAPITALS):

8.6 Appendix 6 – Histograms

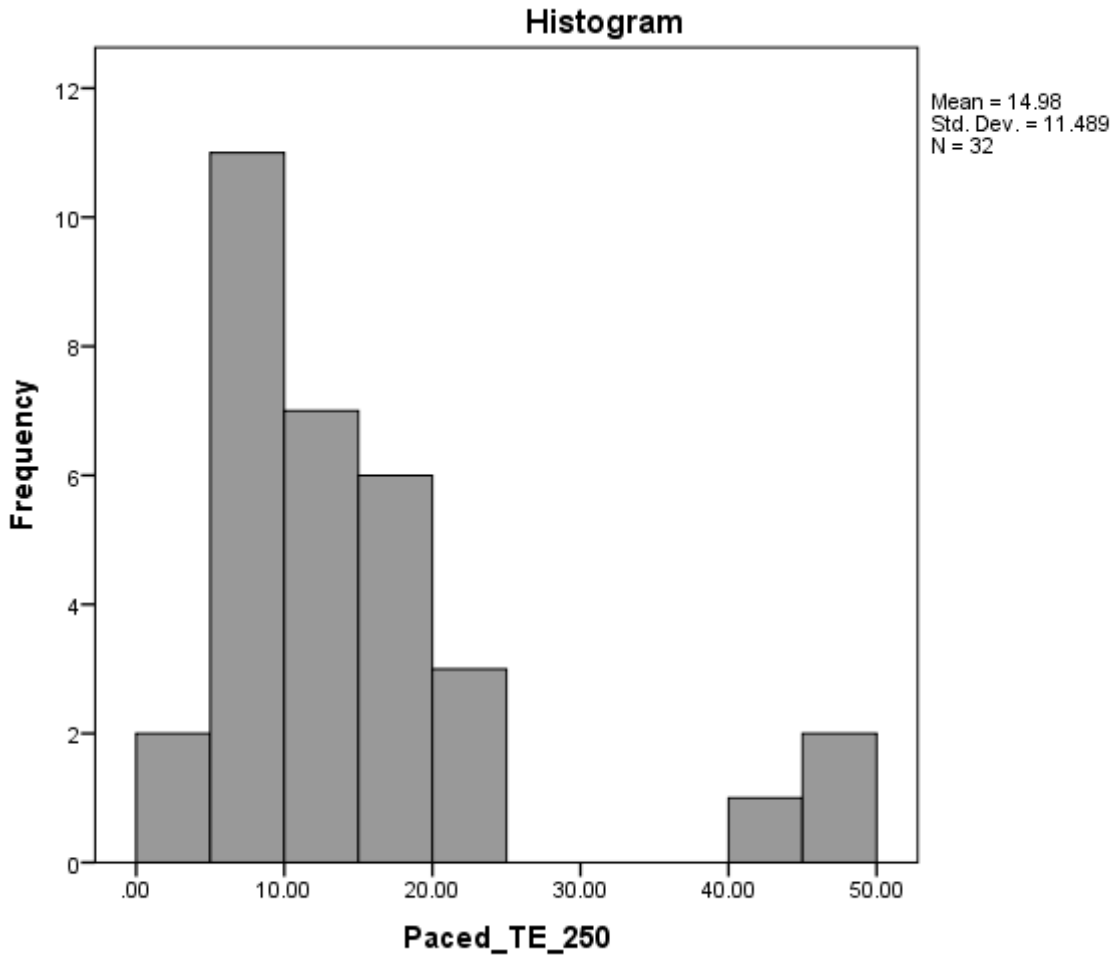


Figure 55 Distribution of mean tapping percentage error in the paced condition (250ms)

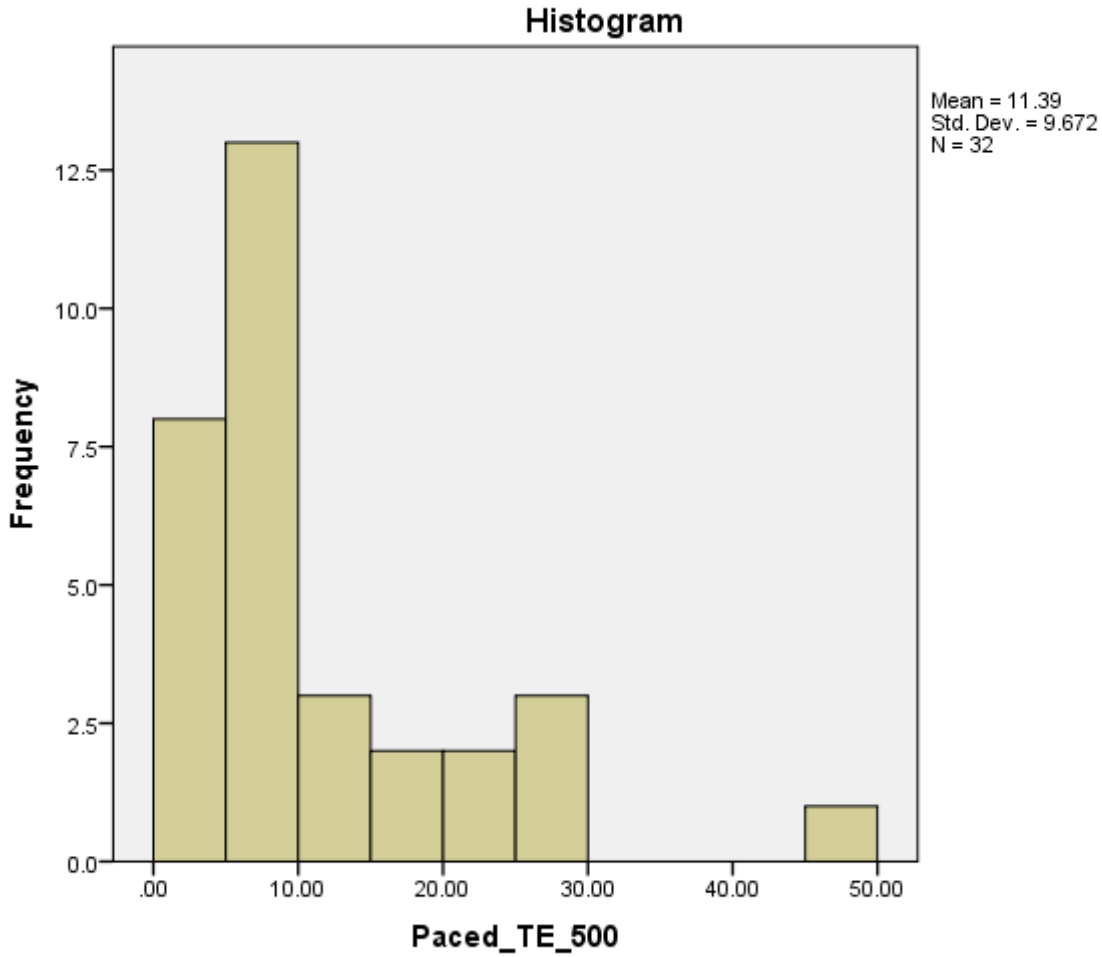


Figure 56 Distribution of mean tapping percentage error in the paced condition (500ms)

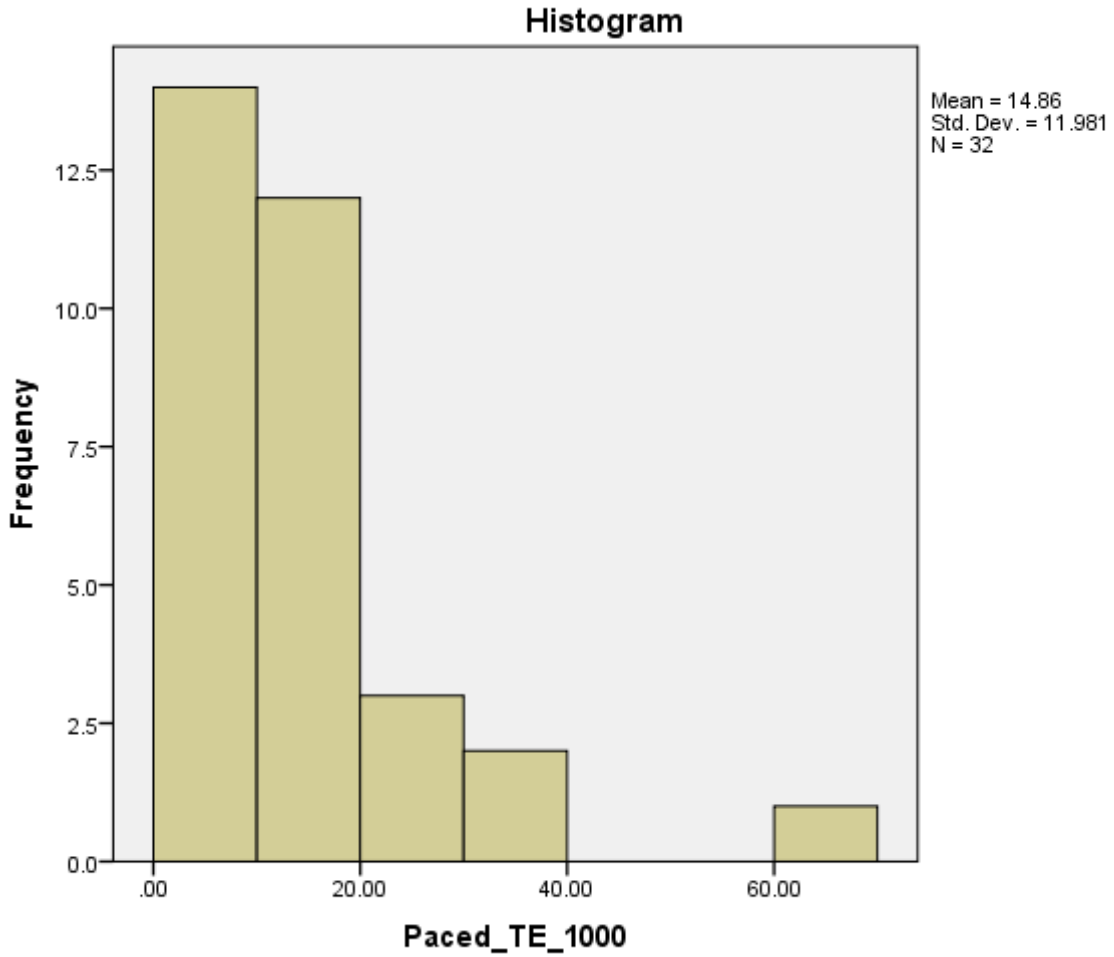


Figure 57 Distribution of mean tapping percentage error in the paced condition (1000ms)

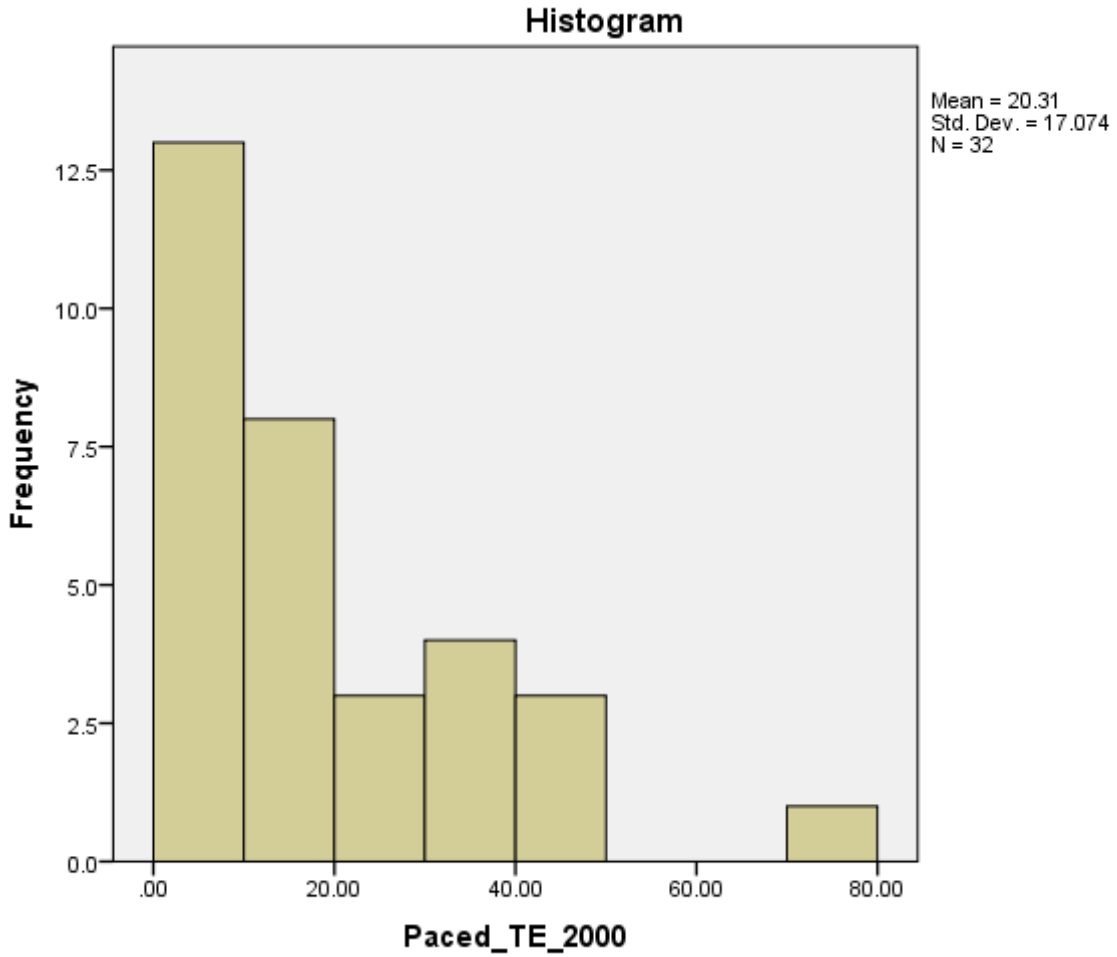


Figure 58 Distribution of mean tapping percentage error in the paced condition (2000ms)

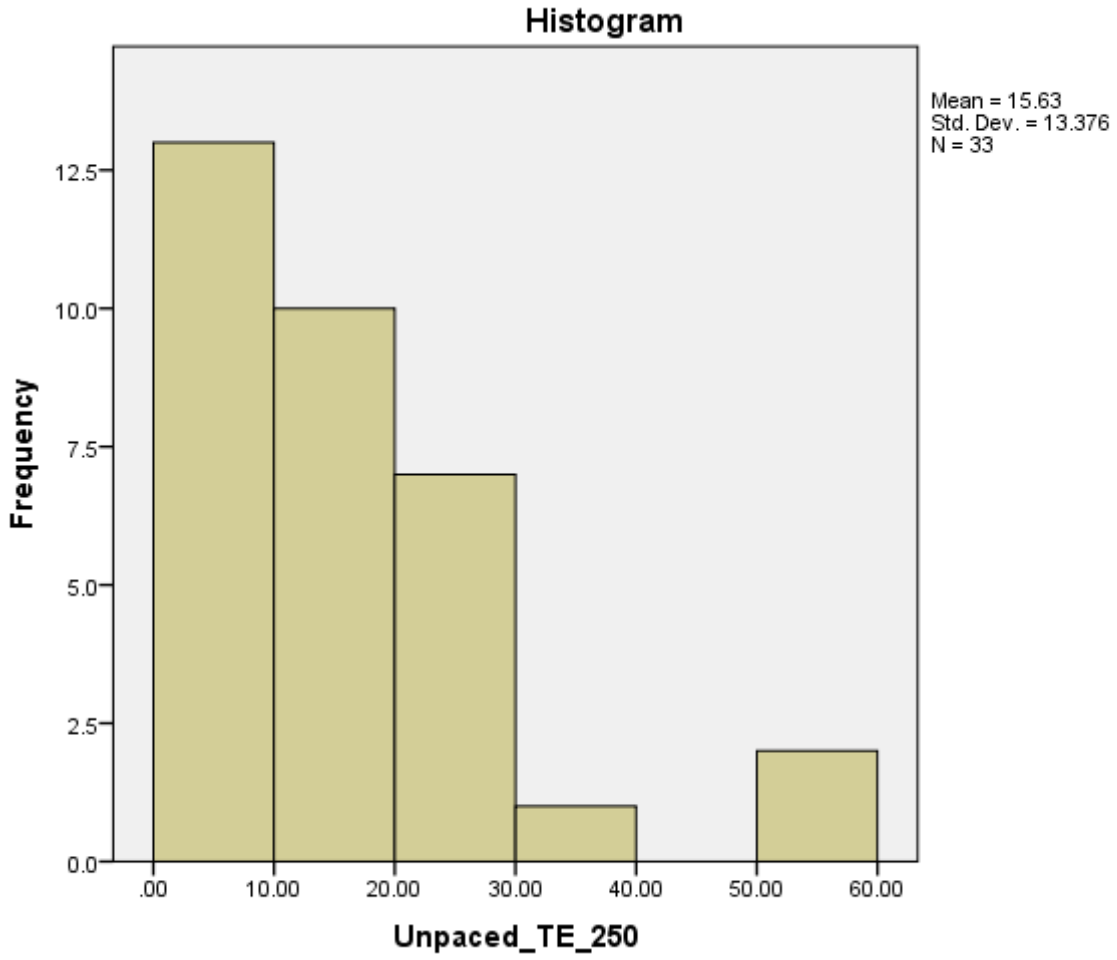


Figure 59 Distribution of mean tapping percentage error in the unpaced condition (250ms)

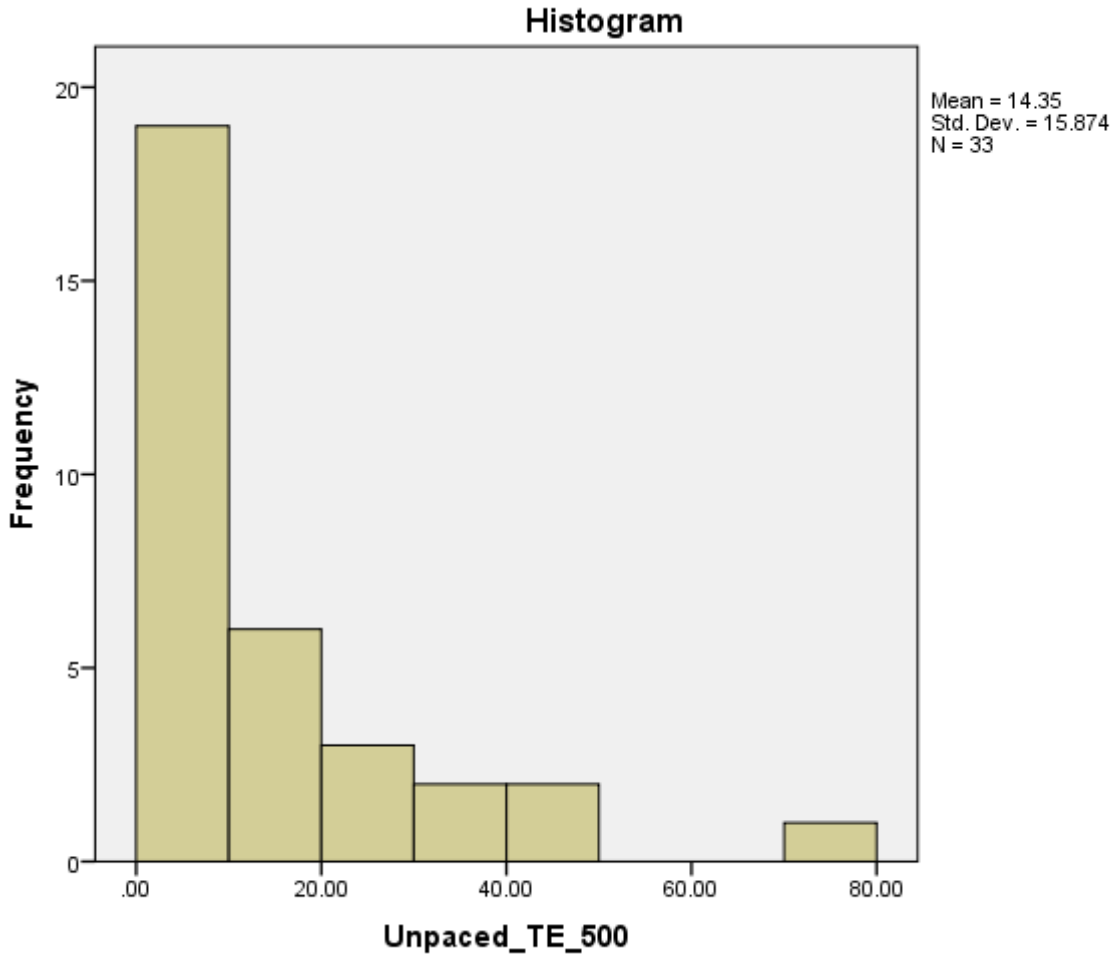


Figure 60 Distribution of mean tapping percentage error in the unpaced condition (500ms)

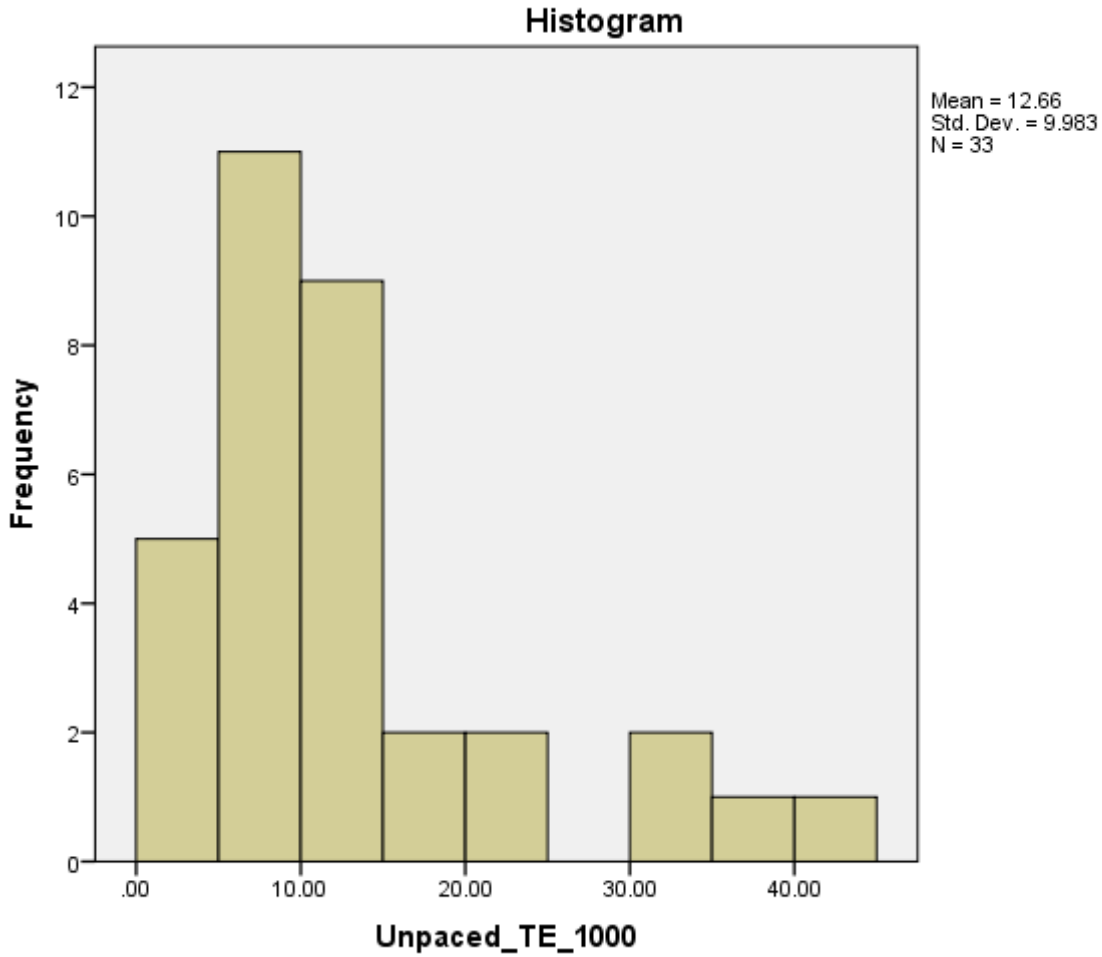


Figure 61 Distribution of mean tapping percentage error in the unpaced condition (1000ms)

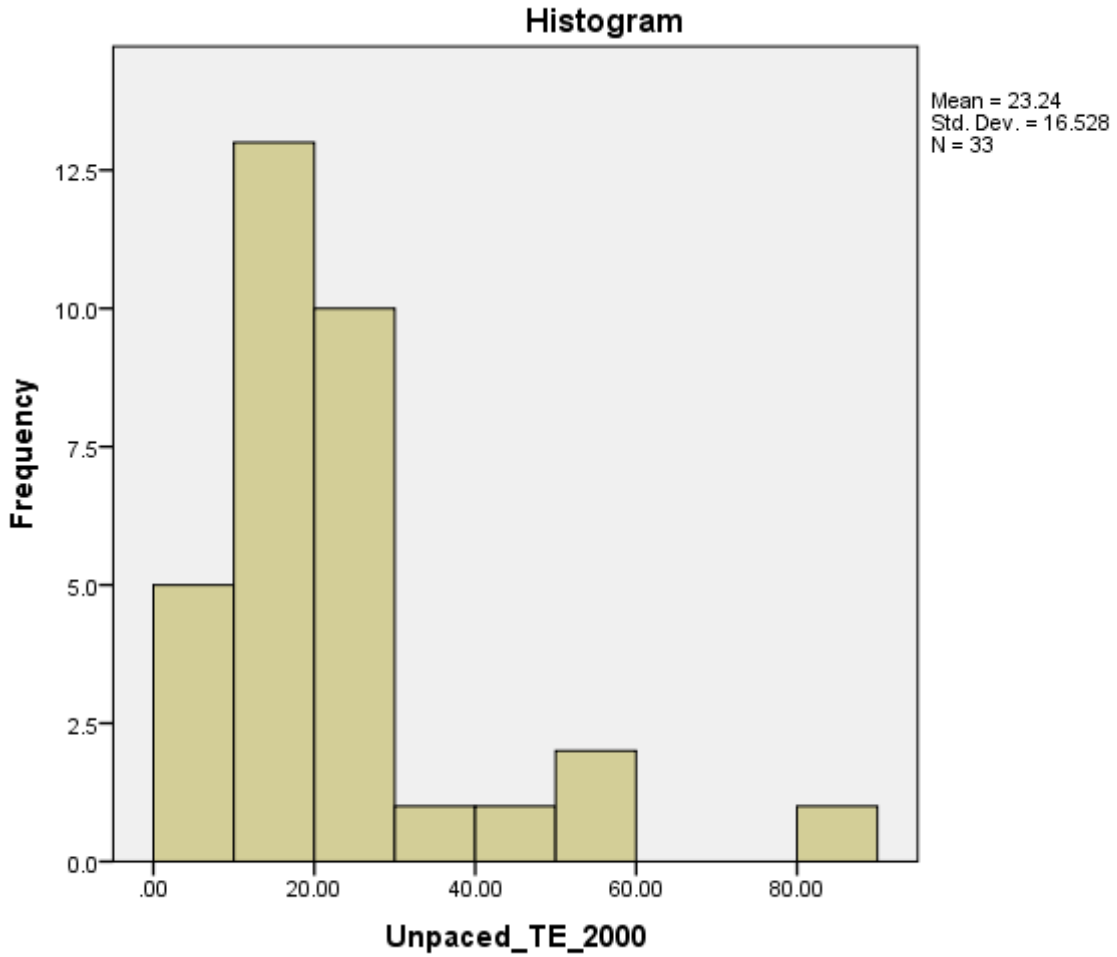


Figure 62 Distribution of mean tapping percentage error in the unpaced condition (2000ms)

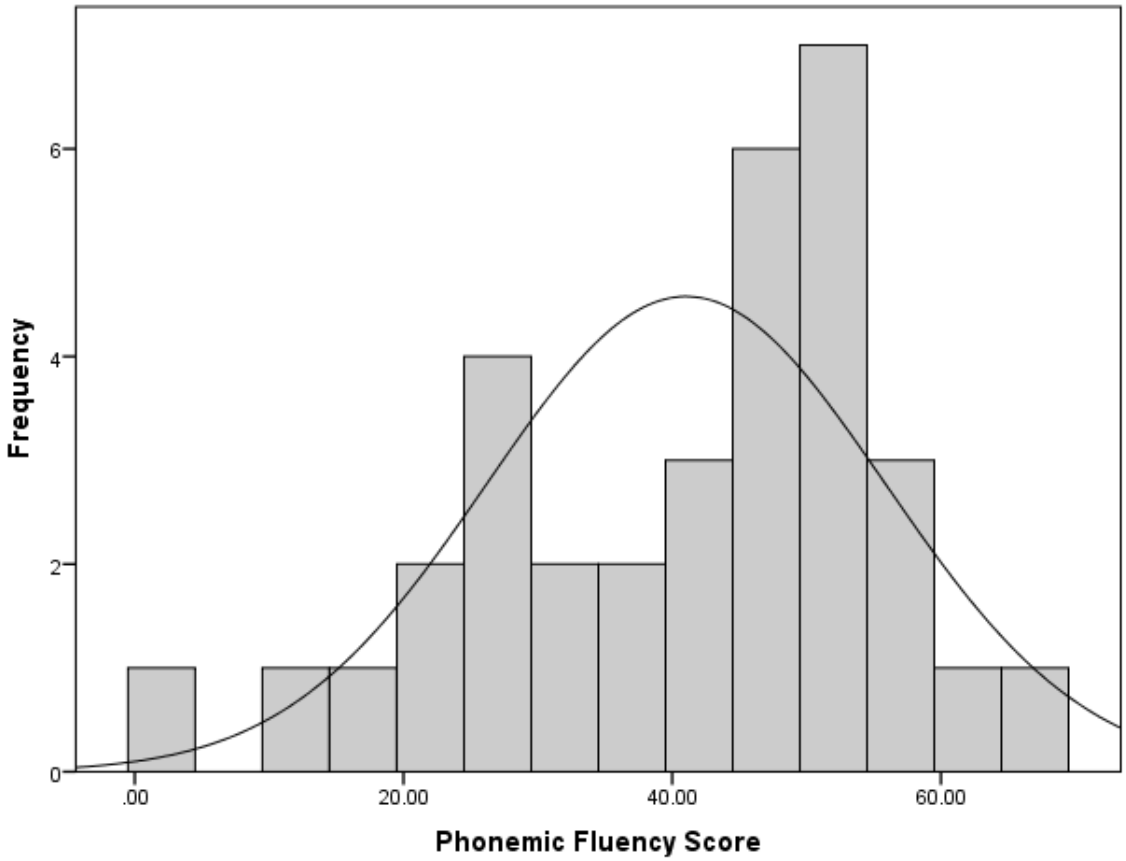


Figure 63 Distribution of letter fluency scores

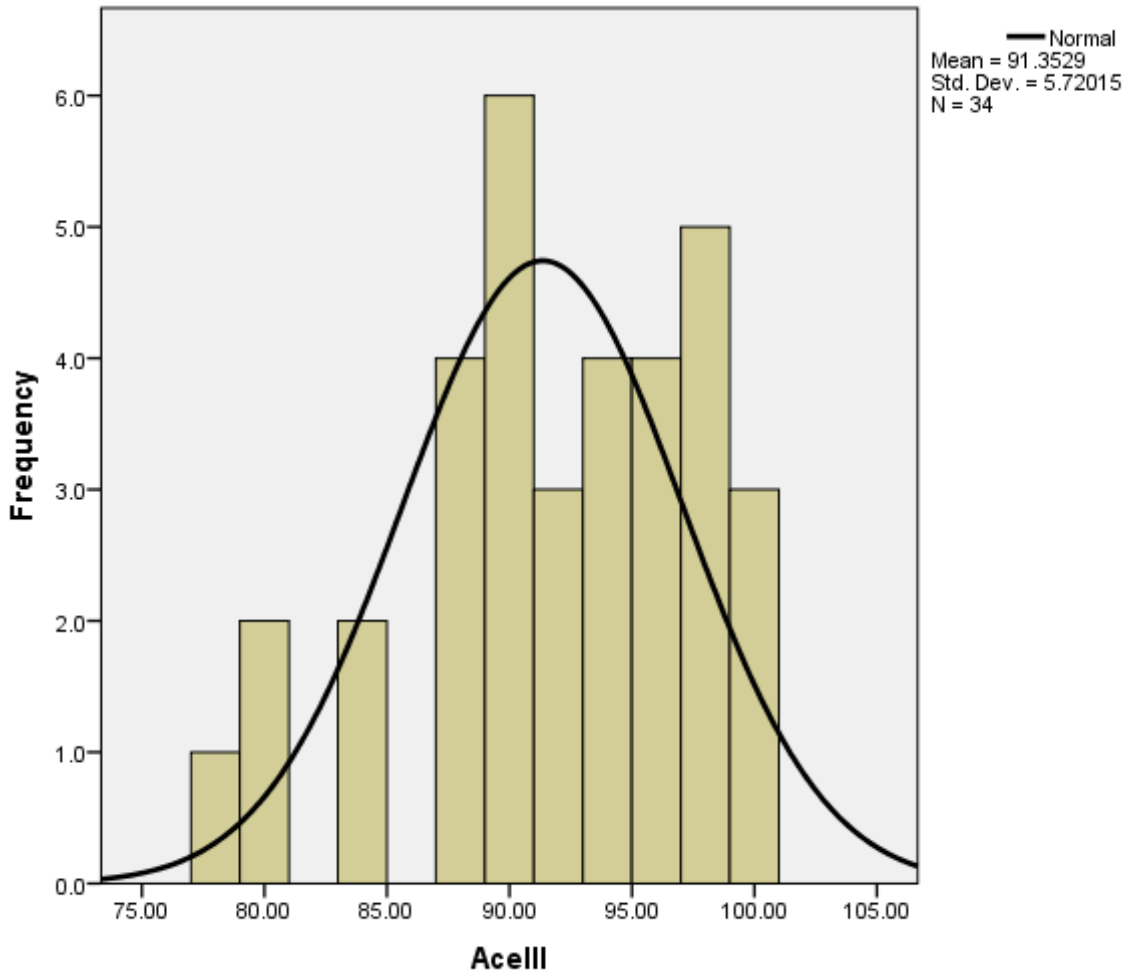


Figure 64 Histogram of ACE III Scores

8.7 Appendix 7 – NMS App Project Group Roles

Table 43 Description of main project group members and roles

Group Member	Role	Description of role
Dr Camille Carroll (CC)	Associate Professor and Honorary Consultant Neurologist	CC is the project lead, and responsible for all decisions related to the project.
Thea Dominey (TD)	Researcher	TD is responsible for leading the design and delivery of the usability studies, and ensuring the app meets user requirements. TD is also responsible for the maintenance of the MHRA Site File.
Dr Stephen Mullin (SM)	Clinical Lecturer	SM is a user representative (HCP) and is responsible for liaising with the app builders.

Group Member	Role	Description of role
Dr Craig Newman* (CN)	Mobile health technology innovation lead	CN contributed towards the initial app and portal design.
Sue Whipps (SW)	Care partner	SW is a user representative (care partner).
John Whipps (JW)	PwP	JW is a user representative (PwP).
Emma Edwards (EE)	Parkinson's Nurse Specialist (PDNS)	EE is a user representative (HCP) and assisted with carrying out the formative usability testing**.
Inocencio Maramba (IM)	Research Assistant, Human Computer Interface and Design	IM joined the project group in December 2018, and assisted with the set up and of the Usability testing.

* Iona Gillies (IG) was N's project student and assisted with various elements of project delivery between July 2017 and July 2018.

** Cathryn Harries (CM) was an Undergraduate Psychology Student and assisted with carrying out the formative usability testing.

Table 44 Description of external collaborators, contractors and roles

Group Member	Role	Description of role
Prof Ray Chaudhuri (RC)	Professor of Neurology/ Movement Disorders, Kings College London	Author of NMS-Quest. RC contributed to development of the scripts for the self-help videos.
Ron Postuma (RP)	Movement Disorders Neurologist, McGill University	Author of 'A Guide to the Non-Motor Symptoms of Parkinson's Disease' *(A Guide to the Non-Motor Symptoms of Parkinson's Diseas*>, n.d.).
Ben Stirling (BS)	App designer (Made with Maturity)	Responsible for designing the app wireframe and developing the animations in line with group comments and feedback.
Peter Hannon (PH)	App builder (SUVO)	Responsible for the build of the app final prototype and nurse portal based on the usability testing findings.

Group Member	Role	Description of role
Ruth D’arcey-Daniels (RD)	User Experience Researcher	Advised TD on the usability testing design, methodology, and objectives.

8.8 Appendix 8 – NMS Questionnaire

Survey Title: Parkinson's non-motor symptoms: self-help behaviours

In addition to the well-known movement symptoms in Parkinson's, other problems can sometimes occur as part of the condition or its treatment. These problems are referred to as non-motor symptoms, and some examples of non-motor symptoms in Parkinson's are listed below. We are interested to find out how frequently you seek help for these problems, and what methods you use to do so.

Some examples of non-motor symptoms in Parkinson's (please note: this is not an extensive list, there are others; not all people with Parkinson's will experience all of these symptoms):

- Changes in taste and smell
- Sleep problems
- Changes in mood
- Dizziness
- Constipation
- Urinary problems
- Problems with thinking and memory
- Pain
- Urinary problems
- Gastrointestinal dysfunction
- Sexual problems

Please start the survey by pressing the start button below, all responses will remain anonymous.

Demographics:

- Age / date of birth
- Gender
- Date of diagnosis
- Country
- City/Region

1. How troublesome do you find your non-motor symptoms?

- Extremely troublesome
- Troublesome
- Moderately troublesome
- Rarely troublesome
- Not troublesome

2. How long is it between appointments with your Parkinson's doctor?

- Less than 6 months
- Between 6 and 12 months
- Between 12 and 18 months
- Longer than 18 months

3. How often do you see your GP about your Parkinson's?

- More than twice in six months
- About twice a year
- About once a year
- About once every 18 months
- Never

4. How long is it between appointments with your Parkinson's Nurse?

- Less than 6 months
- Between 6 and 12 months
- Between 12 and 18 months
- Longer than 18 months
- I don’t have a Parkinson’s Nurse

5. How frequently do you discuss non-motor symptoms with your Parkinson’s doctor in clinic?

- Never
- About a quarter of appointments
- Half of clinic appointments
- 75% of clinic appointments
- At almost all clinic appointments

6. How frequently do you discuss non-motor symptoms with your GP at appointments?

- Never
- About a quarter of appointments
- Half of clinic appointments
- 75% of clinic appointments
- At almost all clinic appointments

7. How frequently do you discuss non-motor symptoms with your Parkinson’s Nurse at appointments?

- Never
- About a quarter of appointments

- Half of clinic appointments
- 75% of clinic appointments
- At almost all clinic appointments

8. How frequently do you seek help from professionals about your non-motor symptoms?

- Very infrequently
- Infrequently
- Occasionally
- Frequently
- Very frequently

9. Whom do you seek help from? (you can select more than one)

- Parkinson's Nurse
- Parkinson's Doctor
- GP
- Other

10. How frequently do you seek self-help advice for your non-motor symptoms?

- Very infrequently
- Infrequently
- Occasionally
- Frequently
- Very frequently

11. In which format would you prefer self-help information?

- Text
- Videos of Expert giving advice
- Animation

- In person
- Other (please give details)

12. What information sources do you currently use to seek self-help advice related to your non-motor symptoms? (You can select more than one):

- Websites –please give details
- Support Groups – please give details
- Reading material – please give details
- Online videos – please give details
- Apps – please give details
- Clinic visits or consultations
- Other – please give details

13. Do you currently use (or have you previously used) any apps associated with your Parkinson's?

- Yes- please give details
- No

14. In future, would you consider using an app to gain self-help advice on how to manage your non-motor symptoms?

- Yes
- No

15. Please select the devices you currently have access to (you can select more than one):

- Smartphone
- Tablet or iPad

- Computer
- None of the above

16. In which environments do you use these devices? (You can select more than one):

- At home
- In clinic
- Out in public (eg. cafes, on buses, the library)

Many thanks for completing this questionnaire; your data will remain anonymous.

8.9 Appendix 9 – Creative Brief

Storyboard Creative Brief

Please complete all sections of this form giving as much information as possible. This allows us to allocate the proper time and resource to each shoot.

From: Dr Camille Carroll **Date:** 28/06/2018

To: Multimedia Teams

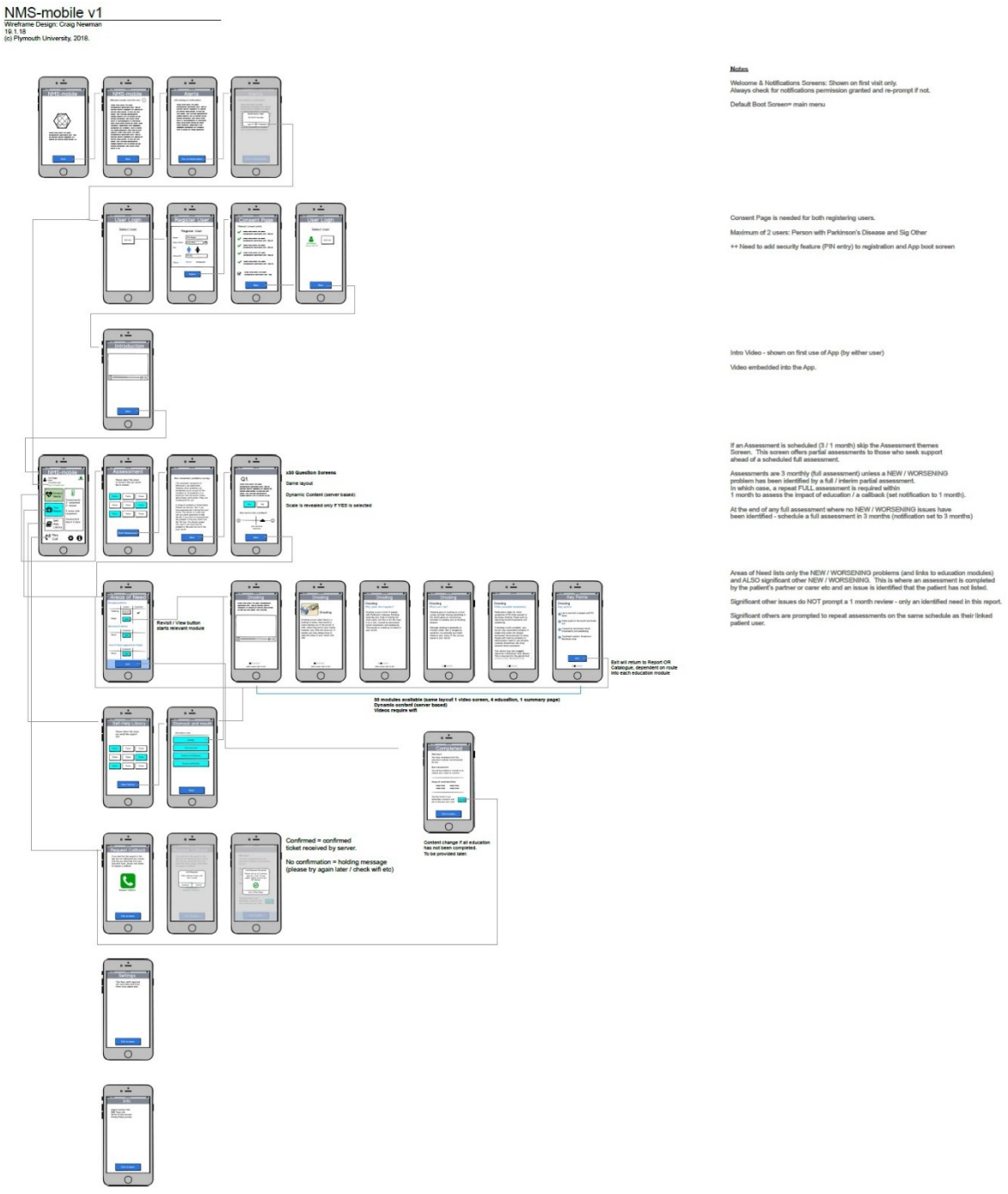
Project working title:	Non Motor Symptoms (NMS) Application

Background:	In addition to the motor symptoms most commonly associated with Parkinson's disease (PD), individuals often develop other health problems, known as non-motor symptoms (NMS), which include problems with decreased swallow and daytime sleepiness. These symptoms often lead to reduced quality of life and increased disease burden for patient and carer. We are developing a non-motor symptom application (NMS Assist) to help individuals manage these symptoms of their Parkinson's. In the app we will include short (approx. 45 secs) videos to describe, explain and advise on the non-motor symptoms. The videos will use animations to provide information on non-motor symptoms, so that there is potential to produce the videos in multiple languages. In the first instance, we would like to focus on using storyboards for 2 of the videos (drooling and excessive daytime sleepiness) to get a feel for what the rest of the animations might look and feel like.
Objectives:	These 2 animation storyboards are aimed at gaining insight into how animation may be used to aid individuals' self-management of PD by educating them on the non-motor symptoms associated with the disease.
Courses:	These animation videos will incorporate information from the Postuma guide to Non-Motor Symptoms of PD. (Link below)

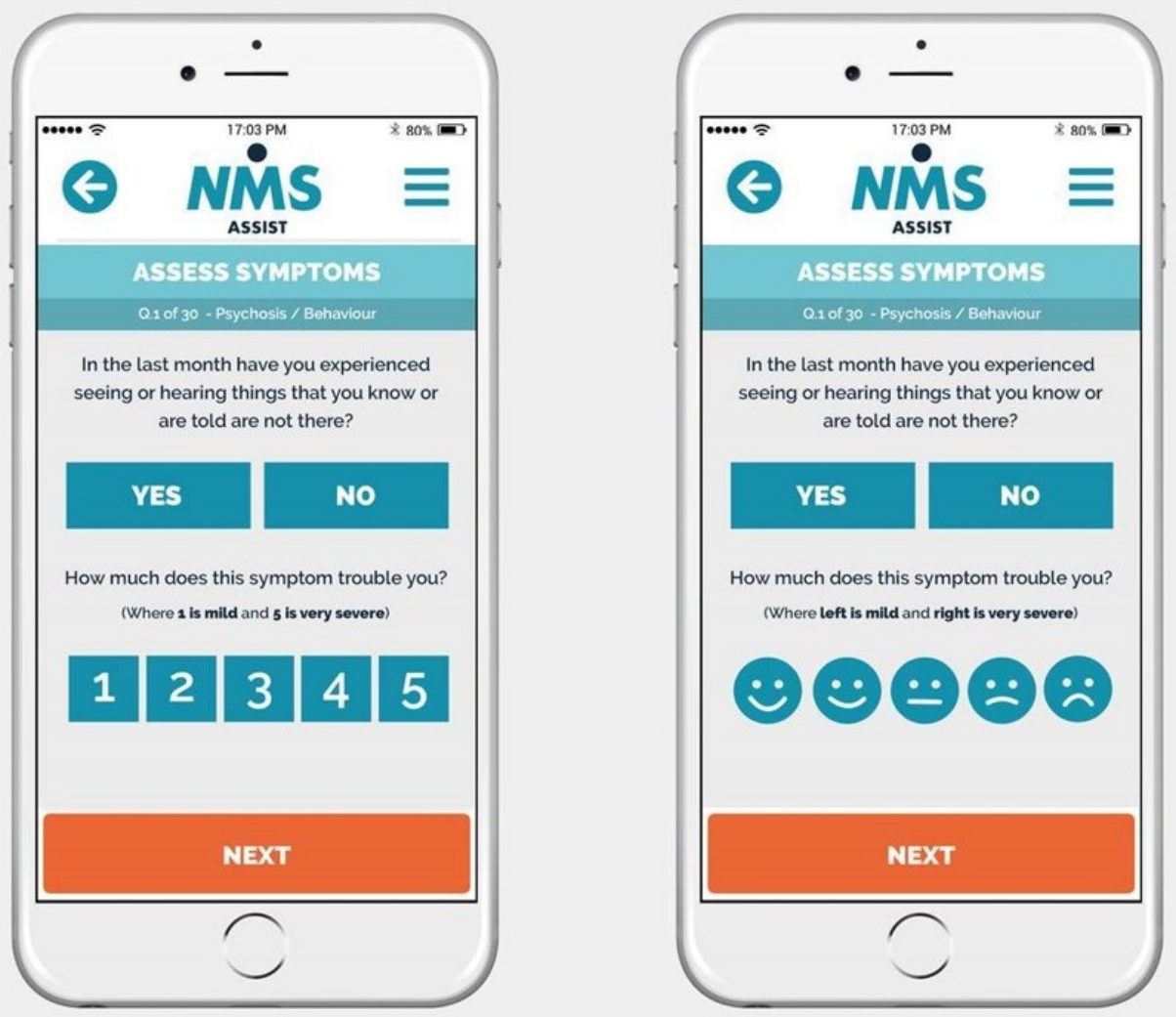
	https://www.parkinson.bc.ca/media/33807/guide-to-the-non-motor-symptoms-of-parkinsons-disease.pdf
Key messages:	Aid individuals' self-management of PD by providing education and advice on the varying non-motor symptoms associated with the disease.
Secondary message:	Direct individuals to additional sources of information regarding PD symptoms.
Inspirations:	Refer to Dr Carroll's previous videos discussing Parkinson's research (generated by Plymouth University). Animation at end of films for schools: https://www.parkinsons.org.uk/professionals/resources/short-film-teachers-listen-my-thoughts
People:	The videos will use animations to provide relevant information on PD non-motor symptoms.
Locations:	As the videos will use animations, all of the video production will be carried out in-house, at the site of the relevant media team.
Schedule:	July-Aug 2018
Delivery Deadline:	Sep-Oct 2018
Length:	Approx. 23 Videos, each 45- 60 secs in length.
Target audiences:	Individuals/carers of Individuals with Parkinson's Disease.
Deliverables:	Deliver storyboards for 2 of the non-motor symptom videos (drooling and excessive daytime sleepiness) that will reflect the style of animation to be used as part of the final 23 animation videos. These storyboards will give some idea of how the information on the relevant non-motor symptoms might be conveyed through animation, with the aim to support the information that the patient has heard, and facilitate learning of this information. This information is derived from Ronald Postuma's guide; using the prepared scripts (attached). Information is likely to be sectioned into 3 components: Why does this symptom happen? Why is this symptom important in Parkinson's Disease? What can be done to help this?

Usage:	These story boards will be used to gain insight into how the animation videos may be used to convey relevant information and aid individuals' self-management of PD.
Formats required:	E.g. Uploaded on University YouTube channel and provided on a DVD or USB.
Budget:	Max £10,000 for all 23 videos (Funding currently available through the Hoover foundation and Plymouth Hospitals Charities)
Who has final sign-off:	Who is the overall owner of this film?
Contacts:	Project Leads: Dr Camille Carroll, Dr Craig Newman Research Assistants: Iona Gillies, Thea Dominey Patient and carer representatives: Sue Whipps, John Whipps

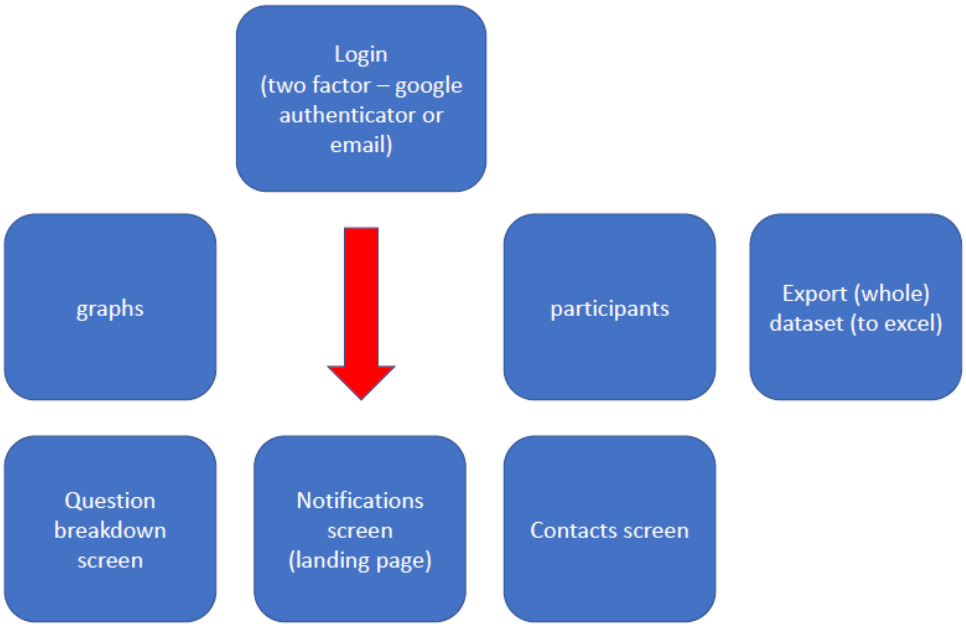
8.10 Appendix 10 – Initial wireframe design

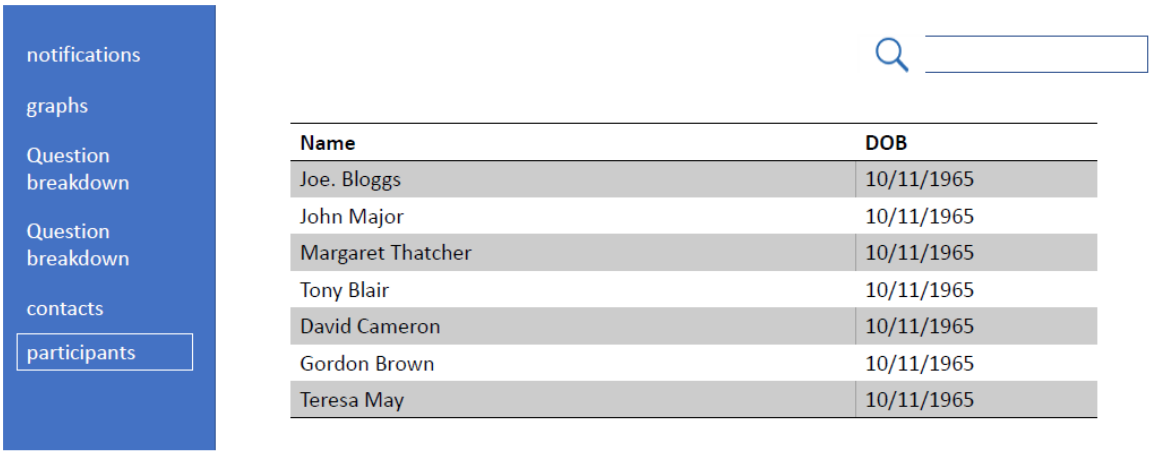


8.11 Appendix 11 – Symptom severity scale

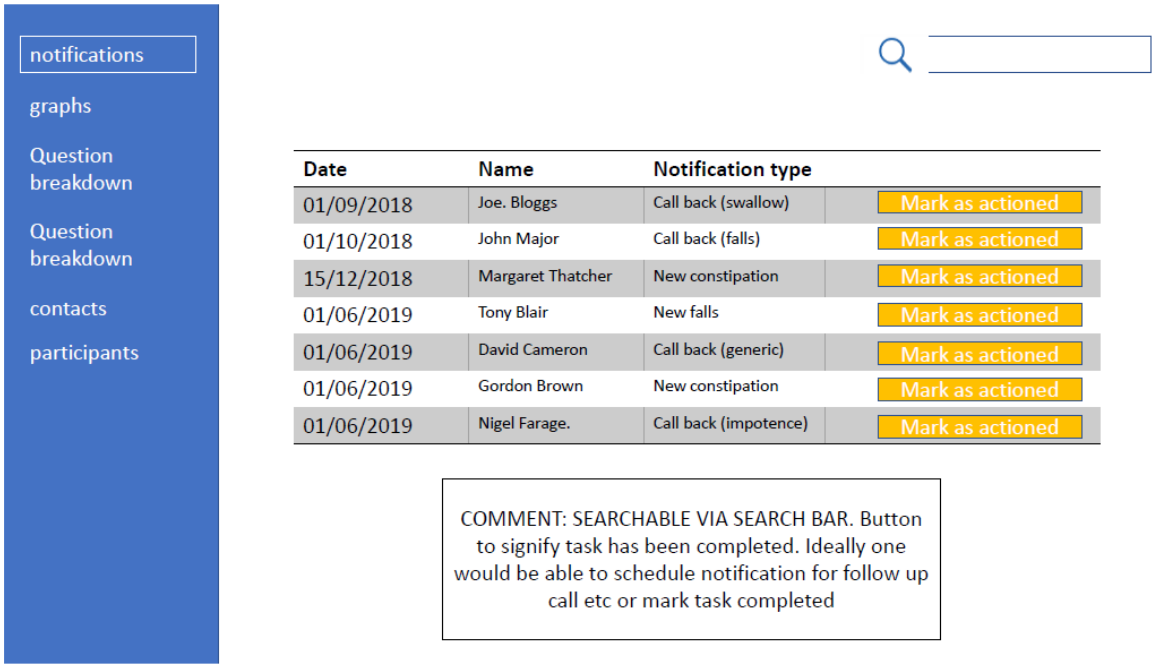


8.12 Appendix 12 – Nurse Portal Mock Up



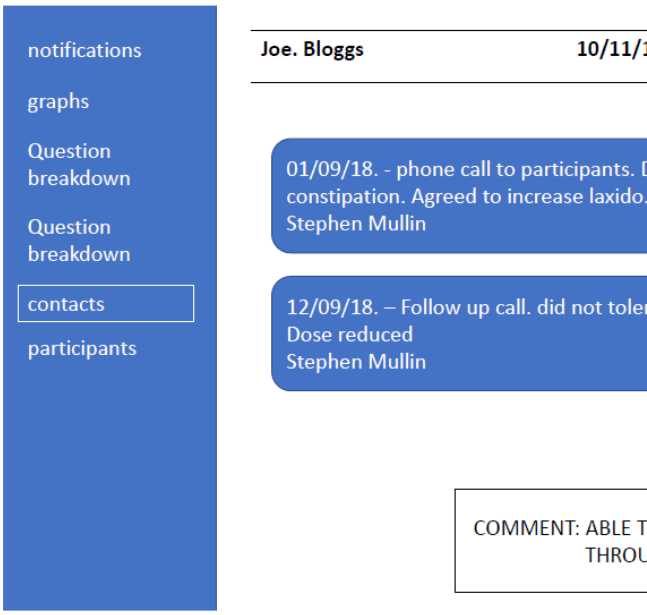


Name	DOB
Joe. Bloggs	10/11/1965
John Major	10/11/1965
Margaret Thatcher	10/11/1965
Tony Blair	10/11/1965
David Cameron	10/11/1965
Gordon Brown	10/11/1965
Teresa May	10/11/1965



Date	Name	Notification type	
01/09/2018	Joe. Bloggs	Call back (swallow)	Mark as actioned
01/10/2018	John Major	Call back (falls)	Mark as actioned
15/12/2018	Margaret Thatcher	New constipation	Mark as actioned
01/06/2019	Tony Blair	New falls	Mark as actioned
01/06/2019	David Cameron	Call back (generic)	Mark as actioned
01/06/2019	Gordon Brown	New constipation	Mark as actioned
01/06/2019	Nigel Farage.	Call back (impotence)	Mark as actioned

COMMENT: SEARCHABLE VIA SEARCH BAR. Button to signify task has been completed. Ideally one would be able to schedule notification for follow up call etc or mark task completed


notifications
graphs
Question breakdown
Question breakdown
contacts
participants
Joe. Bloggs 10/11/1965
01/09/18. - phone call to participants. Discussed constipation. Agreed to increase laxido. Have written to GP
Stephen Mullin
12/09/18. – Follow up call. did not tolerate dose increase. Dose reduced
Stephen Mullin
COMMENT: ABLE TO SWIPE UP AND DOWN THROUGH ENTRIES

notifications

graphs

Question breakdown

Question breakdown

contacts

participants

Joe. Bloggs **10/11/1965**

		01- Nov - 18	01- May - 19	01- Nov - 19
Cognition cluster	Mood (patient)	0	1	1
	Mood (carer)			4
	Memory (patient)	1	2	3
	Memory			2
	Hallucinations (patient)	5	5	5
	Hallucinations (carer)			5
	Anxiety (patient)	2	2	2
	Anxiety (carer)			2
Bowel cluster	Constipation (patient)	4	4	4
	Constipation (carer)			3

COMMENT: TICK BOX FILTERS ALLOW INCLUSION/EXCLUSION OF CLUSTERS OR INDIVIDUAL QUESTIONS. ABLE TO SWIPE LEFT AND RIGHT THROUGH DATES. ALSO ABKLE TO SHOW PATIENT/CARER DATA TOGETHER OR IN ISOLATION

notifications

graphs

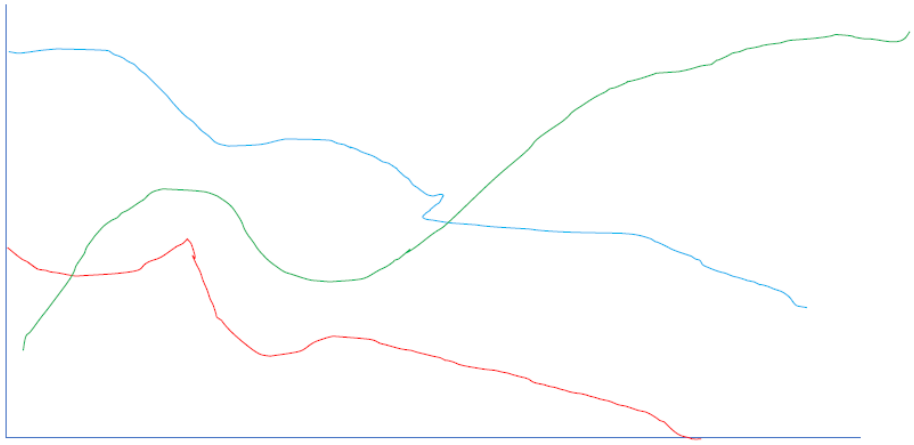
Question breakdown

Question breakdown

contacts

participants

Joe. Bloggs **10/11/1965**



COMMENT: DATES AND GRAPHS SHOWN FILTERED THROUGH TICK BOXES/SLIDERS. ABLE TO SHOW RAW NMS SCORE, ENHANCED NMS SCORE, ENCANCED SCORE OF QUESTIONS OR CLUSTER/ENHANCED CLUSTER SCORE. MULTIPLE GRAPHS CAN BE SHOWN CONCURRENTLY.

8.13 Appendix 13 – Symptom Script

NMS App – Symptoms Script

Only read text in bold.

Theme: Psychosis/behaviour

Hallucinations:

What is it?

Hallucinations mean hearing or seeing things that are not really there and may affect up to one third of people with Parkinson's. They commonly begin as minor, non-threatening visual images. For example, a spot on the floor or the wall may move, or the spot may look like an insect. If hallucinations progress, you may see children, animals or people. Most people are aware that the hallucinations are not real.

Why is this important in Parkinson's disease?

They are partially related to medications and partially related to Parkinson's itself.

What can I do?

Often hallucinations do not need to be treated but you should discuss them with your Parkinson's team, particularly if you are finding them upsetting. Specialist treatments are available.

Key Points:

- Up to one third of people with Parkinson's may have hallucinations.
- Hallucinations are almost always visual (you see things that are not there).

Delusions

What is it?

Delusions are false beliefs that are not based on reality or fact and may be linked to believing hallucinations are real. They can lead to suspicions directed at family members. Common delusions include paranoia, cheating spouses or theft.

Why is this important in Parkinson's disease?

Typically, delusions occur in people who have other problems with thinking and memory. Often, Parkinson's medications can make delusions worse. Delusions may be triggered or worsened by infections.

What can I do?

- **If this has suddenly started or worsened, please speak to your GP in case there is an underlying infection.**
- **Seek specialist help; it may be that medication adjustments are required.**

Seek carer support on a Facebook group

Don't read this link…(https://www.facebook.com/groups/1734404233474754/?ref=share),

or phone the Parkinson's UK helpline (0808 800 0303).

Key Points:

- Delusions are false beliefs not based on fact.
- Delusions often include cheating spouses and theft.
- Specialist treatments are available.

Impulse Control Behaviours

What is it?

Impulse control behaviours can occur in people on Parkinson's medications. These can include:

- **Excessive gambling**
- **Hyper sexuality**
- **Binge eating**
- **Compulsive shopping**
- **Excessive pursuit of hobbies**
- **Punding (repetitive performance of meaningless tasks)**

What can I do?

If you notice any of these behaviours for the first time or an increase in these behaviours, then you must speak to your Parkinson's team.

Seek carer support on a Facebook group.

Don't read this link (https://www.facebook.com/groups/1734404233474754/?ref=share).

Key Points:

- People on some Parkinson's medications can develop impulse control behaviours.
- Excessive gambling and hyper sexuality are the most common ICBs.

- Specialist treatment advice should be sought.

Theme: Falling and balance

Feeling Lightheaded on Standing

What is it?

Feeling lightheaded on standing is due to a drop in blood pressure. Headache and shoulder or neck pain can also occur. If this is severe, you could black out and fall.

Why is this important in Parkinson's disease?

This blood pressure drop can be due to Parkinson's itself, and can be made worse by Parkinson's medications and possibly other blood pressure tablets.

What can I do?

If you have this problem avoid standing up quickly; try counting to 10 before you move off. Increasing salt intake can help. Drink at least 2 litres of water per day and avoid caffeinated drinks. Full length compression stockings may be helpful. Specialist treatments are available.

Key Points:

- Main symptom: Feeling light-headed when standing up.
- Other symptoms include: Shoulder pain, headache or blacking out when standing up.

- Make sure you have adequate salt in your diet and drink at least 2L of water a day.

Theme: Gastrointestinal Tract

Drooling

What is it?

Drooling is a common problem in Parkinson's disease. It is caused by decreased swallowing.

What can I do?

Chewing gum or sucking on a boiled sweet can help; keep your head positioned upright and remember to swallow. A Speech and Language Therapist can discuss swallow timers which may be helpful. At night, try re-positioning your head to a more upright position or covering the pillow with a towel. Specialist medications may be available.

Key Points:

- Up to one half of people with PD drool.
- Saliva pools in the mouth and leaks out.
- It is caused by decreased mouth movements and swallowing.
- Chew gum or suck sweets.
- Specialist treatments are available.

Difficulty Swallowing

What is it?

Occasionally patients notice difficulty in swallowing food, drink, tablets or even saliva.

Why is this important in Parkinson's disease?

Swallowing is a very complex process that requires a high degree of muscle coordination. Food going down the wrong way can lead to chest infections.

What can I do?

It is important not to rush your meals; eating small mouthfuls and sipping water regularly throughout can help. Remember to sit upright and not to talk whilst eating. Adding mango or banana to drinks to make them thicker may help, as well as taking tablets with yoghurt. Try and time meals for when your Parkinson's medications are working well.

Key Points:

- One half of people with PD have trouble swallowing.
- Trouble swallowing can result in choking or chest infections.
- Take frequent sips of water with meals.
- Consider banana or mango to thicken drinks.
- Time meals for when your Parkinson's medications are working well.

Nausea and Vomiting:

Why is this important in Parkinson's disease?

The most common cause of nausea is starting a new Parkinson's drug. However, a feeling of stomach bloating can also be present in Parkinson's, usually related to slow stomach movements.

What can I do?

If nausea and vomiting appear with a new drug, these symptoms often go away by themselves even if you stay on the medication. Taking your medication with meals (or with a small snack) may help. Managing your constipation may also help (link to constipation page).

You should be aware that over-the-counter sickness medications often block the effect of dopamine and can make Parkinson's worse. Specialist prescribed treatments may be available.

Key Points:

- Nausea often begins when starting a new Parkinson's drug.
- This symptom may not persist when related to a new drug.
- Beware of over-the-counter treatments.

Constipation:

What is it?

Constipation is defined as having less than three soft, bulky bowel movements a week, or excessive straining to pass stool. It affects three out of four people with Parkinson's. Generally, constipation is an easy symptom to recognise. Other than the difficulty moving your bowels, you may also feel you are unable to completely empty your bowels or that you are unable to completely relax the muscles that prevent bowel movements.

Why is this important in Parkinson's disease?

Constipation can affect medication absorption and urinary symptoms, as well as causing feelings of nausea. Very severe constipation can cause obstruction of the bowels, with medical complications. Constipation is part of the disease itself, not usually caused by Parkinson's treatment.

What can I do?

Constipation can be treated, and the Bristol Stool Chart can help provide you with an idea of your stool so you can recognise signs of constipation. Drinking at least 2L of water per day, as well as doing moderate exercise and adding fibre to your meals can help relieve symptoms. Foods rich in fibre include: bran fibre, whole wheat products, lentils and beans, prunes or prune juice, dried apricots.

Over-the-counter medications may not be that effective. There are stool softeners that can be prescribed.

Key Points:

- Three in four people with PD suffer from constipation.
- This can be an early sign of Parkinson's disease.
- Treatment options: Drink water, eat fibre, exercise and use bulking agent, or prescribed stool softeners.

Uncontrolled Loss of Stool

Loss of stool is not necessarily due to diarrhoea. It refers more to an inability to control bowel movements, with incontinence, or 'accidents'.

Why is this important in Parkinson's disease?

This is quite a rare feature of Parkinson's; you may have a small amount of leakage when you pass gas.

What can I do?

You can find a range of (incontinence) products at health supply stores. Ensure that you are not constipated, aiming for a soft bulky stool passed every day.

Key Points:

- Rare.
- Parkinson's medications can improve uncontrolled loss of stools.

Theme: Mood and memory:

Problems with Thinking and Memory

What is it?

Problems with thinking and memory are common in Parkinson's.

Why is this important in Parkinson's disease?

This can include problems with planning tasks and concentrating which may be worse when your Parkinson's medications are wearing off.

What can I do?

There is increasing evidence that keeping your brain active can maintain memory and concentration. Consider discussing this with people around you as it may be affecting them too. It is important to keep generally healthy with regular exercise, good diet and good blood pressure control. Specialist treatments may be available.

Key Points:

- Problems with thinking and memory occur with Parkinson's.
- Common symptoms include: difficulty with planning, focussing attention, slowing of thought, decreased memory.
- Some forgetfulness can occur normally with aging.
- Keep mentally and physically active.

Depression and Anxiety

What is it?

Depression is very common in Parkinson's. If you are depressed, you may not be able to experience joy. You may stop hobbies that you once enjoyed, and you may not want to carry out your daily routine. Learning new hobbies may also not interest you. Fatigue is commonly linked with depression. Depression can also affect both your appetite and sleeping patterns. Anxiety often also occurs in Parkinson's. Some have bursts of anxiety called 'panic attacks'. Or you can have excessive worry about everyday things that you cannot control. Anxiety is also common during 'off' periods.

What can I do?

Keep yourself active socially and physically as much as possible. Exercise, particularly while outside, may help. Seek specialist advice early.

Key Points:

- Depression and anxiety are common in Parkinson's.
- Parkinson's disease affects areas of the brain that control mood.
- Anxiety can occur in 'off' periods. This can be improved by preventing the 'off' times.

Theme: Sexual Function

Sexual Dysfunction

What is it?

Sexual dysfunction is common in Parkinson's. For men, it can be hard to obtain or maintain an erection. Problems with having an orgasm or decreased sex drive can also occur. An increased sex drive can occur with some Parkinson's medications.

What can I do?

Regular exercise helps develop stamina for sexual intercourse. Also you may want to consider other forms of intimacy. See the web link below for more information. Don't read this link (https://www.parkinsons.org.uk/information-and-support/sex-and-parkinsons) **Speak with your partner and decide what is best for your relationship. Your local Parkinson's Disease Nurse Specialist can provide you with more information on what help is available. This may include**

speaking with physiotherapists who could advise you on positions. Specialist treatments are available; please let your Parkinson's team know if you think there may be a link with your medications.

Key Points:

- Sexual dysfunction is common in Parkinson's.
- Sexual dysfunction can include: difficulty with erections (men) or orgasm (women), or decreased sex drive (both men and women), increased sex drive related to medications.
- Consider other forms of intimacy (https://www.parkinsons.org.uk/information-and-support/sex-and-parkinsons).

Theme: Urinary

Bladder Problems

What is it?

One third of people experience a bladder related problem with Parkinson's. The most common problem is an over-active bladder. An overactive bladder can cause a sense of urgency, needing to rush to the bathroom, urinate frequently (less than every two hours) as well as get up multiple times at night to go to the bathroom. With Parkinson's, you may also experience an underactive bladder. Symptoms include difficulty starting urination, a sensation of not completely emptying your bladder and the leakage of urine.

What can I do?

Try to plan out and schedule bathroom trips at regular intervals. Try to avoid excessive tea and coffee consumption and reduce your liquid intake prior to going to bed. Make sure you keep well hydrated during the day. Ensure you are not constipated. Consider bladder training exercises. Specialist treatments are available.

Key Points:

- One third of people with Parkinson's have bladder dysfunction.
- Common symptoms: getting up to urinate at night, frequently passing urine and urgency to pass urine.
- Treatment options: Keep well hydrated, ensure you are not constipated, avoid excess caffeine and plan toilet trips.
-
- **Sleep/Fatigue**

Excessive Daytime Sleepiness

What is it?

Excessive daytime sleepiness means falling asleep easily or frequently during the day.

Why is this important in Parkinson's disease?

Daytime sleepiness can be part of Parkinson's, but can also be made worse by Parkinson's medications, poor sleep at night, and other conditions such as sleep apnea (see 'Insomnia' page).

What can I do?

Drinking some extra coffee or tea, going outside, as well as scheduling naps may help. Avoid other medication that can make you feel drowsy such as antihistamines. Specialist treatment is available. Make sure you keep yourself and others safe. Avoid driving if you feel even slightly sleepy. It is important to distinguish daytime sleepiness from sleep attacks. With a sleep attack you will have a sudden desire to sleep which can occur while eating, working, walking or reading. You may even have sleep attacks while driving. If you have sleep attacks, you must seek specialist help.

Key Points:

- Feeling sleepy during the day is common with Parkinson's.
- Always think twice about driving, even if you are just a little bit tired.
- Extra tea and coffee, and scheduled naps may help.

Problems Sleeping

What is it?

Sleep problems are common in Parkinson's and are mostly due to the underlying condition. People with Parkinson's usually have trouble staying asleep more than falling asleep.

What can I do?

- **Falling Asleep: The first step you should take to treat falling asleep problems is 'sleep hygiene'. Sleep hygiene includes making your bedtime and waking time as regular as possible, not spending too long in bed, and not lying in bed for over half an hour if you are struggling to fall asleep. Get up and do something relaxing and then try to sleep again later. Exercise during the day. Reduce naps during the day. Additionally, avoiding (blue light) electronic gadgets can help.**

- **Staying Asleep: If you have trouble staying asleep consider whether this may be due to:**
    a. **Mobility problems/off periods overnight- satin sheets or bed rails may help.**
    b. **Waking to empty your bladder (see 'Bladder' page).**
    c. **Vivid dreams in REM Sleep Behaviour Disorder (see 'RBD' page).**
    d. **Sleep fragmentation due to Parkinson's.**
    e. **Anxiety (see 'Anxiety' page).**
    f. **Restless leg syndrome (see Restless Leg page).**

It might also be useful to review if these sleep problems are due to an overnight off period or mobility issues.

Key Points:

- With insomnia you may have difficulty falling and staying asleep.
- Insomnia contributes to feeling tired during the day.
- Treatment options: try sleep hygiene.
- Specialist Treatments are available.

REM Sleep Behaviour Disorder

What is it?

REM Sleep Behaviour Disorder (RBD) may cause you to act out your dreams. REM, or Rapid Eye Movement sleep is the stage in which the majority of dreaming occurs. Normally, you stop yourself moving during REM sleep, so that you don't act out your dreams; this is lost in RBD. You may punch, kick, shout or talk during this stage, which may cause you to fall out of bed and injure yourself or your bed partner. RBD occurs most often in the early hours of the morning. You may be unaware that this is happening.

What can I do?

If RBD is non-troublesome, no treatment may be needed. If you are having very active movements, think about safety in bed such as bed rails, pillows or mattresses beside the bed. If your RBD is disturbing your bed partner, consider sleeping apart. Specialist treatment is available.

Key Points:

- RBD is common.
- With RBD, dreams are acted out. This includes: shouting, kicking, punching etc.
- Injuries may occur.
- Specialist treatments are available.

Restless Legs Syndrome

What is it?

Restless Legs Syndrome (RLS) is an urge to move the legs, often with pain or difficult-to-describe uncomfortable sensations. Generally, this is felt when sitting or lying down. RLS is worse in the evening, and at night, movement of the legs provides temporary relief. RLS may cause trouble falling asleep.

What can I do?

RLS symptoms can be made worse by caffeine and alcohol. Taking a walk and hot shower before bed can sometimes help. Specialist treatments are available.

Key Points:

- With RLS, you feel an urge to move legs because of uncomfortable or odd feelings.

- RLS tends to be worse at night and can affect sleep.
- Avoid bedtime caffeine and alcohol.
- Specialist treatments are available.

Theme: Miscellaneous

Pain

What is it?

Pain related to other conditions, such as arthritis, lower back pain etc. can be made worse by Parkinson's. However, pain without any explanation may be caused by Parkinson's. One third of people with Parkinson's have pain. This pain can feel like stiffness, cramps, spasms or muscle pain. Often it occurs when medications are 'wearing off'. The cause of pain in Parkinson's is not always clear. Many people have different types of pain all at once.

What can I do?

Stretching the muscles, massage, or warm baths can help. For joint pain in particular, regular exercise and physiotherapy may be beneficial. Over-the-counter painkillers can help. Keeping a pain diary may be helpful to determine if the pain is helped by your Parkinson's medications. Specialist pain treatments are available.

Key Points:

- One third of people with Parkinson's have pain.
- Treatment options: try over-the-counter pain medications if pain persists.
- Keep a pain diary, in relation to medication timing.

Unexplained Changes in Weight

What is it?

In general, weight loss is more common than weight gain.

Why is this important in Parkinson's disease?

Weight loss can be related to nausea from medications. It can also be caused by dyskinesia (excessive movements), as well as issues with nutrient absorption. Excessive eating and weight gain can be due to an impulse control disorder related to some medications.

What can I do?

If nausea/vomiting are stopping you from eating, please click link to 'Nausea Section'. Try taking meals during 'on' times (times when the medication is working well), when swallowing and using cutlery may be easier. If weight loss appears to be associated with constipation, please click link to 'Constipation Section'. You should make sure that you are eating enough; eating frequent, smaller meals may help you achieve this. Consider using milkshakes or calorie supplements (eg. Ensure, Boost). Specialist dietary advice is available. For those struggling with weight gain, consider increasing levels of exercise. Seeking advice from a dietician may help.

Key Points:

- Unexplained changes in weight can happen in PD.
- Treatment option: Try correcting any underlying problems (eg. nausea). Also, eat during 'on' times.

Leg Swelling

What is it?

Leg swelling is common in Parkinson's disease. The lower part of the legs often become bigger, and seemed to be 'filled with water'.

Why is this important in Parkinson's disease?

Legs can also swell as a side effect of Parkinson's treatment. It is important to make sure that there is not another cause such as conditions affecting the heart. If you are concerned, discuss this with your GP.

What can I do?

Leg swelling can be made worse by periods of sitting; try and keep active with regular walking. When leg swelling happens in Parkinson's it usually does not need treating. Compression stockings can be helpful. When sitting, keep your legs raised.

Key Points

- Some people with Parkinson's have swollen legs.
- Swelling can be related to Parkinson's itself or its treatment.
- Other conditions can cause leg swelling (e.g. heart disease).

Double Vision

What is it?

Double vision is when you see two images of the same object. Most often, double vision happens while reading.

Why is this important in Parkinson's disease?

In Parkinson's, double vision is usually caused by the eye muscles working slowly (just like the rest of the muscles in your body). However, there are many other causes for double vision besides Parkinson's.

What can I do?

You may wish to see an optician to rule out other causes. Double vision may be better when your Parkinson's medications are working well.

Key Points:

- Double vision is when you see two images of a single object.
- Many other conditions can cause double vision.

Excessive Sweating

What is it?

With excessive sweating, you may find yourself sweating with no exercise, or sweating profusely with mild exercise.

Why is this important in Parkinson's disease?

Excessive sweating may be worse during off periods or dyskinesia.

What can I do?

There is no specific treatment for excessive sweating. However, you can help limit the amount that you sweat. Try these steps:

- **Avoid hot or humid environments.**
- **Avoid strenuous activity in the heat.**
- **Set the house thermostat lower.**
- **Wear appropriate clothing.**
- **Always keep well hydrated.**

Key Points:

- One third of people with Parkinson's develop excessive sweating.
- Sweating if often associated with 'off periods' or dyskinesias (excessive movements).
- Some practical tips can help (see above).

Change in Taste and Smell

What is it?

Sense of smell is reduced in almost all people with Parkinson's; this can affect your sense of taste. You may have difficulty detecting odours such as smoke, gas, or stale food.

What can I do?

Loss of smell sensation can result in some loss of appetite. Beware of the dangers. Ensure you have working smoke and other gas detectors. Check use-by dates carefully. Monitor your weight and eat healthily.

Key Points: Almost all people with PD have altered sense of taste and smell. Be aware of the dangers.

8.14 Appendix 14 – Group feedback document

Group feedback: Storyboards:

Please see below the storyboards from Ben. Please leave feedback using the prompts below each storyboard. Some things to consider:

1. The arrows on the storyboards signify movement in the animation.

2. The annotations help to explain what is happening in the animation or may describe noises that you will hear in the animation.

3. The text beneath the storyboards is what they voice over will be saying.

Group feedback: Sensitive issues

Ben has sent some initial ideas for how to convey some of the more sensitive topics – please see his ideas below and leave any comments you may have.

Erectile Dysfunction:

- Image of a plant and have it 'flop' and grow.
- A character inflating a balloon and deflating. Orgasms represented as the balloon being let go and flying around the room.

Please give comments below on the appropriateness of these ideas/ if you think will be clear to the user:

Comments:

The group felt that while humorous, they would prefer an image similar to the one below for erectile dysfunction, as they felt it was more direct, easy to interpret, and should not cause any embarrassment.

Story board: Double Vision

Feedback:

The group were confused by the numbers on the screen, and were unsure how these were related to double vision. Otherwise this mood board was liked by the group.

Story board: Nausea & vomiting

Feedback:

The group felt that the bloating in this storyboard looked like somebody being sick. The group suggested that an abdomen swelling slightly might be clearer, but they are open to suggestion.

The group were unsure on the interaction of the anti-sickness pills with dopamine – it needs to be clearer what is happening in this scene.

Instead of making a link to google for constipation, we would like this link to take users to the constipation video – perhaps this could be made clearer in the video.

Story board: Taste and Smell

Feedback:

It was suggested that the food in the first and second screen is replaced by something with a more obvious smell, such as a hot roast dinner or a curry.

The group felt that the picture relating to gas could be made clearer with the addition of a broken gas pipe/flames.

The group felt the slide with the person holding their nose could be improved with the addition of a strong smell image – such as rotting vegetables in the background.

The group felt that the picture of the person standing on the scales could be interpreted as someone expecting to gain weight, not lose it. A picture of someone normal size and then skinny in same clothes hanging off them was suggested instead.

Storyboard: uncontrolled loss of stool

Feedback:

The group felt that the pictures are to the point and tell the story well. It was requested if a sound could be added to demonstrate passing gas.

The group thought there could be a link available to the constipation advice.

Story board: Sleepiness

Feedback:

The group would like variety in the characters being displayed over the clip.

The group said slide 2 could instead reflect a person falling asleep in a comfy chair when it's obviously daytime outside – this is common in Parkinson's.**Storyboard: Drooling**

Feedback:

SALT will need explaining – Speech and Language Therapist (apologies if this was not in the text we sent).

General comments:

The group suspect you have used a limited number of characters in the storyboard for simplicity, but they would like to see more variety of characters being used in the final versions.

8.15 Appendix 15 – Faculty Research Ethics Approval

16th July 2018

CONFIDENTIAL

Dr Craig Newman

N13 ITTC North Building

Plymouth University Peninsula School of Medicine and Dentistry

Plymouth Science Park

Dear Craig,

Application for Approval by Faculty Research Ethics and Integrity Committee

Reference Number: **17/18-961**

Application Title: **A Usability and feedback study on a novel mobile application for the self-management of Parkinson's Disease (NMS Assist) to gauge patients' experiences and views of using the App.**

I am pleased to inform you that the Committee has granted approval to you to conduct this research.

Please note that this approval is for the duration of the research as requested on the application form (1st August 2018 to 31st August 2019), after which you will be required to seek extension of existing approval.

Please note that should any MAJOR changes to your research design occur which effect the ethics of procedures involved you must inform the Committee. Please contact the Faculty Research Administrator, Maurice Bottomley (email hhsethics@plymouth.ac.uk).

Yours sincerely

Professor Paul H Artes, PhD MCOptom

Professor of Eye and Vision Sciences

Co-Chair, Research Ethics and Integrity Committee -

Faculty of Health & Human Sciences and

Faculty of Medicine & Dentistry

8.16 Appendix 16 – Participant Information Sheet

NMS App Usability Study Information Sheet

The University of Plymouth is working in collaboration with Kings College London and University Hospitals Plymouth NHS Trust to develop a smart phone app, known as NMS ASSIST, to encourage and assist people with Parkinson's in the self-management of their condition. The aim of this study is to gather data on the way users interact with and receive the app.

Why have I been invited to take part?

You have been invited to take part in this study as you have Parkinson's, or are the partner/carer of someone with Parkinson's.

What is the purpose of the study?

We are interested in recording the overall experience and satisfaction of people using this app; for example, how easy you find the app to use. Your responses will enable the team to identify areas for improvement that may be modified in later versions of the app.

Do I have to take part in the study?

Participation in this study is completely voluntary. You do not have to take part and can withdraw from the study at any time.

Is this a medical assessment?

This is a research project not a medical assessment. All data collected during the study will be anonymous.

What will I have to do?

The study session will be held at Plymouth Science Park (PSP). On arrival to the session, a member of the research team will discuss the study with you, and there will be an opportunity for you to ask any questions you may have. If you are happy to proceed, you will be asked to sign a consent form. Following consent, there will be some assessments of your Parkinson's, including a thinking and memory task and a quick physical examination.

You will then be asked to interact with the app on a smartphone device.

You will be guided through several different 'user journeys' with the app, and you will be asked to talk aloud while navigating the app. Following this, you will be asked some questions about your experience, and then guided through a usability questionnaire at the end, as well as a questionnaire about your non-motor Parkinson's symptoms.

The study session will be undertaken by 3 members of the research team, one will guide you through the questionnaires and assessments, and the other 2 will guide you through the 'user journeys' and take notes. The session may be filmed or recorded. We expect the session to last approximately 2 hours.

What happens to my responses?

Your responses and any recording of the session will be stored securely on a Plymouth University server managed by the research team. Responses will be stored for 10 years after publication during which only approved members on the research team will be able to access them.

Will the information collected during the study be kept confidential?

This study will be completed in accordance with GDPR guidance and the Data Protection Act (1998) and all information collected will be held with the strictest of confidence. All of the data will remain completely anonymous and information will be identifiable only by a unique participant number. Any identifiable data that we keep during the study will be held securely, and only members of the research team will have access to it. Electronic data collected will be password protected and also only accessible to members of the research team.

Who is organising and supporting the study?

The project has received ethical approval from the University of Plymouth Faculty Research Ethics and Integrity Committee and is supported by PHNT Charitable Fund and The Hoover Foundation. It is being led by Dr Camille Carroll.

Will I receive payment for taking part?

You will not receive any payment for taking part in the study, however your travel expenses will be reimbursed and you will be provided with refreshments during the study visit.

What if I have more questions, concerns or do not understand something?

If you have further questions or concerns please contact Thea Dominey (Research Assistant) using the details provided below.

Thea Dominey

Research Assistant

Email Address: thea.dominey@plymouth.ac.uk

Tel: 07792119415

Thank you for considering taking part in this study, your participation is greatly appreciated.

8.17 Appendix 17 – Consent Form

NMS App Usability Study: Participant Consent Form

Thank you for considering taking part in this research study.

Please initial the boxes if you agree with each section.

1. I confirm that I have read the participant information sheet provided ☐

2. I confirm that I have had the opportunity to discuss the study and have had my questions answered. ☐

3. I understand that I will be filmed during the study, and that this recording will remain strictly confidential, stored on a secure Plymouth university server and accessible only to members of the research team. ☐

4. I understand that personally identifiable information and data collected during the study will be kept confidential and that only anonymised information will be published in a final report of the study. ☐

5. I understand that I can withdraw from the study at any time without having to give a reason.

6. I agree to take part in this study.

Participants name (BLOCK CAPITALS)

_____

Participant's Signature: _____ Date: _____

Investigators Name: _____

Investigators signature: _____

Date: _ _/ _ _/ _ _ _ _

8.18 Appendix 18 – Discussion Guide

Discussion Guide

This discussion guide sets out the format and tasks for the moderator to use during the upcoming NMS App user research.

Contact details

If you have any questions regarding this discussion guide, please contact:

Thea Dominey

thea.dominey@plymouth.ac.uk

07792119415

About this document

This discussion guide details the research project about to be undertaken by the NMS App Project Group. The purpose of this document is to make clear all aspects of the research so there are no surprises.

Please note that the tasks in this guide don't represent a definitive script to be stuck to absolutely; rather, it is intended to provide a basic structure. It is better to remain flexible and to follow the

participants' natural order as much as possible. This often means letting the participant carry on uninterrupted as they would do normally, then coming back to points for further clarification later.

Also be aware, usability testing is conducted in a way that solicits participants' thinking and feelings without interfering with his or her, own discovery process. No judgment should be apparent to the user about their activities, and no direct help is offered as it biases the results.

About this research

The research will consist of one study session, lasting approximately 2 hours. The session will be conducted on a prototype simulating the NMS App (NMS Assist).

Usability testing involves measuring the ease with which users can complete common tasks. The tasks have been designed following discussions with People with Parkinson's, their care partners and healthcare providers. It is also an opportunity to elicit feedback on the overall user experience.

The session will be moderated by an experienced researcher who will probe and question the participant to understand their needs, behaviour and attitudes – participants will not be led or directed

The on-screen interactions by the participant will be filmed using 'Mr Tappy' a screen recording device. Audio will be recording using a dictaphone.

Task list

Each participant will be asked to attempt to perform the following tasks.

Montreal Cognitive Assessment (MOCA) (10 mins)

Non-motor symptoms questionnaire (NMSQ) – PwP only (15mins)

Hoeh & Yahr rating scale – PwP only (5 mins)

Think aloud warm up (5 mins)

User journey 1 – Reading the instructions and requesting contact from the nurse

User journey 2 – NMS full assessment

User journey 3 – NMS partial assessment

User journey 4 – Symptom summary and self-help for an improving symptom

User journey 5 – Accessing self-help information for 2 x symptoms (pain and hallucinations)

User journey 6 – Accessing the drop down menu and turning off alerts

Moderator's introduction

Moderator welcomes the research participant.

Thank you very much for coming in today and agreeing to take part in our study which is all about an app to help manage non motor symptoms in Parkinson's. The app is called 'NMS Assist'.

The app is designed to be used by both People with Parkinson's and their care partners.

(patients only)*The app requires you to fill out an assessment on your non-motor symptoms, similar to the one that you just completed.*

(to carers only) *The app requires you to fill out an assessment* ***on your opinion of the non-motor symptoms the person you care for experiences****.*

(to both) *The app also offers the opportunity to learn more information about non-motor symptoms and how to best manage these, through a series of self-help videos.*

Finally, the app allows you to request contact from a Parkinson's Nurse if you feel like you or your partner are running into trouble from a non-motor symptoms perspective.

We're constantly trying to improve NMS Assist and getting your honest feedback is a really important part of that.

Today's session is approximately 45 minutes so we'll be finished at [specify time].

I'd like to emphasise that I'm not testing you and there are no right or wrong answers. I'm just interested in finding out what you think of our non-motor symptoms app and to see how you get on using it.

And of course, you're free to take a break or stop at any time during the session.

I'd like to start by asking you to complete some warm up tasks. Then I'll show you the app and ask you to complete some tasks. As you work through the tasks, I'd like you to think aloud - this means that you should try to give a running commentary on what you think at each stage.

As you complete the tasks, please tell me if there is anything you like/dislike, if you find anything confusing or if there's something you don't understand. This will really help us. If there's any point at which you think, in real life, you would stop and wouldn't carry on please tell me – I'll probably ask you to carry on, but I do need you to tell me. If you get stuck, I'm going to encourage you to do what you would do if I wasn't here as it's important for me to see where it might not be easy or obvious, and lots of other people are likely to have the same difficulty – but don't worry, I will of course help you if you get completely stuck!

I didn't design this, so you won't hurt my feelings or flatter me. In fact, frank, candid feedback is the most helpful, so I'd really appreciate your honesty. It's the only way we can make sure the app does meet your needs.

Remember, there are no right or wrong answers and I'm not testing you. I just want to hear what you think and understand what the experience is like for you.

Today we're going to use a prototype of the app on this iPhone 6 - it looks and feels very similar to how the real thing will look like, but if you run into something that's not working, I'll let you know. We are using this camera to record your interactions with the app, are you able to see the phone screen ok from there? Sorry if it is in your way a little, but it is important that we are able to record your experience today.

Do you have any questions before we start?

Moderator answers any questions.

Moderator starts recording of audio file and Mr Tappy.

Think aloud warm up questions (5mins)

Think aloud warm up:

As I said previously, as I work through each of the tasks, I would like for you to think aloud - this means that you should try to give a running commentary on what you think at each stage of the task.

As you complete the tasks, please tell me what you are doing, if there is anything you like/dislike, if you find anything confusing or if there's something you don't understand.

As a practice, we are going to do a quick warm up exercise.

Please can describe your journey today from reception, to the room you were in just now.

If user just gives answer without very much detail:

Thank you for your answer. Next time, please try to give some more detailed information about what you saw, what you were thinking, and the decisions you made along the way.

If user just gives answer without very much detail:

Thank you for your answer, now I know a bit more about your thoughts on your journey. Let me give you an example [give detailed thought process]. Would you like to have another go?

That's great thank you, please continue thinking in this way aloud throughout today's session.

8.19 Appendix 19 – Debrief

NMS App Usability Study Debrief

Thank you for taking the time to complete this study. Your participation is greatly appreciated.

This study aimed to examine the usability of the NMS app, such as how easy it is to use, and gather users' opinions of the app. The responses collected from this study will help to identify areas which can be improved and guide the development of later versions of the app.

Your personal details will be stored securely on a Plymouth University computer, accessible only by members of the study team. Your name and address will not appear on any study forms or questionnaires so that you cannot be recognised from them. All other information collected about you during this study will be entered onto a separate, secure database and will only be identifiable by a designated study number.

If you would like to ask any questions, offer feedback or request withdrawal from the study, please contact the Principal Investigator for this study:

Dr Camille Carroll

Tel: 01752 439829

Email: camille.carroll@plymouth.ac.uk

Address:

N14, ITTC Building

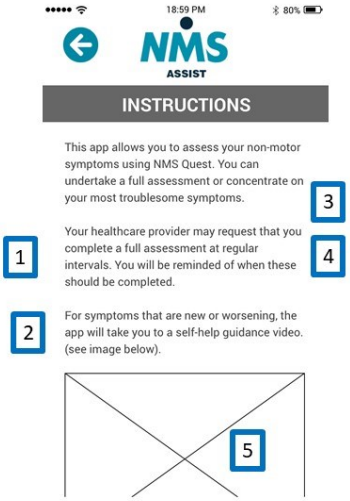
Plymouth Science Park

Plymouth

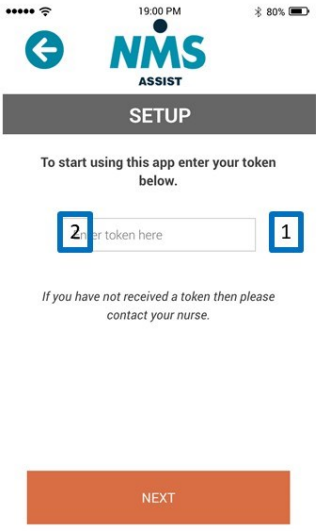
PL6 8BX

8.20 Appendix 20 – Research Report

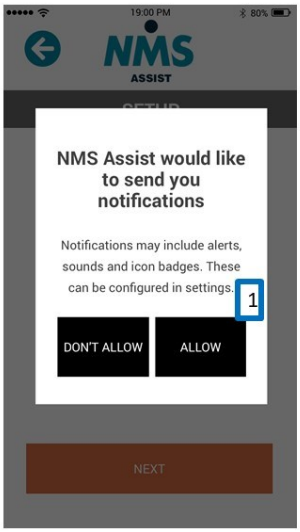
Usability Issue	All pps	PD	CP	Suggested solutions (group)
1. Some users struggled to scroll down (had to be shown how to do this) although they knew there was more information on the page				• Provide a tutorial video called 'getting started' or similar which is easy to access for those who need it but easy for proficient users to skip past • Provide a floating down arrow in the centre bottom of the screen. • Also provide a 'back to top' arrow on long pages.
2.Users commented on the font size being too small.				• Ensure users are shown how to increase text size as part of instruction vid
3. Users commented there was too much text to read, and they did not want to have to remember these instructions throughout.				• Reword in bullet points with catchy subheadings
4. Users commented the content did not make sense from a carer's perspective.				• Reword to make relevant for patients and carers
5. Users attempted to click on the image, expecting it to take them somewhere else.				• Consider leaving the image out – it may be too much for users to remember and can be explained as part of tutorial vid



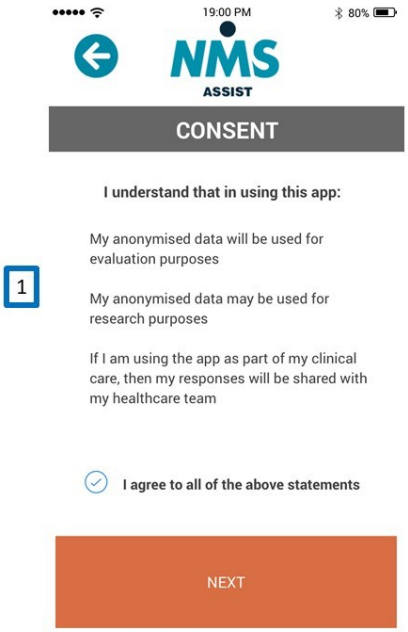
Usability Issue	All pps	PD	CP	Group
1. Users entered token incorrectly (incorrect characters and/or no attention to CAPS)				• Do not let user progress unless enter valid token • Make all tokens lower or upper case – keyboard automatically has caps selected (or not) • If removing case sensitivity has security implications, provide on-screen prompt upfront of required format/case sensitivity. • JW suggested changing the word 'token' to 'password'
2. Users (CP and PD) struggled to accurately hit the correct buttons and this took several attempts. Some users commented that a pen would help, or bigger keyboard size.				• As not all users will have a stylus, could the keyboard size be increased in some way if users select larger font size?



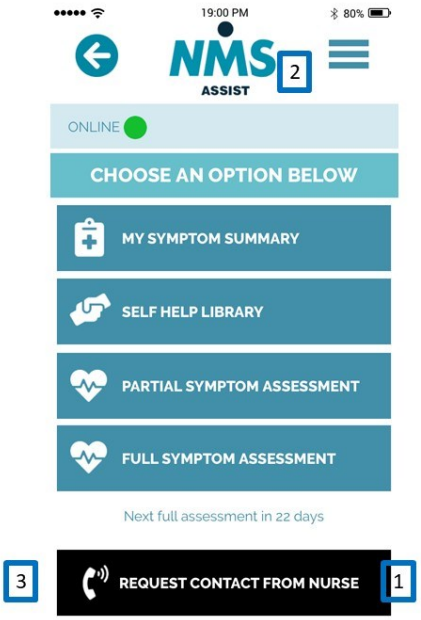
Usability Issue	All pps	PD	CP	Group
1. There was some confusion over what was meant by notifications/alerts/sounds/icon badges and what the purpose of these were (some users selected 'don't allow' because of uncertainty)				• Clarify what notifications and alerts are, the difference between them, and give 1 or 2 examples for what they will receive them for eg. a reminder when next assessment is due



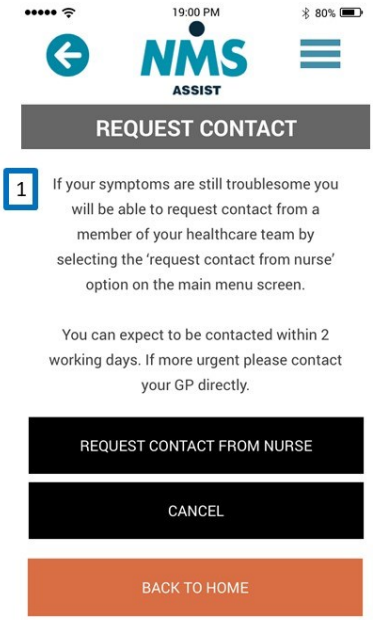
1. No problems, users understood points and all agreed by ticking box



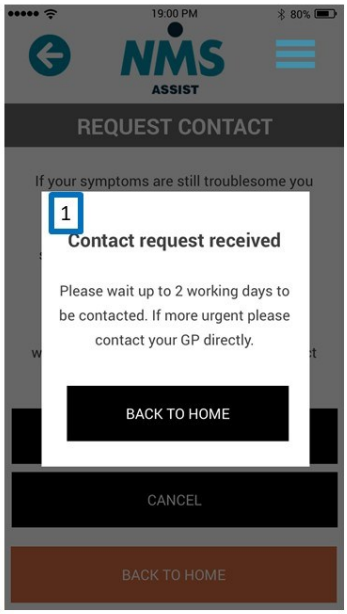
Usability Issue	All Pps	PD	CP	Group
1. Users could not see or find this button				• Request contact button should be shade of green/blue – • there should be consistency across CTAs (calls to action) – users will likely have learnt the format by now
2. Users did not recognise this page as the home screen				• Include the word 'home' somewhere on the screen or an icon of a house • Replace 'choose an option below' (which should be obvious) with something more meaningful
3. Expected this button to initiate a phone call immediately because of the phone icon				• Consider changing the icon – group suggested speech bubble or help icon



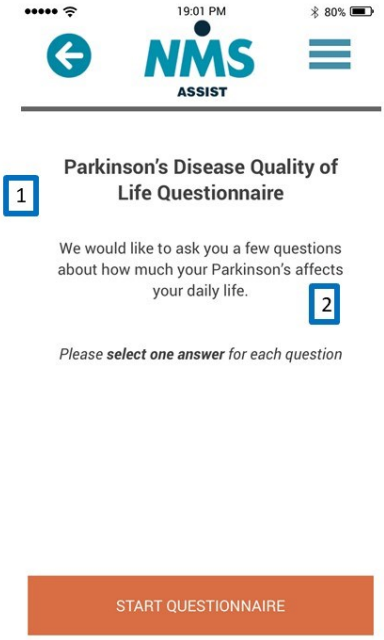
Usability Issue	All pps	PD	CP	Group
1. Confusion over the word 'still' – in comparison to what?				Reword Reduce amount of text – buttons with descriptive labels should not need instructions Consider changing colour of request contact to same as on home page



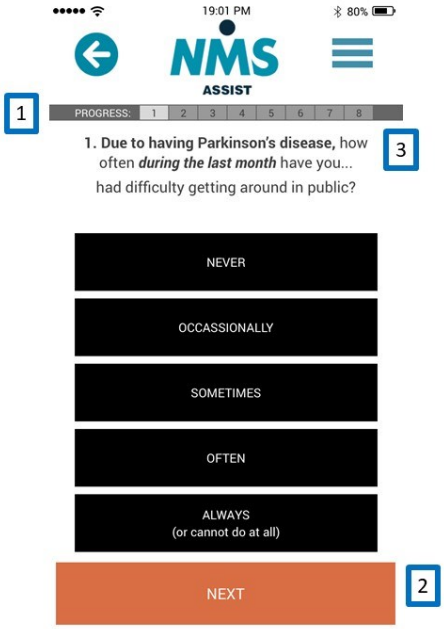
Usability Issue	All pps	PD	CP	Group
1. Confusion whether request had been received, expected to have to give a verbal or written explanation of problems.				No change needed



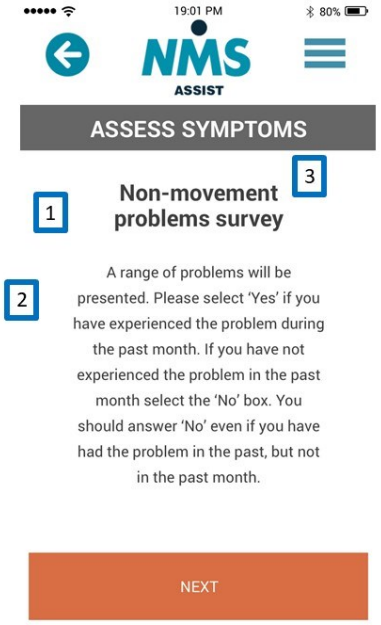
Usability Issue	All pps	PD	CP	Group
1. Users skipped past this page without reading it				Reword to provide more compelling info eg. What's in it for the user? How many questions will there be? Make the page more noticeable/ authoritative
2. There was confusion from the care partners on whether they were to answer on their own QoL or their perspective of the QoL of the person they care for				In carer version, add sentence: "In this assessment, please provide your opinion of the symptoms shown by the person you care for"



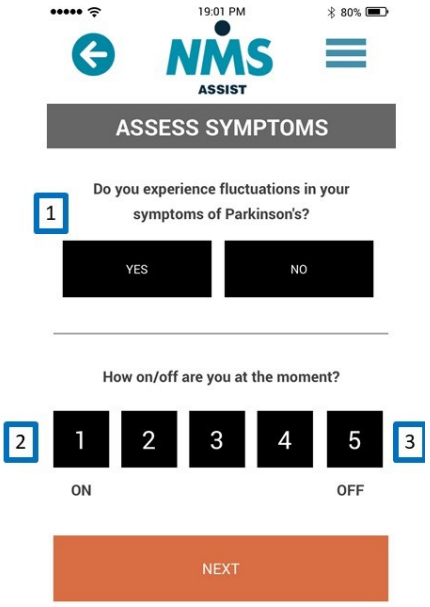
Usability Issue	All pps	PD	CP	Group
1. Users did not notice progress bar				Make progress bar more noticeable with use of colour
2. After pressing next, user did not notice that the question page had changed (kept pressing next, questions were left unanswered)				Make transition between questions more noticeable e.g. question being one colour when unanswered and another when answered or other method
3. Did not like the term 'disease'				Ask PDQ8 owners if we could removed the word 'disease'?



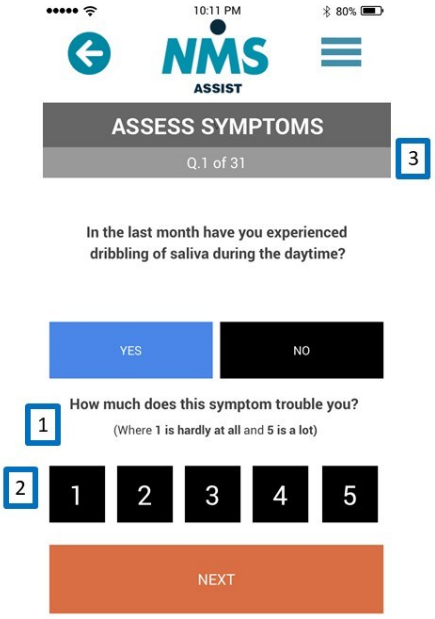
Usability Issue	All pps	PD	CP	Group
1. User skipped past this page without reading it.				Somehow make the page more noticeable/ authoritative
2. Wanted acknowledgement the PDQ8 had finished and were moving onto something new (this would also pertain to end of NMSQ)				Add in another screen prior to this one that says thank you/ end of questionnaire – press to continue to full symptoms assessment
3. Misunderstanding as to what non-motor symptoms were				It is expected that in real life, users would be aware of NMS – would have spoken about with nurse



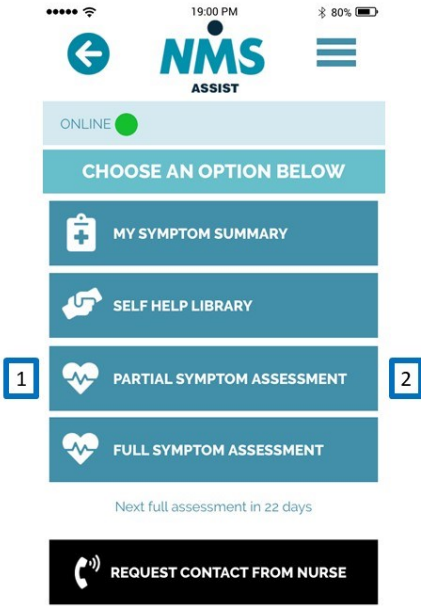
Usability Issue	All pps	PD	CP	Group
1. Confusion regarding meaning of fluctuations				• Provide an info button that explains terminology • Consider embedding a complete glossary with links throughout as relevant.
2. Misinterpretation of ON/OFF scale				Change wording of this question to 'Parkinson's medications working well' at the 1 end, and 'Parkinson's medications not working' at the 5 end Or keep on/off and perhaps have a glossary somewhere
3. Thought would make more sense OFF = 1 and ON = 5				Change direction of scale to OFF to ON (suggested by user)



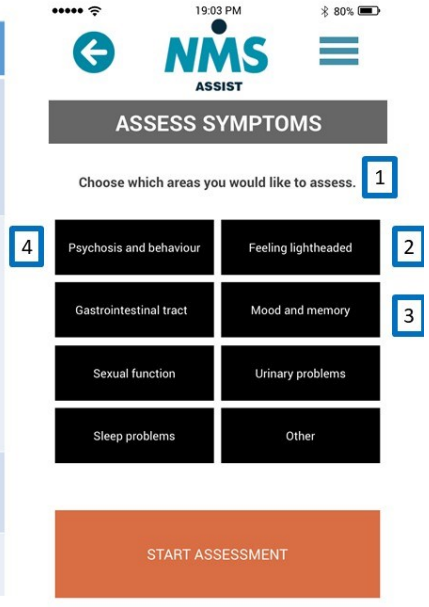
Usability Issue	All pps	PD	CP	Group
1. Misinterpreting scale (eg. interpreted as how much saliva)				• Make the question more noticeable • Include instructions on scale as part of NMSQ intro page
2. Did not notice scale appear				Disable 'next' button till selection made
3. Daunted by 31 questions				• Have save and return as an icon on each page, • Explain this icon upfront and its functionality (if they click it, remind them to return within 48 hours or data will be lost)



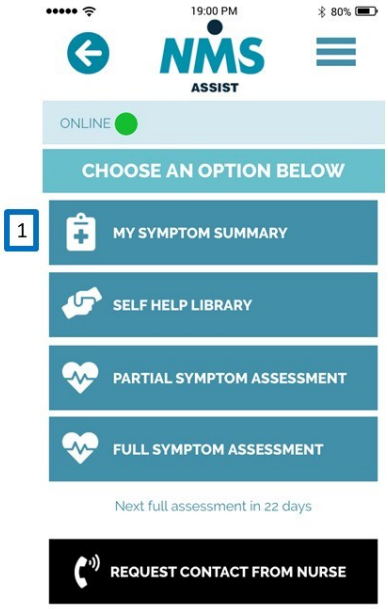
Usability Issue	All pps	PD	CP	
1. Could not find the Partial assessment button on home screen				• Differentiate partial and full assessments eg. use different icons for each and change wording/colour • Consider changing block capitals – hard to read for some
2. Confusion on meaning/purpose of partial assessment				• Explanation of these terms will be provided by Nurse and in instruction vid • Consider giving a pamphlet with glossary? • Consider changing wording. Eg. symptoms you are finding troublesome and • Assess all your non-motor symptoms



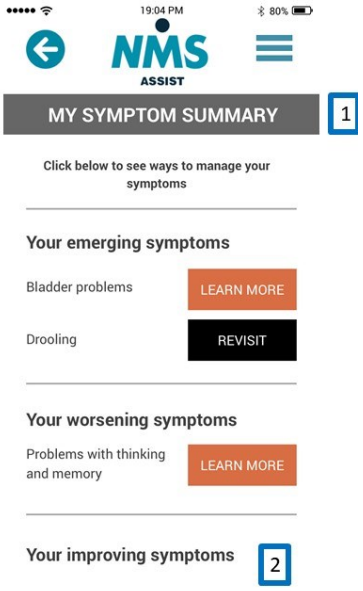
Usability Issue	All pps	PD	CP	Group
1. Users did not realise they could select more than one option				• Consider adding "You can select more than one" • Or Replace existing text with 'Select ALL areas you would like to assess' or similar (rather than adding more text)
2. Users were unsure which symptoms were under which domain				• Consider using an accordion (?) to display symptoms for each category. • Or consider Providing some sort of info button on each domain that shows which symptoms come under each domain • Consider replacing 'other' with meaningful category label
3. Users expected assessment to start automatically once had selected symptom.				• Add to the sentence at the top of the screen: "then press start assessment"
4. Users did not like the term psychosis				• Consider changing word 'psychosis'



Usability Issue	All pps	PD	CP	Solution
1. Took two attempts to find summary				Consider changing the block capitals. It is clearly reading the words that is causing difficulty, so the visual element has to be as easy and clear as possible.

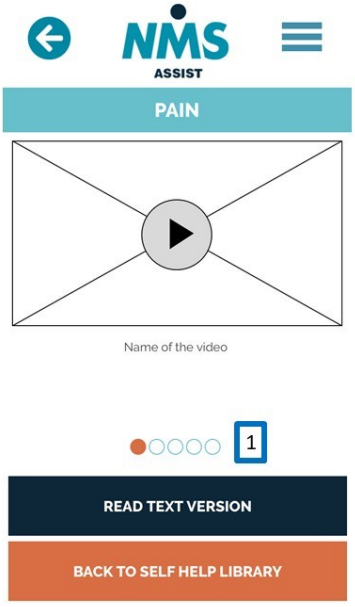


Usability Issue	All pps	PD	CP	
1. Symptom summary did not meet expectations , expected a visual representation or a summary of results from latest assessment				• Provide visual representation of summary • Perhaps there could be a circle (like a polo) with 5 segments, which change from green to amber to red, next to each of the topics listed, so that the patient can easily see how they all rated against each other and which are worst. • Provide info on what this page does on homepage i.e. don't wait for users to get this far to find out what it will give them.
2. Difficulty finding improving symptoms (scrolling)				Provide a floating, persistent down arrow. Also provide a 'back to top' arrow on long pages.

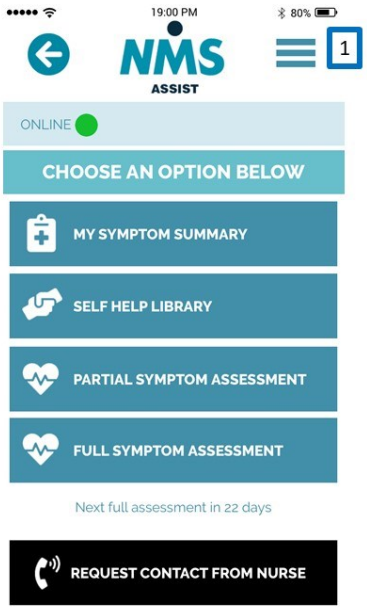


Usability Issue	All pps	PD	CP	
1. Users expected to be able to select more than one option at a time				• Make it clear that you can only choose one at a time in the instructions. • Provide info on when the self-help was last viewed next to each of the symptoms in symptoms summary • Consider having a summary of 'my recently viewed videos', so that they can easily return to one without having to find it again
2. User unsure of correct domain to select				• avoid use of term domain • Consider using an accordion (?) to display symptoms for each category • try to find a meaningful category label instead of other.
3. Commented on similarity of page to partial assessment page (found confusing)				• make it clear that it is a different page to partial assessment.
4. Found white text on dark background cumbersome				• Consider accessibility standards (legal requirement to comply with equality – See WCAG & W3C – see gov.uk) • Change colour scheme
5. Found white text on light blue background hard to read				• Consider accessibility standards (legal requirement to comply with equality – See WCAG & W3C

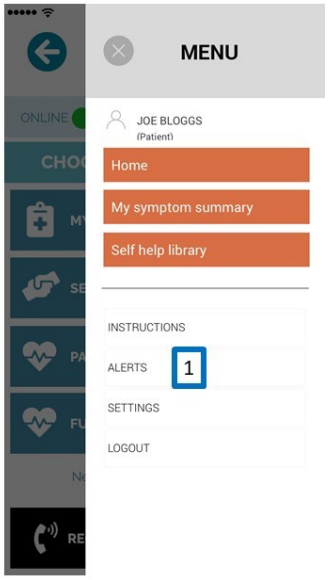
Usability Issue	All pps	PD	CP	Solution
1. User attempted to swipe across/tap dots for next page (due to dots)				• Allow swipe • Or add Page 1 of 3 to each page instead of dots • Dots should not be on this page (should only appear on pages after user has selected to read text version)



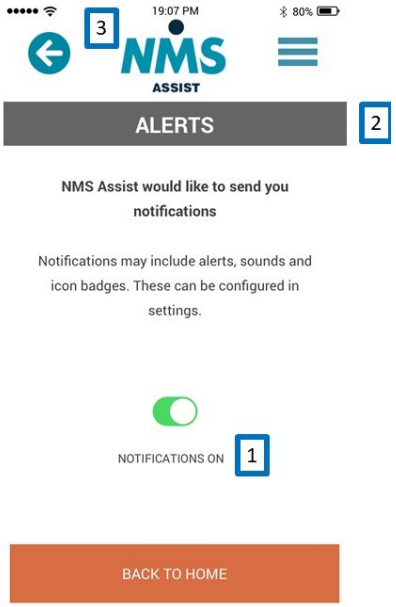
Usability Issue	All pps	PD	CP	Solution
1. Could not find the burger menu. Did not recognise this as a button or where settings would be				• This could be explained in the introductory video/first time log in where features of the app are explained • Avoid use of word burger menu (jargon)



Usability Issue	All pps	PD	CP	Solution
1. Could not find the alerts button within the menu				• Make the buttons in the burger menu more noticeable through use of colour/text (like other buttons on this page)

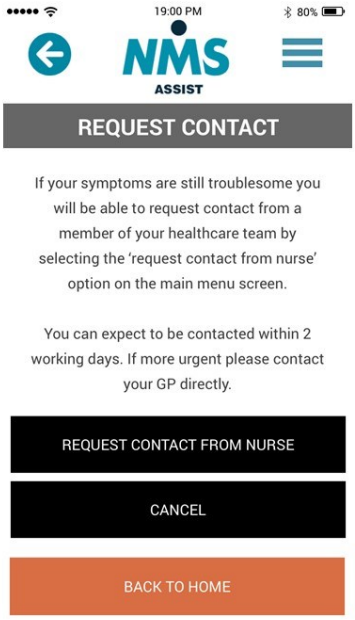


Usability Issue	All PPs	PD	CP	Solution
1. Should change to 'notifications off' when pressed				• Change text to 'off' when pressed
2. Needs to be consistency between word alert/notification				• Best practice: ensure terms appear exactly as they do on the relevant pages, including observing case used. • Change heading to 'Notifications'
3. Attempted to press 'NMS Assist' to go back to home screen				• Allow 'NMS Assist' to take user home

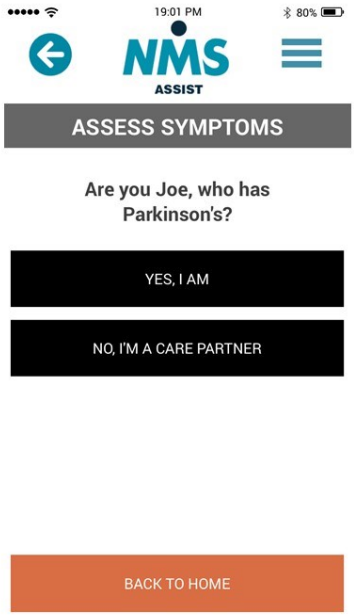


Positive comments		
1. Users found this page very clear, and all pressed start to proceed		

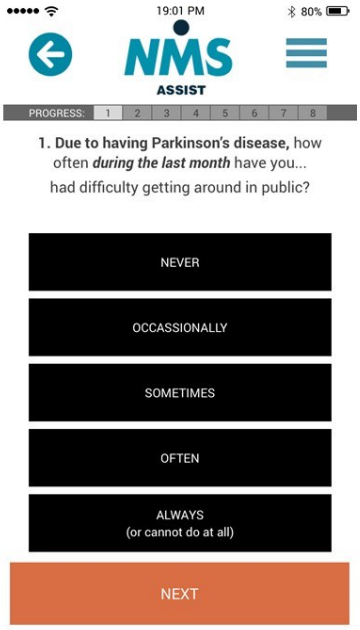
Positive comments		
1. Users appreciated the fact they had the option to change their minds and press cancel		



Positive comments	
1. Users liked the personalisation on this page, some commented it was reassuring that the app 'had the right person'	



Positive comments	
1. Users liked the progress bar - they liked having some idea of how far they had left to go	
2.Users liked the big buttons on this page	
3. Users liked the consistency of the 'next' button being orange throughout the app	
4. Users liked having the menu option and the option to go back on each page	



Positive comments	
1. Users liked the consistency of the question pages throughout the NMS assessment	

8.21 Appendix 21 – PKG Reporting Template

PKG Reporting: Outcome of PD MDT assessment

Patient name:

Patient DOB:

Hosp number:

Date of PKG:

Date of Report:

Reported by:

Reviewed by:

Purpose of recording (including any therapy change that is being evaluated):

Medications at time of recording:

Date of (most recent) previous recording (if applicable): **_ _ / _ _ / _ _**

Medications at time of (most recent) previous recording:

<u>Bradykinesia</u>

<u>No treatment required:</u>

☐ BKS < 23

☐ No wearing off

Consider treatment:

☐ BKS ≥ 23

☐ Any wearing off (not due to sleep or possible hypotension)

Comments:

BKI (50%)

BKII (25%)

BKIII (15%)

BKIV (10%)

Dyskinesia

No treatment required:

☐ DKS < 7

Consider treatment:

☐ DKS ≥ 7

☐ FDS > 13

☐ Observable peak dose dyskinesia (if peak > 9, not due to exercise, not due to tremor bleed through)

Comments:

Sleep

Overnight sleep:

☐ Evidence of fragmentation

Excessive daytime somnolence:

☐ Evidence of daytime somnolence

Comments:

Tremor

Evidence of tremor:

☐ Tremor absent (PTT < 0.6%)

☐ Tremor present (PTT > 1.0%)

Tremor evidence of wearing off:

☐ Tremor worse peri-dose

Comments:

PKG Value	Prev. record Date:	Current Score	Controls
Bradykinesia score (BKS)			18.6 (aim for ≤ 23)
Dyskinesia score (DKS)			4.3
Fluctuation score (FDS)			7.8–12.8 controlled fluctuations
Percent time that tremor was present (PTT)			>1% indicates tremor <0.6% absence of tremor 0.6 - 1% not conclusive
Percent time immobile (PTI)			>5% abnormal

Summary:

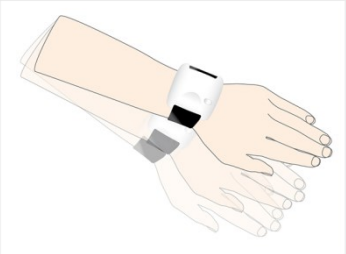
Treatment Suggestions:

8.22 Appendix 22 – PKG Database Variables

PKG record	Sex	Initials	Surname	First Name	PKG Practitioner	Consultant	DoB
Pathway	Prognosis Score	Prognosis Category	Hosp number	NHS number	Date of PKG	Date of report	Clinical Question(s)
BKS	DKS	FDS	PTT (%)	PTI (%)	PKG Findings	Recommend.	Outcome

8.23 Appendix 23 – PKG patient evaluation

PKG Service Questionnaire



We would like to evaluate your experience of the Parkinson's Kinetigraph™ (PKG) service that has formed part of your Parkinson's care. It is important that we regularly collect opinions of service users to ensure a high standard of current and future care. Thank you for taking the time to complete this questionnaire. Once completed, please return in the freepost envelope provided. All responses will remain anonymous. Please think about your **most recent PKG** as you answer the questions throughout.

General Information (please complete in dd/mm/yyyy format)

TODAY'S DATE: _____ Date of most _____

recent

PKG:

D.O.B: _____ _____

DATE OF _____

DIAGNOSIS:

_____

Receiving the PKG (please tick responses)

How many times have you had a PKG fitted?

☐ 1 ☐ 2 ☐ 3 Other

_____

How did you receive your most recent PKG device?

☐ By post ☐ In clinic

Before you received the PKG, what was your level of understanding about the purpose of the device?

No Understanding	☐	☐	☐	☐	☐	Excellent Understanding
	1	2	3	4	5	

How helpful was the information provided to you when you first received the PKG in explaining about the device?

Not at all helpful	☐	☐	☐	☐	☐	Extremely Helpful
	1	2	3	4	5	

Using the PKG

How comfortable did you find wearing the device?

Not at all comfortable	☐	☐	☐	☐	☐	Extremely comfortable

1 2 3 4 5

Please give details:

Did you experience any technical difficulties with the device?

☐ Yes | ☐ No

If ‘YES’ please give details:

How did you return the PKG device?

☐ By post ☐ In clinic

How did you find the process of returning the device?

Not at all simple	☐	☐	☐	☐	☐	Extremely simple
	1	2	3	4	5	

Please let us know how this process could have been improved:

PKG Results

After returning the PKG, how long did it take to receive your results?

☐ Under a month ☐ 1-2 months ☐ 2-3 months

☐3-4 months ☐>4months

Did you receive your results by letter?

☐ Yes ☐ No

If 'YES', how useful did you find the information?

Not at all useful	☐	☐	☐	☐	☐	Extremely useful
	1	2	3	4	5	

Did you receive your results by email?

☐ Yes ☐ No

If 'YES', how useful did you find the information?

Not at all useful	☐	☐	☐	☐	☐	Extremely useful
	1	2	3	4	5	

Did you receive your results by telephone?

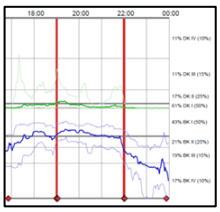
☐ Yes ☐ No

If 'YES', how useful did you find the information?

Not at all useful ☐ ☐ ☐ ☐ ☐ Extremely useful

1 2 3 4 5

Did you receive a copy of the graph (pictured)?



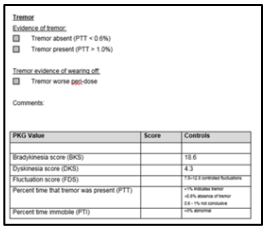
☐ Yes ☐ No

If 'YES', how useful did you find the information?

Not at all useful ☐ ☐ ☐ ☐ ☐ Extremely useful

1 2 3 4 5

Did you receive a copy of the report (pictured)?



Tremor

Evidence of tremor:

Tremor absent (PTT < 0.6%)

Tremor present (PTT > 1.0%)

Tremor evidence of wearing off:

Tremor worse peri-dose

Comments:

PKG Value	Score	Controls
Bradykinesia score (BKS)		18.6
Dyskinesia score (DKS)		4.3
Fluctuation score (FDS)		
Percent time that tremor was present (PTT)		
Percent time immobile (PTI)		

☐ Yes ☐ No

If 'YES', how useful did you find the information?

Not at all useful	☐	☐	☐	☐	☐	Extremely useful
	1	2	3	4	5	

How would you like to receive PKG results in future? (Please tick more than one if necessary)

☐ By letter ☐ By phone ☐ By email

☐ In a report ☐ In a graph ☐ In a report

Did you feel that these results were reflective of your lived experience during the time the PKG was worn?

Not at all reflective	☐	☐	☐	☐	☐	Extremely reflective
	1	2	3	4	5	

Impact on care

How useful were the medication reminders in assisting you with taking your medication on time?

Not at all useful	☐	☐	☐	☐	☐	Extremely useful
	1	2	3	4	5	

If applicable, how useful was the PKG data in assisting with explaining your symptoms to your Doctor or Nurse?

Not at all useful	☐	☐	☐	☐	☐	Extremely useful
	1	2	3	4	5	

How valuable was the PKG in providing data to your Doctor or Nurse about your symptoms that you could not have provided?

Not at all valuable	☐	☐	☐	☐	☐	Extremely valuable
	1	2	3	4	5	

Were any changes to your treatment recommended as a result of the PKG results?

☐ Yes | ☐ No

If ‘YES’ please give details:

If ‘YES’ were these changes made?

☐ Yes | ☐ No

If ‘YES’, how long did it take for these changes to be made from the time of receiving the results?

☐1-4 weeks ☐ 1-2 months ☐ 2-3 months

☐3-4 months ☐>4months

PKG Service Satisfaction

What level of involvement do you feel you have had in your treatment as a result of receiving the PKG?

Not at all involved ☐	☐	☐	☐	☐	Extremely involved
1	2	3	4	5	

What level of involvement do you feel your consultant has had in your treatment as a result of receiving the PKG?

Not at all involved ☐	☐	☐	☐	☐	Extremely involved
1	2	3	4	5	

What level of involvement do you feel your Parkinson's Nurse has had in your treatment as a result of receiving the PKG?

Not at all involved ☐ ☐ ☐ ☐ ☐ Extremely involved

1 2 3 4 5

Please put a tick next to the statement you agree with most:

☐ "I was happy with the PKG as it meant I did not have to travel for my appointment."

☐ "I would have preferred to travel to have a clinic appointment."

☐ Neither of the above.

Areas of concern:

Please tick any areas of concern you may have with the PKG service:

☐The PKG device itself ☐ Consultant Involvement ☐ Treatment

☐No concerns ☐Other

Please give any details of these concerns below:

Would you be willing to use the PKG again to assist in the management of your Parkinson's Disease in the future?

☐ Yes | ☐ No

Thank you

Thank you for taking the time to fill in this questionnaire on the PKG service. Please share any additional comments in the space below.

Please return your completed questionnaire using the freepost return envelope provided.

8.24 Appendix 24 – Data Extraction Form

Study Title	Drug Name	Year of Publication	Year of Registration	CT link	No. of site visits
Phase	Status	Lead Site	Masking	Trial design	Group design
Dose Ranging	No. pps	Study length	Treatment duration	Length of follow up	Extension
Method of distinguish symptomatic effect	Min/Max Age	Disease Stage	Disease duration	H & Y	Cognitive test
Drug Naiive	PD Drug stability	Changes to PD regime	Primary Outcome	Secondary Outcome	Mechanistic Outcome
No. of primary outcomes	Patient Reported Outcome				

8.25 Appendix 25 - Status and key design features of the Phase II Studies

Trial	Yr	Active agent(s)	Status	No. site visits	No. pps	Masking	Trial Design	Study (m)	Tx duration (m)	Follow up Duration	Method for differentiating symptomatic effect
PASADENA	-	PR002	Open + recruiting	11	300	double blind	placebo controlled	48	12	27	-
Ambroxol as a Treatment for PD Dementia	-	Ambroxol	Open + recruiting	11	75	double blind	placebo controlled	37	12	12	-
PD Nilotinib	-	Nilotinib	Finished recruiting	Not known	75	double blind	placebo controlled	42	12	15	wash out - 3 months
NILO-PD	-	Nilotinib	Open + recruiting	11	75	double blind	placebo controlled	35	6	8.5	-
Intermittent Bilateral GDNF for PD	-	GDNF	Completed + reported	21	42	double blind	placebo controlled	27	9	9	-
EXENATIDE-PD	2017	Exenatide	Completed + reported	6	60	double blind	placebo controlled	26	11	14	wash out - 3 months
LixiPark	-	Lixisenatide	Open + recruiting	Not known	158	double blind	placebo controlled	38	12	12	wash out - 2 months
MOVES-PD	-	GZ/SAR402 67	Open + recruiting	8	243	double blind	placebo controlled	63	15	15	-
Deferipron PD	2017	Iron Chelator Deferipron e	Completed + reported	3	36	double blind	placebo controlled	22	6	6	-
FAIR-PARK-I	2015	Iron Chelator Deferipron e	Completed + reported	4	40	double blind	placebo controlled	24	18	18	delayed start - 6 months
FAIRPARK-II	-	Iron Chelator Deferipron e	Open + recruiting	4	338	double blind	placebo controlled	34	9	10	wash out - 1 month
SKY	-	Deferipron e	Open + recruiting	7	140	double blind	placebo controlled	39	9	9	-
NIC-PD	-	Transderm al NICotine	Completed + unreported	Not known	160	double blind	placebo controlled	50	12	14	wash out - 2 months
STEADY-PD	2013	Isradipine	Completed + reported	10	99	double blind	placebo controlled	31	12	12	-
Investigation of the Safety and Efficacy of NTCELL	2017	NTCELL	Completed + reported	Not known	18	double blind	placebo controlled	38	6	Lifelong follow up	-

Trial	Yr	Active agent(s)	Status	No. site visits	No. pps	Masking	Trial Design	Study (m)	Tx duration (m)	Follow up Duration	Method for differentiating symptomatic effect
Lovastatin as a Neuroprotective Treatment for Early Stage PD	-	Lovastatin	Open + recruiting	7	80	double blind	placebo controlled	31	11	12	wash out- 1 month
PD STAT	-	Simvastatin	Finished recruiting	8	235	double blind	placebo controlled	49	24	26	wash out- 2 months
N-Acetylcysteine for Neuroprotection in Parkinson's Disease	-	N-Acetylcysteine	Completed + unreported	2	50	double blind	placebo controlled	55	1	1	-
GM1 Ganglioside Effects on PD	-	GM1 Ganglioside	Completed + reported	6	93	double blind	placebo controlled	127	28	52	wash out - 24 months, delayed start 6 months
Pioglitazone in Early PD	2015	Pioglitazone	Completed + reported	5	210	double blind	placebo controlled	38	10	10	-
Safety and Efficacy of CERE-120 in Subjects With PD	2013	CERE-120	Completed + reported	Not known	60	double blind	placebo controlled	100	- surgical procedure	36	-
Safety and Efficacy of DA-9805 for PD	-	DA-9805	Open + recruiting	Not known	60	double blind	placebo controlled	13	3	3	-
Clinical Trial on the Effectiveness of Traditional Chinese Medicinal Mixture in PD	-	Traditional Chinese Medicinal Mixture	-	Not Known	144	double blind	placebo controlled	21	12	13	wash out - 1 month
Clinical Trial on the Effectiveness of Herbal Medicinal Mixture in PD	-	Herbal Medicinal Mixture	Completed + unreported	Not Known	158	double blind	placebo controlled	30	12	13	wash out - 1 month
Ubiquinol in PD: Safety, Tolerability, and Effects Upon Oidative Damage and Mitochondrial Biomarkers	-	Ubiquinol	Completed + unreported	Not Known	11	double blind	placebo controlled	58	6	6	-

Trial	Yr	Active agent(s)	Status	No. site visits	No. pps	Masking	Trial Design	Study (m)	Tx duration (m)	Follow up Duration	Method for differentiating symptomatic effect
Study of the Neuro-protective Effect of Granulocyte-colony Stimulating Factor on Early Stage PD	-	Granulocyte-colony Stimulating Factor	Terminated	Not known	4	double blind	placebo controlled	42	12	12	-
Exendin-4 as a Treatment for PD - Pilot Study	2013	Exendin-4	Completed + reported	4	44	single blind	open label	32	12	14	wash out - 2 months
Double- blind multicentre,sham surgery controlled study of cere-120 in subjects with pd	2010	Cere-120	Completed + reported		58	double blind	placebo controlled	24	12	12	-
MIREILLE	2016	Bee Venom	Completed + reported	14	50	double blind	placebo controlled	33	12	12	-
SPARK	2018	Exercise	Completed + reported	104	128	single blind	open label	54	6	6	-
A Trial of MitoQ for the treatment of people with PD	2010	MitoQ	Completed + reported	7	128	double blind	placebo controlled	18	12	13	wash out - 1 month
Efficacy and safety of Trigonella seeds as an adjuvant to L-Dopa	2013	Trigonella Seeds	Completed + reported	7	50	double blind	placebo controlled	Not known	6	6	-
Randomized, double-blind, placebo-controlled pilot trial of reduced coenzyme Q10 for Parkinson's disease.	2015	coenzyme Q10	Completed + reported	7	31	double blind	placebo controlled	24	11	13	-
Effect of the myeloperoidase inhibitor AZD3241 on microglia: a PET study in PD	2015	AZD3241	Completed + reported	3	24	double blind	placebo controlled	9	2	2.3	-

Trial	Yr	Active agent(s)	Status	No. site visits	No. pps	Masking	Trial Design	Study (m)	Tx duration (m)	Follow up Duration	Method for differentiating symptomatic effect
Safety and Efficacy of Liraglutide in PD	-	Liraglutide	Open + recruiting	9	57	double blind	placebo controlled	29	12	14	-
Pilot study of H2 therapy in PD	2012	H2	Completed + reported	Not known	17	double blind	placebo controlled	Not known	11	11	-
High-dose transdermal nicotine in Parkinson's disease patients	2017	Transdermal Nicotine	Completed + reported	4	40	single blind	open label	51	10.4	12	wash in 2.5 months, wash out - 1.4 months
SURE-PD	2014	Inosine	Completed + reported	12	75	double blind	placebo controlled	42	24	25	wash in - 3 months, wash out - 1month
GAP-PD	2014	GM 608	Completed + reported	10	6	double blind	placebo controlled	13	0.5	3	-
A Study to Assess Safety and Tolerability of Oral AZD3241 in Patients With PD	2014	Oral AZD3241	Completed + reported	6	51	double blind	placebo controlled	8	2.7	3.2	wash out - 2 weeks
SPARK	-	BIIB054	Open + recruiting	38	311	double blind	placebo controlled	54	12	24	-
Study of Zonisamide in Early PD	-	Zonisamide	In set-up, not yet started	7	60	double blind	placebo controlled	14	12	12	-
High-intensity Exercise and Fall Prevention Boot Camp for PD	-	Exercise	Completed + unreported	25	27	double blind	open label	16	2	8	-
PASADENA	-	PR002	Open + recruiting	11	300	double blind	placebo controlled	48	12	27	-
Ambroxol as a Treatment for PD Dementia	-	Ambroxol	Open + recruiting	11	75	double blind	placebo controlled	37	12	12	-
PD Nilotinib	-	Nilotinib	Finished recruiting	Not known	75	double blind	placebo controlled	42	12	15	wash out - 3 months
NILO-PD	-	Nilotinib	Open + recruiting	11	75	double blind	placebo controlled	35	6	8.5	-
Intermittent Bilateral GDNF for PD	-	GDNF	Completed + reported	21	42	double blind	placebo controlled	27	9	9	-
EXENATIDE-PD	2017	Exenatide	Completed + reported	6	60	double blind	placebo controlled	26	11	14	wash out - 3 months

Trial	Yr	Active agent(s)	Status	No. site visits	No. pps	Masking	Trial Design	Study (m)	Tx duration (m)	Follow up Duration	Method for differentiating symptomatic effect
LixiPark	-	Lixisenatide	Open + recruiting	Not known	158	double blind	placebo controlled	38	12	12	wash out - 2 months
MOVES-PD	-	GZ/SAR402 67	Open + recruiting	8	243	double blind	placebo controlled	63	15	15	-
Deferipron PD	2017	Iron Chelator Deferipron e	Completed + reported	3	36	double blind	placebo controlled	22	6	6	-
FAIR-PARK-I	2015	Iron Chelator Deferipron e	Completed + reported	4	40	double blind	placebo controlled	24	18	18	delayed start - 6 months
FAIRPARK-II	-	Iron Chelator Deferipron e	Open + recruiting	4	338	double blind	placebo controlled	34	9	10	wash out - 1 month
SKY	-	Deferipron e	Open + recruiting	7	140	double blind	placebo controlled	39	9	9	-
NIC-PD	-	Transderm al NICotine	Completed + unreported	Not known	160	double blind	placebo controlled	50	12	14	wash out - 2 months
STEADY-PD	2013	Isradipine	Completed + reported	10	99	double blind	placebo controlled	31	12	12	-
Investigation of the Safety and Efficacy of NTCELL	2017	NTCELL	Completed + reported	Not known	18	double blind	placebo controlled	38	6	Lifelong follow up	-
Lovastatin as a Neuroprotect ive Treatment for Early Stage PD	-	Lovastatin	Open + recruiting	7	80	double blind	placebo controlled	31	11	12	wash out- 1 month
PD STAT	-	Simvastatin	Finished recruiting	8	235	double blind	placebo controlled	49	24	26	wash out- 2 months
N-Acetylcystein e for Neuroprotect ion in Parkinson's Disease	-	N-Acetylcystei ne	Completed + unreported	2	50	double blind	placebo controlled	55	1	1	-
GM1 Ganglioside Effects on PD	-	GM1 Ganglioside	Completed + reported	6	93	double blind	placebo controlled	127	28	52	wash out - 24 months, delayed start 6 months
Pioglitazone in Early PD	2015	Pioglitazon e	Completed + reported	5	210	double blind	placebo controlled	38	10	10	-

Trial	Yr	Active agent(s)	Status	No. site visits	No. pps	Masking	Trial Design	Study (m)	Tx duration (m)	Follow up Duration	Method for differentiating symptomatic effect
Safety and Efficacy of CERE-120 in Subjects With PD	2013	CERE-120	Completed + reported	Not known	60	double blind	placebo controlled	100	- surgical procedure	36	-
Safety and Efficacy of DA-9805 for PD	-	DA-9805	Open + recruiting	Not known	60	double blind	placebo controlled	13	3	3	-
Clinical Trial on the Effectiveness of Traditional Chinese Medicinal Mixture in PD	-	Traditional Chinese Medicinal Mixture	-	Not Known	144	double blind	placebo controlled	21	12	13	wash out - 1 month
Clinical Trial on the Effectiveness of Herbal Medicinal Mixture in PD	-	Herbal Medicinal Mixture	Completed + unreported	Not Known	158	double blind	placebo controlled	30	12	13	wash out - 1 month
Ubiquinol in PD: Safety, Tolerability, and Effects Upon Oidative Damage and Mitochondrial Biomarkers	-	Ubiquinol	Completed + unreported	Not Known	11	double blind	placebo controlled	58	6	6	-
Study of the Neuro-protective Effect of Granulocyte-colony Stimulating Factor on Early Stage PD	-	Granulocyte-colony Stimulating Factor	Terminated	Not known	4	double blind	placebo controlled	42	12	12	-
Exendin-4 as a Treatment for PD - Pilot Study	2013	Exendin-4	Completed + reported	4	44	single blind	open label	32	12	14	wash out - 2 months
Double- blind multicentre,sham surgery controlled study of cere-120 in subjects with pd	2010	Cere-120	Completed + reported		58	double blind	placebo controlled	24	12	12	-
MIREILLE	2016	Bee Venom	Completed + reported	14	50	double blind	placebo controlled	33	12	12	-

Trial	Yr	Active agent(s)	Status	No. site visits	No. pps	Masking	Trial Design	Study (m)	Tx duration (m)	Follow up Duration	Method for differentiating symptomatic effect
SPARK	2018	Exercise	Completed + reported	104	128	single blind	open label	54	6	6	-
A Trial of MitoQ for the treatment of people with PD	2010	MitoQ	Completed + reported	7	128	double blind	placebo controlled	18	12	13	wash out - 1 month
Efficacy and safety of Trigonella seeds as an adjuvant to L-Dopa	2013	Trigonella Seeds	Completed + reported	7	50	double blind	placebo controlled	Not known	6	6	-
Randomized, double-blind, placebo-controlled pilot trial of reduced coenzyme Q10 for Parkinson's disease.	2015	coenzyme Q10	Completed + reported	7	31	double blind	placebo controlled	24	11	13	-
Effect of the myeloperoidase inhibitor AZD3241 on microglia: a PET study in PD	2015	AZD3241	Completed + reported	3	24	double blind	placebo controlled	9	2	2.3	-
Safety and Efficacy of Liraglutide in PD	-	Liraglutide	Open + recruiting	9	57	double blind	placebo controlled	29	12	14	-
Pilot study of H2 therapy in PD	2012	H2	Completed + reported	Not known	17	double blind	placebo controlled	Not known	11	11	-
High-dose transdermal nicotine in Parkinson's disease patients	2017	Transdermal Nicotine	Completed + reported	4	40	single blind	open label	51	10.4	12	wash in 2.5 months, wash out - 1.4 months
SURE-PD	2014	Inosine	Completed + reported	12	75	double blind	placebo controlled	42	24	25	wash in - 3 months, wash out - 1month
GAP-PD	2014	GM 608	Completed + reported	10	6	double blind	placebo controlled	13	0.5	3	-
A Study to Assess Safety and Tolerability of Oral AZD3241 in Patients With PD	2014	Oral AZD3241	Completed + reported	6	51	double blind	placebo controlled	8	2.7	3.2	wash out - 2 weeks

Trial	Yr	Active agent(s)	Status	No. site visits	No. pps	Masking	Trial Design	Study (m)	Tx duration (m)	Follow up Duration	Method for differentiating symptomatic effect
SPARK	-	BIIB054	Open + recruiting	38	311	double blind	placebo controlled	54	12	24	-
Study of Zonisamide in Early PD	-	Zonisamide	In set-up, not yet started	7	60	double blind	placebo controlled	14	12	12	-
High-intensity Exercise and Fall Prevention Boot Camp for PD	-	Exercise	Completed + unreported	25	27	double blind	open label	16	2	8	-

8.26 Appendix 26 – Status and key design features of the Phase III studies

Trial	Year of record	Active agent(s)	Status	Number of site visits	No. PPS	Mask	Trial Design	Group Design	Dose ranging	Study Length (months)	Treatment Duration (months)	Follow up Duration	Treatment Extension (months)	Method
STEADY-PD III	2017	Isradipine	Completed + reported	12	(336)	double blind	placebo controlled	parallel group	N	54	36	36	-	-
SURE-PD3	-	Inosine	Finished recruiting	14	(270)	double blind	placebo controlled	parallel group	N	50	24	27	-	wash in - 3 months, wash out- 3 months
Study of Mirapex Pramipeole for the Early Treatment of Parkinson's disease	2013	Pramipeole	Completed + reported	6	(535)	double blind	placebo controlled	parallel group	N	35	15	15	-	delayed start- 9 months
NET-PD LS-1 Creatine in Parkinson's Disease	2015	Creatine	Terminated	9	(1741)	double blind	placebo controlled	parallel group	N	86	60	60	-	-
QE3	2014	Coenzyme Q10 with Vitamin E	Terminated	5	(600)	double blind	placebo controlled	parallel group	Y	32	16	16	-	-
PD4PD	2012	Partnered Dance	Completed + reported	4	62	single blind	placebo controlled	parallel group	N	23	12	12	-	-
ADAGIO	2009	Rasagiline	Completed + reported	11	(1176)	double blind	placebo controlled	parallel group	Y	43	16.5	16.5	-	delayed start- 8 months

8.27 Appendix 27 – Outcome measures in Phase II studies

Trial	Year published	Active agent(s)	Status	Primary Endpoints met	Primary Outcome Domain(s)	Outcome Measure(s)	Number of Primary Outcome	Mechanistic Secondary Outcome	Patient Reported Outcome
PASADENA	-	PR002	Open + recruiting	-	Motor	MDS-UPDRS I-III total score (OFF state)	1	DaTSCAN, Blood Test	N
Ambroxol as a Treatment for PD Dementia	-	Ambroxol	Open + recruiting	-	Cognition	Alzheimer's Disease Assessment Scale - cogntive subscale (ADAS-cog), ADCS - Clinican's Global impression of change (CGIC)	2	CSF, Blood Test, MRI	N
PD Nilotinib	-	Nilotinib	Finished recruiting	-	Safety	Number of participants with abnormal lab values/adverse events/serious adverse events	1	CSF	N
NILO-PD	-	Nilotinib	Open + recruiting	-	Safety, Tolerability	Number of treatment-related serious adverse events, Ability to complete study on assigned dose	2	-	N
Intermittent Bilateral GDNF for PD	2016	GDNF	Completed + reported	N	Motor	MDS-UPDRS Part III (OFF)	1	MRI, PET	N
EXENATIDE-PD	2017	Exenatide	Completed + reported	Y	Motor	MDS-UPDRS Part III (OFF)	1	-	N

Trial	Year published	Active agent(s)	Status	Primary Endpoints met	Primary Outcome Domain(s)	Outcome Measure(s)	Number of Primary Outcome	Mechanistic Secondary Outcome	Patient Reported Outcome
LixiPark	-	Liisenatide	Open + recruiting	-	Motor	MDS-UPDRS Part III (ON)	1	-	N
MOVES-PD	-	GZ/SAR402 67	Open + recruiting	-	Motor	MDS-UPDRS Part II and III score (OFF/ON state not reported)	1		N
Deferipron PD	2017	Iron Chelator Deferipron e	Complet ed + reported	Y	Safety, Mechanism of Action	Blood, MRI	2	-	N
FAIR-PARK-I	2015	Iron Chelator Deferipron e	Complet ed + reported	Y	Mechanism of Action	MRI	1	Blood Test, CSF, MRI	Y
FAIRPARKII	-	Iron Chelator Deferipron e	Open + recruiting	-	Motor	MDS-UPDRS I-III total score (OFF state)	1	-	N
SKY	-	Deferipron e	Open + recruiting	-	Motor	MDS-UPDRS part III (OFF/ON state not reported)	1	Blood Test	N
NIC-PD	-	Transderma l NICotine	Complet ed + unreport ed	-	Motor	MDS-UPDRS I-III total score (OFF/ON state not reported)	1	-	N
STEADY-PD	2013	Isradipine	Complet ed + reported	Y	Tolerability	Proportion of subjects who complete study or to the time of iniation of dopaminergic therapy	1	-	Y
Investigation of the Safety and Efficacy of NTCELL	2017	NTCELL	Complet ed + reported	Y	Safety	the incidence of treatment emergent adverse events	1	-	Y

Trial	Year published	Active agent(s)	Status	Primary Endpoints met	Primary Outcome Domain(s)	Outcome Measure(s)	Number of Primary Outcome	Mechanistic Secondary Outcome	Patient Reported Outcome
Lovastatin as a Neuroprotective Treatment for Early Stage PD	-	Lovastatin	Open + recruiting	-	Motor	MDS-UPDRS part III (OFF)	1	PET	N
PD STAT	-	Simvastatin	Finished recruiting	-	Motor	MDS-UPDRS Part III (OFF)	1	-	N
N-Acetylcysteine for Neuroprotection in Parkinson's Disease	-	N-Acetylcysteine	Completed + unreported	-	Mechanism of Action	MRI	1	-	Y
GM1 Ganglioside Effects on PD	-	GM1 Ganglioside	Completed + reported	Y	Motor	MDS-UPDRS I-III total score (week 24) (OFF), MDS-UPDRS I-III total score (week 120) (OFF)	2	-	N
Pioglitazone in Early PD	2015	Pioglitazone	Completed + reported	N	Motor	MDS-UPDRS I-III total score (OFF)	1	-	N
Safety and Efficacy of CERE-120 in Subjects With PD	2013	CERE-120	Completed + reported	N	Motor	MDS-UPDRS part III (OFF)	1	Brain Imaging	N
Safety and Efficacy of DA-9805 for PD	-	DA-9805	Open + recruiting	-	Motor	MDS-UPDRS part III (OFF)	1	-	N
Clinical Trial on the Effectiveness of Traditional Chinese Medicinal Miture in PD	-	Traditional Chinese Medicinal Miture	-	-	Motor	MDS-UPDRS I-III total score (OFF/ON state not reported)	1	-	N

Trial	Year published	Active agent(s)	Status	Primary Endpoints met	Primary Outcome Domain(s)	Outcome Measure(s)	Number of Primary Outcome	Mechanistic Secondary Outcome	Patient Reported Outcome
Ubiquinol in PD: Safety, Tolerability, and Effects Upon Oidative Damage and Mitochondrial Biomarkers	-	Ubiquinol	Completed + unreported	-	Safety	Number and severity of any adverse event	1	MRI	N
Study of the Neuro-protective Effect of Granulocyte-colony Stimulating Factor on Early Stage PD	-	Granulocyte-colony Stimulating Factor	Terminated	-	Motor	MDS-UPDRS part III (OFF)	1	-	N
Exendin-4 as a Treatment for PD - Pilot Study	2013	Eendin-4	Completed + reported	Y	Motor	MDS-UPDRS part III (OFF)	1	DaTSCAN	N
Clinical Trial on the Effectiveness of Herbal Medicinal Mixture in PD	-	Herbal Medicinal Mixture	Completed + unreported	-	Time to event	Levodopa Equivalent Dose (LED)	1	-	N
Double- blind multicentre,sham surgery controlled study of cere-120 in subjects with pd	2010	Cere-120	Completed + reported	N	Motor	MDS-UPDRS part III (OFF)	1	-	N
MIREILLE	2016	Bee Venom	Completed + reported	N	Motor	MDS-UPDRS part III (OFF)	1	DaTSCAN	N
SPARX	2018	Exercise	Completed + reported	Y	Adherence	Maximum heart rate	1	-	N

Trial	Year published	Active agent(s)	Status	Primary Endpoints met	Primary Outcome Domain(s)	Outcome Measure(s)	Number of Primary Outcome	Mechanistic Secondary Outcome	Patient Reported Outcome
A Trial of MitoQ for the treatment of people with PD	2010	MitoQ	Completed + reported	N	Motor	MDS-UPDRS I-III total score (OFF)	1	-	N
Efficacy and Safety of Trigonella seeds as adjuvant to L-Dopa	2013	Trigoneela L seeds	Completed + reported	Y	Motor	MDS-UPDRS I-III total score (OFF/ON state not reported)	1	-	N
Randomized, double-blind, placebo-controlled pilot trial of reduced coenzyme Q10 for Parkinson's disease.	2015	coenzyme Q10	Completed + reported	Y	Motor	MDS-UPDRS I-III total score (ON)	1	-	N
Effect of the myeloperoidase inhibitor AZD3241 on microglia: a PET study in PD	2015	AZD3241	Completed + reported	N	Target Engagement	PET	1	Blood	N
Liraglutide	-	Liraglutide	Open + recruiting	-	Motor, Non-motor, Cognition	MDS-UPDRS Part III (OFF), NMSS score, MADRS-2 score	3	Blood	Y
H2 Therapy	2012	H2	Completed + reported	Y	Motor	MDS-UPDRS I-III total score (OFF/ON state not reported)	1	-	N
High-dose transdermal nicotine in Parkinson's disease patients	2017	Transdermal Nicotine	Completed + reported	-	Motor	MDS-UPDRS Part III (OFF)	1	DaTSCAN, Urine	Y

Trial	Year published	Active agent(s)	Status	Primary Endpoints met	Primary Outcome Domain(s)	Outcome Measure(s)	Number of Primary Outcome	Mechanistic Secondary Outcome	Patient Reported Outcome
SURE-PD	2014	Inosine	Completed + reported	Y	Tolerability, Safety, Site of action	Extent assigned treatment could continue without prolonged dose reduction due to adverse experiences (AEs) at 6 and 24 months, absence of serious AEs, CSF Urate levels	3	-	N
GAP-PD	2014	GM 608	Completed + reported	Y	Motor, Safety, Tolerability	MDS-UPDRS I-III total score (OFF), Safety/tolerability outcomes not specified	3	-	N
A Study to Assess Safety and Tolerability of Oral AZD3241 in Patients With PD	2014	Oral AZD3241	Completed + reported	Y	Safety, Tolerability	change in vital sign measurements, number and severity of Aes, change in neuro/phyiscal examination or clin lab test data, ECGs, Suicidality Score, CSSRS	6	Blood Test	Y
SPARK	-	BIIB054	Open + recruiting	-	Safety	Percentage of participants with Aes	1	Blood Test, SPECT	N
Study of Zonisamide in Early PD	-	Zonisamide	In set-up, not yet started	-	Time to Event	Time to need dopaminergic therapy	1	-	N
High-intensity Exercise and Fall Prevention Boot Camp for PD	-	Exercise	Completed + unreported	Y	Tolerability/Adherence/ Safety	Number of participants that complete exercise, AEs	7	Blood Test	Y

8.28 Appendix 28 - Outcome measures in Phase III studies

Trial	Year published	Active agent(s)	Status	Primary Endpoints met	Primary Outcome Domain(s)	Outcome Measure(s)	Number of Primary Outcome	Mechanistic Secondary Outcome	Patient Reported Outcome
STEADY-PD III	2017	Isradipine	Completed + reported	N	Motor	MDS-UPDRS I-III total score (OFF)	1	-	Y
SURE-PD3	-	Inosine	Finished recruiting	-	Motor	MDS-UPDRS I-III total score (OFF)	1	-	Y
Study of Mirapex Pramipeole for the Early Treatment of Parkinson's disease	2013	Pramipexole	Completed + reported	N	Motor	MDS-UPDRS I-III total score (OFF)	1	SPECT	Y
NET-PD LS-1 Creatine in Parkinson's Disease	2015	Creatine	Terminated	N	Efficacy	Global outcome combined information from Schwab England ADL, PDQ-39, Ambulatory capacity,Symbol digit modalitites, modified rankin	1	-	Y
QE3	2014	Coenzyme Q10 with Vitamin E	Terminated	N	Motor	MDS-UPDRS I-III total score (OFF)	1	Blood	Y
PD4PD	2012	Partnered Dance	Completed + reported	Y	Motor	MDS-UPDRS part III (OFF)	1	-	N
ADAGIO	2009	Rasagiline	Completed + reported	Y	Motor	MDS-UPDRS I-III total score (OFF)	1	-	N

8.29 Appendix 29 – Inclusion criteria Phase II studies

				Participant Characteristics										
Trial	**Year published**	**Active agent(s)**	**Status**	**Min Age**	**Ma Age**	**Disease Duration**	**Inferred Disease Stage**	**H&Y Stage**	**H&Y On/Off State**	**Inclusion Criteria: Cognition**	**Cut-off Score**	**Inclusion Criteria: Depression**	**Cut-off Score**	**Drug naïve**
PASADENA	-	PR002	Open + recruiting	40	80	-	early	1 or 2	-	MMSE	>25	-	N/A	N
Ambroxol as a Treatment for PD Dementia	-	Ambroxol	Open + recruiting	50	-	PD diagnosis 1 yr prior to dementia	early-advanced	2-3.5	-	MOCA ≤ 24 and MMSE ≥16	≤ 24 and ≥16	-	N/A	N
PD Nilotinib	-	Nilotinib	Finished recruiting	40	90	-	moderate	≥2.5 ≤ 3	-	MOCA	≥22	-	N/A	N
NILO-PD	-	Nilotinib	Open + recruiting	40	79	> 5yrs since diagnosis	mod - advanced	>2<4	ON	MOCA	≥21	Becks	≤ 17	N
Intermittent Bilateral GDNF for PD	-	GDNF	Completed + reported	35	75	≥ 5yrs since diagnosis	early-mod	≤3	OFF	MOCA	≥24	Becks	<14	N
EXENATIDE-PD	2017	Exenatide	Completed + reported	25	75	-	early	≤ 2.5	ON	MDRS	≥120	MADRS	≤ 16	N
LixiPark	-	Lixisenatide	Open + recruiting	40	75	Within 3 yrs of diagnosis	early-mod	<3	ON	MOCA	>26	-	N/A	N
MOVES-PD	-	GZ/SAR40267	Open + recruiting	18	80	≥2 yrs of symptoms	early	≤ 2	-	MOCA	≥20	-	N/A	N

				Participant Characteristics										
Trial	**Year published**	**Active agent(s)**	**Status**	**Min Age**	**Ma Age**	**Disease Duration**	**Inferred Disease Stage**	**H&Y Stage**	**H&Y On/Off State**	**Inclusion Criteria: Cognition**	**Cut-off Score**	**Inclusion Criteria: Depression**	**Cut-off Score**	**Drug naïve**
Deferipron PD	2017	Iron Chelator Deferiprone	Completed + reported	50	75	Within 5 years of diagnosis	early	1-2	ON	None Specified	N/A	-	N/A	N
FAIR-PARK-I	2015	Iron Chelator Deferiprone	Completed + reported	30	80	< 2-3 Years	early-mod	< 3	OFF	MMSE	>24	-	N/A	N
FAIRPARKII	-	Iron Chelator Deferiprone	Open + recruiting	18	80	Within 18 months of diagnosis	early-mod	<3	-	MMSE	≥24	-	N/A	Y
SKY	-	Deferiprone	Open + recruiting	18	80	Within 3 yrs of diagnosis	early-mod	<3	-	None Specified	N/A	-	N/A	N
NIC-PD	-	Transdermal NICotine	Completed + unreported	30	-	Within 18 months of diagnosis	early	≤ 2	-	MMSE	>24	Becks	≤ 24	N
STEADY-PD	2013	Isradipine	Completed + reported	30	-	-	early	≤ 2.5	-	MMSE	≥26	Becks	≤ 15	N
Investigation of the Safety and Efficacy of NTCELL	2017	NTCELL	Completed + reported	40	65	> 5yrs since diagnosis	-	-	-	None Specified	N/A	-	N/A	N
Lovastatin as a Neuroprotective Treatment	-	Lovastatin	Open + recruiting	30	90	-	early	1	OFF	None Specified	N/A	-	N/A	N

				Participant Characteristics										
Trial	**Year published**	**Active agent(s)**	**Status**	**Min Age**	**Ma Age**	**Disease Duration**	**Inferred Disease Stage**	**H&Y Stage**	**H&Y On/Off State**	**Inclusion Criteria: Cognition**	**Cut-off Score**	**Inclusion Criteria: Depression**	**Cut-off Score**	**Drug naïve**
for Early Stage PD														
PD STAT	-	Simvastatin	Finished recruiting	40	90	-	early-mod	≤ 3	ON	MOCA	≥21	MADRS	≤ 31	N
Trial	**Year published**	**Active agent(s)**	**Status**	**Min Age**	**Ma Age**	**Disease Duration**	**Inferred Disease Stage**	**H&Y Stage**	**H&Y On/Off State**	**Inclusion Criteria: Cognition**	**Cut-off Score**	**Inclusion Criteria: Depression**	**Cut-off Score**	**Drug naïve**
N-Acetylcysteine for Neuroprotection in Parkinson's Disease	-	N-Acetylcysteine	Completed + unreported	50	75	<15 years since diagnosis	-	-	-	MMSE	>24	-	N/A	N
GM1 Gangliosid e Effects on PD	-	GM1 Ganglioside	Completed + reported	39	85	-	early-mod	1-3	OFF	MMSE	>25	Becks	<10	N
Pioglitazone in Early PD	2015	Pioglitazone	Completed + reported	30	-	Within 5 years of diagnosis	early	<2	-	None Specified	N/A	-	N/A	N
Safety and Efficacy of CERE-120 in Subjects With PD	2013	CERE-120	Completed + reported	35	70	-	early-mod	≤ 3	OFF	None Specified	N/A	-	N/A	N
Safety and Efficacy of DA-9805 for PD	-	DA-9805	Open + recruiting	30	79	Within 2 years of diagnosis	early	1 or 2	-	MMSE	≥24	-	N/A	N

				Participant Characteristics										
Trial	**Year published**	**Active agent(s)**	**Status**	**Min Age**	**Ma Age**	**Disease Duration**	**Inferred Disease Stage**	**H&Y Stage**	**H&Y On/Off State**	**Inclusion Criteria: Cognition**	**Cut-off Score**	**Inclusion Criteria: Depression**	**Cut-off Score**	**Drug naïve**
Clinical Trial on the Effectiveness of Traditional Chinese Medicinal Miture in PD	-	Traditional Chinese Medicinal Miture	-	50	-	-	early-mod	1-3	-	None Specified	N/A	-	N/A	N
Ubiquinol in PD: Safety, Tolerability, and Effects Upon Oidative Damage and Mitochondrial Biomarkers	-	Ubiquinol	Completed + unreported	40	75	Within 5 years of diagnosis	-	-	-	MMSE	>26	-	N/A	N
Study of the Neuro-protective Effect of Granulocyte-colony Stimulating Factor on Early Stage PD	-	Granulocyte-colony Stimulating Factor	Terminated	40	65	-	early-mod	1-3	OFF	MMSE	>24	-	N/A	N
Exendin-4 as a Treatment for PD - Pilot Study	2013	Eendin-4	Completed + reported	45	70	> 5yrs since diagnosis	early	2-2.5	-	MDRS	>120	MADRS	<16	N
Clinical Trial on the Effectiveness of Herbal Medicinal Miture in PD	-	Herbal Medicinal Miture	Completed + unreported	50	-	-	early-mod	1-3	-	None Specified	N/A	-	N/A	N

				Participant Characteristics										
Trial	**Year published**	**Active agent(s)**	**Status**	**Min Age**	**Ma Age**	**Disease Duration**	**Inferred Disease Stage**	**H&Y Stage**	**H&Y On/Off State**	**Inclusion Criteria: Cognition**	**Cut-off Score**	**Inclusion Criteria: Depression**	**Cut-off Score**	**Drug naïve**
Double-blind multicentre,sham surgery controlled study of cere-120 in subjects with pd	2010	Cere-120	Completed + reported	35	75	≥ 5yrs since diagnosis	N/A	-	-	Folstein Mini Mental eamination	>27	-	N/A	N
MIREILLE	2016	Bee Venom	Completed + reported	40	-	-	early-mod	1.5-3	OFF	MMSE	≥24	-	N/A	N
SPAR	2018	Exercise	Completed + reported	40	80	Within 5 years of diagnosis	early	1-2	-	MOCA	>26/30	Becks	<13	N
Trial	**Year published**	**Active agent(s)**	**Status**	**Min Age**	**Ma Age**	**Disease Duration**	**Inferred Disease Stage**	**H&Y Stage**	**H&Y On/Off State**	**Inclusion Criteria: Cognition**	**Cut-off Score**	**Inclusion Criteria: Depression**	**Cut-off Score**	**Drug naïve**
A Trial of MitoQ for the treatment of people with PD	2010	MitoQ	Completed + reported	30	-	-	early	<2.5	-	None Specified	N/A	Hamilton Scale	<10	N
Trigonella														
Randomized, double-blind, placebo-controlled pilot trial of reduced coenzyme Q10 for Parkinson's	2015	coenzyme Q10	Completed + reported	48	75	Not known	early	1	-	None Specified	N/A	-	N/A	Y

				Participant Characteristics										
Trial	**Year published**	**Active agent(s)**	**Status**	**Min Age**	**Ma Age**	**Disease Duration**	**Inferred Disease Stage**	**H&Y Stage**	**H&Y On/Off State**	**Inclusion Criteria: Cognition**	**Cut-off Score**	**Inclusion Criteria: Depression**	**Cut-off Score**	**Drug naïve**
disease. Group A														
Effect of the myeloperoidase inhibitor AZD3241 on microglia: a PET study in PD	2015	AZD3241	Completed + reported	35	70	≥ 3 years or treated by L-dopa for ≥2 years with motor fluctuations	early - advanced	4 ma (OFF) and 3 ma (ON)	Either	Mattis	>125	-	N/A	N
Safety and Efficacy of Liraglutide in PD	-	Liragluti de	Open + recruiting	25	85	>2 yrs of symptoms	-	-	-	MOCA	≥22	Becks	≤ 29	N
H2 therapy														
High-dose transdermal nicotine in Parkinson's disease patients	2017	Transdermal Nicotine	Completed + reported	45	65	-	early-mod	1-3	-	MOCA	≥26	-	N/A	N
SURE-PD	2014	Inosine	Completed + reported	30	-	Within 3 yrs of diagnosis	-	-	-	None Specified	N/A	-	N/A	N
GAP-PD	2014	GM 608	Completed + reported	30	-	<10 years since diagnosis	early-mod	<3	-	None Specified	N/A	-	N/A	N
A Study to Assess Safety and Tolerability of Oral AZD3241	2014	Oral AZD3241	Completed + reported	30	80	-	early	1-2.5	-	None Specified	N/A	-	N/A	N

				Participant Characteristics										
Trial	**Year published**	**Active agent(s)**	**Status**	**Min Age**	**Ma Age**	**Disease Duration**	**Inferred Disease Stage**	**H&Y Stage**	**H&Y On/Off State**	**Inclusion Criteria: Cognition**	**Cut-off Score**	**Inclusion Criteria: Depression**	**Cut-off Score**	**Drug naïve**
in Patients With PD														
SPARK	-	BIIB054	Open + recruiting	40	80	Within 3 yrs of diagnosis	early	≤ 2.5	-	MOCA	≥ 23	-	N/A	N
Study of Zonisamide in Early PD	-	Zonisamide	In set-up, not yet started	45	85	<1 month of symptoms	-	-	-	None Specified	N/A	-	N/A	Y
High-intensity Exercise and Fall Prevention Boot Camp for PD	-	Exercise	Completed + unreported	62	73	-	early-mod	1-3	ON	None Specified	N/A	-	N/A	N

8.30 Appendix 30 – Inclusion criteria Phase III studies

				Participant Characteristics										
Trial	**Year published**	**Active agent(s)**	**Status**	**Min Age**	**Ma Age**	**Disease Duration**	**Inferred Disease Stage**	**H&Y Stage**	**H&Y On/Off State**	**Inclusion Criteria: Cognition**	**Cut-off Score**	**Inclusion Criteria: Depression**	**Cut-off Score**	**Drug naïve**
STEADY-PD III	2017	Isradipine	Completed + reported	30	-	Within 3 yrs of diagnosis	early	≤ 2	-	MOCA	≥26	Becks	≤ 15	N
SURE-PD3	-	Inosine	Finished recruiting	30	-	Within 3 yrs of diagnosis	early	1-2.5	-	MMSE	≥25	-	N/A	N
Study of Mirapex Pramipeole for the Early Treatment of Parkinson's disease	2013	Pramipeole	Completed + reported	30	79	Within 2 yrs of diagnosis	early	1-2	-	None Specified	N/A	-	N/A	N
NET-PD LS-1 Creatine in Parkinson's Disease	2015	Creatine	Terminated	-	-	Within 5 yrs of diagnosis	N/A	-	-	None Specified	N/A	-	N/A	N
QE3	2014	Coenzyme Q10 with Vitamin E	Terminated	30	-	Within 5 yrs of diagnosis	early	<2.5	-	MMSE	>25	Hamilton Scale	<11	N
PD4PD	2012	Partnered Dance	Completed + reported	30	-	-	early-advanced	1-4	OFF	None Specified	N/A	-	N/A	N

				Participant Characteristics										
Trial	**Year published**	**Active agent(s)**	**Status**	**Min Age**	**Ma Age**	**Disease Duration**	**Inferred Disease Stage**	**H&Y Stage**	**H&Y On/Off State**	**Inclusion Criteria: Cognition**	**Cut-off Score**	**Inclusion Criteria: Depression**	**Cut-off Score**	**Drug naïve**
ADAGIO	2009	Rasagiline	Completed + reported	30	80	< 18 months since diagnosis	early-mod	<3	-	MMSE	≥26	Becks	<15	N