Fatigue Management in Parkinson's Disease: Evidence Synthesis and a Pilot Randomised Controlled Trial of the *ReFresh* Online Intervention

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Abstract

Fatigue is one of the most prevalent and disabling non-motor symptoms in Parkinson's disease (PD), yet it remains poorly understood and inadequately treated. People with Parkinson's consistently identify fatigue as among the most burdensome aspects of their condition, often with greater impact on daily functioning and quality of life than motor symptoms. Despite this, fatigue remains under-recognised in clinical care and there is limited evidence to guide effective management strategies.

This thesis aimed to advance the evidence base for non-pharmacological approaches to fatigue management in PD through a multi-stage research programme. First, a systematic review synthesised randomised controlled trials of non-pharmacological interventions for fatigue in PD. Findings highlighted the scarcity of available evidence, with only a small number of underpowered studies—predominantly exercise-based—providing modest indications of benefit but insufficient to establish robust conclusions. To broaden the perspective, a scoping review mapped fatigue management strategies across other neurodegenerative conditions, including multiple sclerosis and motor neurone disease. This review identified a wider range of interventions, such as cognitive behavioural therapy, energy management, psychoeducation, and self-management programmes, many of which demonstrated promise and provided transferable insights for PD.

Building on this evidence, a pilot randomised controlled trial evaluated the feasibility, acceptability, and preliminary outcomes of *ReFresh*, an online fatigue management programme for people with PD adapted from the Multiple Sclerosis-based *FACETS* programme. The pilot trial demonstrated good feasibility and acceptability, with encouraging short-term trends towards improved fatigue self-efficacy. However, challenges were noted in

sustaining engagement and retention, highlighting the need for further adaptation and digital support strategies in future research.

Together, these studies contribute to understanding fatigue management in PD, emphasising the limited existing evidence, the value of cross-condition learning, and the potential of structured, patient-centred programmes. The findings support the case for further development and rigorous evaluation of non-pharmacological fatigue interventions in PD, with patient involvement central to design and implementation.

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Author's Note: Use of AI Tools

Artificial intelligence (AI) tools, specifically ChatGPT (OpenAI), were used in the preparation of this thesis. Their use was limited to paraphrasing, restructuring, and grammatical correction of draft text. No AI tools were used to generate original academic content, interpret data, conduct analysis, or write substantive arguments.

All content was critically reviewed, edited, and finalised by the author to ensure academic integrity, methodological accuracy, and alignment with disciplinary standards. This use of AI is in full compliance with the University of East Anglia's Generative AI Policy for Research and Innovation (v1.2, approved 7 May 2025).

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List of abbreviations

ADL — Activities of Daily Living

ALS — Amyotrophic Lateral Sclerosis

AMED — Allied and Complementary Medicine Database

CBT — Cognitive Behavioural Therapy

CFQ — Chalder Fatigue Questionnaire

CI — Confidence Interval

CINAHL — Cumulative Index to Nursing and Allied Health Literature

CIS-20R — Checklist Individual Strength, Revised

CONSORT — Consolidated Standards of Reporting Trials

COPM — Canadian Occupational Performance Measure

EDSS — Expanded Disability Status Scale

ELEVIDA — (Name of a self-guided online fatigue programme)

EQ-5D — EuroQol Five-Dimension Scale

FACETS — Fatigue: Applying Cognitive behavioural and Energy-effectiveness Techniques to lifeStyle

FIS — Fatigue Impact Scale

FM+ — Fatigue Self-Management plus Physical Activity

FSMC — Fatigue Scale for Motor and Cognitive Functions

FSS — Fatigue Severity Scale

GDS-15 — Geriatric Depression Scale, 15 items

HD — Huntington's Disease

H&Y — Hoehn and Yahr (staging scale)

HPA — Hypothalamic–Pituitary–Adrenal (axis)

HRV — Heart Rate Variability

iCBT — Internet-based Cognitive Behavioural Therapy

ICF — International Classification of Functioning, Disability and Health

ITT — Intention to Treat

JBI — Joanna Briggs Institute

MA — Meta-analysis

MCID — Minimal Clinically Important Difference

MEDLINE — Medical Literature Analysis and Retrieval System Online

MeSH — Medical Subject Headings

MFIS — Modified Fatigue Impact Scale

MFIS-5 — Modified Fatigue Impact Scale, 5 items

MND — Motor Neuron Disease

MRC — Medical Research Council

MS — Multiple Sclerosis

MS-FSE — Multiple Sclerosis Fatigue Self-Efficacy Scale

MSA — Multiple System Atrophy

NMA — Network Meta-analysis

NMS — Non-Motor Symptoms

NRCT — Non-randomised Controlled Trial

OSF — Open Science Framework

PAS — Parkinson Anxiety Scale

PBA — Person-Based Approach

PCC — Population, Concept, Context

PD — Parkinson's Disease

PDDS — Patient Determined Disease Steps

PDQ-39 — Parkinson's Disease Questionnaire, 39 items

PFS — Parkinson's Fatigue Scale

PFS-16 — Parkinson's Fatigue Scale, 16 items

PP — Per Protocol

PPI — Patient and Public Involvement

PRISMA — Preferred Reporting Items for Systematic Reviews and Meta-Analyses

PRISMA-ScR — PRISMA Extension for Scoping Reviews

PSP — Progressive Supranuclear Palsy

PSQI — Pittsburgh Sleep Quality Index

PsycINFO — Psychological Information Database

PwP — People with Parkinson's

QoL — Quality of Life

RCT — Randomised Controlled Trial

ReFresh — Rebalancing Fatigue and Enhancing Self-Help

RoB2 — Risk of Bias, Version 2

RPE — Rating of Perceived Exertion

RRMS — Relapsing-Remitting Multiple Sclerosis

ScR — Scoping Review

SMD — Standardised Mean Difference

SR — Systematic Review

TAU — Treatment as Usual

TFA — Theoretical Framework of Acceptability

tDCS — Transcranial Direct Current Stimulation

TIDieR — Template for Intervention Description and Replication

UC — Usual Care

UEA — University of East Anglia

VO2peak — Peak Oxygen Uptake

Short Glossary of Key Terms

Term	Definition
PD — Parkinson's Disease	Progressive neurodegenerative disorder with motor and non-motor features; the target condition for this thesis.
PwP — People with Parkinson's	Abbreviation used throughout the thesis to refer to people living with Parkinson's disease.
ReFresh — Rebalancing Fatigue & Enhancing Self-Help	Six-week online fatigue-management programme adapted from FACETS and piloted in Chapter 4.
FACETS	Fatigue: Applying Cognitive behavioural and Energy-effectiveness Techniques to lifeStyle — manualised programme for people with multiple sclerosis; the basis for ReFresh adaptation.
MFIS — Modified Fatigue Impact Scale	Multidimensional instrument measuring the impact of fatigue on physical, cognitive and psychosocial domains; used in measurement discussions.
PFS — Parkinson's Fatigue Scale (PFS-16)	PD-specific 16-item self-report measure of fatigue presence and impact referenced in the thesis.
COPM — Canadian Occupational Performance Measure	Client-centred occupational therapy outcome measure capturing performance and satisfaction in meaningful activities; used in the pilot trial.
ITT — Intention-to-treat	Primary analysis strategy including all randomised participants in their allocated groups regardless of adherence.
PP — Per-protocol	Sensitivity analysis including participants who adhered to the intervention protocol as defined a priori.
MCID — Minimal Clinically Important Difference	Smallest change in an outcome that patients perceive as important; used when interpreting clinical significance of results.

PPI — Patient and Public Involvement	Active involvement of patients/public (lay advisors) in co-design, development and evaluation of ReFresh.
TFA — Theoretical Framework of Acceptability	Seven-component framework used to assess acceptability of interventions (affective attitude, burden, perceived effectiveness, ethicality, intervention coherence, opportunity costs, self-efficacy).

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"Each day I walk through, with ever stiffening legs, what feels like deepening sand. I hope that people with Parkinson's disease who read this will feel it strikes a chord and understand that they are not alone in their journey with this disease."

(Ravenhill, 2023, p.3)

This thesis is grounded in lived experience and addresses the persistent challenge of fatigue in Parkinson's disease.

Chapter 1: Introduction

This chapter establishes the context and rationale for the thesis. It begins by outlining the burden of neurodegenerative diseases, highlighting fatigue as a highly prevalent and disabling symptom that is often under-recognised in clinical practice. It then considers the challenges of defining and measuring fatigue, alongside a review of theoretical models and current management strategies. The chapter concludes by presenting the overarching aims and objectives of the thesis and situating the work within the wider clinical and research landscape.

1.1 Background and Rationale

Neurological and neurodegenerative disorders collectively impose a major and growing burden on populations and health systems worldwide. Global estimates indicate that the number of people living with Parkinson's disease (PD) has risen sharply over the last few decades; in 2019 there were over 8.5 million people living with PD, and PD-related disability and mortality are increasing faster than for any other neurological disorder (World Health Organization, 2023). PD is widely recognised as the second most common neurodegenerative disorder after Alzheimer's disease (de Lau and Breteler, 2006; Kouli, Torsney and Kuan, 2018). Demographic ageing and improved survival are expected to drive further increases in prevalence, intensifying the clinical and societal imperative to address PD's multidimensional impact (Feigin et al., 2019; Steinmetz et al., 2024).

Clinically, PD is characterised by its cardinal motor features—bradykinesia, rigidity, rest tremor and postural instability—but it is now unequivocally established that non-motor symptoms (NMS) are ubiquitous, often emerge early, and contribute substantially to disability and reduced quality of life (Chaudhuri, Healy and Schapira, 2006). NMS encompass sleep disturbance, mood and anxiety symptoms, cognitive changes, autonomic dysfunction (e.g., orthostatic hypotension, constipation, urinary symptoms), pain and sensory phenomena, among others (Chaudhuri, Healy and Schapira, 2006; Seppi et al., 2019). Despite their clinical salience, NMS frequently remain under-recognised and under-treated in routine care, partly because they are variably reported, can be mistakenly attributed to ageing or comorbidity, and cut across traditional disciplinary boundaries in neurology and rehabilitation (Chaudhuri, Healy and Schapira, 2006; Seppi et al., 2019).

Among NMS, fatigue stands out as persistent, distressing and function-limiting. Consensus and review work emphasise that fatigue in PD is not simply "tiredness" or sleepiness; rather,

it is typically described as an overwhelming, disproportionate sense of physical and/or mental exhaustion that is not fully relieved by rest and should be distinguished from related constructs such as excessive daytime sleepiness, apathy, depression and motor fatigability (Kluger et al., 2016). This definitional clarity matters because conflation with neighbouring constructs obscures mechanisms and blunts treatment evaluation, especially when studies rely on heterogeneous screening questions or scales (Kluger et al., 2016).

Epidemiologically, fatigue is common and clinically meaningful in PD. A meta-analysis of 44 studies reported a pooled prevalence of ~50% in PD, with between-study variation largely attributable to differences in instruments and thresholds (Siciliano et al., 2018). Cohort studies and reviews commonly report ranges from roughly one-third to two-thirds of people with PD, with prevalence observable early in the disease course, including in levodopa-naïve patients (Schifitto et al., 2008; Kostić, Filippi and Santangelo, 2016; Siciliano et al., 2018). Importantly, patients consistently rate fatigue among their most troublesome or disabling symptoms; in several series, around one-third identify it as their single most disabling problem (Rabo, Cha and Kim, 2009; Friedman, 2010). These patient-reported perspectives align with observational data linking fatigue to poorer quality of life, greater functional limitations and reduced participation, independent of motor severity (Garber and Friedman, 2003; Herlofson and Larsen, 2003; Elbers et al., 2014).

Despite its high prevalence and impact, effective evidence-based management for PD-related fatigue remains limited. Pharmacological trials have been inconclusive overall, with some signals (e.g., for rasagiline on certain domains) not consistently replicated, and no agent currently supported by strong, generalisable evidence (Elbers et al., 2015; Seppi et al., 2019). Conversely, non-pharmacological approaches (e.g., structured exercise and self-management/behavioural interventions) show promising but underpowered benefits; a recent

synthesis suggests small, positive effects of exercise on fatigue across heterogeneous modalities in PD, though better-designed, adequately powered trials are needed (Folkerts et al., 2023). Collectively, these factors highlight a critical need for rigorous evaluation of tailored non-pharmacological strategies for fatigue in PD, and for embedding systematic assessment of fatigue into routine clinical pathways (Seppi et al., 2019).

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1.2 Conceptual Challenges in Defining and Measuring Fatigue

A central challenge in Parkinson's disease (PD) fatigue research is conceptual clarity. Fatigue is inherently multidimensional and subjective, and in clinical practice as well as research it is frequently conflated with excessive daytime sleepiness, apathy, depressed mood, and motor fatigability—overlapping but distinct constructs that differ in aetiology, measurement, and management (Kluger et al., 2016). The Movement Disorder Society Task Force proposed a case definition to distinguish PD-related fatigue from neighbouring phenomena, emphasising an overwhelming sense of physical and/or mental exhaustion that is disproportionate to exertion and not fully relieved by rest; they also highlighted the need to separate subjective fatigue from motor fatigability (decline in motor performance with sustained effort) and from sleepiness (propensity to fall asleep) (Kluger et al., 2016). In PD populations, construct boundaries are further blurred by medication effects (e.g., dopaminergic therapy influencing alertness), comorbid sleep disorders, and mood symptoms, which can each modulate fatigue scores and complicate phenotyping and treatment evaluation (Kluger et al., 2016).

Measurement presents an additional set of challenges. Several widely used fatigue instruments in PD originated in other conditions. The Fatigue Severity Scale (FSS) was developed in multiple sclerosis (MS) and systemic lupus erythematosus (Krupp et al., 1989), and the Modified Fatigue Impact Scale (MFIS) was adapted from the MS-specific Fatigue Impact Scale to capture perceived functional impact across physical, cognitive, and psychosocial domains. Although these tools are commonly used in PD, they were not designed for PD's specific phenotype and comorbidities. Importantly, the MFIS has been formally validated in PD (e.g., factor structure and convergent validity in PD without dementia) and can perform adequately as a multidimensional measure (Schiehser et al.,

2013), but variations in cut-offs and scoring conventions across studies still limit comparability and pooled inference (Schiehser et al., 2013).

In response to these limitations, PD-specific instruments have been developed. The Parkinson's Fatigue Scale (PFS-16) was created from patient-generated items to capture the presence of fatigue and its impact on daily function (7 and 9 items, respectively) with an administration time of only a few minutes (Brown et al., 2005). Psychometric work—including in advanced PD—supports the PFS-16's acceptability, internal consistency, and construct validity, with emerging evidence for responsiveness (Martínez-Martín et al., 2019). Notably, the PFS-16 preferentially targets physical aspects of fatigue and intentionally down-weights emotional/cognitive items to reduce overlap with mood constructs, which helps specificity but may under-represent cognitive fatigue in some patients (Brown et al., 2005; Niimi et al., 2019). Cross-cultural validations (e.g., Spanish, Brazilian adaptations of MFIS-PD) also indicate acceptable reliability and structural validity, yet measurement invariance across languages and disease stages remains incompletely characterised (Schiehser et al., 2013; Martínez-Martín et al., 2019).

Critically, there is still no universally accepted gold standard for PD fatigue. Heterogeneity in definitions, inclusion thresholds, reference periods (e.g., past week vs past month), and scale selection reduces between-study comparability and complicates meta-analysis. These issues impede precise estimation of prevalence, severity, and treatment response, and they contribute to apparently wide prevalence ranges in the literature (Kluger et al., 2016; Schiehser et al., 2013). For clinical trials, inconsistent instrument choice and limited data on interpretability (e.g., minimal important change) make it harder to judge whether statistically significant changes reflect meaningful improvement for patients. Consolidating on a core measurement set—and ensuring consistent construct boundaries distinguishing fatigue from

sleepiness, apathy, depression, and motor fatigability—would materially strengthen future PD fatigue research and trial design (Kluger et al., 2016).

1.3 Theoretical Models of Fatigue

Understanding the mechanisms underlying fatigue in PD requires a biopsychosocial perspective. Neurobiological theories implicate basal ganglia–cortical circuit dysfunction, impaired dopaminergic and serotonergic signalling, hypothalamic–pituitary–adrenal axis dysregulation, and neuroinflammatory processes. Behavioural and psychosocial factors, such as coping strategies, mood disorders, and disrupted sleep, further interact with biological vulnerability to exacerbate fatigue.

Understanding fatigue in Parkinson's disease (PD) is best approached through a biopsychosocial lens in which biological vulnerability interacts with behavioural, cognitive, and contextual factors to generate a persistent sense of effort and exhaustion that is disproportionate to activity and not fully relieved by rest (Kluger et al., 2016). A useful cross-condition taxonomy distinguishes fatigue (the subjective symptom) from fatigability (objective performance decline) and further differentiates central (brain-mediated) from peripheral (muscle/neuromuscular) contributors—distinctions that guide both measurement and intervention design (Kluger, Krupp and Enoka, 2013).

1.3.1 Neurobiological mechanisms (central contributors)

Multiple converging lines of evidence implicate fronto–basal-ganglia–limbic circuits and non-dopaminergic neurotransmission in PD-related fatigue. Positron emission tomography (PET) studies using the serotonin transporter ligand ^{11}C-DASB demonstrate reduced

serotonergic binding in striatal and limbic regions among fatigued compared with non-fatigued PwP, supporting a role for serotonergic dysfunction in the genesis of fatigue (Pavese et al., 2010). Contemporary reviews integrate these data with evidence for neurotransmitter imbalance (dopamine–serotonin), abnormal BG-cortical loops, and possible hypothalamic–pituitary–adrenal (HPA) axis dysregulation, all of which may alter effort perception and motivational drive (Kostić, Filippi and Santangelo, 2016).

1.3.2 Immune–inflammatory signalling

Emerging work implicates immune activation and neuroinflammation in PD generally, with several meta-analyses and reviews reporting elevated peripheral and CSF cytokines (e.g., IL-6, IL-1β, TNF-α) in PD (Qu et al., 2023; Dzamko et al., 2023). At the symptom level, higher CSF inflammatory markers have been associated with greater fatigue (and related non-motor features) in PD cohorts, suggesting a mechanistic link between inflammatory tone and fatigue expression, although causality is unproven (Lindqvist et al., 2013). Taken together, these findings support the inclusion of inflammatory pathways within biopsychosocial models of PD fatigue.

1.3.3 Behavioural, cognitive, and contextual influences

Symptoms that commonly co-travel with fatigue—sleep disturbance, low mood/anxiety, maladaptive coping, reduced physical activity, and autonomic symptoms—likely amplify biological vulnerability, shaping day-to-day fluctuations and the lived experience of effort (Kluger et al., 2016; Kostić, Filippi and Santangelo, 2016). This interaction helps explain why interventions that target behavioural regulation (e.g., sleep hygiene, graded activity), cognitive appraisals (e.g., catastrophising, perceived control), and self-management skills can

reduce the impact of fatigue in related neurological conditions, even when disease biology is unchanged.

1.3.4 A transdiagnostic perspective

Across neurological conditions such as multiple sclerosis (MS) and motor neurone disease (MND/ALS), leading reviews characterise fatigue as a multidimensional phenomenon arising from the interplay of central neurophysiology with psychological and contextual drivers (Penner and Paul, 2017). This transdiagnostic framing justifies careful knowledge transfer: for example, in MS the group-based FACETS programme (a cognitive-behavioural and energy-management intervention) produces reduced fatigue severity and improved fatigue self-efficacy, with benefits maintained at one year (Thomas et al., 2013; Thomas et al., 2014). Such programme logic—combining education, cognitive-behavioural techniques, pacing/energy conservation, goal setting, and peer support—is theoretically compatible with PD fatigue mechanisms and provides a structured starting point for PD-specific adaptation and evaluation.

1.3.5 Positioning fatigue within the ICF

Beyond disease-mechanism models, the International Classification of Functioning, Disability and Health (ICF) offer a practical scaffold for linking symptoms to activity limitations and participation restrictions and for aligning outcomes with what matters to people's lives (WHO, 2001). Framing PD-related fatigue within the ICF encourages measurement and intervention targets that extend beyond symptom severity (e.g., fatigue self-efficacy, goal-concordant activity, participation), thereby supporting comprehensive rehabilitation planning and evaluation.

Summary. In PD, fatigue likely reflects network-level alterations (fronto–basal-ganglia–limbic circuits; serotonergic imbalance) modulated by immune–inflammatory tone and stress-system dynamics, with expression shaped by behavioural, cognitive, and contextual factors. This model supports multimodal, skills-based interventions (e.g., CBT-informed self-management plus activity regulation) alongside targeted biological research.

1.4 Existing Management Strategies

Despite its prevalence and impact, there is no established, widely effective treatment for Parkinson's disease (PD)–related fatigue. Evidence syntheses consistently conclude that pharmacological options remain limited and inconsistent, and that higher-quality trials—using appropriate fatigue measures—are needed before firm recommendations can be made (Elbers et al., 2015; Seppi et al., 2019). In the Cochrane Review of interventions for PD fatigue, the authors could not provide clear treatment recommendations overall; small studies suggested possible benefits for doxepin and rasagiline on specific fatigue domains, but findings were low-certainty or not consistently replicated, and most agents—including modafinil, methylphenidate, caffeine, memantine and levodopa-carbidopa—did not show robust effects on subjective fatigue (Elbers et al., 2015).

1.4.1 Pharmacological options: signals and limits

Individual trials report signals of benefit that have not translated into a reproducible standard of care:

- MAO-B inhibitors (rasagiline). A small, double-blind RCT in PD with moderate–severe fatigue reported improvement with rasagiline 1 mg over 12 weeks (Lim et al.,

2015). However, analyses from larger multicentre trials found trivial effect sizes for rasagiline on fatigue endpoints, underscoring uncertainty about clinically meaningful benefit (Tsuboi et al., 2022). Overall, the balance of evidence is inconclusive (Elbers et al., 2015; Seppi et al., 2019).

- Psychostimulants (methylphenidate). One small RCT reported reduced fatigue scores after 6 weeks of methylphenidate versus placebo (Mendonça, Menezes and Jog, 2007), but replication is lacking and safety/acceptability data are limited, so this has not become standard practice (Elbers et al., 2015).
- Modafinil and other agents. Although modafinil can improve excessive daytime sleepiness in PD, trials have not demonstrated consistent benefit for fatigue as a distinct construct; similarly, caffeine and other agents have not produced reliable fatigue improvements (Elbers et al., 2015; Seppi et al., 2019).

Across pharmacological studies, common limitations include small samples, heterogeneous outcomes (often not fatigue-specific), short durations, and unclear interpretability (e.g., minimal important change), all of which constrain clinical inference (Elbers et al., 2015; Seppi et al., 2019).

1.4.2 non-pharmacological approaches: emerging but under-tested in PD

In contrast, non-pharmacological strategies are increasingly studied and, in some cases, show promising signals in PD:

- Exercise. A recent systematic review and meta-analysis found a small but statistically significant pooled effect of exercise on fatigue in PD across varied modalities (standardised mean difference ≈ –0.37), whereas acupuncture did not outperform

sham (Folkerts et al., 2023). Although encouraging, heterogeneity and small samples warrant cautious interpretation and more rigorous RCTs (Folkerts et al., 2023).

- Psychological/self-management approaches. In PD, cognitive-behavioural therapy (CBT) has demonstrated benefits for depression, anxiety, and sleep, but no consistent effect on fatigue to date (Luo et al., 2021). By contrast, in multiple sclerosis (MS), structured programmes that combine education, CBT-informed strategies, pacing/energy conservation, goal setting and peer support (e.g., FACETS) reduce fatigue severity and improve fatigue self-efficacy with effects sustained at one year (Thomas et al., 2013; Thomas et al., 2014). These MS results provide transdiagnostic rationale for carefully adapting such content to PD, while recognising the need for PD-specific trials.

1.4.3 Practice gap and implications

Real-world clinical practice often under-assesses fatigue and lacks standardised care pathways for its management in PD. Authoritative reviews of non-motor symptom (NMS) treatment note the limited evidence base and highlight the need to validate and implement effective strategies within routine services (Seppi et al., 2019). Accordingly, current best practice emphasises systematic assessment (clear distinction from sleepiness/apathy), optimising sleep and mood, encouraging graded physical activity, and considering skills-based self-management approaches—pending results from larger, well-designed PD-specific RCTs (Elbers et al., 2015; Seppi et al., 2019; Folkerts et al., 2023).

Summary. In PD, no medication has established itself as a reliable, generalisable treatment for fatigue. Exercise shows small but consistent benefits, and CBT-informed self-management is theoretically compelling—supported by strong evidence in MS—but remains under-tested for PD-specific fatigue endpoints. These gaps motivate the evaluation of

tailored, non-pharmacological interventions that use PD-appropriate fatigue measures and target both symptom burden and participation outcomes.

1.5 Rationale for the Thesis

Fatigue is highly prevalent, clinically important, and under-addressed in Parkinson's disease (PD), yet the current evidence base is fragmented. Conceptual heterogeneity (fatigue vs sleepiness, apathy, and motor fatigability) and inconsistent measurement have constrained cumulative knowledge and impeded robust synthesis (Kluger et al., 2016). Pharmacological trials are small and heterogeneous, with no agent demonstrating consistent, generalisable effects on subjective fatigue outcomes (Elbers et al., 2015; Seppi et al., 2019). By contrast, non-pharmacological strategies—particularly structured exercise—show small but statistically significant pooled benefits on fatigue in PD, though heterogeneity and underpowered trials warrant caution (Folkerts et al., 2023). Evidence from other neurological conditions, especially multiple sclerosis (MS), indicates that cognitive-behavioural and self-management programmes (e.g., FACETS) can reduce fatigue severity and improve fatigue self-efficacy with sustained effects (Thomas et al., 2013; Thomas et al., 2014). However, such approaches remain under-tested for PD-specific fatigue endpoints and often target related outcomes (mood, sleep) rather than fatigue per se (Luo et al., 2021).

These gaps motivate a staged programme of work that (i) clarifies what is already known in PD via a focused systematic review of non-pharmacological randomised controlled trials (RCTs), (ii) broadens scope through a scoping review to identify transferable intervention components from other neurodegenerative diseases, and (iii) adapts and pilots a theoretically grounded, skills-based, online fatigue-management programme for people with Parkinson's

(PwP). Grounding the work in the International Classification of Functioning, Disability and Health (ICF) foregrounds outcomes that matter to patients—fatigue severity and fatigue self-efficacy, but also the ability to participate in daily activities—ensuring alignment with rehabilitation priorities (World Health Organization, 2001).

Accordingly, this thesis proceeds in three integrated stages:

- Systematic Review (Chapter 2) — A rigorous synthesis of randomised controlled trials testing non-pharmacological interventions for Parkinson's-related fatigue, quantifying effects where possible and mapping gaps in the evidence.
- Scoping Review (Chapter 3) — A broader mapping of fatigue-management strategies across neurodegenerative conditions to identify transferable components (for example, CBT-informed self-management and energy conservation/pacing) that may be adapted for Parkinson's.
- Pilot RCT (Chapter 4) — A feasibility and acceptability evaluation of *ReFresh*, an online fatigue-management programme adapted from the MS-based FACETS model for people with Parkinson's, with preliminary assessment of change in fatigue severity and fatigue self-efficacy (Thomas et al., 2013; Thomas et al., 2014; Luo et al., 2021).

These three stages are intentionally linked: Chapter 2 provides a focused, PD-specific evidence synthesis to identify efficacy and gaps; Chapter 3 maps transferable components, delivery strategies and measurement/acceptability lessons; and Chapter 4 uses these inputs to specify and preliminarily evaluate a tailored intervention, following the MRC complex-interventions framework from evidence synthesis to programme specification and feasibility testing (Craig et al., 2008; Skivington et al., 2021). This staging also responds to gaps and

heterogeneity highlighted in prior PD fatigue reviews (Elbers et al., 2015; Seppi et al., 2019; Folkerts et al., 2023).

1.6 Aims and Objectives

The overarching aim of this thesis is to evaluate and advance non-pharmacological approaches to managing fatigue in Parkinson's disease. Its specific objectives are to:

- Systematic Review (Chapter 2): Critically appraise and, where appropriate, meta-analyse RCT evidence on non-pharmacological interventions for PD-related fatigue
- Scoping Review (Chapter 3): Identify transferable components of effective fatigue-management interventions from other neurodegenerative conditions to inform PD-specific intervention logic.
- Pilot RCT (Chapter 4): Adapt and pilot-test ReFresh for PwP, evaluating feasibility (recruitment, retention, adherence), acceptability (satisfaction, qualitative feedback), and preliminary change in fatigue severity and fatigue self-efficacy.
- Methodological and ethical reflection (Chapter 5): Reflect on conceptual, measurement, and ethical issues (e.g., construct boundaries; minimal important change; participant involvement) to shape priorities for a fully powered RCT and implementation.

This introduction has outlined the burden of fatigue in Parkinson's disease, the limited effectiveness of existing management strategies, and the need for a stronger evidence base to inform intervention development. To address this, the next chapter presents a systematic review of non-pharmacological interventions for fatigue in PwP.

Note on search windows: the systematic review (Chapter 2) and the scoping review (Chapter 3) used different database cut-off dates (SR search completed 01 October 2024; ScR search completed 15 February 2025). The scoping review employed a broader strategy and was used to cross-check for any additional PD RCTs published after the SR window. In that later search, we did not identify any PD RCTs that met the SR eligibility criteria.

1.7 Discussion

The argument developed across sections 1.1–1.6 is that PD-related fatigue warrants dedicated, theoretically coherent intervention research. First, definitional and measurement heterogeneity (Kluger et al., 2016) has contributed to under-recognition and diluted treatment signals. Second, while medication trials remain inconclusive (Elbers et al., 2015; Seppi et al., 2019), structured exercise shows small, pooled benefits and offers a tractable behavioural target (Folkerts et al., 2023). Third, transdiagnostic evidence—especially from MS—demonstrates that skills-based, CBT-informed self-management can meaningfully reduce fatigue impact (Thomas et al., 2013; Thomas et al., 2014), supporting adaptation to PD provided disease-specific features (bradykinesia, fluctuating "ON–OFF," autonomic symptoms) are addressed. Finally, aligning outcomes to the ICF reframes success beyond symptom scores toward confidence in managing fatigue, goal-concordant activity, and participation (World Health Organization, 2001). This logic underpins the thesis design: synthesise, map, adapt, and pilot.

1.8 Conclusion

Fatigue in PD is common, disabling, and currently under-served by evidence-based care. The field's progress depends on conceptual clarity, consistent measurement, and the development of tailored non-pharmacological interventions that target both symptom burden and everyday functioning. This thesis contributes by consolidating PD-specific evidence, bringing across transferable learning from related conditions, and piloting a pragmatic, theory-informed programme (ReFresh) for PwP. The next chapter presents a systematic review of non-pharmacological interventions for fatigue in PD.

Chapter 2: Non-Pharmacological Interventions for Managing Fatigue in Parkinson's Disease: A Systematic Review and Meta-Analysis

This chapter presents a systematic review of non-pharmacological interventions for fatigue in people with Parkinson's disease. It outlines the methods of literature searching, screening, and appraisal, followed by a synthesis of the included studies. The evidence is then critically evaluated with attention to methodological quality, strength of findings, and sources of bias. The chapter concludes by identifying key limitations in the current literature and highlighting the gaps that shaped the rationale for the subsequent scoping review and empirical work.

This systematic review and meta-analysis has been accepted for publication in Clinical Parkinsonism & Related Disorders (accepted 12 March 2026).

Protocol registered prospectively on PROSPERO (CRD42023394180).

2.1 Introduction

Parkinson's disease (PD) is a progressive neurodegenerative disorder characterised by a constellation of motor and non-motor symptoms. Classically, motor manifestations such as bradykinesia, tremor, rigidity, and postural instability are attributed to the degeneration of dopaminergic neurons within the substantia nigra and basal ganglia circuitry (DeMaagd and Philip, 2015; Ou et al., 2021). However, the disease burden extends far beyond motor dysfunction. Non-motor symptoms, including fatigue, depression, cognitive impairment, sleep disturbances, and autonomic dysfunction, reflect widespread involvement of non-dopaminergic systems and exert a profound influence on quality of life (Fernandes et al., 2021; Tibar et al., 2018). Importantly, non-motor symptoms frequently precede motor onset, progress independently, and remain undertreated in routine care (Sprenger and Poewe, 2013).

Among these, fatigue stands out as particularly disabling. It is defined as a persistent, overwhelming sense of physical, emotional, and cognitive exhaustion that is disproportionate to activity or exertion (Kluger et al., 2016). Prevalence estimates in PD vary widely, ranging from one-third to almost 90% of individuals, depending on diagnostic criteria and measurement tools used (Falup-Pecurariu, 2013; Kluger, Krupp and Enoka, 2013; Lin et al., 2021; Siciliano et al., 2018). Fatigue is consistently rated by people with Parkinson's (PwP) as one of the most distressing symptoms, often more disabling than motor deficits, yet remains under-recognised by clinicians and inadequately addressed in care pathways (Armstrong and Okun, 2020; Tinazzi et al., 2025). The aetiology of fatigue in PD is multifactorial and misunderstood. Hypothesised mechanisms include basal ganglia–cortical dysfunction (particularly in prefrontal circuits), dopaminergic and serotonergic imbalance, hypothalamic–pituitary–adrenal (HPA) axis dysregulation, neuroinflammation, and cardiac sympathetic denervation (Kostić, Tomić and Ječmenica-Lukić, 2016b). Contributing clinical

factors include motor demands, medication-related side effects (e.g. daytime somnolence, motor fluctuations), and psychiatric comorbidities such as anxiety, apathy, and depression (Armstrong and Okun, 2020; Friedman et al., 2007; Herlofson and Kluger, 2017; Kouli, Torsney and Kuan, 2018). These issues have also been discussed in the context of pragmatic management (Kostić, Tomić and Ječmenica-Lukić, 2016a). Environmental triggers such as disrupted sleep, overheating, and excessive activity may exacerbate symptoms (Lin et al., 2021). This complexity reflects an interaction between central neurobiological mechanisms and behavioural or lifestyle influences.

2.1.1 Fatigue across neurodegenerative diseases

Many of these mechanisms may be common with other neurodegenerative disorders. In multiple sclerosis (MS), fatigue is the most frequently reported symptom and is associated with inflammatory activity, cortical–subcortical disconnection, and maladaptive coping (Motl et al., 2017; Knoop, van Kessel and Moss-Morris, 2012).

In motor neurone disease (MND), fatigue is prevalent and strongly linked to respiratory impairment, sleep disturbance, and systemic metabolic strain (Lo Coco et al., 2012). In Huntington's disease (HD), fatigue overlaps with apathy and slowed cognition, reflecting disruption of basal ganglia–thalamocortical circuits (Aziz et al., 2010). These transdiagnostic observations suggest that fatigue is not a disease-specific phenomenon but rather reflects shared neurobiological and behavioural mechanisms across neurological conditions.

Neuroimaging evidence further supports this view: studies consistently implicate disrupted connectivity in frontal and limbic circuits regulating motivation and effort perception, alongside altered serotonergic and dopaminergic signalling (Jellinger, 2010; Gan et al., 2018;

Mahad, Trapp and Lassmann, 2015). Such convergence supports a biopsychosocial model of fatigue that integrates central neurobiological vulnerability with behavioural and contextual contributors (Engel, 1977; Knoop, van Kessel & Moss-Morris, 2012), a perspective that has been pivotal in shaping fatigue interventions in multiple sclerosis and now offers a framework for advancing fatigue management in Parkinson's disease (Motl et al., 2017).

2.1.2 Management of fatigue in Parkinson's disease

Despite the burden of fatigue in PD, there is currently no consensus on effective management strategies. Longitudinal cohort studies highlight that fatigue tends to worsen over time, underscoring the need for early identification and intervention (Ongre et al., 2021). Pharmacological trials have generally yielded disappointing results. A Cochrane review identified 11 randomised controlled trials (RCTs) testing agents such as doxepin, rasagiline, levodopa–carbidopa, modafinil, and methylphenidate, but concluded that no clear recommendations could be made due to inconsistent and low-quality evidence (Elbers et al., 2015).

In contrast, non-pharmacological strategies offer broader therapeutic potential. In MS, structured fatigue management programmes (e.g. FACETS), exercise, energy conservation techniques, and CBT have demonstrated significant efficacy (Motl et al., 2017; Knoop et al., 2012). In PD, however, non-drug approaches remain under-investigated, and clinical practice is inconsistent. Given the parallels in aetiology and patient-reported experience of fatigue across neurological conditions, adapting and testing these approaches in PD is both feasible and urgently needed. This systematic review addresses this gap by synthesising the available evidence from RCTs of non-pharmacological interventions for fatigue in PD.

2.1.3 Measurement of fatigue in Parkinson's disease

A further challenge is the measurement of fatigue. Fatigue in PD is multidimensional, fluctuating, and subjective, complicating efforts to capture its severity and functional impact (Weintraub et al., 2015; Kluger, Krupp and Enoka, 2013). Most studies have relied on tools originally validated in MS or general populations. The Modified Fatigue Impact Scale (MFIS), originally developed for multiple sclerosis (Fisk et al., 1994), has been applied in PD populations. Internal consistency in small PD samples is typically high ($\alpha \approx 0.9$), but comprehensive PD-specific validation of its construct validity and responsiveness remains limited. The Parkinson Fatigue Scale (PFS-16) is a PD-specific measure, validated in Greek and Spanish cohorts with very high internal consistency ($\alpha \approx 0.95$) and good test–retest reliability (Dagklis et al., 2019; Martinez-Martin et al., 2019). The Fatigue Severity Scale (FSS) is a widely used generic measure that has also been applied in PD, with acceptable internal consistency but less evidence of PD-specific validity (e.g., Martinez-Martin et al., 2019). The Chalder Fatigue Scale (CFS) measures physical and mental fatigue, with acceptable convergent validity but limited sensitivity to change in PD (Chalder et al., 1993; Morriss, Wearden and Mullis, 1998; Wong and Fielding, 2010).

While these tools are widely used, their limited specificity for PD fatigue hampers comparability across trials and may contribute to inconsistent findings. The absence of a fully validated, PD-specific fatigue outcome continues to represent a major barrier for intervention studies.

2.1.4 Aim of the review

This systematic review and meta-analysis evaluate the efficacy of non-pharmacological interventions for reducing fatigue in PD. By synthesising data from RCTs, it aims to estimate the effect sizes of intervention categories (exercise, psychological, educational), assess study quality, and identify methodological and conceptual gaps. The chapter also highlights the translational potential of interventions developed in other neurological populations and provides a rationale for advancing fatigue management research in PD.

2.2 Methods

2.2.1 Review Registration and Framework

The protocol for this systematic review was prospectively registered on PROSPERO (CRD42023394180). The review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines (Page et al., 2021), with the completed checklist included in Appendix 2.A. This registration enhanced transparency and minimised risk of post hoc decision-making.

2.2.2 Search Strategy

A systematic literature search was carried out across MEDLINE (Ovid), CINAHL (EBSCOhost), AMED (EBSCOhost) and PsycINFO (EBSCOhost) from database inception. The initial search was completed on 13 February 2023; searches were updated on 01 October 2024, which served as the cut-off for the synthesis reported in this chapter. Citation tracking and reference checking of included trials were completed to the same cut-off (full strategies in Appendix 2.B).

The strategy combined controlled vocabulary (e.g. MeSH terms) with free-text keywords to maximise sensitivity. Terms included “Parkinson’s disease”, “fatigue”, “tiredness”, “lack of energy”, and “exhaustion”, combined with randomised controlled trial filters. Using RCT filters increased precision but risked missing eligible studies; this trade-off was accepted due to resource constraints. We also manually screened reference lists of included studies and relevant reviews. Non-English-language papers were excluded due to resource limitations and potential translation inaccuracies without specialist support.

2.2.3 Eligibility Criteria

Studies were eligible for inclusion if they met the following criteria:

Study design

Full-text, peer-reviewed randomised controlled trials (RCTs). Cross-over RCTs were included only if pre-cross-over data were available for analysis.

Population

Adults (≥18 years) with a clinical diagnosis of idiopathic Parkinson's disease at any disease stage. Studies including mixed neurological populations were excluded unless data for Parkinson's disease participants were reported separately. Studies of Parkinson's plus syndromes were excluded.

Interventions

Non-pharmacological interventions explicitly targeting fatigue management, including but not limited to physiotherapy, occupational therapy, exercise-based interventions, psychological therapies (e.g. cognitive behavioural therapy), and complementary therapies. Interventions aimed solely at sleep duration or sleep quality were excluded. Pharmacological therapies were excluded unless medication formed part of usual care and was not modified specifically to target fatigue during the trial.

Comparators

Eligible comparators included inactive controls (e.g. wait list, placebo, treatment as usual) and active controls (e.g. alternative non-pharmacological intervention, variation in delivery

mode, intensity, or provider). Trials comparing non-pharmacological interventions with pharmacological interventions were excluded.

Outcomes

Studies were required to report fatigue severity using validated fatigue-specific outcome measures (e.g. Parkinson's Fatigue Scale (PFS), Fatigue Severity Scale (FSS), Modified Fatigue Impact Scale (MFIS), Multidimensional Fatigue Inventory (MFI)). Trials in which fatigue was measured only incidentally or embedded within broader quality-of-life measures without fatigue-specific reporting were excluded.

Publication date

Studies published up to 01 October 2024 were included.

Restricting inclusion to RCTs that explicitly targeted fatigue as a primary therapeutic objective preserved conceptual focus and improved interpretability. Trials in which fatigue was measured only incidentally often differ in design, statistical power, and outcome prioritisation; excluding them reduced heterogeneity and strengthened the validity of a fatigue-specific synthesis. This approach aligns with calls to conceptualise fatigue as a distinct clinical construct rather than a subsidiary feature of broader symptom clusters (Kluger, Krupp and Enoka, 2013).

2.2.4 Study Selection

All search results were exported to EndNote for reference management. Duplicate records were identified and removed within EndNote prior to screening.

Titles and abstracts were independently screened by two reviewers (SA and KD) against the predefined eligibility criteria. Full-text articles of potentially relevant studies were then retrieved and independently assessed for inclusion by the same two reviewers. Disagreements at any stage were resolved through discussion and consensus.

A PRISMA flow diagram summarises the study selection process, including reasons for exclusion at full-text stage (Figure 2.1).

2.2.5 Risk of Bias Assessment

Risk of bias was independently assessed by two reviewers (SA and KD) using the Cochrane Risk of Bias 2 (RoB2) tool (Sterne et al., 2019). This tool was selected over alternatives such as the PEDro scale or ROBINS-I because it provides a domain-based evaluation tailored specifically for RCTs and offers clear signalling questions to guide judgements.

The five domains assessed were: (1) randomisation process; (2) deviations from intended interventions; (3) missing outcome data; (4) measurement of the outcome; and (5) selection of the reported result. Each study was rated as low risk, some concerns, or high risk. Discrepancies were resolved through discussion to ensure consensus. A summary of ratings is presented in Table 2.1, while detailed domain-level justifications are provided in Appendix 2.C.

By providing both a tabular summary and narrative explanation, the review balances transparency with readability. It also reflects an awareness that risk of bias is particularly challenging in behavioural interventions, where blinding is often unfeasible and outcomes such as fatigue are inherently subjective (Boutron et al., 2007).

2.2.6 Statistical Analysis

Meta-analyses were conducted using random-effects models, selected a priori to account for anticipated clinical and methodological heterogeneity across interventions, populations, and outcome measures (Higgins et al., 2022). The primary outcome was fatigue severity. Effect sizes were synthesised using standardised mean differences (SMDs) to allow pooling across studies employing different fatigue scales. Where identical measures were used, group mean differences were also reported for clarity.

Effect sizes were interpreted according to Cohen's conventional thresholds (0.20 = small, 0.50 = moderate, 0.80 = large) (Cohen, 1988). Statistical heterogeneity was assessed using both the chi-squared (Q) test ($p < 0.05$ indicating statistical heterogeneity) and the I^2 statistic, interpreted as low (25%), moderate (50%), and high (75%) heterogeneity, in line with Cochrane guidance (Higgins et al., 2022).

Publication bias was not formally assessed due to the small number of included studies, as funnel plot asymmetry is unreliable when fewer than ten studies are available (Sterne et al., 2011).

The certainty of evidence for key outcomes was evaluated using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach (Guyatt et al., 2008; Schünemann et al., 2019). Summary of Findings tables are presented in the Results, with detailed GRADE evidence profiles provided in Appendix 2.D.

2.2.7 Secondary Outcomes

Where available, secondary outcomes such as quality of life, sleep, depression, and anxiety were extracted and summarised. However, because reporting was inconsistent and outcome measures were heterogeneous, these results were synthesised narratively rather than statistically. Particular attention was given to whether trials employed PD-specific tools (e.g. PDQ-39, PAS, GDS-15), as the absence of such measures represents a key limitation in the evidence base.

By adopting strict eligibility criteria, applying a structured risk of bias assessment, and conducting both quantitative and narrative syntheses, this review sought to balance rigour with clinical relevance. The inclusion of only randomised controlled trials ensured a focus on interventions with the highest level of evidence for causal inference, while the narrative treatment of secondary outcomes allowed exploration of broader impacts such as sleep and mood, despite heterogeneity in measurement. Taken together, these methodological decisions provide a robust foundation for the results that follow, while also highlighting where gaps in reporting and trial design continue to limit the evidence base for fatigue management in Parkinson's disease.

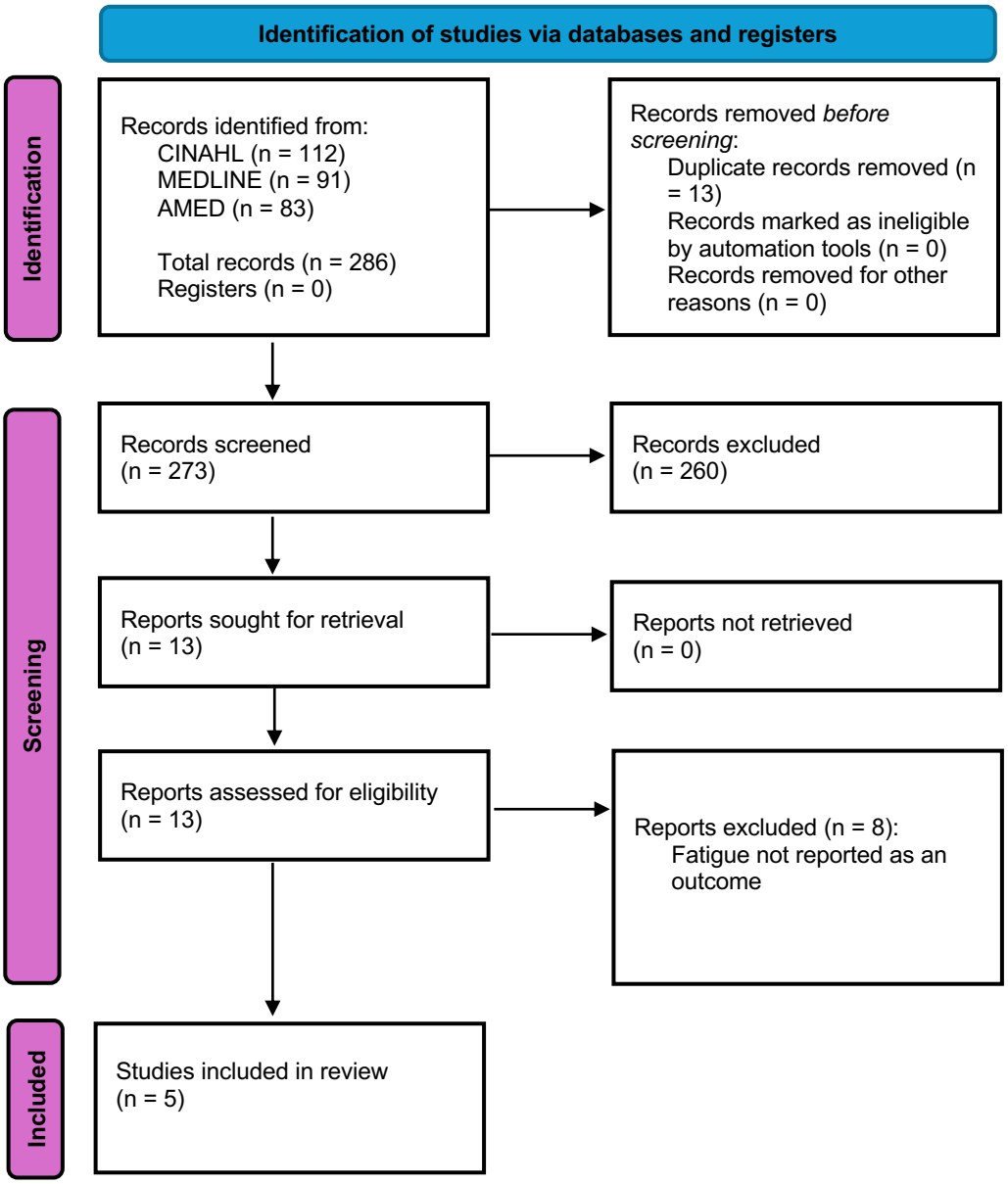
2.3 Results

2.3.1 Literature Search

The electronic searches yielded 286 records across the three databases (CINAHL = 112, MEDLINE = 91, AMED = 83). Following removal of 13 duplicate records, 273 records remained for title and abstract screening. Of these, 260 were excluded, leaving 13 full-text articles assessed for eligibility. Eight studies were excluded because fatigue was not reported as an outcome, leaving five RCTs meeting the eligibility criteria and included in the final synthesis (Figure 2.1).

This relatively small yield underscores the scarcity of fatigue-targeted intervention research in Parkinson's disease, particularly when compared with more extensively studied symptoms such as motor decline or depression. It also highlights a structural gap in the field: although fatigue is widely reported as one of the most disabling non-motor symptoms, it remains under-investigated as a primary therapeutic target.

Figure 2.1. PRISMA Flow Diagram of the study selection process (adapted from Page et al., 2021).



1 Figure 2.1. PRISMA Flow Diagram

2.3.2 Risk of Bias Assessment

Methodological quality was evaluated using the Cochrane Risk of Bias 2 (RoB2) tool (Sterne et al., 2019). Two studies (Kluger et al., 2016; Kong et al., 2018) were rated at overall low risk of bias across all domains. The remaining three trials (Abasi et al., 2020; Ribas et al., 2017; Wu et al., 2021) were rated as having some concerns, primarily relating to deviations from intended interventions and outcome measurement. These issues largely reflected the practical challenges of blinding in behavioural and exercise-based interventions and the reliance on self-reported fatigue measures. A summary of risk of bias judgements is presented in Table 2.1, with full domain-level assessments provided in Appendix 2.C.

Risk of bias assessments for the included trials across the five domains of the RoB2 tool, with overall ratings.

0-1 Table 2.1. Risk of Bias Summary Table

Study	Randomisation (D1)	Deviations (D2)	Missing Data (D3)	Measurement (D4)	Reporting (D5)	Overall Risk
Kluger et al. (2016)	Low	Low	Low	Low	Low	Low
Kong et al. (2018)	Low	Low	Low	Low	Low	Low
Abasi et al. (2020)	Some concerns	Some concerns	Low	Some concerns	Low	Some concerns
Ribas et al. (2017)	Some concerns	Some concerns	Low	Some concerns	Low	Some concerns

Wu et al. (2021)	Some concerns	Some concerns	Low	Some concerns	Low	Some concerns

Legend: Domains (D1–D5) correspond to the RoB2 tool (Sterne et al., 2019).

2.3.3 Study Size

Sample sizes varied substantially across the five included trials. Abasi et al. (2020) enrolled 24 participants (12 per arm), while Wu et al. (2021) recruited 98 participants. The total number of participants across all trials was 270. The generally modest recruitment numbers reflect ongoing challenges in conducting fatigue-specific trials in Parkinson's disease populations.

2.3.4 Study Characteristics

The five included trials were conducted across diverse international settings: Taiwan, Iran, Singapore, Brazil, and the United States. Together they enrolled 270 participants, with a mean age of 64.7 years and a near-equal sex distribution (48.6% male).

Fatigue outcomes were assessed using four different instruments: the Modified Fatigue Impact Scale (MFIS), the Fatigue Severity Scale (FSS and its Brazilian version), and the Multidimensional Fatigue Inventory (MFI). This variation in outcome measurement necessitated the use of standardised mean differences in the meta-analysis.

Diagnostic criteria were inconsistently reported. Two trials used the UK Parkinson's Disease Society Brain Bank criteria (Kluger et al., 2016; Ribas et al., 2017), one used NIH/NINDS criteria (Kong et al., 2018), and two reported Hoehn and Yahr staging without specifying formal diagnostic criteria (Wu et al., 2021; Abasi et al., 2020). Such variation may limit

comparability and generalisability across Parkinson's disease populations. Key study characteristics are summarised in Table 2.2.

Table 2.2. Summary of Included Study Characteristics

0-2 Table 2.2. Summary of Included Study Characteristics

Study	Design	Country	Sample Characteristics	Fatigue Measure	PD Diagnostic Criteria
Wu et al. (2021)	Parallel RCT	Taiwan	N = 98 (49 intervention; 49 comparator); mean age 65.1 years; 57.1% male; mean 5.3 years with PD	FSS	Hoehn and Yahr stage I–II (Hoehn and Yahr, 1967); no formal criteria specified
Abasi et al. (2020)	Parallel RCT	Iran	N = 24 (12 intervention; 12 comparator); mean age 63.1 years; 41.5% male; mean 3.5 years with PD	MFIS	Hoehn and Yahr stage 1–4 (Hoehn and Yahr, 1967); no formal diagnostic criteria
Kong et al. (2018)	Parallel RCT	Singapore	N = 34 (18 intervention; 16 comparator); mean age 64.6 years; 32.5% male; mean 5.7 years with PD	MFI	Gelb et al. (1999), NIH/NINDS
Ribas et al. (2017)	Parallel RCT	Brazil	N = 20 (10 intervention; 10 comparator); mean age 61 years; 40% male; mean 6.8 years with PD	FSS-BR	UK Brain Bank criteria (Gibb and Lees, 1988)
Kluger et al. (2016)	Parallel RCT	USA	N = 94 (47 intervention; 47 comparator); mean age 63.7	MFIS	UK Brain Bank criteria (Gibb and Lees, 1988)

			years; 59% male; PD duration not reported		

Legend: PD = Parkinson's disease; RCT = randomised controlled trial; FSS = Fatigue Severity Scale; MFIS = Modified Fatigue Impact Scale; MFI = Multidimensional Fatigue Inventory; FSS-BR = Brazilian adaptation of the Fatigue Severity Scale.

2.3.5 Intervention Characteristics

The included trials evaluated two broad categories of non-pharmacological interventions: exercise (three trials) and acupuncture (two trials). Exercise programmes comprised vestibular rehabilitation (Abasi et al., 2020), exergaming with Wii Fit (Ribas et al., 2017), and home-based aerobic and resistance training (Wu et al., 2021). Sessions typically lasted 30–60 minutes, delivered two to three times weekly for 8–12 weeks. Comparators ranged from no additional intervention to conventional physiotherapy.

The acupuncture studies (Kluger et al., 2016; Kong et al., 2018) applied Traditional Chinese Medicine acupoint selection, with interventions delivered twice weekly for 5–6 weeks. Both employed rigorous sham controls; either toothpick stimulation or non-penetrating devices; to reduce expectancy effects. Intervention characteristics are presented in Table 2.3**.**

Table 2.3. Characteristics of Interventions in Included Studies

Details of intervention type, duration, frequency, and comparator conditions.

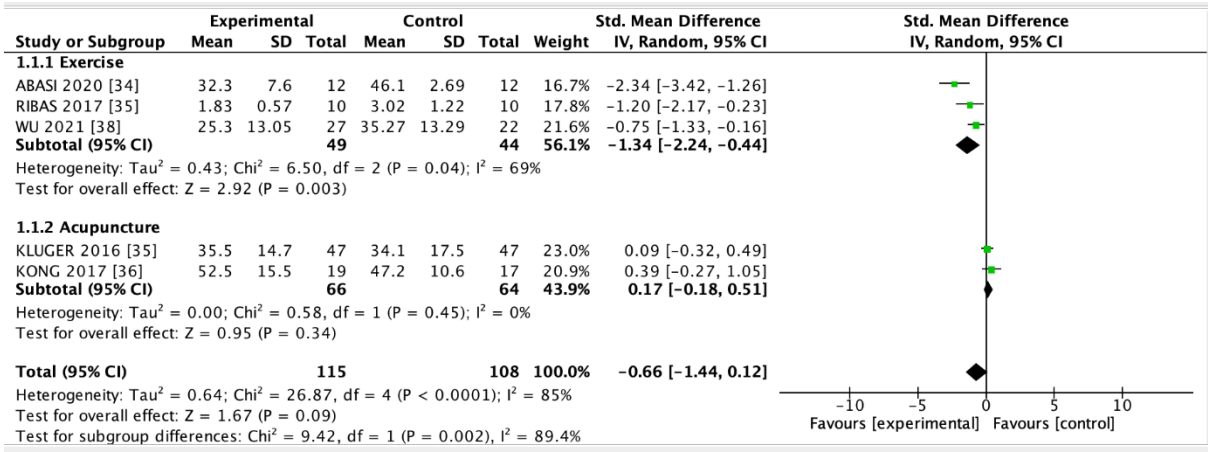
0-3Table 2.3. Characteristics of Interventions in Included Studies

Intervention Type	Study	Intervention Details	Comparator	Comparator Details
Home-based exercise	Wu et al. (2021)	30–50 min/session, 3×/week or 10–15 min/day; 150 min/week for 8 weeks. Supervised home-based aerobic and resistance training.	Usual care	Routine daily activities with no added exercise for 8 weeks.
Vestibular rehabilitation	Abasi et al. (2020)	24 sessions (60 min), 3×/week for 8 weeks. Vestibular rehab including gaze stabilisation, eye–head coordination, and balance tasks.	Conventional exercise	24 sessions (35 min), 3×/week. Warm-up, stretching, and axial rotation.
Exergaming (digital exercise)	Ribas et al. (2017)	Wii Fit (7 games), 30 min/session, 2×/week for 12 weeks (24 sessions). Supervised sessions using motion sensors.	Conventional physiotherapy	Stretching, resistance, and functional exercises. Same frequency/duration.
Real acupuncture	Kong et al. (2018)	30 min/session, 2×/week for 5 weeks (10 sessions). 11 acupoints per session. Sessions spaced ≥3 days apart.	Sham acupuncture	Non-invasive acupuncture mimicking, same schedule.

Real acupuncture	Kluger et al. (2016)	30 min/session, 2×/week for 6 weeks (12 sessions). Needling at 11 acupoints per participant protocol.	Sham acupuncture	Toothpick stimulation in guide tubes. Same frequency/duration.

2.4 Meta-Analysis

All five trials were synthesised in the quantitative analysis. Exercise interventions (Abasi et al., 2020; Ribas et al., 2017; Wu et al., 2021) demonstrated a statistically significant reduction in fatigue compared with controls (SMD = −1.34, 95% CI −2.24 to −0.44, p = 0.003). These pooled estimates combined studies that used different control conditions, including one usual-care comparator (Wu et al., 2021) and two active control comparators (Abasi et al., 2020; Ribas et al., 2017). Given the small number of available exercise trials (n = 3), stratification by comparator type was not feasible without producing unstable subgroup estimates. Substantial heterogeneity was observed (I^2 = 69%), which likely reflects variation in comparator type as well as differences in intervention modality, delivery format, and adherence monitoring across trials. By contrast, acupuncture interventions (Kluger et al., 2016; Kong et al., 2018) did not produce a significant pooled effect (SMD = 0.17, 95% CI −0.13 to 0.51, p = 0.26). Pooled estimates are shown in Figure 2.2. (forest plot)**.**



2 Figure 2.2. Forest Plot of Pooled Effects on Fatigue

Legend: Pooled estimates expressed as standardised mean differences (SMD) using a random-effects model.

2.4.1 Secondary Outcomes

Secondary outcomes were variably assessed across trials and demonstrated heterogeneous patterns of change (Table 2.4). While several studies reported statistically significant within-group improvements in quality of life, mood, motor function, or sleep, between-group differences were frequently absent or dependent on adherence thresholds.

Quality of Life

Quality of life was assessed using Parkinson's Disease Questionnaire measures in three trials.

In Wu et al. (2021)**,** participants achieving ≥150 minutes of exercise per week demonstrated significant improvements in PDQ-8 scores at both 4 and 8 weeks compared with controls after adjustment using a Generalised Estimating Equation model ($p < 0.05$). Improvements were adherence-dependent and were not uniformly observed across all exercise thresholds.

In contrast, Ribas et al. (2017) reported no significant group or time-by-group effects for PDQ-39 domains despite improvements in balance and fatigue following 12 weeks of exergaming. Quality of life gains were therefore not sustained nor statistically superior to control.

Similarly, in Kluger et al. (2016), both real and sham acupuncture groups showed significant within-group improvements in PDQ-39 scores at 6 weeks; however, no significant between-group differences were detected on ANCOVA analysis ($p = 0.61$).

Overall, improvements in quality of life were either adherence-sensitive or occurred equally in intervention and control groups, limiting conclusions regarding intervention-specific effects.

Mood and Psychological Outcomes

Psychological outcomes were assessed inconsistently and with non-Parkinson's-specific tools.

In Wu et al. (2021), significant improvements were observed in Geriatric Depression Scale scores among participants achieving ≥120 or ≥150 minutes per week of exercise ($p < 0.05$). However, Hospital Anxiety Scale scores did not differ significantly between groups after adjustment.

In Kluger et al. (2016), both real and sham acupuncture groups demonstrated significant within-group reductions in HADS depression and anxiety subscales; however, no significant between-group differences were identified.

In Kong et al. (2018), baseline GDS scores were comparable between groups and no significant differential changes were observed following acupuncture versus sham treatment.

Importantly, none of the included trials utilised Parkinson's Anxiety Scale or GDS-15 versions validated specifically for Parkinson's populations, limiting interpretability of mood outcomes.

Sleep Outcomes

Sleep was examined in two acupuncture trials and one exercise trial.

In Wu et al. (2021), PSQI scores improved significantly in participants achieving ≥150 minutes per week compared with controls at 8 weeks ($p < 0.05$), although improvements were not observed consistently at lower exercise thresholds.

In Kluger et al. (2016), Epworth Sleepiness Scale scores improved within both real and sham groups, but no significant between-group differences were detected.

Sleep outcomes therefore appeared responsive to participation but not uniquely attributable to the experimental intervention.

Functional and Motor Outcomes

Functional measures demonstrated more consistent improvements.

In Abasi et al. (2020), vestibular rehabilitation produced significant improvements in total Functional Independence Measure scores and motor subscale scores compared with controls ($p < 0.001$), although cognitive FIM scores did not significantly differ between groups.

In Wu et al. (2021), significant improvements were observed in UPDRS Parts II and III among participants achieving ≥150 minutes per week ($p < 0.05$).

In Ribas et al. (2017)**,** balance improved significantly following 12 weeks of exergaming ($p = 0.043$), but benefits were not maintained at 60-day follow-up.

These findings suggest that motor and functional domains may be more responsive to exercise-based interventions than broader psychosocial outcomes.

Summary of secondary outcomes assessed across trials, including quality of life, sleep, mood, and functional measures.

0-4 Table 2.4. Secondary Outcomes Reported in Included Studies

Study	Secondary Outcomes Assessed	Measurement Tools	Between-Group Findings
Wu et al. (2021)	Quality of life, mood, motor function, sleep	PDQ-8; GDS; UPDRS II–III; PSQI; HAS	Significant improvements in PDQ-8, GDS, UPDRS II–III and PSQI in participants achieving ≥150 min/week compared with controls; anxiety not significantly different. Effects adherence-dependent.
Abasi et al. (2020)	Activities of daily living	FIM (total, motor, cognitive)	Significant improvements in total and motor FIM scores versus control; no significant difference in cognitive FIM.
Ribas et al. (2017)	Quality of life, balance, functional capacity	PDQ-39; Berg Balance Scale; 6MWT	Significant improvements in balance and fatigue post-intervention; no significant group effects for PDQ-39; benefits not sustained at follow-up.
Kong et al. (2018)	Fatigue total score, motor function	MFI; UPDRS Motor	Both real and sham acupuncture improved fatigue; no significant between-group differences using ANCOVA.
Kluger et al. (2016)	Quality of life, mood, sleep, apathy	PDQ-39; HADS; ESS; AES	Significant within-group improvements in both real and sham groups; no significant between-group differences across primary and secondary outcomes.

2.4.2 Summary of findings (SoF) and certainty of evidence (GRADE)

We used GRADE to rate the certainty of evidence for outcomes prioritised a priori (fatigue severity, quality of life, sleep quality, and adverse events). Table 2.5 summarises pooled effects and certainty ratings; detailed evidence profiles by outcome and comparison are

provided in Appendix 2.D. The SoF table highlights that exercise programmes are associated with a reduction in fatigue versus controls (low-certainty evidence due to heterogeneity and risk of bias), whereas acupuncture shows little to no effect versus sham (moderate-certainty, downgraded for imprecision

Table 2.5. Summary of findings (SoF) — Non-pharmacological interventions for PD-related fatigue

0-5 Table 2.5. Summary of findings (SoF) — Non-pharmacological interventions for PD-related fatigue

Population	Intervention	Comparator	Outcome (time point)	Effect (95% CI)	Certainty (GRADE) / Key reasons
Adults with idiopathic PD in RCTs	Exercise-based programmes (vestibular rehab; exergaming; home-based aerobic/resistance)	Usual care / conventional physiotherapy / minimal intervention	Fatigue severity (post-intervention)	SMD −1.34 (−2.24 to −0.44) — pooled from 3 trials (Abasi; Ribas; Wu), total N=142	LOW — Downgraded for risk of bias (all 3 trials "some concerns") and inconsistency ($I^2 \approx 89\%$); imprecision noted.
Adults with PD in sham-controlled RCTs	Acupuncture (10–12 sessions over 5–6 weeks)	Credible sham acupuncture (non-penetrating / toothpick)	Fatigue severity (post-intervention)	SMD 0.17 (−0.13 to 0.51) — pooled from 2 trials (Kluger n=94 [47;47]; Kong n=40 [20;20]), total N=134	MODERATE — Downgraded for imprecision (CI spans small benefit to small harm); low RoB due to credible shams.
Adults with PD in RCTs	Exercise-based programmes	Usual care / active control	Quality of life (PDQ) — post-intervention	No pooled estimate; narrative: no clear between-group effect	VERY LOW — Imprecision, inconsistency of instruments/reporting, and indirectness (QoL distal to fatigue target).
Adults with PD in RCTs	Exercise-based programmes	Usual care / active control	Sleep quality (PSQI) — post-intervention	No pooled estimate; narrative: negligible change	VERY LOW — Single small study reporting PSQI; indirectness and imprecision.
Adults with PD in RCTs	Exercise or acupuncture	Usual care / sham	Adverse events (AEs)	Infrequently and inconsistently reported; no serious AEs attributed	VERY LOW — Sparse/unsystematic AE capture; imprecision.

SMD = standardised mean difference. Different fatigue scales were used (MFIS, FSS, MFI); SMDs were used for pooling. Certainty labels follow GRADE (High→Moderate→Low→Very low). Total N for acupuncture reflects Kong et al. = 40 (20 vs 20) and Kluger et al. = 94 (47 vs 47

2.5 Discussion

Previous work has primarily focused on pharmacological treatments (Elbers et al., 2015) or on broader narrative reviews of fatigue management across neurological conditions, where Parkinson's disease was considered alongside other diagnoses without PD-specific synthesis (Khan, Amatya and Galea, 2018). By narrowing the scope to RCTs explicitly targeting fatigue in PD, this chapter provides a condition-specific evaluation of the evidence base.

2.5.1 Exercise-based interventions: promise and limitations

Among the interventions evaluated, exercise-based programmes; particularly those incorporating balance or whole-body activity; demonstrated the greatest potential for reducing fatigue severity. This finding is consistent with evidence from MS, where exercise is recognised as a first-line strategy for fatigue management (Motl et al., 2017). However, substantial heterogeneity ($I^2 = 89\%$) in the pooled estimate limits certainty. Contributing factors include wide variation in exercise modality (from vestibular rehabilitation to exergaming), differences in intervention intensity and adherence monitoring, and inconsistency in comparator conditions. While the use of a random-effects model accounted for some variation, the pooled effect must be interpreted with caution. These findings highlight both the promise of exercise and the need for greater methodological standardisation to establish reproducibility and clinical applicability.

Interpreting these findings using GRADE, the exercise estimate is low-certainty (downgraded for risk of bias and inconsistency), while the moderate-certainty acupuncture estimate suggests little or no benefit over sham (see Table 2.5 and Appendix 2.D).

2.5.2 Secondary outcomes: underexplored domains

Beyond fatigue, secondary outcomes such as quality of life, sleep, and psychological wellbeing were inconsistently measured and rarely improved. Importantly, none of the included studies employed validated Parkinson's-specific scales such as the Parkinson Anxiety Scale (PAS) (Leentjens et al., 2014) or the Geriatric Depression Scale-15 (Vinkers et al., 2004). Where mood was assessed, trials most often used generic depression scales (for example the Beck Depression Inventory), and these measures were usually included as secondary outcomes rather than primary endpoints (Schrag et al., 2007; Goodarzi et al., 2016; Wang et al., 2021). This omission is problematic, as fatigue in PD is closely interwoven with mood, sleep, and broader wellbeing (Herlofson and Kluger, 2017). The lack of standardised, disease-specific tools restricts the interpretability of secondary findings and represents a missed opportunity to capture patient-centred outcomes such as coping ability or fatigue self-efficacy.

2.5.3 Conceptual framing: a biopsychosocial and transdiagnostic model

Findings from this review support the view that fatigue in PD cannot be explained by motor impairment alone but is instead the product of overlapping neurobiological and psychosocial mechanisms. The convergence of evidence across neurodegenerative conditions strengthens the case for a biopsychosocial model. Shared mechanisms; including basal ganglia–cortical dysfunction, dopaminergic and serotonergic imbalance, hypothalamic–pituitary–adrenal (HPA) axis dysregulation, neuroinflammation, and autonomic imbalance; have been

implicated in PD, MS, motor neurone disease (MND), and Huntington's disease (Jellinger, 2010; Gan et al., 2018; Mahad, Trapp and Lassmann, 2015). Neuroimaging studies further suggest that altered functional connectivity of frontal, limbic and striatal networks — including reduced coupling within fronto-striatal and fronto-limbic circuits — is associated with fatigue across neurological conditions and in Parkinson's disease specifically (Tessitore et al., 2016; Hou et al., 2022; Prell, 2018; Tessitore, Cirillo & De Micco, 2019). These commonalities provide theoretical justification for adapting interventions that are effective in other conditions, such as exercise, cognitive behavioural therapy (CBT), and energy conservation, for use in Parkinson's disease.

2.5.4 CBT as an underexplored but theoretically robust option

The lack of trials evaluating CBT for fatigue in PD is a striking omission. CBT has shown large effect sizes in improving depression and anxiety in PwP (Alnajjar et al., 2023) and is well established in MS fatigue management, where it acts through mechanisms such as enhancing sleep hygiene, reducing unhelpful fatigue beliefs, and promoting behavioural activation (Knoop, van Kessel and Moss-Morris, 2012). Given the multidimensional nature of fatigue in PD, CBT represents a promising but under-investigated strategy that could complement exercise-based approaches by addressing emotional, cognitive, and behavioural dimensions of fatigue. Future research should prioritise this avenue.

2.5.5 Methodological strengths and limitations of the evidence base

The strength of this review lies in its exclusive inclusion of RCTs and rigorous adherence to PRISMA guidelines, reducing the risk of bias in evidence synthesis. However, the evidence base itself remains limited. Only five trials were eligible, with modest sample sizes ranging from 20 to 98 participants, and few studies employed validated PD-specific outcome measures. Diagnostic criteria varied across studies, with some relying only on Hoehn and Yahr staging rather than established frameworks (Hoehn and Yahr, 1967; Gibb and Lees, 1988; Gelb, Oliver and Gilman, 1999). This inconsistency introduces further heterogeneity and undermines comparability.

The methodological limitations of primary studies extend beyond sample size. Blinding is inherently difficult in exercise or behavioural interventions, leading to risks of performance and detection bias (Boutron et al., 2007). To improve transparency, the CONSORT extension for non-pharmacologic treatments recommends detailed reporting of intervention content, provider expertise, and adherence strategies (Boutron et al., 2008), while the TIDieR checklist provides structured guidance for intervention description and replication (Hoffmann et al., 2014). However, few included trials adhered to these recommendations, limiting confidence in reproducibility.

The small number and heterogeneity of PD trials limit confident recommendations. In contrast, fatigue management interventions in multiple sclerosis have been evaluated across numerous randomised controlled trials and synthesised in systematic reviews, including structured cognitive behavioural and energy conservation programmes (Khan, Amatya and Galea, 2014; Asano and Finlayson, 2014; Thomas et al., 2013); Chapter 3 therefore examines the structural reasons for MS's dominance (trial networks, measurement conventions,

historical funding/priorities) and extracts transferable components to inform PD-specific intervention design.

2.6 Implications for future trials

Future trials should prioritise fatigue as a primary endpoint and be adequately powered to detect clinically meaningful change. Transparent reporting consistent with CONSORT extensions for non-pharmacological trials is essential to enhance reproducibility and reduce performance and detection bias. Standardisation of fatigue measurement through agreement on a Parkinson's-specific core outcome set would reduce heterogeneity and strengthen comparability across studies. Incorporating feasibility work and explicit programme theory, consistent with MRC guidance for complex interventions, will be critical before definitive evaluation.

2.6.1 Towards multimodal, co-designed interventions

Fatigue in Parkinson's disease reflects interacting motor, cognitive, emotional, and behavioural processes. The limited impact of unimodal interventions suggests that integrated approaches combining physical training, behavioural strategies, and psychological components may better address this multidimensional profile. Co-design with people with Parkinson's disease is particularly important given the variability in fatigue presentation and coping strategies. Multimodal programmes should therefore be theoretically informed, tailored, and designed with explicit fidelity and engagement plans.

2.7 Conclusion

This systematic review and meta-analysis demonstrates that exercise-based interventions produce modest short-term reductions in fatigue in Parkinson's disease, although certainty of evidence is low due to inconsistency and imprecision. Evidence for acupuncture shows no clear superiority over sham, and other non-pharmacological approaches remain under-evaluated. Secondary outcomes, including quality of life and sleep, show variable and adherence-dependent effects.

Overall, the current evidence base is narrow and methodologically heterogeneous, limiting definitive clinical recommendations. These findings justify further development of theory-informed, multimodal interventions and provide the rationale for the subsequent scoping review and pilot work presented in later chapters.

Chapter 3: Scoping Review of Fatigue Management in Neurodegenerative Diseases

This chapter presents a scoping review of non-pharmacological interventions for fatigue across neurodegenerative diseases. Building on the systematic review in Chapter Two, which revealed limited evidence specific to Parkinson's disease, this broader review was undertaken to map the wider landscape of fatigue management strategies in related conditions. The chapter begins with the methodological framework, including search strategy, eligibility criteria, and data charting. It then synthesises findings from a diverse body of literature, encompassing exercise, psychological, educational, and complementary and lifestyle approaches. The evidence is appraised in terms of scope, quality, and transferability, with particular attention to interventions that may be adapted for Parkinson's disease.

Protocol: Scoping review registered on the Open Science Framework (OSF; DOI: 10.17605/OSF.IO/MJEYP; osf.io/r38sh).

3.1 Introduction

Neurological disorders affect a substantial proportion of the global population and are consistently associated with high levels of disability. Among the wide spectrum of symptoms, fatigue emerges as one of the most common and debilitating. Its prevalence varies considerably across conditions, with estimates ranging from 37% to 78% in MS and 33% to 90% in PD (Siciliano et al., 2018; Lin et al., 2021). Fatigue is not only pervasive but also functionally disabling, reducing participation in daily life and undermining quality of life. Given its clinical relevance, fatigue requires nuanced approaches to assessment and management across different neurological conditions.

Chapter Two systematically reviewed fatigue management interventions in Parkinson's disease but found limited evidence, with few intervention types tested and small, heterogeneous trials. To address this paucity, the present chapter broadens the scope to a scoping review of non-pharmacological interventions across neurodegenerative conditions. This wider mapping allows insights from conditions such as multiple sclerosis, Huntington's disease, and amyotrophic lateral sclerosis to be considered for their potential transferability to Parkinson's disease, while also identifying shared gaps in evidence and directions for future research. The objective of this scoping review is not to estimate pooled effects, but to map the breadth of non-pharmacological fatigue interventions tested in neurodegenerative conditions other than PD, and to extract candidate components, delivery features, engagement/acceptability considerations, and measurement approaches that are potentially transferable to PD. Findings are intended to complement the PD-specific synthesis in Chapter 2 and to inform specification of the ReFresh intervention and its evaluation plan in Chapter 4.

This scoping review synthesised evidence from 27 studies published between 2006 and 2025 examining non-pharmacological interventions for fatigue in progressive neurodegenerative diseases other than dementias. The included evidence comprised systematic reviews and

meta-analyses, randomised controlled trials (RCTs), non-randomised controlled trials (NRCTs), and uncontrolled pre–post intervention studies. In line with the eligibility criteria, only interventional studies evaluating fatigue outcomes were included; observational studies were excluded.

3.1.1 Understanding Fatigue

Fatigue in neurological disorders is typically classified into central and peripheral mechanisms. Central fatigue originates in the central nervous system, where disease processes such as demyelination in MS or dopaminergic degeneration in PD disrupt neural pathways involved in sustaining effort. Peripheral fatigue arises within the muscles themselves, often linked to impaired energy metabolism or neuromuscular dysfunction (Davis & Walsh, 2010).

While these broad categories apply across conditions, the mechanisms of fatigue vary according to disease pathology. In MS, inflammatory activity, demyelination, and disrupted nerve conduction are thought to contribute strongly to central fatigue. By contrast, in PD, basal ganglia dysfunction, dopaminergic deficits, and fluctuations in motor performance play a more prominent role, with cognitive fatigue also emerging as a key driver. These mechanistic differences are important when considering interventions: for example, psychological and behavioural strategies such as CBT, education-based fatigue management, and structured exercise programmes may be particularly effective in MS, where coping strategies and reconditioning can counter central mechanisms. In PD, however, adaptations that integrate both motor and cognitive elements are likely to be required, since purely

physical interventions may not address the dopaminergic and cognitive contributors to fatigue.

In other neurodegenerative disorders, such as amyotrophic lateral sclerosis (ALS) or Huntington's disease (HD), fatigue may result from different combinations of muscle weakness, motor neuron loss, or progressive cognitive demands. These distinctions are important when considering intervention design, as both mechanisms of action and potential for benefit differ between conditions.

Table 3.1 summarises the principal arguments for and against adapting non-pharmacological fatigue interventions across different neurodegenerative conditions. The table draws on systematic and scoping evidence (Hulme et al., 2018; Walker et al., 2019), mechanistic accounts of central fatigue (Morris et al., 2015; Passaro et al., 2021) and condition-specific trial literature (Khan et al., 2014; Pazzaglia et al., 2020; Folkerts et al., 2023), together with exemplar implementation studies of home/VR delivery (Standen et al., 2017; Threapleton et al., 2018). Where conceptual cells are stated without a single trial citation this reflects broad consensus in the reviews cited; the following text expands these points and cites additional condition-specific measurement and trial literature.

6 Table 3.1: Arguments for and against generalisability of non-pharmacological fatigue interventions across neurodegenerative diseases

Aspect	Arguments supporting generalisability	Arguments against generalisability
Psychological responses to fatigue	Common behavioural and cognitive patterns (activity-avoidance, unhelpful beliefs, low self-efficacy) appear across long-term conditions and are amenable to psychological/behavioural approaches (Hulme et al., 2018; Walker et al., 2019).	Neurocognitive differences (cognitive decline, apathy) and disease-specific neuroinflammatory pathways may limit response to psychological interventions in some diagnoses (Morris et al., 2015; Walker et al., 2019).
Exercise-based benefits	Exercise and structured physical programmes show benefit for function and some fatigue outcomes across neurological groups (Folkerts et al., 2023; Langeskov-Christensen et al., 2024); disease-specific VR/exercise trials also demonstrate modality-specific gains (Pazzaglia et al., 2020).	Motor features (tremor, dyskinesia, progressive weakness) and autonomic/respiratory comorbidity constrain feasibility and dosing of exercise interventions across diagnoses (Pazzaglia et al., 2020; Khan et al., 2014).
Multidisciplinary approaches	Combining physical, cognitive and occupational elements targets multiple fatigue mechanisms and therefore has potential cross-condition value (Hulme et al., 2018; Khan et al., 2014).	Resource intensity, specialist skill requirements and the need for diagnosis-specific tailoring limit

		simple one-size-fits-all translation (Standen et al., 2017; Threapleton et al., 2018).
Measurement and outcomes	Many fatigue constructs (severity, impact, self-efficacy) are conceptually comparable, and several validated scales exist that permit cross-study comparison (Whitehead, 2009; Amtmann et al., 2012).	Heterogeneity in outcome selection, timing and psychometric evidence across conditions complicates pooling and interpretation (Whitehead, 2009; Amtmann et al., 2012).
Implementation and accessibility	Digital and home-based delivery (including low-cost VR) can increase reach and acceptability when feasible (Standen et al., 2017; Threapleton et al., 2018); scoping reviews show scalable delivery formats are being trialled across long-term conditions (Hulme et al., 2018).	Digital literacy, sensory or cognitive impairments, and unequal access to support services create differential engagement risks across diagnostic groups (Standen et al., 2017; Threapleton et al., 2018).

3.1.2 Measuring Fatigue

Capturing fatigue reliably remains challenging because of its multidimensional nature. While objective tests such as muscle endurance assessments provide information on physical capacity, they fail to encompass the broader cognitive and emotional dimensions of fatigue that are particularly relevant in neurodegenerative conditions. Consequently, subjective self-report tools remain the most widely used.

~~Across the studies included in this scoping review, the Modified Fatigue Impact Scale (MFIS) (Fisk et al.,1994) and Fatigue Severity Scale (FSS) (Krupp et al.,1989) were the most frequently applied, reflecting their broad uptake in both MS and PD populations. The Chalder Fatigue Scale (CFS) (Chalder et al.,1993) was used less commonly, but it offered a general measure of severity that has been adapted in some mixed-neurological samples. Importantly, the choice of tool often varied by condition: MFIS was more commonly used in MS studies, given its detailed subscales capturing cognitive and psychosocial impact, whereas FSS was frequently employed in PD trials because of its brevity and ease of administration.~~

Despite this variety, concerns persist regarding sensitivity, specificity, and responsiveness to change. For example, the MFIS is comprehensive but can be burdensome in populations with cognitive impairment, while the FSS has been criticised for floor and ceiling effects in milder disease groups. Heterogeneity in measurement approaches complicates direct comparison across conditions and interventions, limiting opportunities for pooled synthesis.

From a research perspective, inconsistency in outcome measurement represents a key barrier to synthesising findings across neurodegenerative conditions (Whitehead, 2009; Amtmann et al., 2012; Hulme et al., 2018; Walker et al., 2019). From a clinical perspective, tools that

capture not only fatigue severity but also the lived impact on activity and participation are particularly valuable in guiding intervention design and evaluation (Whitehead, 2009; Amtmann et al., 2012; Hulme et al., 2018). For example, the MFIS derives from the Fatigue Impact Scale (Fisk et al., 1994) and the FSS was originally developed and validated by Krupp and colleagues (Krupp et al., 1989); comparative psychometric work further examines differences in dimensionality and respondent burden between these instruments (Amtmann et al., 2012; Whitehead, 2009).

3.1.3 The Role of Non-Pharmacological Interventions

Pharmacological treatments for fatigue remain limited, with modest benefits and frequent adverse effects (MacAllister & Krupp, 2005). Consequently, non-pharmacological interventions have become central to fatigue management research across neurodegenerative conditions. These interventions include structured exercise programmes, cognitive behavioural therapy, psychoeducation, and mind–body approaches such as yoga and mindfulness (Khan & Amatya, 2018; Moss-Morris et al., 2012; Branas et al., 2000).

The distribution of intervention types varies between conditions. In multiple sclerosis, structured exercise and energy management programmes have been extensively evaluated in randomised trials (e.g., Heine et al., 2015; Moss-Morris et al., 2012). In Parkinson's disease, the literature remains smaller and has included exercise-based trials alongside exploratory cognitive and behavioural approaches (Elbers et al., 2015). By contrast, fatigue interventions in amyotrophic lateral sclerosis and Huntington's disease are limited to small-scale feasibility or observational studies, with few condition-specific trials (Khan & Amatya, 2018).

In this scoping review, the focus is not on evaluating effectiveness, which is addressed in the systematic review, but rather on mapping the diversity of approaches and highlighting where evidence remains sparse. This perspective provides the necessary foundation for identifying gaps, assessing transferability between conditions, and informing priorities for future research.

3.1.4 Objective of This Review

This scoping review aimed to systematically map and synthesise quantitative evidence on non-pharmacological interventions for managing fatigue in progressive neurodegenerative diseases. By excluding dementia populations due to distinct cognitive and intervention considerations, the review sought to identify intervention types, reported outcomes, methodological limitations, and key gaps in the evidence base to inform future intervention development and adaptation.

3.2 Methods

3.2.1 Scoping Review Approach

A scoping review was conducted to comprehensively map the evidence on non-pharmacological interventions for fatigue management in neurological disorders without limiting the analysis to specific study designs. This approach enabled a broad exploration of available evidence and aligned with the review's objectives. A scoping review was selected rather than a systematic review because the primary aim was to chart the range and characteristics of interventions across multiple neurodegenerative conditions, rather than to evaluate effectiveness within a single disorder. Scoping reviews are particularly suited to

topics where evidence is heterogeneous, dispersed across different methodologies, and where knowledge gaps need to be identified (Munn et al., 2018).

3.2.2 Review Framework

The review adhered to the Joanna Briggs Institute (JBI) guidelines for conducting and reporting scoping reviews, with the completed checklist provided in Appendix 3.D. (Peters et al., 2020) and adhered to the PRISMA Extension for Scoping Reviews (PRISMA-ScR) checklist (Tricco et al., 2018). The PRISMA-ScR flow diagram (Figure 3.1) and checklist (Appendix 3.B) were utilised to ensure transparency and standardisation throughout the review process.

Registration

The review protocol was pre-registered with the Open Science Framework (OSF) to ensure methodological transparency (Alageel et al. 2024).

3.2.3 Search Strategy

A comprehensive search strategy was implemented in MEDLINE, Cochrane Library, CINAHL, AMED, and PsycINFO for records published from January 2006 onwards. The start date of January 2006 was selected to capture contemporary non-pharmacological intervention research and the more consistent use of validated fatigue outcome measures in neurological populations. Earlier studies were less standardised in intervention reporting and outcome measurement, limiting comparability with current practice. Searches were conducted up to 15 February 2025 to ensure currency prior to thesis submission. The updated search did not identify any additional eligible studies. In each database, a structured Boolean

string combined a fatigue concept with neurodegenerative diagnoses and a non-pharmacological intervention concept. An example summary string (MEDLINE/PubMed; adapted for database-specific subject headings and syntax) was:

(fatigue[MeSH] OR fatigue OR fatig* OR “fatigue management” OR “fatigue intervention”)

AND (Parkinson Disease[MeSH] OR Parkinson* OR Multiple Sclerosis[MeSH] OR “Huntington Disease” OR ataxia* OR “progressive supranuclear palsy” OR “multiple system atrophy” OR “amyotrophic lateral sclerosis” OR “motor neuron* disease*” OR “frontotemporal dementia”) AND (non-pharmacologic* OR nonpharmacologic* OR “occupational therap*” OR “physi* therap*” OR exercise OR “cognitive behavioral therap” OR CBT OR “self-management” OR education OR mindfulness OR acupuncture OR “light therap*”).

The strategy was tailored to each database (e.g., MeSH in MEDLINE; CINAHL Headings in CINAHL), with truncation and spelling variants applied consistently; no study-design filters were applied at the search stage. Reference lists of relevant reviews and included studies were also screened to identify additional records. Full, database-specific strategies are provided in Appendix 3.A and detailed search string provided in Appendix 3.C. The scoping review was intentionally performed after the systematic review (which used a database cut-off of 01 October 2024) to broaden the evidence base and to capture more recent, transferable intervention studies from other neurodegenerative conditions that could inform intervention adaptation (see Chapter 4). Where identical trials were identified in both reviews, they were handled according to each review’s pre-specified inclusion criteria and cross-referenced in the text.

3.2.4 Inclusion and Exclusion Criteria

Eligibility criteria were defined using the Population, Concept, and Context (PCC) framework recommended for scoping reviews (Peters et al. 2020; Peters et al. 2024). In keeping with scoping review methodology, both systematic reviews and primary empirical studies were eligible for inclusion in order to comprehensively map intervention approaches and reported components across levels of evidence. Table 3.2 provides a detailed summary of inclusion and exclusion criteria across the PCC domains.

Rationale for population scope

The review focused specifically on progressive neurodegenerative conditions because fatigue in these disorders is typically chronic, fluctuating, and closely linked to underlying neurological pathology rather than recovery trajectories. In conditions such as Parkinson's disease and multiple sclerosis, fatigue is recognised as a persistent and multifactorial symptom associated with neurobiological changes, disease progression, and reduced functional capacity (Friedman et al., 2007; Kluger et al., 2016). Restricting the population to progressive conditions therefore enhanced conceptual coherence and increased the relevance of transferable intervention components to Parkinson's disease, which is the primary focus of this thesis.

Inclusion Criteria:

- Systematic reviews, quantitative studies, or mixed-methods studies evaluating non-pharmacological interventions for fatigue, provided that fatigue-related quantitative data were extractable and the non-pharmacological effects could be isolated.

- Eligible interventions included behavioural and psychological approaches (e.g., cognitive behavioural therapy and motivational interviewing), education-based fatigue management programmes, exercise interventions (including aerobic, resistance, aquatic, yoga-based or multidisciplinary rehabilitation), light therapy, acupuncture, dietary interventions, and digitally delivered or telehealth fatigue management programmes.
- Studies presenting numerical data on fatigue as an outcome.
- Adult participants diagnosed with progressive neurodegenerative conditions, including PD, MS, motor neurone disease (MND), Huntington's disease (HD), ataxia, multiple system atrophy (MSA), and progressive supranuclear palsy (PSP).
- Studies published in English or Arabic from January 2006 onwards in peer-reviewed journals.

Exclusion Criteria:

- Qualitative studies.
- Studies solely focusing on pharmacological, surgical, herbal, or homeopathic interventions.
- Studies in populations with dementias (e.g., Alzheimer's disease, FTD). *Rationale:* the review focused on non-dementia neurodegenerative conditions; dementia trials typically require different intervention adaptations and outcome strategies (learning/memory supports), which would introduce substantial heterogeneity.

Search note: Dementia-related terms were included in the database search to maximise sensitivity; records involving dementia populations were excluded at title/abstract or full-text screening per protocol.

7 Table 3.2. Inclusion Criteria Based on PCC (Population, Concept, Context) Guidelines

Population	Include: Adults with Ataxia, Huntington's disease, Parkinson's disease, Motor neuron disease, Multiple system atrophy, Progressive supranuclear palsy, and Multiple sclerosis. Exclude: Patients with dementia
Concept	Non-pharmacological fatigue management interventions.The study had to include at least one measure of fatigue (quantitative) or explore the impact of the intervention on fatigue (qualitative).
Context	Any community or healthcare setting; hospitals, medical centres, rehabilitation centres, community-based settings, patient's homes, long-term care facilities. The interventions could be delivered in any modality e.g. face-to-face, telehealth, virtual. It could be delivered in groups or to individuals. It could be of any duration, intensity, and any length of follow-up. The interventions could be delivered by any professional, lay leader, or peers.

For clarity, study designs were classified into four categories: systematic reviews and meta-analyses; randomised controlled trials (RCTs); non-randomised controlled trials (NRCTs), defined as studies including a concurrent comparator but without random allocation; and uncontrolled pre–post intervention studies, in which outcomes were measured before and

after the intervention within a single group without a concurrent control. Studies described by authors as pilot or feasibility studies were classified according to their underlying design (e.g., pilot RCT or uncontrolled pre–post study) rather than treated as a separate methodological category.

3.2.5 Selection of Studies

Search results were exported into EndNote (Clarivate Analytics) for reference management and duplicate removal. Automated duplicate detection was followed by manual verification to ensure accuracy.

Title and abstract screening was conducted by the primary reviewer. Where eligibility was unclear, decisions were discussed with the supervisory team to ensure consistency with the inclusion criteria. The same procedure was applied during full-text assessment.

A three-step selection process was adopted:

- Title and Abstract Screening: Titles and abstracts were screened against the inclusion criteria.
- Full-Text Assessment: Potentially relevant full texts were retrieved for detailed eligibility evaluation.
- Resolution of Queries: Inclusion decisions were made through discussions with the review team to ensure consistency.

To prevent double counting, overlap between included systematic reviews and primary studies was assessed. Because this scoping review included both evidence syntheses and individual empirical studies, primary studies cited within included reviews were cross-

checked against the pool of eligible studies. Each primary study was included only once in the data charting process.

Where a systematic review was excluded, its reference list was screened to identify any potentially eligible primary studies not otherwise captured in the search. These were assessed independently against the inclusion criteria.

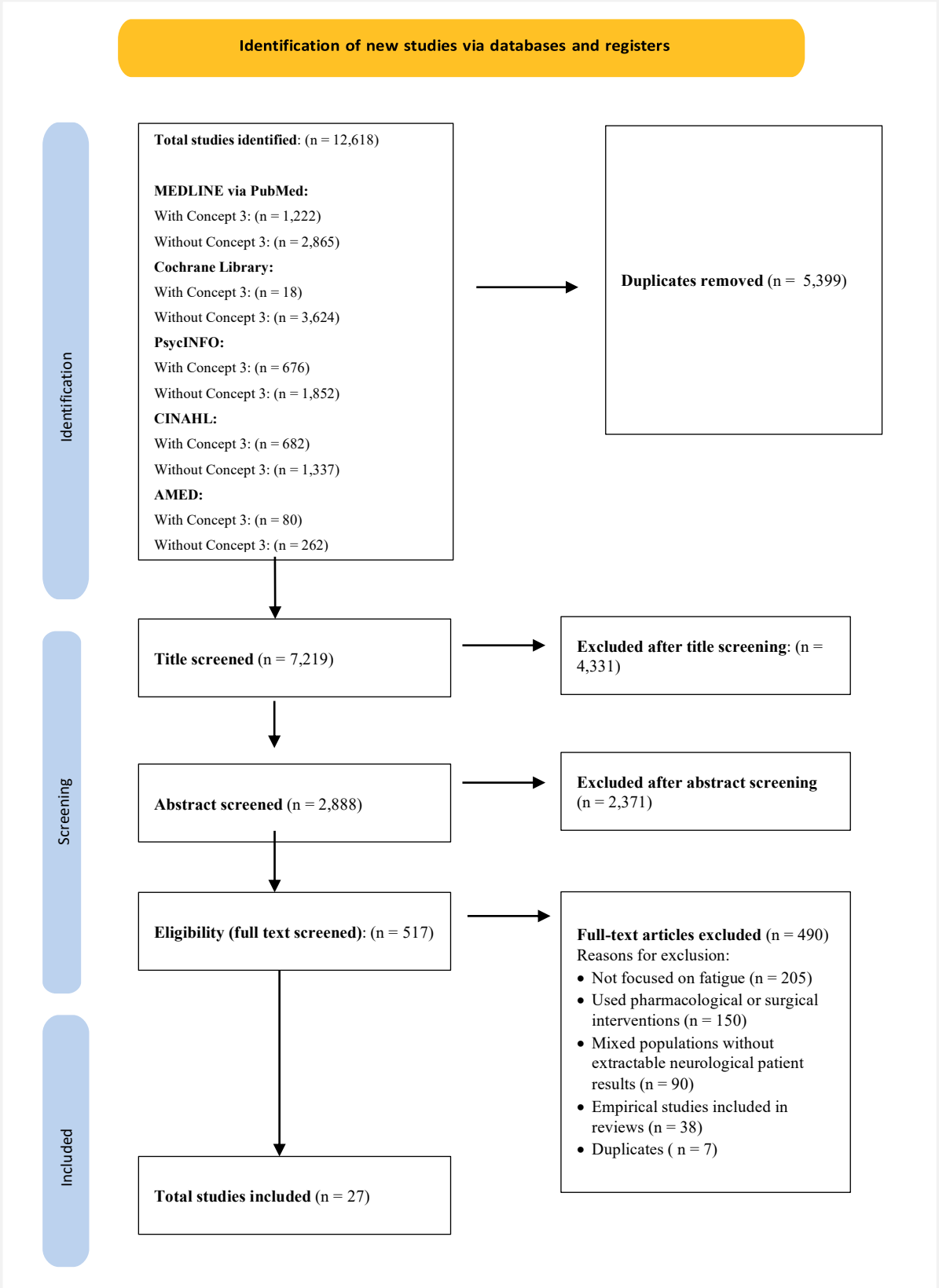
3.2.6 Data Extraction and Synthesis

A customised data extraction tool captured key study details, including:

- Study title, author(s), publication year, and design.
- Methodology, population characteristics, intervention details, and setting.
- Outcomes, key findings, conclusions, and limitations.

Quantitative data were summarised in tabular form, and a narrative synthesis approach was used to integrate findings. The results were organised by intervention type and evidence strength, starting with systematic reviews and meta-analyses, followed by RCTs and observational studies.

3.3 Results



3Figure 3.1. Flow diagram for searching and screening studies

The initial literature search identified 12,618 records across MEDLINE, Cochrane Library, CINAHL, AMED, and PsycINFO. After removal of 5,399 duplicates, 7,219 records remained for title screening. Of these, 4,331 were excluded as not relevant to the review topic, leaving 2,888 records for abstract screening. A further 2,371 records were excluded at this stage, resulting in 517 full-text articles retrieved for detailed assessment.

At full-text screening, 490 articles were excluded for the following reasons:

- Not focused on fatigue (n = 205)
- Used pharmacological or surgical interventions (n = 150)
- Mixed populations without extractable neurological patient data (n = 90)
- Empirical studies already included within systematic reviews (n = 38)
- Other reasons (protocols, duplicates, or unsuitable study design) (n = 7)

A total of 27 studies met the inclusion criteria, grouped as follows:

1. Systematic reviews and meta-analyses (n = 7)

   These syntheses covered between 9 and 113 primary studies per review (participant totals per review ~315 to ~6,909). Interventions spanned exercise modalities, cognitive-behavioural therapy/Internet-based Cognitive Behavioural Therapy (CBT/iCBT), education-based programmes, electrical stimulation, and mixed approaches. Where pooling was feasible, we report between-group post-treatment effects (standardised mean differences) and note statistically significant findings ($p < 0.05$).

2. Randomised controlled trials (RCTs, n = 16)

   Trials in MS (including RRMS) and PD evaluated CBT (with and without boosters), internet-delivered CBT, structured aerobic, resistance, aquatic and yoga-based exercise, individualised versus guideline-based exercise, multidisciplinary rehabilitation, bright-light therapy, acupuncture, and dietary interventions. Across these RCTs, approximately 1,100–1,235 participants were randomised/analysed in total.

3. Non-randomised controlled (NRCT) (n = 1)

   One non-randomised controlled– study (Pilates vs usual care), n=40.

4. Uncontrolled pre-post design (n=3)

   Three single-arm pre–post studies (motivational interviewing; aerobic cycling, MS TeleCoach). Sample sizes ranged from small pilots to n = 75, with fatigue assessed before and after the intervention.

These 27 studies represent the unit of inclusion for this scoping review. Seven were systematic reviews or meta-analyses synthesising substantially larger pools of primary trials. In this chapter, we report findings from both primary trials and synthesis-level studies, while maintaining 27 as the total number of included studies.

Fatigue outcomes were most commonly the MFIS and FSS, alongside other validated measures (e.g., Chalder Fatigue Scale, CIS-20R, FIS, FSMC).

Comprehensive details of the included studies are presented in Table 3.3, which

summarises both primary intervention studies and secondary evidence syntheses (systematic reviews and meta-analyses) identified in the scoping review. Reviews are included to provide contextual evidence regarding broader intervention effectiveness but were not treated as primary data sources in the narrative synthesis.

8 Table 3.3. Characteristics and findings of included studies on non-pharmacological fatigue management interventions in neurodegenerative diseases

#	Study reference	Study design	Pathology	Intervention(s) / comparator	Fatigue outcome(s)	Key findings
Systematic reviews & meta-analyses						
1	Wendebourg et al., 2024	Systematic review & meta-analysis (15 RCTs; n=1,473; MFIS outcomes from 9 RCTs; n=824)	MS	Education for fatigue management vs control	MFIS	Pooled analyses showed significant improvement with education interventions; heterogeneity across programs.
2	Wu et al., 2023	Systematic review (10 studies; n=315)	MS	Electrical stimulation vs sham	FSS, MFIS	Some improvement in fatigue; protocols heterogeneous; certainty limited.

3	Torres-Costoso et al., 2022	Network meta-analysis (58 RCTs; n=2,644)	MS	Exercise types vs control	Various validated self-reported fatigue questionnaires (results reported as SMD)	Combined exercise and resistance training significantly better than control (SMD ∼−1.5 and −1.15 respectively).
4	Moss-Morris et al., 2021	Included studies/participants: 34 trials; n≈2,434 (31 trials contributed to the meta-analysis)	MS	Exercise vs Behavioural vs Combined	Validated self-reported fatigue scales (results as SMD)	Exercise most effective; behavioural better than combined
5	Harrison et al., 2021	Network meta-analysis (113 studies; n=6,909)	MS	Balance exercises, non-balance, behavioural (incl./excl. CBT)	multiple validated self-report scales (reported as SMD)	Balance exercise outperformed other exercise/behavioural comparators; CBT outperformed energy conservation.

6	Heine et al., 2015	Cochrane review	MS	Exercise therapy (endurance, resistance, mixed)	Various (incl. MFIS/FSS)	Exercise therapy shows beneficial effects on fatigue; more well-reported, powered RCTs needed.
7	Phyo et al., 2018	Systematic review & meta-analysis (20 studies; n=1,249; 12 studies meta-analysed, n=745)	MS	Psychological interventions (incl. CBT, relaxation, mindfulness) vs inactive or active controls	Multiple validated fatigue scales	CBT reduced fatigue vs both inactive and active controls; heterogeneity noted.
Randomised controlled trials (RCTs)						
8	de Gier et al., 2024	RCT (n=103)	MS	CBT booster programme vs usual care after prior CBT	MFIS	No statistically significant between-group difference in fatigue outcomes at 1-year follow-up; CBT booster sessions provided

						no additional benefit beyond prior CBT.
9	Royer et al., 2024	RCT (2-arm; n=29 randomized, ~14% dropout)	MS	Individualized exercise vs Traditional guideline-based combined exercise (12 weeks, supervised)	FSS, MFIS	Fatigue (FSS, MFIS) decreased similarly in both groups (no between-group superiority); individualized training produced greater gains in VO_2peak and lower RPE at a given workload; strength gains similar.
10	Gay et al., 2024 (JNNP)	RCT (n=105; RRMS)	RRMS	CBT with 4 booster sessions vs standard care	MFIS	Statistically significant between-group reduction in fatigue in the CBT group compared with standard care at 12 months ($p < 0.01$).
11	Voggenberger et al., 2022	Sham-controlled RCT (n=26)	MS	Bright white light vs dim red light	FSS	No statistically significant between-group difference in fatigue severity measured using the FSS.

12	Moss-Morris et al., 2012	RCT (pilot) (n=40 randomized; 112 screened)	MS	Internet-based CBT (MS Invigor8) vs usual care	Fatigue (Chalder), MFIS (substudy)	Statistically significant between-group reduction in fatigue severity favouring internet-delivered CBT compared with usual care; the follow-up period was short.
13	van Kessel et al., 2008	RCT (n=72)	MS	CBT vs relaxation therapy/usual care	MFIS/Chalder	Statistically significant between-group reduction in fatigue in the CBT group compared with relaxation/usual care, with effects maintained at approximately 6-month follow-up.
14	Pöttgen et al., 2018	RCT (n=139)	MS	Self-guided online fatigue programme vs control	Chalder fatigue scale	Statistically significant between-group reduction in fatigue at 12 weeks for the ELEVEDIA intervention compared with wait-list control (Chalder Fatigue Scale; d = 0.53; p = 0.0007), with improvements maintained at 24 weeks.

15	Plow et al., 2019	RCT (n=208)	MS	Physical activity + fatigue self-management (FM+) vs physical activity only vs control	FIS	Statistically significant between-group improvement in fatigue for the combined fatigue management plus physical activity programme compared with the control group; no statistically significant difference between the combined programme and physical activity alone.
16	Rietberg et al., 2014	RCT (n=48)	MS	Multidisciplinary outpatient rehab vs nurse consultation	CIS-20R	No significant between-group differences in overall fatigue at 12 or 24 wks.
17	Khodaie et al., 2023	RCT (n=50)	MS (RRMS)	Acupuncture vs sham	FSS	Statistically significant between-group reduction in fatigue favouring true acupuncture compared with sham ($p < 0.05$); small sample size.

18	Chase et al., 2023	RCT (n=39)	MS	Low-fat diet vs wait-list	MFIS	Statistically significant between-group reduction in fatigue favouring the low-fat diet compared with wait-list control (mean difference −13.9; 95% CI −20.7 to −7.2).
19	Wahls et al., 2021	RCT (n=87)	RRMS	Swank diet vs Wahls elimination	MFIS, FSS	Significant within-group improvements; no between-group difference.
20	Kargarfard et al., 2012	RCT (n=32)	RRMS	Aquatic exercise vs control	MFIS	Statistically significant between-group improvement in fatigue favouring the aquatic exercise group compared with control over 4–8 weeks; small female-only sample.

21	Kluger et al., 2016	RCT (n=94)	PD	Acupuncture vs sham	MFIS	Both groups improved; no between-group difference.
22	Winward et al., 2012	Single-blinded RCT (n=39)	PD	12-wk community exercise vs control	FSS	No improvement in fatigue; adherence variable.
23	Karbandi et al., 2015	Randomised trial (n = 85 randomised; 57 analysed)	MS	Group-based yoga/stretching vs individual/home-based yoga/stretching (6 weeks; twice daily; 10 to 15 min)	MFIS	No significant between-group difference in fatigue at follow-up; within-group reduction over time reported in the individual arm; interpretation limited by lack of non-exercise control and high attrition.
Non-randomised controlled & uncontrolled pretest–posttest / feasibility						
24	Borji et al., 2018	Non-randomised uncontrolled pre-post; n=60)	MS	Motivational interviewing (5 sessions)	FIS	Significant reduction post-intervention; no long-term follow-up.

25	D'Hooghe et al., 2018	Prospective open-label (n=75)	MS	MS TeleCoach (12 wks)	FSMC	Total FSMC improved to wk 12 (p=0.009); uncontrolled, heterogeneous.
26	Miri et al., 2023	Non-randomised controlled pre–post study (n = 40)	MS	Pilates training vs non-randomised control	FIS	Statistically significant reduction in fatigue in the Pilates group compared with the control group following the 8-week intervention (FIS; $p < 0.001$).
27	Simmons et al., 2023	Preliminary single-arm study	MS	Aerobic cycling	MFIS	Within-group reduction in fatigue following the intervention; uncontrolled design with no long-term follow-up.

Abbreviations: CBT, Cognitive Behavioural Therapy; CIS-20R, Checklist Individual Strength, Revised; FIS, Fatigue Impact Scale; FSS, Fatigue Severity Scale; FSMC, Fatigue Scale for Motor and Cognitive Functions; iCBT, Internet-based Cognitive Behavioural Therapy; MFIS, Modified Fatigue Impact Scale; MS, Multiple Sclerosis; PD, Parkinson's Disease; RRMS, Relapsing-Remitting Multiple Sclerosis; RCT, Randomised Controlled Trial; SMD, Standardised Mean Difference; VO_2peak, Peak Oxygen Uptake; RPE, Rating of Perceived Exertion; n.s., not significant.

3.3.1 Study Focus and Populations

All 27 included studies evaluated fatigue outcomes, with the literature heavily dominated by multiple sclerosis cohorts. Interventions encompassed behavioural and psychological approaches (CBT, internet-delivered CBT, education and energy-conservation programmes), a range of exercise modalities (aerobic, resistance, balance, aquatic and multimodal programmes), and other non-pharmacological strategies including electrical stimulation, bright-light therapy, acupuncture and dietary modification. Twenty of the included records were primary intervention studies (16 RCTs; 4 non-randomised or pre–post designs). Fatigue was assessed using established self-report instruments, most frequently the Modified Fatigue Impact Scale (MFIS; used in 11 studies) and the Fatigue Severity Scale (FSS; used in 5 studies), with additional use of the Chalder Fatigue Scale, CIS-20R, FIS and FSMC.

Across populations, the evidence base was dominated by studies in MS, with only two small RCTs enrolling participants with Parkinson's disease. Within MS cohorts, samples most frequently involved individuals with relapsing–remitting MS (RRMS), although several studies also included progressive phenotypes. Levels of disability were generally mild to moderate, with most studies requiring participants to be ambulatory (for example, able to walk at least 100 metres) and reporting Expanded Disability Status Scale scores consistent with community mobility (Kurtzke, 1983). A subset of primary trials recruited participants based on predefined fatigue eligibility criteria (for example, scale-specific thresholds such as FSS ≥4, Chalder/CFS cut-offs, CIS-20R ≥35 or FSMC cut-points), whereas other studies enrolled unselected clinical cohorts and analysed fatigue as a planned outcome.

Demographically, participants were adults, most commonly in mid-adulthood, with women disproportionately represented, reflecting MS epidemiology (Walton et al., 2020). Disease duration varied across studies, and some explicitly excluded individuals with major psychiatric comorbidities or unstable neurological status. Sample sizes ranged from small pilot and feasibility cohorts to multicentre RCTs enrolling over 100 participants. Interventions were delivered in a range of settings, including outpatient clinics, community facilities, home-based or online platforms, and, in the case of aquatic exercise, swimming pools. Comparators included usual care, wait-list and attention/education controls, active comparators (for example relaxation therapy or alternative exercise modalities), and sham interventions including electrical stimulation, acupuncture and light therapy. A *sham control* is a placebo-like procedure that reproduces the non-specific aspects of the active intervention (appearance, contact, ritual and participant expectancy) while omitting the putative therapeutic element; sham controls are used to control for expectation and attention effects (Boutron et al., 2008; Howick et al., 2020). Examples from this review include dim red light used as the sham in a bright-light trial and superficial/sham acupuncture procedures (Voggenberger et al., 2022; Kluger et al., 2016). Follow-up durations varied from immediate post-treatment assessment to 12 months.

Taken together, the body of evidence primarily evaluates ambulatory adults with MS and mild to moderate disability, using fatigue-specific eligibility criteria and validated patient-reported outcomes. Evidence for Parkinson's disease populations remains very limited, restricted to two small RCTs.

3.3.2 Measurement Tools

Across the 19 primary intervention studies (RCTs and non-randomised designs), fatigue was assessed using six validated self-report instruments. The most frequently applied tool was the Modified Fatigue Impact Scale (MFIS), used in 11 studies. The MFIS is a 21-item instrument derived from the 40-item Fatigue Impact Scale and captures physical, cognitive, and psychosocial dimensions of fatigue impact (Fisk et al., 1994; Multiple Sclerosis Council for Clinical Practice Guidelines, 1998). In validation studies in multiple sclerosis, the MFIS demonstrated high internal consistency (Cronbach's $\alpha > 0.90$ for the total score) and good test–retest reliability (Fisk et al., 1994). Its multidimensional structure enables domain-specific analysis of fatigue impact, which has supported its widespread use in MS trials and intervention studies (Amtmann et al., 2012).

The Fatigue Severity Scale (FSS) was employed in five studies. The FSS is a 9-item unidimensional measure assessing the impact of fatigue on daily functioning (Krupp et al., 1989). It has demonstrated strong internal consistency (α typically reported between 0.88 and 0.95) and good test–retest reliability in neurological populations (Krupp et al., 1989). However, because it assesses global fatigue severity rather than distinct cognitive and physical domains, it does not allow domain-level differentiation. Comparative psychometric analyses have noted that while the FSS is practical and widely validated, it may be less sensitive to multidimensional change compared to instruments such as the MFIS (Amtmann et al., 2012).

Three studies used the Chalder Fatigue Questionnaire (CFQ; Chalder et al., 1993), an 11-item measure assessing physical and mental fatigue. The CFQ has demonstrated acceptable internal consistency (α generally >0.85) and has been widely used in behavioural intervention research, particularly in chronic fatigue and general medical populations (Chalder et al.,

1993; Whitehead, 2009). However, it was not developed specifically for neurological conditions and does not provide condition-specific validation for MS or Parkinson's disease populations.

The Fatigue Impact Scale (FIS), used in three studies, is the original 40-item instrument from which the MFIS was derived (Fisk et al., 1994). It assesses fatigue-related impact across physical, cognitive, and psychosocial domains and demonstrated high internal consistency and reliability in MS validation samples (Fisk et al., 1994). Its comprehensiveness provides breadth of measurement but is associated with greater respondent burden relative to shorter tools.

One study used the Checklist Individual Strength – Fatigue subscale (CIS-20R), a multidimensional fatigue instrument developed in chronic fatigue populations (Vercoulen et al., 1994; Beurskens et al., 2000). The CIS fatigue subscale has demonstrated good internal consistency and test–retest reliability, although it is a generic measure and not disease-specific to neurological populations.

Finally, one study applied the Fatigue Scale for Motor and Cognitive Functions (FSMC), a 20-item instrument developed specifically for MS that differentiates motor and cognitive fatigue (Penner et al., 2009). Validation studies reported high internal consistency for total and subscale scores and supported its ability to distinguish between cognitive and motor fatigue domains in MS cohorts (Penner et al., 2009).

Although all instruments demonstrate acceptable reliability within their development populations, differences in item number, dimensional structure, and conceptual focus (severity versus impact) limit direct comparability across studies. This heterogeneity is particularly notable given the limited representation of Parkinson's disease populations.

To demonstrate variability in fatigue measurement characteristics across studies, Table 3.4 summarises instrument frequency, item number, conceptual focus, dimensional structure, and validation context.

9 Table 3.4. Summary of Fatigue Measurement Tools Used in Included Studies

Tool	Studies (n)	Items (n)	Fatigue Construct	Structure	Developed / Initially Validated In
MFIS	11	21	Impact	Multidimensional (physical, cognitive, psychosocial)	MS
FSS	5	9	Severity	Unidimensional	MS / SLE
CFQ	3	11	Severity (physical + mental)	Bidimensional	General medical populations
FIS	3	40	Impact	Multidimensional	MS
CIS-20R (fatigue subscale)	1	8	Severity	Unidimensional	Chronic fatigue populations
FSMC	1	20	Motor vs Cognitive fatigue	Multidimensional	MS

As shown in Table 3.4, instruments varied substantially in length (8 to 40 items), dimensional structure (unidimensional versus multidimensional), and construct focus (severity versus impact). While the MFIS and FSS were most commonly used, their structural differences illustrate the absence of a unified measurement framework across neurodegenerative fatigue research. This variability complicates cross-study synthesis and underscores the need for greater consensus in outcome selection, particularly in under-represented conditions such as Parkinson's disease.

3.3.3 Intervention Types

The 27 included studies explored a range of non-pharmacological fatigue management interventions. These were categorised into four groups: exercise interventions, psychological interventions, educational interventions, and complementary and lifestyle interventions. To provide an overview of how studies were distributed across these categories and study designs, a summary is presented in Table 3.5. These categories also form the basis for the detailed synthesis in the sections that follow. For clarity, this category is labelled "complementary and lifestyle interventions" because it includes dietary interventions, which are not typically classified as complementary therapies alon

10 Table 3.5: Summary of Included Studies by Intervention Type

Intervention type	Study (author, year)	Population / sample	Comparator	Duration & intensity	Fatigue outcome(s)	Key findings
Exercise interventions	Torres-Costoso et al., 2022 (Network meta-analysis, 58 RCTs; n=2,644)	MS	Control	≥8 weeks; varied types	Validated self-report questionnaires (MFIS, FSS, etc.)	Combined exercise and resistance training significantly better than control (SMD ~−1.5 and −1.15).
	Harrison et al., 2021 (Network meta-analysis, 113 studies; n=6,909)	MS	Exercise/behavioural comparators	Varied	Multiple validated self-report fatigue scales	Balance exercise outperformed other modalities; CBT outperformed energy conservation.

Intervention type	Study (author, year)	Population / sample	Comparator	Duration & intensity	Fatigue outcome(s)	Key findings
	Moss-Morris et al., 2021 (Meta-analysis, 34 trials; n≈2,434)	MS	Exercise vs behavioural vs combined	Varied	Validated self-report fatigue scales	Exercise most effective; behavioural better than combined approaches.
	Heine et al., 2015 (Cochrane review)	MS	Control	Endurance, resistance, and mixed exercise therapy	MFIS, FSS, others	Exercise therapy shows beneficial effects; need well-reported RCTs.
	Royer et al., 2024 (RCT, n=29)	MS	Traditional guideline-based combined exercise	12 weeks, supervised	FSS, MFIS	Fatigue decreased similarly in both groups; VO_2peak higher with individualised training.

Intervention type	Study (author, year)	Population / sample	Comparator	Duration & intensity	Fatigue outcome(s)	Key findings
	Kargarfard et al., 2012 (RCT, n=32)	RRMS	Control	4–8 weeks, aquatic exercise	MFIS	Significant improvements in aquatic group.
	Karbandi et al., 2015 (RCT, n = 85 randomised; n = 57 analysed)	MS	Individual vs group yoga/stretching (no non-exercise control)	6 weeks; twice daily 10 to 15 min mild stretching + yoga	MFIS	No between-group difference; within-group improvement in individual arm; attrition >30%, so findings mainly inform delivery format rather than efficacy versus usual care.
	Winward et al., 2012 (Single-blinded RCT, n=39)	PD	Control	12-week community exercise programme	FSS	No significant improvement; adherence variable.
	Simmons et al., 2023	MS	None	Aerobic cycling (short course)	MFIS	Within-group reductions in fatigue were reported following aerobic cycling; no statistically

Intervention type	Study (author, year)	Population / sample	Comparator	Duration & intensity	Fatigue outcome(s)	Key findings
	(Uncontrolled pre–post intervention study)					significant between-group analysis was conducted and long-term follow-up was not reported.
	Miri et al., 2023 (Non-randomised pre/post, n=40)	MS	Non-randomised control	Pilates training	FIS	Within-group reductions in fatigue were observed following the Pilates training intervention; however, statistical testing showed no statistically significant between-group difference in fatigue between the Pilates and control groups.
Psychological interventions	Phyo et al., 2018 (systematic	MS	inactive (waitlist, usual care) and active	varied: CBT typically 6–16	MFIS, FSS, FSMC, FAI,	CBT significantly reduced fatigue versus both inactive

Intervention type	Study (author, year)	Population / sample	Comparator	Duration & intensity	Fatigue outcome(s)	Key findings
(CBT and motivational interviewing)	review & meta-analysis, 20 studies; n=1,249, of which 12 studies; n=745 contributed to meta-analyses)		(relaxation, psychotherapy)	weeks, 45–90 min sessions; relaxation 8–12 sessions (~45–60 min); mindfulness ~8 weekly 2-h sessions with home practice.	and other validated scales	(SMD −0.32, 95% CI −0.63 to −0.01) and active controls (SMD −0.71, 95% CI −1.05 to −0.37). Relaxation (SMD −0.90, 95% CI −1.30 to −0.51) and mindfulness (SMD −0.62, 95% CI −1.12 to −0.12) also demonstrated benefits. Heterogeneity was none to moderate.
	de Gier et al., 2024 (RCT, n=103)	MS	Usual care after CBT	Booster CBT programme	MFIS (12 months)	Lower MFIS overall; boosters gave no added benefit.

Intervention type	Study (author, year)	Population / sample	Comparator	Duration & intensity	Fatigue outcome(s)	Key findings
	Gay et al., 2024 (Multicentre RCT, n=105)	RRMS	Standard care	Structured CBT + 4 boosters	MFIS (12 months)	CBT significantly better at 12 months ($p<0.01$).
	Moss-Morris et al., 2012 (Pilot RCT, n=40 randomised)	MS	Usual care	Internet-based CBT (MS Invigor8), 8–10 weeks	Chalder Fatigue, MFIS (substudy)	Significant treatment effects favouring iCBT; short follow-up.
	van Kessel et al., 2008 (RCT, n=72)	MS	Relaxation/usual care	~8 CBT sessions	Chalder Fatigue, MFIS	Greater fatigue reductions with CBT; sustained at ~6 months.
	Pöttgen et al., 2018 (RCT, n=139)	MS	Wait-list control	ELEVIDA self-guided online CBT, 12 weeks	Chalder Fatigue Scale;	Significant reduction vs control at 12 weeks (mean diff

Intervention type	Study (author, year)	Population / sample	Comparator	Duration & intensity	Fatigue outcome(s)	Key findings
					baseline, 12, 24 weeks	2.74; d=0.53; p=0.0007); effect sustained at 24 weeks.
	Borji et al., 2018 (Non-randomised, n=60)	MS	None	Motivational interviewing (5 sessions)	FIS	Significant reduction post-intervention; no long-term follow-up.
Educational interventions	Wendebourg et al., 2024 (Systematic review & meta-analysis, 15 RCTs; n=1,473)	MS	Varied controls	Varied; CBT-based and energy-conservation approaches	MFIS, FSS, Chalder	Fatigue severity reduced (SMD −0.28, 95% CI −0.53 to −0.03, low certainty); fatigue impact reduced (SMD −0.21, 95% CI −0.42 to 0.00, moderate certainty). Long-term results mixed. *Note: for MFIS*

Intervention type	Study (author, year)	Population / sample	Comparator	Duration & intensity	Fatigue outcome(s)	Key findings
						outcomes specifically, 9 RCTs (n=824) contributed data.
	Plow et al., 2019 (RCT, n=208)	MS	Physical activity only; control	Multi-session, telephone delivered	FIS	FM+ superior to control; no difference vs PA only.
	Rietberg et al., 2014 (RCT, n=48)	MS	Nurse consultation	Multidisciplinary outpatient rehab, 12 weeks	CIS-20R; 12 and 24 weeks	No significant between-group differences.
	D'Hooghe et al., 2018 (Prospective open-label, n=75)	MS	None	MS TeleCoach, 12 weeks	FSMC	FSMC improved at week 12 (p=0.009); uncontrolled, heterogeneous sample.

Intervention type	Study (author, year)	Population / sample	Comparator	Duration & intensity	Fatigue outcome(s)	Key findings
Complementary and lifestyle interventions	Wu et al., 2023 (Systematic review, 10 studies; n=315)	MS	Sham/control	Varied electrical stimulation protocols	FSS, MFIS	Some improvements; protocols heterogeneous; certainty limited.
	Voggenberger et al., 2022 (Sham-controlled RCT, n=26)	MS	Dim red light	Bright white light, 2 weeks	FSS	No significant between-group difference in FSS.
	Khodaie et al., 2023 (RCT, n=50)	RRMS	Sham	Acupuncture, 6 weeks	FSS	Significant between-group reduction with true acupuncture ($p<0.05$).

Intervention type	Study (author, year)	Population / sample	Comparator	Duration & intensity	Fatigue outcome(s)	Key findings
	Kluger et al., 2016 (RCT, n=94)	PD	Sham	Acupuncture	MFIS	Both groups improved; no between-group difference.
	Chase et al., 2023 (RCT, n=39)	MS	Wait-list	Low-fat diet, 16 weeks	MFIS	Significant reduction (mean diff −13.9; 95% CI −20.7 to −7.2).
	Wahls et al., 2021 (RCT, n=87)	RRMS	Swank vs Wahls diets	36 weeks	MFIS, FSS	Significant within-group improvements; no between-group difference.

Abbreviations: CBT, Cognitive Behavioural Therapy; CIS-20R, Checklist Individual Strength, Revised; ELEVIDA, Self-guided online CBT programme; FIS, Fatigue Impact Scale; FM+, Fatigue Self-Management plus Physical Activity; FSS, Fatigue Severity Scale; FSMC, Fatigue Scale for Motor and Cognitive Functions; iCBT, Internet-based Cognitive Behavioural Therapy; MA, Meta-analysis; MFIS, Modified Fatigue Impact Scale; MS, Multiple Sclerosis; NMA, Network Meta-analysis; PD, Parkinson's Disease; RCT, Randomised Controlled Trial; RRMS, Relapsing-Remitting Multiple Sclerosis; SMD, Standardised Mean Difference; SR, Systematic Review; VO_2peak, Peak Oxygen Uptake.

Note on design labels:

NRCT = non-randomised controlled study.

Pre–post single-arm = uncontrolled before–after design.

Between-group difference = comparison between intervention and control arms

Within-group change = change over time within the same group

Delivery Methods

Most interventions were delivered face to face (n = 12), either individually or in groups, exemplified by therapist-led CBT and supervised rehabilitation or exercise programmes in MS that reported fatigue outcomes (e.g., van Kessel et al., 2008; Kargarfard et al., 2012; Rietberg et al., 2014; Karbandi et al., 2015). One study directly compared individual versus group-based delivery of yoga and stretching and found no significant between-group differences in fatigue outcomes (Karbandi et al., 2015), suggesting that delivery format alone may not determine fatigue response, although interpretation is limited by attrition and the absence of a non-exercise control. Three trials evaluated fully online programmes, including internet-based CBT and app-supported telecoaching (Moss-Morris et al., 2012; Pöttgen et al., 2018; D'Hooghe et al., 2018). Two studies used telephone or remote delivery formats (Plow et al., 2019; D'Hooghe et al., 2018). Finally, two studies adopted hybrid models that blended in-person sessions with remote or digital components, reflecting pragmatic delivery in real-world settings.

3.3.3.1 Exercise Interventions

Evidence for exercise-based interventions is strongest in multiple sclerosis (MS), where several high-level syntheses converge on a beneficial effect for self-reported fatigue. In a network meta-analysis of 58 RCTs (n = 2,644), combined exercise demonstrated large effects (SMD ≈ −1.51), and resistance training moderate-to-large effects (SMD ≈ −1.15) compared with control (Torres-Costoso et al., 2022). A second network meta-analysis of 113 trials (n =

6,909) identified balance-focused exercise as superior to other exercise and behavioural comparators for fatigue (Harrison et al., 2021). The Cochrane review by Heine et al. (2015) similarly concluded that endurance, resistance and mixed modalities produce beneficial effects, although with ongoing concerns regarding reporting quality and power. Moss-Morris et al. (2021) also identified that exercise demonstrated significant short-term improvements in fatigue, although comparative effectiveness relative to behavioural approaches varied across analyses.

Further individual trials not included in the reviews listed above are supportive of their findings but heterogeneous. Some RCTs demonstrate clear between-group improvements (e.g., aquatic exercise improving MFIS; Kargarfard et al., 2012), whereas others report no significant fatigue advantage over active comparators (Rietberg et al., 2014; Winward et al., 2012, Karbandi et al., 2015). A non-randomised controlled study (Miri et al., 2023) and an uncontrolled pre–post study (Simmons et al., 2023) reported within-group improvements, but the certainty about causality is inherently limited.

Synthesising across evidence tiers, exercise, particularly resistance, combined and balance-focused formats, demonstrates moderate-to-large short-term effects on self-reported fatigue in MS. However, heterogeneity in intensity, supervision and follow-up limits precise prescription guidance. In Parkinson's disease (PD), evidence remains sparse and inconsistent, preventing confident extrapolation.

3.3.3.2 Psychological Interventions

Psychological interventions, particularly cognitive behavioural therapy (CBT), demonstrate the most consistent and durable evidence for fatigue reduction in MS. A systematic review and meta-analysis of 20 studies (n = 1,249; 12 meta-analysed, n = 745) found CBT superior to both inactive and active comparators (Phyo et al., 2018). Network meta-analysis similarly ranked CBT above energy-conservation education (Harrison et al., 2021).

At RCT level, CBT effects are consistently demonstrated across therapist-delivered and digital formats, with some trials reporting sustained benefits up to 6–12 months (Gay et al., 2024; van Kessel et al., 2008; Pöttgen et al., 2018; Thomas et al., 2013). However, booster sessions do not uniformly enhance durability (de Gier et al., 2024), and some effects attenuate by 52 weeks (van den Akker et al., 2017).

Taken together, CBT represents the most robust, disease-specific evidence base for MS-related fatigue, with consistent between-group improvements and replication across formats. In contrast, PD-specific CBT trials targeting fatigue were not identified, limiting the confidence in recommending this therapy for this patient group.

Motivational interviewing was evaluated in one uncontrolled pre–post study in people with MS (Borji et al., 2018). In that study, a five-session motivational interviewing intervention was associated with a statistically significant post-intervention reduction in fatigue measured using the Fatigue Impact Scale (FIS). However, because the study did not include a concurrent control group, random allocation, or long-term follow-up, the findings should be interpreted cautiously and cannot support causal conclusions regarding effectiveness.

3.3.3.3 Educational Interventions

Education-based meta-analysis data Wendebourg et al. (2024) reported statistically significant short-term reductions in fatigue severity (8 studies, n = 878; SMD −0.28, 95% CI −0.53 to −0.03; low certainty) and fatigue impact (9 studies, n = 824; SMD −0.21, 95% CI −0.42 to 0.00; moderate certainty).The magnitude of effect is modest, and heterogeneity in content and delivery constrains conclusions regarding optimal format.

The ELEVIDA trial (Pöttgen et al., 2018; n = 275) demonstrated moderate between-group reductions in fatigue severity at 12 weeks (d = 0.53), maintained at 24 weeks, supporting the potential of scalable digital self-management formats.

Overall, educational programmes appear beneficial, particularly when structured and grounded in behavioural principles. However, effect sizes are generally smaller than those reported for exercise or CBT, and durability beyond short-to-medium follow-up remains uncertain.

3.3.3.4 Complementary Therapies and lifestyle interventions

Complementary approaches show the weakest and most inconsistent evidence base. Acupuncture trials in PD reported no significant between-group effects (Kluger et al., 2016). In MS, an small (n=50) controlled trial of adjunctive acupuncture showed short-term benefit (MD −1.14 on FSS; Khodaie et al., 2023), but small sample size limits confidence.

Massage and bright light therapy trials primarily demonstrate within-group improvements but no significant between-group differences (Voggenberger et al., 2022).

Individual RCTs show clinically meaningful within-group improvements (Chase et al., 2023), yet between-group superiority is inconsistent (Wahls et al., 2021).

Across complementary and lifestyle interventions types, only a small controlled studies of low-fat diet (Chase et al., 2023) and of adjunctive acupuncture in MS (Khodaie et al., 2023) demonstrated between-group fatigue reductions. Overall, evidence remains exploratory, with small samples and methodological limitations precluding firm conclusions.

3.3.4 Overall Synthesis

Although 27 studies were included, seven were systematic reviews or meta-analyses synthesising larger pools of primary trials. Therefore, the apparent breadth of evidence reflects synthesis-level aggregation rather than a large number of unique primary RCTs, particularly outside multiple sclerosis (MS).

Across intervention categories, the most consistently supported intervention types, based on the volume of studies, level of evidence (systematic reviews and RCTs), and direction of findings, were:

• Structured exercise programmes (including aerobic, resistance, aquatic, and balance-based formats)

• Psychological interventions, particularly cognitive behavioural therapy (CBT)

• Structured educational or fatigue self-management programmes

Exercise interventions included a range of formats across studies (e.g., aerobic, resistance, aquatic, balance, and multimodal programmes), but these were considered collectively as

exercise-based interventions in the synthesis because the number of studies evaluating each specific modality was limited.

In MS populations, several high-level syntheses reported statistically significant short-term reductions in fatigue for both exercise-based interventions and cognitive behavioural therapy, although individual trials demonstrated heterogeneity in effect size and durability. Educational interventions showed statistically significant but generally smaller effects and were supported by a more limited number of trials. Complementary and lifestyle interventions were characterised by smaller samples, greater methodological limitations, and inconsistent between-group findings.

The evidence base remains heavily weighted toward MS. Trials in Parkinson's disease (PD) were comparatively sparse, frequently small, and rarely powered specifically for fatigue outcomes. No fatigue-focused intervention trials were identified in other progressive neurodegenerative conditions such as Huntington's disease, multiple system atrophy, progressive supranuclear palsy, motor neurone disease, or hereditary ataxias. While non-pharmacological fatigue interventions appear promising in MS, cross-condition generalisability cannot be assumed and requires direct empirical evaluation.

A structured synthesis by intervention category is presented in Table 3.6.

Table 3.6. Overview of intervention categories, evidence base, and strength of findings

11 Table 3.6. Overview of intervention categories, evidence base, and strength of findings

Intervention Category	Evidence Base	Participants	Summary of Effects	Certainty / Limitations
Exercise	systematic reviews/meta-analyses (n = 4); RCTs (n = 4); non-randomised controlled studies (n = 1); uncontrolled pre–post studies (n = 2)	Primarily MS; limited PD	Consistent evidence from high-level syntheses for combined, resistance and balance-focused exercise in MS. Individual RCTs show heterogeneous effects; some demonstrate between-group improvements (e.g., aquatic exercise), whereas others show no superiority or only within-group change (e.g., yoga format comparison). Evidence in PD remains limited.	High certainty for MS; evidence in PD limited; heterogeneity in exercise protocols and follow-up durations
Psychological	systematic reviews/meta-analyses (n = 3); RCTs (n = 5);	Predominantly MS; limited PD	CBT consistently reduces fatigue with clinically meaningful effects; motivational interviewing and multimodal behavioural	Strongest and most consistent evidence base in MS: durability beyond 12 months rarely tested;

	uncontrolled pre–post studies (n = 1)		strategies show promise but with weaker evidence	generalisability outside MS uncertain
Educational	systematic review/meta-analysis (n = 1); RCTs (n = 2); uncontrolled pre–post studies (n = 1)	Exclusively MS	Structured programmes (e.g., self-management, energy conservation) improve MFIS and FSMC scores; facilitator-led delivery models most effective	Evidence confined to MS; small number of trials; heterogeneity in programme design and delivery
Complementary and lifestyle	systematic review (n = 1); RCTs (n = 4)	MS and PD	Some evidence of benefit for acupuncture (MS) and low-fat diet; other approaches (acupuncture/acupressure in PD, massage, bright light therapy, dietary modifications) show inconsistent or non-significant effects	Overall low certainty; small samples; methodological weaknesses; possible indirect effects via sleep or diet

Footnote: Participant numbers are approximate because some studies did not report complete sample sizes or presented pooled data. Where systematic reviews and meta-analyses were included, the combined sample sizes reflect the total number of participants across eligible trials rather than unique individuals and overlap between reviews is possible.

3.4 Discussion

For clarity, study designs were classified into four categories: systematic reviews and meta-analyses; randomised controlled trials (RCTs); non-randomised controlled trials (NRCTs), defined as studies including a concurrent comparator but without random allocation; and uncontrolled pre–post intervention studies, in which outcomes were measured before and after the intervention within a single group without a concurrent control. Studies described by authors as pilot or feasibility studies were classified according to their underlying design (e.g., pilot RCT or uncontrolled pre–post study) rather than treated as a separate methodological category.

To determine relative strength of evidence across intervention categories, consistency was judged based on: (1) the number of independent RCTs demonstrating statistically significant between-group effects; (2) the presence of supporting systematic reviews or meta-analyses; (3) replication across delivery formats; and (4) durability of effects at follow-up where reported.

Across intervention categories, psychological approaches, particularly CBT, are the most consistently supported, with multiple RCTs and systematic reviews in MS demonstrating statistically significant between-group improvements in fatigue outcomes. Educational programmes, especially structured fatigue self-management courses, also show benefit, although heterogeneity in delivery methods limits identification of an optimal format.

Exercise-based interventions, including aerobic, resistance, and aquatic training, demonstrate beneficial effects in MS across several RCTs and meta-analyses. However, effects are not uniform across formats. For example, a randomised trial comparing individual versus group yoga-based stretching (n = 85 randomised; 57 analysed) found no significant between-group difference in fatigue, with improvements confined to within-group change and attrition exceeding 30%, limiting causal inference (Karbandi et al., 2015). Applicability to PD remains uncertain given differing fatigue mechanisms and motor constraints.

Complementary and lifestyle interventions yield more variable results. Only two interventions, low-fat diet (n = 39; Chase et al., 2023) and acupuncture (n = 60; Khodaie et al., 2023) in MS, demonstrated significant between-group effects, though both had small samples and require replication in larger, adequately powered RCTs. Other approaches, such as acupuncture/acupressure in PD, Swedish massage, and bright light therapy, either failed to reach significance or showed benefits confined to within-group analyses.

Taken together, the most consistent evidence supports CBT as the strongest and most consistently replicated intervention in MS, followed by structured exercise and educational self-management programmes. Evidence in PD remains limited and less conclusive.

3.4.1 Measurement Challenges and Future Directions

As noted in the Results, fatigue outcomes were most assessed using the MFIS and FSS alongside less frequently applied tools such as the Chalder Fatigue Scale, FIS, Fatigue Scale for Motor and Cognitive Functions (FSMC), and CIS-20R. The predominance of MFIS and FSS reflects their strong validation in MS, but their transferability to other conditions is limited. The MFIS captures physical, cognitive, and psychosocial dimensions but does not

adequately address motor fatigability, which is particularly relevant in PD (Fisk et al., 1994). Conversely, the FSS yields a global severity score without distinguishing cognitive from physical fatigue, reducing its specificity in PD where cognitive fatigue is often dominant (Krupp et al., 1989; Kluger et al., 2013).

Beyond tool choice, methodological issues further complicate interpretation. Assessments are often administered at inconsistent times relative to daily fatigue fluctuations, and fatigue is frequently evaluated as a secondary rather than primary outcome, leaving studies underpowered. Almost exclusive reliance on self-report introduces vulnerability to bias from mood, recall error, and behavioural adaptations such as pacing. These limitations reduce comparability across trials and make it difficult to establish whether reported effects represent true physiological change or artefacts of measurement.

To strengthen the field, future studies should adopt integrated, multi-method approaches. Patient-reported outcome measures should remain central, as they capture the lived experience and functional impact of fatigue, but they need to be complemented by objective markers. These include wearable activity monitors to track diurnal variation and real-world energy expenditure, actigraphy-based sleep analysis, heart rate variability (HRV) and other autonomic indicators, and task-based fatigability tests that detect decline in motor or cognitive performance under sustained effort. Triangulating subjective reports with these objective measures can help distinguish perceived fatigue from measurable performance decline, identify when behavioural adaptations (for example., reduced activity to avoid symptoms) inflate fatigue scores, and allow earlier detection of change. Integrating multiple data streams can also improve sensitivity to intervention effects and support personalised management strategies.

Finally, trials should be explicit about whether their aim is to reduce fatigue severity or to improve fatigue self-management. These are conceptually distinct outcomes, each requiring different measurement strategies and analytic approaches. Embedding this distinction, alongside longitudinal and multi-modal assessment, will not only enhance the sensitivity and validity of research but also ensure that findings translate into clinically actionable strategies across neurodegenerative conditions.

3.4.2 Fatigue reduction vs. improved self-management

An important conceptual question is whether the primary aim of interventions should be to reduce fatigue severity or to enhance the individual's ability to manage fatigue effectively. Findings from this review suggest that self-management skills; pacing, energy conservation and strategic activity planning; can improve participation and quality of life even when absolute fatigue scores remain unchanged. In chronic, progressive conditions where complete resolution of fatigue is unlikely, targeting self-efficacy and adaptive coping strategies may deliver more sustainable and meaningful benefits.

Future trials should be explicit about which of these outcomes they are designed to achieve, choose measures accordingly, and power analyses to detect clinically meaningful change in both domains.

3.4.3 Intervention-specific considerations and integration with broader evidence

3.4.3.1 Psychological Interventions: CBT & Motivational Interviewing

CBT remains the most consistently supported intervention for fatigue in MS, with benefits observed across a wide range of programme lengths and delivery modes. The durability of effects even in brief online formats (~150 minutes total) suggests that lower-intensity, scalable models may be viable in routine practice. However, the transferability of CBT to PD is uncertain. Motor impairments, executive dysfunction, and apathy; all common in PD; may reduce engagement and diminish treatment effects unless programmes are adapted to integrate motor rehabilitation, cognitive supports, and condition-specific pacing strategies.

Motivational interviewing (MI) has been explored only in a very limited way within this evidence base. One uncontrolled pre–post study in people with MS reported a statistically significant reduction in fatigue following a five-session MI intervention (Borji et al., 2018). However, the absence of a concurrent control group, randomisation, and long-term follow-up substantially limits confidence in causal inference and generalisability. MI may still be of interest as a potential adjunct to fatigue self-management programmes because of its focus on motivation, self-efficacy, and behavioural engagement, but more rigorous controlled trials are needed before its contribution to fatigue management can be determined.

3.4.3.2 Exercise Interventions: Efficacy & Variability

Exercise-based interventions are consistently associated with reductions in self-reported fatigue in multiple sclerosis (MS), particularly in higher-level syntheses. Large network meta-analyses indicate moderate-to-large short-term effects for resistance, combined, and balance-focused exercise formats compared with control conditions, although effect

magnitudes vary across modalities and follow-up periods. These findings are supported, though less uniformly, by individual RCTs demonstrating improvements following aerobic, aquatic, and mixed-modality training. However, effect estimates at trial level are more heterogeneous than pooled syntheses suggest, reflecting differences in comparator choice, intensity, progression, and adherence.

Not all exercise formats demonstrate clear between-group superiority. For example, a randomised trial comparing delivery format of mild stretching and yoga (individual versus group; n = 85 randomised, 57 analysed) reported no significant between-group differences in fatigue. Improvements were confined to within-group change in the individual arm, and attrition exceeded 30%, reducing statistical power and limiting causal inference regarding exercise efficacy (Karbandi et al., 2015). Importantly, the absence of a non-exercise control arm in this study means conclusions relate to delivery format rather than exercise effectiveness per se. Such design features illustrate how comparator selection and adherence patterns can materially influence observed outcomes.

Variability in exercise effects likely reflects both methodological and mechanistic factors. Methodologically, trials differ in intervention dose, supervision, progression, and follow-up duration. Many studies are small and rely exclusively on self-report fatigue measures, increasing susceptibility to expectancy effects and regression to the mean. Mechanistically, fatigue in MS is strongly influenced by central inflammatory and cognitive processes, which may be responsive to structured physical activity. In Parkinson's disease (PD) and other neurodegenerative conditions, fatigue profiles are more heterogeneous and often intertwined with motor impairment, apathy, autonomic dysfunction, and dopaminergic fluctuations. These differences complicate direct extrapolation of MS findings.

For progressive conditions such as motor neuron disease (MND) and Huntington's disease (HD), mobility limitations and rapid functional decline further constrain feasible exercise intensity and progression. In such populations, adaptive and lower-burden formats may prioritise safety and maintenance of participation over fatigue reduction as a primary outcome.

The absence of standardised exercise prescriptions across trials hampers synthesis and clinical translation. Establishing condition-specific guidelines with clearly defined parameters for type, intensity, frequency, progression, and monitoring would enable more precise evaluation of efficacy and facilitate replication. Future research should also incorporate objective markers of fatigability alongside patient-reported outcomes to determine whether observed improvements reflect physiological adaptation, behavioural pacing, or changes in fatigue perception.

3.4.3.3 Complementary and Lifestyle Interventions

Complementary and lifestyle interventions for fatigue in neurodegenerative disease include manual therapies, acupuncture-based interventions, light-based treatments, and dietary modification. Evidence is mixed across all modalities. For example, Swedish massage has been associated with short-term fatigue reduction in MS, but the absence of long-term follow-up and the treatment of fatigue as a secondary outcome limit its interpretive weight. Acupuncture and acupressure studies, including those in PD, have generally failed to outperform sham controls, with methodological weaknesses such as small samples, heterogeneous protocols, and inadequate blinding making it difficult to separate genuine physiological effects from placebo responses.

Bright light therapy trials report modest improvements in some populations, but these effects are inconsistent and often short-lived, reflecting small sample sizes and the absence of standardised light exposure protocols. Dietary interventions offer an emerging avenue: low-fat and ketogenic diets in MS, and Mediterranean-style diets in PD, have each demonstrated short-term benefits that may be mediated by anti-inflammatory or metabolic effects. However, adherence challenges, lack of sustained effects, and methodological variability restrict confidence in these findings.

Overall, the complementary therapies evidence base is constrained by small-scale, heterogeneous studies, short follow-up, and inconsistent primary fatigue outcomes. While some modalities; particularly certain dietary strategies; show potential, robust trials with standardised protocols and adequate power are needed to clarify their contribution to comprehensive fatigue management models.

3.4.3.4 Educational Interventions

Educational interventions, particularly structured fatigue self-management programmes, demonstrate moderate efficacy in MS, with systematic reviews and RCTs (e.g., Wendebourg et al., 2024; Pöttgen et al., 2018) showing improvements in both fatigue outcomes and patient engagement. Programmes that integrate self-management with physical activity or deliver content digitally appear to enhance reach and accessibility, but their evidence base remains almost entirely confined to MS.

The absence of robust data in PD and other neurodegenerative conditions limits conclusions about transferability. Moreover, long-term sustainability of benefits is rarely tested. Extending these interventions to under-represented conditions, incorporating strategies

tailored to cognitive and motor profiles, and embedding follow-up assessments beyond 6–12 months are priorities for strengthening their clinical applicability.

3.4.4 Mechanisms Underlying Varying Effectiveness

Differences in intervention effectiveness across neurodegenerative diseases likely reflect interaction between biological, behavioural, and delivery-related mechanisms rather than a single causal pathway. Fatigue is a multidimensional symptom encompassing subjective exhaustion, reduced motivation, and measurable performance decline. Interventions may therefore exert effects through distinct but overlapping pathways.

At a neurobiological level, fatigue in MS is strongly associated with central inflammation, demyelination, and disrupted neural connectivity within cortico-striatal and fronto-parietal networks. Structured exercise may improve fatigue by enhancing cerebral perfusion, modulating inflammatory cytokines, and improving mitochondrial efficiency, while CBT may reduce cognitive load and maladaptive stress responses that amplify central fatigue perception. In contrast, fatigue in PD is closely linked to dopaminergic dysfunction within basal ganglia circuits, autonomic dysregulation, and apathy-related motivational deficits. These differences suggest that interventions effective in MS may require adaptation in PD to address motor–cognitive integration and reward-processing systems rather than solely inflammatory mechanisms.

At a behavioural level, fatigue can be perpetuated by maladaptive activity patterns, including overexertion followed by prolonged rest, avoidance behaviours, and reduced participation leading to physical deconditioning. CBT and structured self-management programmes may interrupt this cycle by targeting illness beliefs, enhancing self-efficacy, promoting pacing

strategies, and reframing fatigue as manageable rather than catastrophic. Improvements in perceived control may reduce central amplification of fatigue signals, even when underlying pathology remains unchanged.

At a physiological–performance level, exercise interventions may reduce fatigue through improved cardiorespiratory fitness, enhanced motor unit recruitment, and better autonomic regulation. However, where motor impairment is severe or rapidly progressive, as in MND or advanced PD, the capacity to induce meaningful physiological adaptation may be constrained. In such contexts, observed improvements may reflect improved activity structuring and energy conservation rather than reversal of biological fatigue drivers.

Implementation mechanisms remain relevant. Fidelity, engagement, and delivery format influence whether core behaviour-change ingredients are sufficiently activated. Digital interventions improve accessibility but may reduce therapeutic alliance and individual tailoring, whereas blended models may optimise both reach and responsiveness. The interaction between mechanistic plausibility and delivery feasibility likely determines real-world effectiveness.

Taken together, intervention impact depends on alignment between:
(1) the dominant biological fatigue drivers in a given condition,
(2) the behavioural processes sustaining fatigue-related disability, and
(3) the degree to which intervention components directly target these pathways while remaining feasible for the population.

3.4.5 Integration with Evidence & Future Research

The findings from this review indicate that CBT, structured exercise programmes, and educational fatigue self-management interventions remain the most consistently supported strategies for fatigue management in MS, underpinned by multiple high-quality RCTs and systematic reviews. However, the applicability of these interventions to other neurodegenerative conditions such as PD, Huntington's Disease (HD), and MND is less certain. This reflects both the disproportionate concentration of evidence in MS and the underlying differences in fatigue mechanisms across conditions.

The overwhelming concentration of evidence in MS populations; accounting for nearly three-quarters of all included studies; likely reflects both its relatively high prevalence and the strong clinical research infrastructure that has evolved around this condition. However, this imbalance risks perpetuating structural inequity in the field. Fatigue is a pervasive and disabling symptom across PD, HD, MND, and other neurodegenerative disorders, yet these groups remain markedly under-represented in intervention research. The result is a cycle in which the best-resourced condition continues to accumulate evidence and refine interventions, while other populations with equally urgent clinical needs are left without robust, tailored approaches. Unless research investment and trial infrastructure are deliberately extended to non-MS conditions, fatigue management risks becoming disproportionately advanced for MS while remaining underdeveloped for PD, MND, and HD, thereby widening rather than reducing disparities in patient care.

MS fatigue often has a strong central and cognitive component, which may explain why CBT and self-management approaches demonstrate robust effects. In PD, fatigue arises from a complex interplay of motor impairment, cognitive decline, and non-motor symptoms, suggesting that both the content and delivery of interventions may require adaptation. In

rapidly progressive diseases such as MND, the feasibility of structured, high-intensity programmes is a critical limitation, pointing towards the need for lower-burden, flexible formats. These condition-specific considerations underline the importance of aligning intervention targets with the dominant mechanisms and functional realities of each disease.

Future research should broaden its scope beyond MS, using adequately powered, multicentre RCTs to examine fatigue management in PD, HD, and MND. Intervention protocols require greater standardisation in terms of session frequency, intensity, duration, and follow-up to enable meaningful cross-study comparisons and support reproducibility. Alongside established self-report tools such as the Modified Fatigue Impact Scale (MFIS) and Fatigue Severity Scale (FSS), incorporating objective physiological and behavioural measures, such as accelerometery, actigraphy-based sleep analysis, and heart rate variability (HRV) monitoring; would capture real-time fluctuations and better characterise fatigue phenotypes (Srinivasan et al., 2024; Mulcahy et al., 2019; Alfini et al., 2020). Given the multidimensional nature of fatigue, future work should prioritise multimodal approaches that integrate psychological, physical, and educational components. For example, combining CBT with individually tailored exercise programmes may offer synergistic benefits, particularly in PD where both motor and cognitive fatigue drive symptom burden. Educational strategies that embed self-management skills could further strengthen adherence and sustain benefits over time. Addressing these priorities; expanding the evidence base beyond MS, standardising methodologies, embedding objective metrics, and testing integrated intervention models; will be essential to optimise fatigue management and improve quality of life for people living with neurodegenerative diseases.

3.4.6 Limitations and implications

As highlighted in the earlier synthesis of intervention categories (Sections 3.3.3.1–3.3.3.4), the evidence base is dominated by studies in Multiple Sclerosis, with only sporadic exploration of fatigue interventions in other neurodegenerative conditions. Across the included trials, most enrolled fewer than 100 participants, restricting statistical power to detect clinically meaningful effects and limiting generalisability. Heterogeneity in intervention content, delivery formats, and follow-up durations further constrained comparability.

High attrition rates were observed in several small exercise trials (for example, >30% in Karbandi et al., 2015), raising concerns regarding engagement, feasibility, and potential attrition bias, and further reducing statistical power in already modest samples. Where improvements are observed primarily in completers, selective retention of more adherent or motivated participants may inflate apparent benefit.

Risk of bias was common. Fatigue outcomes were almost always assessed using self-report instruments, which are indispensable for capturing a symptom that is fundamentally subjective. However, because behavioural and rehabilitation interventions cannot usually be blinded, improvements may partly reflect expectation effects. Results should therefore be interpreted cautiously, with recognition that apparent benefits may reflect both genuine change and non-specific influences. Additional risks of bias arose from the absence of blinded outcome assessment in some trials and inconsistent reporting of adverse events.

Few studies incorporated economic evaluation, and long-term follow-up was the exception rather than the rule. Collectively, these limitations weaken the confidence with which practice recommendations can be made.

3.4.7 Acceptability and feasibility evaluation (TFA)

To assess and address the acceptability challenges identified across the scoping evidence (for example, digital access, perceived burden, and motivation), the ReFresh acceptability plan was framed using Sekhon et al.'s Theoretical Framework of Acceptability (TFA) and the Person-Based Approach (PBA) to intervention adaptation. In practice, the plan operationalised acceptability using a low-burden set of brief post-module items and weekly free-text comments, with iterative refinements made to wording, examples and pacing based on participant feedback (see Chapter 4 and Appendix 4.J for full operational details). This theoretical framing directed us to measure both affective and cognitive dimensions of acceptability (for example, perceived usefulness, intervention coherence, burden, and self-efficacy) and to prioritise small, participant-led changes that preserve core behaviour-change ingredients. (Sekhon, Cartwright & Francis, 2017; Yardley et al., 2015)

3.5 Conclusion

This scoping review mapped the landscape of non-pharmacological fatigue interventions across neurodegenerative diseases and identified CBT, structured exercise programmes, and self-management education as the most promising approaches, evidence that is, however, overwhelmingly concentrated in MS. The dominance of MS in the fatigue literature reflects pragmatic and historical factors rather than greater clinical importance of fatigue in MS alone. MS has benefited from earlier and sustained research investment and well-organised trial infrastructure, which facilitated development and widespread adoption of MS-specific measures (for example, the MFIS) and standardised eligibility criteria. By contrast, PD and

other neurodegenerative conditions have received less targeted funding for fatigue trials, exhibit greater heterogeneity in fatigue phenotypes (motor versus cognitive versus central mechanisms), and lack a single, widely accepted disease-specific fatigue instrument, all of which complicate trial design, recruitment and outcome harmonisation. These structural factors limit direct generalisability of MS findings to PD and emphasise the need for PD-specific feasibility and effectiveness testing.

Methodological and measurement issues further constrain confidence in the evidence base. Across studies, sample sizes were typically small, intervention content and delivery varied widely, and fatigue was often measured with instruments developed for other conditions or as a secondary outcome. Reliance on self-report alone is vulnerable to mood and expectation effects, and the absence of objective, real-world measures (for example, accelerometry, actigraphy, heart-rate variability, or task-based fatigability tests) reduces sensitivity to change and complicates interpretation. Risk of bias is also a recurrent issue in behavioural and rehabilitation trials where blinding is frequently infeasible. Taken together, these limitations mean that, while CBT, exercise and educational programmes show promise (especially in MS), the overall certainty of evidence for non-pharmacological fatigue management in PD and other non-MS conditions is low and further well-designed, adequately powered trials are required.

To advance the field, future research should prioritise: (1) condition-specific feasibility work and adequately powered RCTs in under-represented populations (PD, HD, MND, PSP); (2) harmonisation of outcome measurement through consensus on core fatigue measures (including PD-relevant instruments) and routine inclusion of objective physiological/behavioural markers alongside validated patient-reported outcomes; (3) standardised reporting of interventions following CONSORT and TIDieR guidance to

improve reproducibility and enable pooled synthesis; and (4) testing of multimodal, co-designed interventions that integrate physical, psychological and educational components and explicitly target either fatigue severity or fatigue self-management (or both) depending on trial aims.

Following the MRC complex-interventions framework and using TIDieR to specify intervention components, Chapter 4 describes the development, PD-specific adaptation and pilot evaluation of ReFresh, a six-week online programme integrating CBT, fatigue self-management education and practical pacing, designed to improve fatigue severity and fatigue self-efficacy in PwP. The programme's logic model and full TIDieR checklist are provided in Appendices 4.O and 4.N to support feasibility testing and replication (Skivington et al., 2021; Hoffmann et al., 2014).

Chapter 4: Pilot Randomised Controlled Trial of the Rebalancing Fatigue & Enhancing Self-Help (ReFresh) Online Fatigue Management Program for People with Parkinson's

This chapter reports on a pilot randomised controlled trial (RCT) of the ReFresh online fatigue management programme for people with Parkinson's disease. The programme was adapted from the evidence-based FACETS intervention originally developed for multiple sclerosis, with modifications made to ensure relevance and accessibility for Parkinson's populations. The chapter begins by outlining the development of ReFresh, including co-creation with people with Parkinson's, followed by the study design, recruitment processes, and outcome measures. Results are then presented for feasibility, acceptability, and preliminary efficacy, including both quantitative outcomes and qualitative feedback.

This pilot randomised controlled trial has been accepted for publication in Neurodegenerative Disease Management (accepted 13 March 2026).

Trial registration: Pilot randomised controlled trial registered with ISRCTN (ISRCTN62114944).

4.1 Background and Rationale

Fatigue is one of the most prevalent and disabling non-motor symptoms of Parkinson's disease (PD), affecting a large proportion of people with Parkinson's and substantially impairing daily activities, social participation and wellbeing (Friedman et al., 2007; Friedman et al., 2016; Ongre et al., 2017). Pharmacological treatments have shown limited and inconsistent benefit for Parkinson's-related fatigue, leaving patients with few reliable, evidence-based options (Kluger et al., 2017).

The systematic review undertaken for this thesis (Chapter 2) highlights a narrow Parkinson's-specific evidence base for fatigue interventions: only five randomised controlled trials met inclusion criteria, and benefits were most evident for exercise programmes, whereas CBT and occupational therapy approaches showed mixed or limited evidence (see Chapter 2). To broaden the potential intervention pool, a scoping review was undertaken (see Chapter 3) which examined fatigue management across other neurodegenerative conditions. That review identified a wider array of non-pharmacological strategies, particularly interventions combining cognitive behavioural techniques, activity-based approaches, and energy-management or occupational strategies (Foster et al., 2014; Tofani et al., 2020), many of which have demonstrated benefit in multiple sclerosis.

Taken together, the findings from Chapters 2 and 3 indicate both (i) a clear gap in robust, diverse trials specifically addressing fatigue in Parkinson's disease, and (ii) a set of potentially transferable, evidence-informed intervention components from related neurological populations (particularly multiple sclerosis) that warrant adaptation and feasibility testing in a Parkinson's cohort. One such programme is FACETS (Fatigue:

Applying Cognitive behavioural and Energy-effectiveness Techniques to lifeStyle), a manualised group programme integrating cognitive behavioural and energy effectiveness strategies. In a pragmatic, multi-centre randomised controlled trial in multiple sclerosis, FACETS improved fatigue outcomes and fatigue self-efficacy at four months, with effects largely sustained at twelve months (Thomas et al., 2013; Thomas et al., 2014). Its manualised content and reproducible structure strengthen suitability for adaptation into a Parkinson's-specific online format, particularly as it targets mechanisms aligned with the priorities emerging from Chapters 2 and 3, including pacing, cognitive reframing, and behavioural regulation. These mechanisms provide a plausible pathway for improving perceived control and coping even when short-term reductions in fatigue severity are limited.

The intervention reported here (ReFresh) was specified using the combined insights of Chapters 2 and 3: Chapter 2 identified the paucity and direction of PD-specific evidence, while Chapter 3 supplied a broader set of candidate components and delivery and measurement options from related conditions. This integration follows the Medical Research Council pathway from evidence synthesis to programme theory and feasibility testing (Craig et al., 2008; Skivington et al., 2021).

4.1.1 The ReFresh Programme

The Rebalancing Fatigue & Enhancing Self-Help (ReFresh) programme was developed as a six-week online fatigue management intervention, adapted from FACETS to address the unique needs of PwP. Key adaptations included:

- tailoring pacing and energy conservation strategies to account for motor impairments and fluctuating mobility.

- integrating components targeting the emotional and cognitive dimensions of fatigue in PD.
- ensuring digital accessibility for individuals with physical limitations, including the provision of printed alternatives.
- embedding patient and public involvement (PPI) throughout, ensuring relevance, clarity, and acceptability of the materials.

Development of the programme followed an iterative and collaborative, informed by evidence synthesis, contributions from the multidisciplinary research team (three occupational therapists, one person with MS, and one person with a functional movement disorder), and co-adaptation with eleven PwP recruited via the Parkinson's UK Research Support Network. This co-creation process was essential in aligning the intervention with lived experiences of fatigue, thereby enhancing both ecological validity and potential clinical relevance.

Development was informed by principles of the Person-Based Approach (PBA), which emphasises the integration of user feedback to optimise engagement and usability of complex interventions (Yardley et al., 2015). In this study, feedback from people with Parkinson's was gathered through structured surveys and iterative review of draft materials rather than formal qualitative interviews. Survey responses were used to identify areas requiring clarification, simplification, or contextual adaptation. Refinements included reducing language complexity, incorporating Parkinson's-specific examples, modifying layout and formatting, and ensuring alternative printable options were available. This approach aimed to enhance usability and relevance while remaining proportionate to the feasibility stage of development.

4.1.2 Study Objectives and Research Questions

The overarching aim of this pilot RCT was to evaluate the feasibility, acceptability, and preliminary efficacy of delivering ReFresh online to PwP. Specifically, the study objectives were to:

1. Assess the feasibility of delivering ReFresh online, including recruitment, retention, adherence, and engagement.
2. Evaluate the acceptability of the programme content and delivery format, using quantitative satisfaction measures and qualitative participant feedback.
3. Explore preliminary efficacy trends across fatigue-related outcomes, including fatigue severity, fatigue self-efficacy, quality of life, sleep, and mood.
4. Examine whether occupational performance, as measured by the Canadian Occupational Performance Measure (COPM), can be feasibly self-administered and provide meaningful insights in this population. Although the COPM is conventionally delivered via a semi-structured interview with an occupational therapist (Law et al., 1990), its psychometric evidence and prior feasibility studies in Parkinson's disease and in remote/telerehabilitation contexts support cautious use of a participant-completed version as an exploratory outcome in a pilot trial (Ohno et al., 2021; Kobayashi et al., 2023; Tanner et al., 2021).

The pilot trial was not powered to detect definitive efficacy outcomes. Instead, it was designed to establish feasibility benchmarks, identify engagement challenges, and generate preliminary effect size estimates to inform the design of a future fully powered randomised controlled trial. These effect size estimates were subsequently used to conduct an indicative sample size calculation using G*Power version 3.1 (Faul et al., 2009), assuming a two-tailed significance level of $\alpha = 0.05$ and statistical power of 80% ($1-\beta = 0.80$).

4.2 Methods

This study was conducted as a parallel-group, open-label pilot randomised controlled trial (RCT) and is reported in accordance with the CONSORT 2025 guidelines for randomised trials (Hopewell et al., 2025); a completed CONSORT checklist is provided in Appendix 4.B. No blinding was implemented: both participants and members of the research team were aware of group allocation. Outcome measures were completed independently by participants via the online survey platform rather than through researcher-administered interviews; that is, participants completed validated questionnaires in their own setting without a researcher present. Independent, self-administered completion was employed to reduce interviewer administration bias and experimenter expectancy effects (which can arise from an interviewer's wording, tone or non-verbal cues) and to ensure consistency in question presentation (Bowling, 2005; Podsakoff et al., 2003). Standardised instruments and uniform on-screen instructions were used to minimise variation in administration. It should be noted, however, that independent completion does not remove other sources of measurement error (for example, response style, recall error or differential attrition), which are addressed in the Limitations section. All data were handled in accordance with the UK General Data Protection Regulation (ICO, 2018) and the University of East Anglia Research Data Management Policy (UEA, 2024); full details of data storage, anonymisation procedures and information governance are provided in the Data Management Plan (Appendix 4.C).

4.2.1 Study design

The trial was designed as a parallel-group RCT in which participants were randomly allocated in a 1:1 ratio to either the intervention group, who received immediate access to the

ReFresh online fatigue management programme, or to a waitlist control group, who continued their usual care and gained access to the programme after sixteen weeks. The study was prospectively registered with ISRCTN (ISRCTN62114944), and ethical approval was obtained from the University of East Anglia's Faculty of Medicine and Health Sciences Research Ethics Committee (reference: ETH2324-0159). All participants provided informed consent prior to enrolment using a standardised form, which is reproduced in Appendix 4.D. For pragmatic reasons linked to online delivery, ability to engage with study materials was inferred from completion of the online Participant Information Sheet and consent checklist; no formal language-proficiency or digital-skills screening was performed.

4.2.2 Patient and public involvement

Patient and public involvement (PPI) was embedded throughout the study. Eleven PwP acted as lay advisers and were actively engaged in co-design, implementation, and evaluation processes. Meetings with advisers were held approximately every two months and included discussions on trial design, recruitment approaches, and refinements to the intervention content. Advisers received basic training on trial methodology to support meaningful contributions. Their insights informed language, accessibility, and content relevance of the ReFresh materials. A full summary of lay adviser contributions across all stages of the study, including intervention adaptation, outcome selection, and feedback on preliminary results, is provided in Appendix 4.E. Following completion of the trial, an outcome prioritisation survey was distributed to the lay advisers to guide selection of the most meaningful primary outcome for a future fully powered RCT. The survey format is provided in Appendix 4.F, with anonymised responses in Appendix 4.G.

4.2.3 Participants and recruitment

Participants were eligible for inclusion if they self-identified as having idiopathic Parkinson's disease, reported experiencing fatigue, were aged 18 years or older, and had reliable access to the internet with an appropriate device for engaging in an online intervention. Participants were also required to have sufficient English proficiency and basic digital literacy to complete the programme and associated study procedures. Sufficiency of English proficiency and digital literacy was not assessed through separate screening items. Instead, participants self-reported eligibility and indicated consent by completing the online Participant Information Sheet and the consent checklist (see Appendix 4.H). Specifically, participants were required to confirm that they had read the Participant Information Sheet, had downloaded a copy for their records, and were able to complete the online consent and baseline survey. This pragmatic approach preserved feasibility for online delivery but has implications for generalisability that are discussed in the Limitations section. No formal assessment of English language ability or a discrete digital-skills test was performed. Eligibility was self-reported, and no clinical verification (such as neurologist confirmation), fatigue severity threshold, or cognitive screening assessment (e.g., MMSE) was conducted. The Participant Information Sheet (Appendix 4.H) explicitly advised potential participants with Parkinson's plus syndromes or with contraindications to moderate exercise not to enrol. Participants were encouraged to consult their own healthcare teams if they had concerns regarding exercise-based elements of the programme. Use of Parkinsonian medication and any changes during the study were neither controlled nor monitored.

A minimum recruitment target of 40 participants was specified a priori, consistent with methodological guidance for pilot randomised controlled trials recommending approximately

12–20 participants per arm to estimate feasibility parameters and outcome variability for future definitive studies (Julious, 2005; Whitehead et al., 2016). Allowing for anticipated attrition commonly observed in unguided digital interventions (Eysenbach, 2005), a target of 40 participants was considered sufficient to assess feasibility outcomes while remaining manageable within the scope of a pilot trial.

Recruitment was conducted online between 14 June 2024 and 25 June 2024. Recruitment materials were disseminated through multiple channels, including the Parkinson's UK Research Support Network, Parkinson's UK newsletters, and targeted social media advertisements. Interest in the study exceeded expectations: 150 individuals were assessed for eligibility during the recruitment period. After exclusions (n = 32), a total of 118 participants were randomised, as shown in the CONSORT flow diagram (Figure 4.1). This recruitment approach facilitated broad engagement with the target population.

4.2.4 Randomisation and allocation

Randomisation was undertaken using the Sealed Envelope online randomisation system (Sealed Envelope Ltd, n.d.), employing permuted blocks of size four and six to ensure balanced allocation. The allocation sequence was generated automatically within the Sealed Envelope system using computer-generated random permuted blocks of varying sizes (four and six). The lead researcher configured the randomisation parameters prior to recruitment; however, the sequence itself was system-generated and not visible in advance. Allocation was concealed at the point of enrolment, as assignments were revealed sequentially by the platform only after confirmation of eligibility and completion of baseline measures. Once generated, the randomisation schedule could not be manually edited. The allocation list

remained stored securely within the Sealed Envelope platform and was not accessible to participants. Participants were assigned in a 1:1 ratio to either the ReFresh intervention group or the waitlist control group. Due to the nature of the intervention, participants could not be blinded and were informed of their allocation via email. Outcome measures were collected via Qualtrics (Qualtrics, Provo, UT), with participants completing the same set of validated measures at baseline and at the 12-week endpoint.

The lead researcher was responsible for both dataset preparation and statistical analysis and was therefore not blinded to allocation. This lack of blinding during analysis is acknowledged as a limitation and potential source of bias. Full baseline and endpoint questionnaires are reproduced in Appendix 4.I, and the weekly feedback survey items are provided in Appendix 4.J.

4.2.5 The intervention: ReFresh programme

The ReFresh programme was a six-week online fatigue management intervention adapted from the FACETS programme originally developed for people with multiple sclerosis. The intervention retained core cognitive behavioural and energy effectiveness components from FACETS but was modified to ensure relevance and accessibility for people with Parkinson's. Content wording and examples had been iteratively refined during development using principles of the Person-Based Approach (see Section 4.1.1).

Each of the six modules targeted a distinct domain of fatigue management: understanding fatigue mechanisms, activity pacing and energy conservation, cognitive restructuring, adaptive movement and physical activity planning, sleep and rest regulation, and sustaining behavioural change. Content was delivered through pre-recorded video sessions,

downloadable worksheets, structured reflection exercises, and optional diaries. A detailed breakdown of module objectives and exercises is provided in Appendix 4.A.

ReFresh Intervention lineage and adaptation process

ReFresh was derived from the manualised FACETS programme but was structurally and contextually adapted for a Parkinson's population and for independent online delivery. Core therapeutic components retained included cognitive reframing of fatigue-related beliefs, structured pacing and energy effectiveness strategies, behavioural experiments, and reflective practice exercises. However, several substantive modifications were introduced.

First, content examples were revised to reflect Parkinson's-specific challenges, including motor fluctuations, bradykinesia, rigidity, and variable energy patterns across the day. Second, delivery was modified from facilitated face-to-face group sessions to self-directed online modules. This removed live peer discussion and therapist facilitation as active ingredients, replacing them with structured reflection prompts and guided exercises. While this format increased accessibility and scalability, it may alter the social reinforcement mechanisms inherent in the original group-based FACETS model. Third, module duration was reduced and video content segmented to minimise cognitive load and accommodate fatigue-related concentration difficulties. Fourth, optional printable materials were incorporated to enhance accessibility for participants experiencing screen-related fatigue or dexterity limitations.

Adaptations were informed by evidence synthesis (Chapters 2 and 3) and structured survey feedback from eleven people with Parkinson's recruited via the Parkinson's UK Research Support Network. Feedback focused on clarity, tone, usability, and contextual relevance rather than formal qualitative interviews. Survey responses were reviewed iteratively, and

refinements were made to language complexity, example scenarios, formatting, and navigation. Although a formal co-design framework involving qualitative interview cycles was not employed, development was guided by principles of the Person-Based Approach, ensuring that modifications addressed user-identified barriers and engagement needs (see Section 4.1.1).

Acceptability framework and analytical use

Acceptability was conceptualised using the Theoretical Framework of Acceptability (TFA), which defines acceptability as a multi-dimensional construct capturing participants' cognitive and emotional responses to an intervention, including affective attitude, burden, perceived effectiveness, ethicality, intervention coherence, opportunity costs and self-efficacy (Sekhon, Cartwright & Francis, 2017). TFA was selected because the primary objective of this pilot RCT was to assess feasibility and participant experience of a newly adapted intervention, rather than implementation, scalability or organisational integration. As such, an individual-level acceptability framework was more appropriate than implementation-oriented models. Alternative frameworks were considered. Normalisation Process Theory focuses on the work required to embed interventions into routine practice and is more appropriate for implementation-stage research. RE-AIM provides a systems-level evaluation framework emphasising reach, adoption and maintenance across organisational contexts. Given that the present study was an early-phase feasibility trial evaluating participant experience of a newly adapted digital intervention, TFA was conceptually aligned with the study aims and provided a structured basis for both measurement and interpretive analysis at the individual level.

TFA informed both measurement and analysis. Weekly acceptability survey items were aligned to key TFA domains, including perceived usefulness, clarity, burden, engagement, and ease of application. In addition, free-text feedback was analysed using reflexive thematic analysis, followed by a deductive mapping step in which themes were examined against TFA constructs to enhance conceptual coherence. Full item wording and domain mapping are provided in Appendix 4.J.

Acceptability items were rated using a 5-point Likert scale to minimise cognitive burden and respondent fatigue while preserving sufficient discrimination for descriptive comparisons across modules in a population experiencing fatigue and fluctuating concentration. Wider response formats, such as 7-point scales, may increase response burden without materially improving measurement precision in brief repeated assessments. Visual analogue scales were considered but were deemed potentially less accessible across devices and screen formats. Post-intervention interviews or structured usability instruments were also considered; however, the study prioritised low-burden, repeated measurement compatible with online delivery and feasibility constraints.

Intervention delivery and adherence monitoring

The intervention was hosted on the University of East Anglia website, and the intervention link was provided only to participants randomised to the intervention arm during the active study period. Although access was restricted in this way, the platform did not support extraction of participant-level web analytics. Consequently, user-specific data such as time-on-page, module completion timestamps, or device type could not be linked to individual participants.

The original protocol anticipated capturing page hits and download activity as objective engagement indicators; however, the live platform did not permit retrieval of individualised usage data during the trial. Adherence was therefore assessed using (i) participant self-report of accessed modules within the weekly feedback surveys and (ii) Qualtrics survey timestamps to corroborate survey completion timing. Participants were not asked to return completed diaries or worksheets, as these were intended for personal use within the programme. The platform did not support extraction of participant-level analytics such as module completion logs or download activity.

The intervention did not require individual log-in credentials and did not include automated progress tracking or saved completion status. Participants accessed each module via a direct web link provided after randomisation. Progress within modules was not automatically stored, and participants were not required to formally mark modules as complete. Device type was not captured, and no participant-level information was available regarding whether materials were accessed via desktop, tablet, or mobile devices.

Engagement prompts were limited to weekly email reminders to complete the outcome survey. Access to the subsequent module link was provided following survey completion, functioning as a structured progression mechanism rather than an automated behavioural engagement tool. No additional automated prompts or scheduled researcher contact were built into the intervention beyond standard trial communications.

The pre-specified per-protocol threshold of accessing at least four of six modules was operationalised using participant self-report, corroborated by available submitted materials where possible. While this pragmatic approach enabled feasibility assessment under real-world conditions, it limited precision in objective engagement measurement, a limitation discussed in Section 4.5.

Control participants were offered access to the intervention following completion of endpoint assessment.

Introductory information remains publicly accessible at:
https://www.uea.ac.uk/groups-and-centres/projects/fatigue-management-in-parkinson-s
and intervention materials at:
https://www.uea.ac.uk/groups-and-centres/projects/fatigue-management-in-parkinson-s/refresh-study-getting-started

4.2.6 Comparator: waitlist control

Participants in the control group continued to receive their usual clinical care during the study period, which did not include any structured fatigue management. After the 16-week follow-up assessments, control group participants were provided with full access to the ReFresh programme.

4.2.7 Outcome measures

The study evaluated both feasibility and preliminary efficacy outcomes. Feasibility was assessed through recruitment rates, retention at 12 weeks, adherence to the intervention, and levels of participant engagement. All outcome measures were collected at two predefined timepoints: baseline prior to randomisation (Week 0) and endpoint at 12 weeks post-randomisation. The 12-week endpoint was selected to allow completion of the six-week intervention period followed by a consolidation phase, enabling assessment of short-term sustainability of effects rather than immediate post-module responses alone. Weekly

engagement and acceptability measures were collected during the initial six-week intervention period for participants in the intervention arm only. Adherence was operationalised as the number of ReFresh modules completed, with completion defined as engagement with at least four of the six modules. Engagement was measured using weekly survey responses, which included participant ratings of module content on a 5-point Likert scale (1 = strongly disagree to 5 = strongly agree) in response to the statement: "I found the content of this module helpful and engaging." Open-text feedback was also collected weekly in response to the question: "Please provide any comments or suggestions regarding this week's module or your experience with the programme."

Acceptability was assessed through overall satisfaction ratings collected at the endpoint using a 5-point Likert scale, in addition to qualitative feedback addressing participants' perceptions of programme relevance, usability, and perceived impact.

Preliminary efficacy was assessed using validated measures administered at baseline (Week 0) and at the 12-week endpoint. Fatigue severity was measured using the 16-item Parkinson's Fatigue Scale (PFS) (Brown et al., 2005) and the 21-item Modified Fatigue Impact Scale (MFIS) (Fisk et al., 1994). Fatigue self-efficacy was measured using the 9-item Multiple Sclerosis Fatigue Self-Efficacy Scale (MS-FSE) (Thomas et al., 2015). Quality of life was assessed with the 39-item Parkinson's Disease Questionnaire (PDQ-39) (Peto et al., 2001). Sleep quality was measured using the 19-item Pittsburgh Sleep Quality Index (PSQI) (Buysse et al., 1989). Mood was measured through the 15-item Geriatric Depression Scale (GDS-15) (Yesavage et al., 1982) and the 12-item Parkinson's Anxiety Scale (PAS) (Leentjens et al., 2014). Occupational performance was evaluated using the Canadian Occupational Performance Measure (COPM), a semi-structured, client-centred tool widely used in rehabilitation (Law et al., 1990).

The COPM was completed at baseline (Week 0), during which participants identified and rated up to five personally meaningful occupational goals, and these same goals were re-rated at the 12-week endpoint to assess change in perceived performance and satisfaction.

The COPM is traditionally administered as a semi-structured interview facilitated by a trained occupational therapist, allowing clarification, probing, and guided goal identification (Law et al., 1990). In this pilot study, the COPM was completed independently by participants via online self-report to accommodate remote delivery and minimise burden. While prior research has explored remote and modified administration formats, the absence of therapist facilitation may influence goal formulation clarity, rating consistency, and score comparability. Accordingly, COPM findings are interpreted as exploratory indicators of change within the context of a modified administration format.

4.2.8 Use of artificial intelligence tools

Generative artificial intelligence tools were used during the drafting process solely to support paraphrasing, grammatical correction, and reorganisation of text. No content, interpretation, or data analysis was produced by AI. All material was critically reviewed, edited, and finalised by the author to ensure accuracy, academic integrity, and compliance with the University of East Anglia's policy on the responsible use of generative AI.

4.2.9 Quantitative analysis

Descriptive statistics were used to summarise demographic characteristics and feasibility outcomes. Preliminary efficacy outcomes were analysed using independent-sample t-tests to

compare between-group differences and paired-sample t-tests for within-group changes. Both intention-to-treat (ITT) and per-protocol (PP) analyses were undertaken. In addition to p-values, effect sizes (Cohen's d) and 95% confidence intervals were calculated to estimate the magnitude and precision of observed differences. This approach is recommended in pilot and feasibility trials where studies are typically not powered to detect statistically significant effects, and effect estimates are intended to inform the design and sample size calculations of future definitive trials (Eldridge et al., 2016).

The ITT analysis employed last observation carried forward (LOCF) to impute missing endpoint data (Lachin, 2016). LOCF was selected because this pilot trial had a relatively small sample size and short follow-up period, and the primary aim was feasibility estimation rather than definitive treatment effect modelling. LOCF preserves the original randomisation and provides a conservative estimate when deterioration is expected over time.

However, LOCF assumes that participants' outcomes would have remained stable after their last recorded measurement. This assumption may be problematic in Parkinson's disease, where fatigue, mood, and functional status fluctuate over time and may worsen or improve unpredictably. LOCF can underestimate variability and potentially bias treatment effects towards the null or inflate stability where change may have occurred. Given these limitations, per-protocol analyses were also conducted and are presented in Appendix 4.K to allow comparison of analytic approaches. Findings should therefore be interpreted cautiously as exploratory estimates appropriate for a pilot feasibility study rather than confirmatory efficacy conclusions.

4.2.10 Qualitative analysis

Qualitative data comprised anonymous weekly open-text responses collected after each module (Weeks 1 to 6), in addition to endpoint reflection responses collected at 12 weeks. Open-text response occasions were analysed. Because weekly surveys were completed anonymously and not linked to persistent participant identifiers, it was not possible to determine the number of unique individuals contributing qualitative responses.

Data were analysed using Braun and Clarke's six-phase reflexive thematic analysis approach. Analysis began with familiarisation through repeated reading of all responses. Initial codes were generated inductively at a semantic level, capturing explicit meanings within participant accounts. Codes were then collated into candidate themes, which were iteratively reviewed, refined, and defined to ensure internal coherence.

The qualitative analysis was conducted by the lead researcher. Given the feasibility focus of the trial, the brief nature of responses, and the descriptive purpose of the qualitative component, formal independent double coding was not undertaken. Theme development and interpretation were discussed with supervisory team members to enhance analytic credibility and reflexivity.

Coding and theme organisation were conducted manually using Microsoft Excel. Following inductive theme generation, themes were examined in relation to domains of the Theoretical Framework of Acceptability to support conceptual integration with quantitative findings.

As responses were anonymised and not linked to participant identifiers, it was not possible to present participant-level evidence tables demonstrating the distribution of quotes across individuals.

4.3 Results

4.3.1 Feasibility Outcomes

4.3.1.1 Recruitment Feasibility

The ReFresh pilot RCT exceeded its initial recruitment target of 40 participants. In total, 150 individuals accessed the online baseline survey; 118 completed the full baseline assessment, provided informed consent, and were randomised (intervention n = 58; control n = 60). The remaining 32 individuals did not progress to randomisation: 22 accessed the survey but did not complete consent or the baseline survey, while 10 provided consent but withdrew before completing baseline measures. Consent was obtained via mandatory items in the Qualtrics platform prior to progression. Because the digital recruitment system did not consistently record reasons for non-completion, precise causes for early attrition are unavailable. Attrition between expression of interest and formal enrolment is common in digital trials of complex behavioural interventions and should be considered when interpreting recruitment results (Eysenbach, 2005; Christensen et al., 2009). A CONSORT flow diagram summarising participant progression is provided in Figure 4.1.

Characteristics for the intervention and control groups are summarised in Table 4.1.

12 Table 4.1. Baseline characteristics of participants randomised to intervention and control groups

	Intervention (n=58)	**Control (n=60)**	**Total (n=118)**
Gender (%)	**Intervention (n=58)**	**Control (n=60)**	**Total (n=118)**
Female, %	53.3	46.2	50.0
Male, %	46.7	53.8	50.0
Years since diagnosis, mean (SD)	**Intervention (n=58)**	**Control (n=60)**	**Total (n=118)**
Years since diagnosis	6.4 (3.1)	6.7 (3.5)	6.6 (3.3)
Age group (%) — uses endpoint respondents	**Intervention (n=27)**	**Control (n=30)**	**Total (n=57)**
45–54 years	3 (11.1%)	0 (0.0%)	3 (5.3%)
55–64 years	7 (25.9%)	7 (23.3%)	14 (24.6%)
65–74 years	13 (48.1%)	15 (50.0%)	28 (49.1%)
75+ years	4 (14.8%)	8 (26.7%)	12 (21.1%)
Employment status (n, % of randomised)	**Intervention (n=58)**	**Control (n=60)**	**Total (n=118)**
Retired	32 (55.2%)	30 (50.0%)	62 (52.5%)
Working	12 (20.7%)	15 (25.0%)	27 (22.9%)
Other	14 (24.1%)	15 (25.0%)	29 (24.6%)
Living status (n, % of randomised)	**Intervention (n=58)**	**Control (n=60)**	**Total (n=118)**
Living alone	20 (34.5%)	18 (30.0%)	38 (32.2%)
Living with others	38 (65.5%)	42 (70.0%)	80 (67.8%)
Assistive device use (n, % of randomised)	**Intervention (n=58)**	**Control (n=60)**	**Total (n=118)**
Uses device	15 (25.9%)	12 (20.0%)	27 (22.9%)
Does not use device	43 (74.1%)	48 (80.0%)	91 (77.1%)
Ethnicity (n, % of randomised)	**Intervention (n=58)**	**Control (n=60)**	**Total (n=118)**
White	55 (94.8%)	54 (90.0%)	109 (92.4%)
Other	3 (5.2%)	6 (10.0%)	9 (7.6%)

Note. Age was not collected at baseline due to a survey design error. Age values shown use endpoint age bands for participants matched to endpoint records (Intervention n=27; Control n=30; Total n=57). Percentages are within-column for those denominators. Abbreviation: SD = standard deviation.

Baseline characteristics were broadly comparable between the intervention and control groups across the measured demographic and disease-related variables (Table 4.1). The distribution of gender, years since diagnosis, employment status, living arrangements, assistive device use, and ethnicity appeared similar across groups, suggesting that randomisation achieved reasonable balance between trial arms. Consistent with recommendations for reporting randomised controlled trials, formal statistical testing of baseline differences was not performed, as any observed differences following randomisation are expected to arise by chance (Moher et al., 2010; de Boer et al., 2015). Baseline characteristics are therefore presented descriptively to allow readers to assess group comparability.

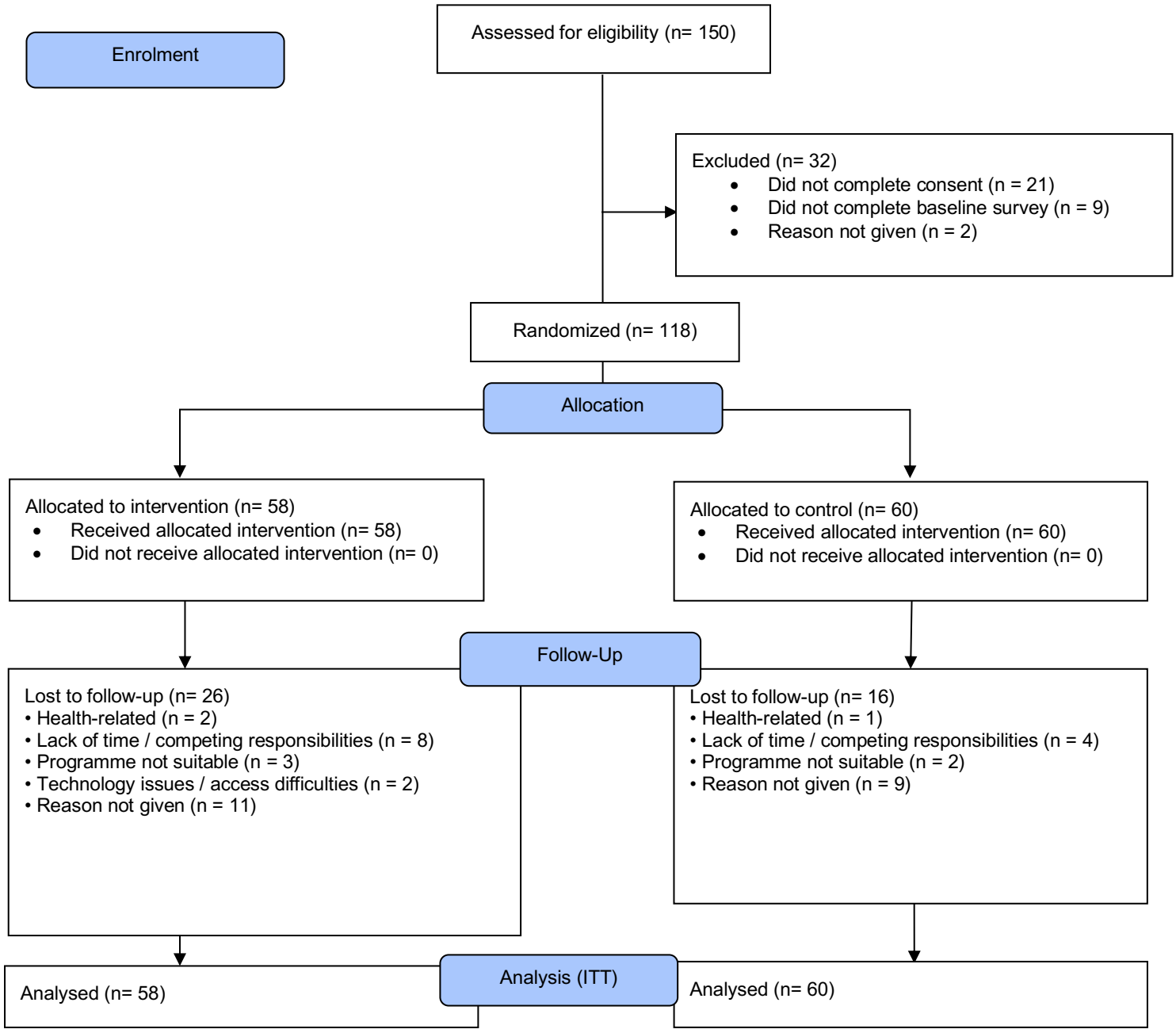
Recruitment strategies leveraging Parkinson's UK networks, particularly the Research Support Network (RSN), newsletters, and social media, proved highly effective, with approximately 65% of participants reporting that they had heard about the study through these channels.

4.3.1.2 Retention feasibility

At the 12-week endpoint, 76 participants (64.4%) completed the outcome survey, while 42 participants (35.6%) withdrew during the study period. Retention was lower in the intervention group (55.2%, 32/58) compared to the control group (73.3%, 44/60), indicating potential barriers to sustained engagement with the ReFresh programme. Reported reasons for withdrawal included health challenges, the perceived burden of the programme, and competing personal or family responsibilities.

In line with CONSORT 2010 recommendations (Schulz, Altman and Moher, 2010), all 118 randomised participants were retained within the intention-to-treat (ITT) analysis. In contrast, 62 participants who failed to complete endpoint assessments were excluded from the per-protocol (PP) analysis. A further three participants who completed endpoint surveys were excluded due to missing key outcome data (e.g., incomplete fatigue or self-efficacy measures). The PP analysis was therefore based on 53 participants in total (32 intervention, 21 control), reflecting only those who adhered to the protocol and provided complete outcome data.

Figure 4.1. CONSORT 2010 Flow Diagram of Participant Progression [1]



4 *Figure 4.1. CONSORT 2010 Flow Diagram of Participant Progression*

[1] Reasons are taken from withdrawal logs and weekly feedback forms; 'reason not given' indicates participants withdrew without providing a reason

Participants described their struggle with continuing with the ReFresh program:

"I was really interested at the start, but after a few weeks, I found it hard to keep up. It wasn't that I didn't find it useful, I just didn't have the energy to stay engaged."

"I was overenthusiastic when I signed up. I really do not have the time to give the programme my full commitment."

4.3.1.3 Adherence and Engagement Feasibility

Adherence to the ReFresh programme was evaluated using completion of weekly feedback surveys associated with each of the six modules. Among the 58 participants allocated to the intervention arm, engagement declined progressively across the intervention period. Weekly feedback responses decreased from 34 in Week 1 to 31 in Week 2 and 27 in Week 3, followed by a sharper decline in later modules (18 in Week 4, 22 in Week 5, and 14 in Week 6). Across the six modules, a total of 149 weekly response occasions were recorded.

Because participant-level web analytics were not available, module access could not be objectively verified. Engagement was therefore inferred using self-reported weekly surveys, worksheet submissions, and survey timestamps. Although participation declined over time, early module engagement suggests that the programme was initially acceptable and accessible to many participants with Parkinson's disease. Detailed weekly item-level descriptive statistics for acceptability ratings are presented in Appendix 4.J (Table J2). Although engagement declined over time, a substantial proportion of participants interacted with the programme during the early modules, indicating that the ReFresh intervention was acceptable and usable for many participants with Parkinson's disease. These engagement patterns are consistent with attrition commonly observed in unguided digital behavioural

interventions and support the feasibility of further refinement and evaluation in a future definitive trial.

4.3.2 Inclusivity Measures

To enhance accessibility, printed versions of ReFresh programme resources were provided upon request. The materials provided were in both PDF and Word formats: Exercise Videos, Activity Diary, Energy Measures Sheet, Rest/Activity/Sleep Planner, Deep Breathing Exercises, Prioritisation Sheet, Weekly Planner, Thought Diary Sheet, Thought Challenge Technique, Forcefield Sheet, Keeping on Track Planner, and a Bumper Pack containing all homework sheets. Twelve participants opted to receive printed materials, citing reasons such as small on-screen font (Age UK, 2024; Ofcom, 2024), difficulty typing into digital forms, and lack of access to Microsoft Word licences. All materials were made available in both Word and PDF formats, with participants able to request either standard (12-point) or large (16-point) font. No participants requested large-print materials.

This inclusive approach was informed by participant feedback such as:

- *"I can't write on the diary or energy docs, so could you please send a printable copy in the standard font?"*
- *"Having trouble opening Word docs; I don't have a licence."*
- *"Please send me the ReFresh study document pack."*

While not all requesters specified a reason, these comments reflect varied needs related to readability, usability, and digital compatibility. This underscores the importance of offering programme materials in multiple accessible formats for future digital health interventions (Spreadbury et. al, 2022)

One participant noted:

"I struggled with the website at first, but having the printed materials helped me follow along."

4.3.3 Acceptability of the ReFresh Programme

Participants rated their satisfaction with the ReFresh programme on a 5-point Likert scale (1 = low, 5 = high). Mean ratings across domains exceeded 4.5 (Table 4.2), indicating favourable participant appraisal. Pooled across all completed weekly feedback forms (n = 149 response occasions), ratings remained consistently high (see Appendix 4.J, Table J1). Because weekly survey completion varied across modules, pooled estimates reflect total response occasions rather than unique individuals. Week-specific denominators and item-level distributions are reported in Appendix 4.J (Table J2) to enable transparent interpretation of temporal response patterns. A weekly summary of quantitative satisfaction and qualitative feedback is also presented in Appendix 4.J.

13 Table 4.2. Participant Satisfaction Ratings for the ReFresh Programme

Programme Aspect	Mean (SD)
Programme Content	4.7 (±0.5)
Format and Usability	4.6 (±0.6)
Relevance to Participants' Needs	4.8 (±0.4)

Abbreviation: SD = standard deviation

Participants' open-ended responses to the prompt "*Please share any other feedback about the programme, including what you found most helpful, anything you struggled with, or anything you think should be changed*" identified several strengths and challenges of the programme:

Participants described practical, relevant content:

> *"This programme gave me practical tools to manage my fatigue in a way that fit into my daily routine without feeling overwhelming."*

They suggested improvements. Some participants reported difficulty maintaining motivation and suggested more interactive elements, such as peer discussion groups or regular facilitator check-ins. Among those in the intervention arm (n=58), the following barriers to participation were reported:

- Technical difficulties: 12.1% (n=7)
- Cognitive overload: 10.3% (n=6)
- Limited motivation: 8.6% (n=5)

Participants highlighted these barriers clearly:

"I wanted to stick with it, but I needed more check-ins or support to stay motivated."

However, acceptability findings should be interpreted with caution. Retention in the intervention arm was relatively low (55.2%), meaning that satisfaction ratings largely reflect the views of participants who remained engaged with the programme. Individuals who withdrew may have had less favourable experiences but did not complete acceptability surveys. As a result, the reported satisfaction ratings may overestimate the true acceptability

of the intervention. This potential attrition bias is common in digital behavioural interventions and should be considered when interpreting participant feedback.

4.3.4 Preliminary Efficacy Outcomes

Preliminary efficacy outcomes (intention-to-treat analysis) are summarised in Table 4.3. In brief, neither primary fatigue measure (PFS, MFIS) showed a statistically significant between-group difference at 12 weeks (see Table 4.3). By contrast, fatigue self-efficacy (MS-FSE) improved in the intervention group compared with control (between-group mean difference +6.72 points, 95% CI 1.68 to 11.76, Cohen's d = 0.48, p = 0.05). reflecting a mean increase of 5.45 points (SD 13.80) in the intervention group compared with a mean decrease of 1.27 points (SD 14.18) in the control group. Secondary outcomes including sleep (PSQI), quality of life (PDQ-39), anxiety (PAS) and depression (GDS) showed small, non-significant changes. Full numerical results (baseline and endpoint means, SDs, and between-group p-values) are presented in Table 4.3.

Table 4.3. Intention-to-treat analysis of primary and secondary outcome measures at 12 weeks

14 Table 4.3. Intention-to-treat analysis of primary and secondary outcome measures at 12 weeks

Measure	Group	Baseline Mean (SD)	Endpoint Mean (SD)	Change Mean (SD)	T test (Intervention vs. Control mean change)
Fatigue Measures					

PFS	Intervention (n=58)	56.18 (14.93)	53.13 (16.24)	-3.05 (9.54)	P=0.102
	Control (n=60)	57.31 (13.09)	57.52 (13.04)	0.21 (7.84)	
MFIS	Intervention (n=58)	40.61 (15.60)	39.85 (18.62)	-0.75 (11.38)	P=0.33
	Control (n=60)	42.70 (14.01)	42.87 (15.43)	0.16 (8.25)	
Secondary Measures					
MS-FSE	Intervention (n=58)	47.06 (25.12)	52.52 (24.13)	5.45 (13.80)	P=0.05*
	Control (n=60)	45.77 (20.60)	44.50 (20.28)	-1.27 (14.18)	
PSQI	Intervention (n=58)	9.47 (3.03)	9.17 (2.99)	-0.30 (1.21)	P=0.09
	Control (n=60)	10.49 (3.24)	10.16 (3.02)	-0.39 (1.46)	
PDQ	Intervention (n=58)	26.10 (15.92)	29.34 (20.84)	3.25 (15.35)	P=0.47
	Control (n=60)	29.49 (16.09)	32.00 (24.56)	2.84 (17.27)	
PAS	Intervention (n=58)	24.79 (11.72)	25.26 (11.31)	0.48 (5.06)	P=0.72
	Control (n=60)	25.59 (10.71)	25.95 (9.73)	0.36 (5.78)	
GDS	Intervention (n=58)	4.41 (3.80)	5.00 (4.54)	0.59 (1.86)	P=0.25

	Control (n=60)	4.91 (3.66)	5.91 (4.18)	1.00 (1.94)	

Abbreviations**:** GDS = Geriatric Depression Scale; MFIS = Modified Fatigue Impact Scale; MS-FSE = Multiple Sclerosis Fatigue Self-Efficacy Scale; PAS = Parkinson's Anxiety Scale; PDQ = Parkinson's Disease Questionnaire-39; PFS = Parkinson's Fatigue Scale; PSQI = Pittsburgh Sleep Quality Index; SD = Standard Deviation; ITT = Intention-To-Treat; n= number of participants.

Scale ranges: PFS (16–80); MFIS (0–84); MS-FSE (0–90); PSQI (0–21); PDQ-39 (0–100); PAS (0–48); GDS-15 (0–15).

4.3.5 Primary outcomes

Fatigue is a complex construct that requires multi-dimensional assessment. In this pilot trial, two validated tools were used to evaluate fatigue severity and impact: the Parkinson's Fatigue Scale (PFS) and the Modified Fatigue Impact Scale (MFIS). Neither measure demonstrated a statistically significant between-group difference at 12 weeks, and the observed changes were small in magnitude. The change in MFIS scores in the intervention group (mean change -0.75, p = 0.33) was substantially below the minimal clinically important difference (MCID) of 13.8 points reported for people with Parkinson's disease (Kluger et al., 2017). No agreed MCID is available for the PFS; however, the magnitude of change observed in this study (mean change -3.05, p = 0.102) was modest and should be interpreted as exploratory rather than clinically meaningful.

4.3.6 Secondary outcomes

4.3.6.1 Fatigue Self-Efficacy

The MS-Fatigue Self-Efficacy Scale (MS-FSE) showed a statistically significant improvement in the intervention group compared to control, a between-group difference of +6.72 (p=0.05).

Participants reflected positively on this aspect, noting:

"I used to feel helpless when my fatigue hit, but now I have strategies I can rely on, even if they don't always work perfectly."
"I think the programme helped me pace myself better, but my fatigue levels didn't change overnight."

To determine the most meaningful outcome for a future fully powered trial, a follow-up outcome prioritisation survey was conducted with the eleven s who contributed to programme development. Seven responded, and six prioritised *"improved ability to manage fatigue"* over *"reduction in fatigue."* They described fatigue as persistent and complex, emphasising the value of coping strategies over symptom eradication. One respondent prioritised fatigue reduction. These results support the selection of fatigue self-efficacy as the primary outcome in future trials (see Appendices 4.F and 4.G).

4.3.6.2 Quality of Life

Quality of life, assessed using the Parkinson's Disease Questionnaire-39 (PDQ-39), showed a small, non-significant improvement in the intervention group (mean change 3.25 points). This change was below the reported minimal clinically important difference (MCID) of 4.7 for PwP disease, suggesting limited clinical impact (Horváth et al., 2017).

4.3.6.3 Sleep

Sleep quality, measured using the Pittsburgh Sleep Quality Index (PSQI), also showed small, non-significant reductions in both groups (mean change ~0.3 points). This is well below the MCID of 4.4 reported in clinical populations (Longo et al., 2021), suggesting that the intervention did not meaningfully affect sleep quality. These findings highlight the complex and often bidirectional relationship between sleep disturbance and fatigue in neurological conditions (Schütz et al., 2022).

4.3.6.4 Depression and Anxiety

Depression and anxiety were assessed using the Geriatric Depression Scale (GDS-15) and the Parkinson's Anxiety Scale (PAS), respectively. In the intention-to-treat (ITT) analysis, no

statistically significant between-group differences were observed (Table 4.3). In the per-protocol analysis (Appendix 4.K), a small numerical improvement in depression scores was observed in the intervention group (mean change = −0.17, SD = 2.73) compared with a worsening in the control group (mean change = +0.83, SD = 2.48), with a between-group p-value of 0.05. However, the high attrition rate and associated risk of bias limit the interpretability of these findings. Anxiety scores remained stable across both groups with negligible change. Given the small sample size and the exploratory nature of this pilot study, the trial was not powered to detect small changes in mood outcomes; therefore, these findings should be interpreted cautiously.

4.3.6.5 Occupational Performance

Only ten participants in the ReFresh group completed self-evaluations of their current occupational performance and satisfaction using (COPM)[2] (Law et al., 1990).

This measure is typically administered in collaboration with an occupational therapist to support the identification of personal goals and performance challenges (Canadian Occupational Performance Measure, 2024). The self-directed nature of completion may have contributed to the low response rate due to its cognitive complexity.

A thematic analysis of participant-specified COPM goals identified five key areas:

1. Physical activities and mobility: Increased endurance and independence
2. Social engagement: Greater involvement in social activities
3. Household management: Improved ability to manage daily tasks

[2] Note: In this pilot the COPM was completed by participants as a self-administered instrument rather than via the standard therapist-led semi-structured interview. Only ten participants in the intervention arm completed the COPM; consequently these data are exploratory and should be interpreted cautiously given the altered administration mode and small sample size (Law et al., 1990; Kobayashi et al., 2023).

4. Personal care: Enhanced self-care routines
5. Cognitive and creative activities: Renewed participation in hobbies and mental stimulation

The data showed that participant-identified goals demonstrated improvements, these exceeded the two-point threshold commonly cited in the COPM literature as indicative of a clinically meaningful change (Eyssen et al., 2011). Mean change in performance was +2.28 and in satisfaction was +2.44 (Table 4.4).

15 Table 4.4. Canadian Occupational Performance Measure (COPM) outcomes for intervention participants

COPM Component	Baseline Mean (SD)	Endpoint Mean (SD)	Mean Change
Performance	6.14	8.42	+2.28
Satisfaction	6.12	8.56	+2.44

Abbreviation: SD = standard deviation

Themes from participant-identified goals highlighted improvements in mobility, social engagement, household management, personal care, and cognitive/creative activities. Reflections reinforced these findings, including: *"It's not that I have more energy, but I'm using my energy in a smarter way now"* and *"I'm able to do more of what I want to do; not necessarily because I have more energy, but because I'm using it better."*

4.3.7 Participant Reflections on the ReFresh Programme

Participants were asked three open-ended questions; whether the programme helped them achieve their initial goals, what positive or negative experiences they had during participation, and what suggestions they had for improvement. Their responses revealed four interrelated themes that provide additional context to the quantitative findings.

4.3.7.1 Challenges of using an online resource:

Several participants expressed that the absence of structured support limited their engagement. They emphasised that more interactive elements or regular check-ins could have sustained their motivation. One participant explained, *"An occasional check-in with a facilitator might have kept me more engaged,"* while another noted, *"The strategies were helpful, but I needed more reminders or encouragement to keep going."* These perspectives underscore the broader literature on digital interventions for Parkinson's disease, which highlights that structured human support—whether from facilitators or peers—can be critical for retention (Gerritzen et al., 2022).

4.3.7.2 Digital literacy:

Several participants reported difficulty accessing programme materials, with one commenting, *"I had trouble accessing materials initially; a phone call or video guide would have helped."* These barriers likely reflect the lower levels of digital confidence within an older population (Age UK, 2024; Ofcom, 2024). National data confirm this trend: Ofcom (2024) reported that 6% of UK households (approximately 1.7 million) lacked internet

access, often due to concerns about complexity or online safety. Motivational barriers such as low confidence, fear of scams, and limited skills remain prevalent among older adults and those with long-term conditions (POST, 2024; Romanowski and Lally, 2024). More recent evidence indicates that digital exclusion among older adults remains a significant problem. Age UK's national analysis found that around 4.7 million people aged 65+ lack the basic skills needed to use the internet successfully (Age UK, 2024) and, in July 2025, Age UK estimated 2.4 million older people (≈19%) use the internet less than once a month or not at all. These data confirm that offering printed or offline alternatives and tailored digital support remains necessary when delivering online interventions for older people. These findings suggest that future iterations of ReFresh should integrate tailored digital support strategies, such as telephone helplines, visual "how-to" guides, or peer "tech buddy" systems, to mitigate digital exclusion and improve engagement (Age UK, 2024). These steps are likely to increase accessibility and retention for older participants and those with limited digital skills.

4.3.7.3 Increased awareness and self-management

Many participants described a heightened awareness of how their behaviours influenced fatigue patterns. One reflected, *"I never realised how much overdoing it one day affected me for days after."* Such comments indicate that, even without measurable reductions in fatigue severity, participants developed greater insight into pacing and energy management. This aligns with the intervention's emphasis on cognitive–behavioural and occupational therapy techniques, which prioritise behaviour change and coping strategies over immediate symptom reduction.

4.3.7.4 Emotional and psychological impact.

Several participants reported that their emotional response to fatigue shifted because of the programme. One participant observed, *"I still get fatigued, but now I don't let it overwhelm me as much."* These reflections reinforce the quantitative finding of improved fatigue self-efficacy, illustrating how participants reinterpreted their fatigue experiences in ways that enhanced resilience and psychological wellbeing. Such outcomes are consistent with the literature on self-management interventions, where increased self-efficacy is often a more reliable early indicator of success than symptom reduction (Thomas et al., 2015).

Taken together, these qualitative insights demonstrate that while ReFresh may not have significantly reduced fatigue severity, it enabled participants to reconceptualise and manage fatigue more effectively in daily life. This highlights the importance of integrating participant feedback and digital inclusion strategies into the design of future interventions.

4.3.8 Adverse Events

No adverse events were formally reported by participants in either the intervention or control group. Specifically, although participants were asked about falls during endpoint data collection, no falls were reported

4.4 Discussion

The findings from this pilot study indicate that the ReFresh online fatigue management programme is both feasible and acceptable. High levels of participant satisfaction were reported, and preliminary analyses demonstrated a statistically significant between-group difference in fatigue self-efficacy (mean difference +6.72, 95% CI 1.68 to 11.76, Cohen's d = 0.48). Changes in occupational performance were observed in a small subgroup; however, these findings should be interpreted cautiously due to limited sample size and non-standard administration procedures.

Recruitment to the trial exceeded expectations, reflecting both the high level of interest in the management of fatigue and the paucity of structured support available in routine clinical practice. The programme initially attracted 150 individuals, of whom 118 proceeded to full consent and randomisation. This level of engagement highlights the perceived relevance of fatigue as a target for intervention and underscores the extent to which people with Parkinson's (PwP) are willing to engage with digital solutions when conventional options are lacking.

Despite successful recruitment, retention presented a significant challenge. At the twelve-week endpoint, 42 participants (35.6%) had withdrawn from the study, with dropout rates notably higher in the intervention arm (44.8%, 26/58) than in the control arm (26.7%, 16/60). Qualitative feedback indicated that the most frequently cited reasons for disengagement included health-related complications, the perceived burden of participation, and competing personal or family responsibilities. Participants also reported difficulties with digital literacy, a lack of structured support, and reduced motivation once the initial novelty of the programme had diminished. These factors reflect challenges common to many digital health interventions.

High dropout rates in online programmes have been well documented. For example, Okusa et al. (2025) reported a 48.5% attrition rate in a six-month telerehabilitation intervention for Parkinson's disease, and Zhang et al. (2024) identified dropout rates between 29% and 48% across more than 290,000 participants in internet-based mental health interventions. Importantly, these reviews also show that attrition can be substantially reduced by adding structured human support such as peer contact or facilitator check-ins. This aligns with Eysenbach's (2005) "law of attrition," which emphasises the tendency of participants to disengage from digital programmes in the absence of accountability. Consistent evidence (Elbers et al., 2015; MacLean et al., 2025) indicates that interventions offering opportunities for human interaction are associated with higher adherence. Taken together, these findings suggest that future iterations of ReFresh should consider embedding light-touch human support (peer mentoring, group discussion, facilitator check-ins) to enhance motivation and retention.

Despite engagement challenges, participants valued the programme content. Satisfaction ratings averaged above 4.6/5 across domains of programme content, usability, and relevance. Consistent with high pooled TFA ratings (Appendix 4.J, Table J1), participants valued the content, although week-by-week patterns indicate variability in "ease of application" and "engagement" (Appendix 4.J, Table J2). Open-text feedback indicated a preference for more interactive components, consistent with evidence that social support enhances engagement and effectiveness in digital interventions (MacLean et al., 2025). Future refinements may therefore combine the self-directed format with optional interactive components.

Accessibility also emerged as a key issue. Although the programme was delivered online to maximise reach, several participants encountered digital barriers (navigation, screen readability, low confidence). Twelve participants requested printed resources, citing small

on-screen font, difficulty editing electronic files, or lack of compatible software. These findings reinforce the need for printable alternatives and tailored digital support in future trials.

The intervention appeared to exert a greater effect on fatigue self-efficacy than on fatigue severity. The between-group difference in fatigue self-efficacy corresponded to a moderate effect size (Cohen's d = 0.48), whereas fatigue severity measures (PFS and MFIS) showed small, non-significant changes. The mean difference in MS-FSE between groups was +6.72 points (95% CI 1.68 to 11.76, p = 0.05). Lay advisers prioritised "improved ability to manage fatigue" over "fatigue reduction" when asked about meaningful outcomes, supporting fatigue self-efficacy as a candidate primary outcome for a definitive trial.

These findings are broadly consistent with previous behavioural fatigue management interventions developed for other neurological conditions. For example, the FACETS programme for people with multiple sclerosis demonstrated improvements in fatigue self-efficacy and fatigue coping, while reductions in fatigue severity were modest (Thomas et al., 2013). Similar patterns have been reported in other behavioural fatigue management interventions, where improvements in perceived control and fatigue management strategies often precede measurable reductions in fatigue severity. The present findings therefore align with emerging evidence suggesting that behavioural fatigue interventions may exert their primary effects by strengthening coping strategies and self-management skills rather than directly reducing fatigue intensity.

It should also be noted that the observed changes in fatigue severity (PFS and MFIS) did not approach established thresholds for minimal clinically important difference (MCID), indicating that fatigue severity itself was not meaningfully altered within the timeframe of this pilot intervention.

COPM showed clinically meaningful improvements in the small subgroup that completed the measure, suggesting the value of embedding occupational therapy strategies. These results are promising but must be interpreted cautiously due to the small sample and the non-standard, self-completed COPM administration.

No adverse events were reported, including no falls. While reassuring, safety monitoring relied on passive self-report at follow-up and thus may have missed minor events. Larger trials should incorporate prospective, structured safety monitoring and standardised adverse event logs (see Appendices 4.L–4.M).

The findings of this pilot trial suggest that progression to a fully powered randomised controlled trial is warranted; however, several refinements should be implemented first. In particular, future studies should incorporate light-touch human support to improve retention, implement objective platform analytics to measure engagement more accurately, and introduce structured safety monitoring procedures. Refinement of outcome selection may also be required, with fatigue self-efficacy emerging as a potentially more appropriate primary outcome than fatigue severity. Once these methodological considerations have been addressed, a definitive multi-centre RCT would be needed to determine the effectiveness and cost-effectiveness of the ReFresh programme for people with Parkinson's disease.

4.5 Limitations

Several limitations affect the interpretation and generalisability of these pilot findings.

First, this was a small, underpowered pilot trial and was not designed to provide definitive estimates of efficacy. The absence of statistically significant effects on fatigue severity

should therefore be interpreted as preliminary and hypothesis-generating rather than conclusive.

Second, the study relied predominantly on self-reported outcomes and self-reported module engagement. This increases the risk of recall bias, measurement error, and social desirability bias (Bowling, 2005; Podsakoff et al., 2003). Objective platform analytics originally planned in the protocol, such as page hits, time-on-page, and individual logins, were not retrievable at participant level during implementation. Adherence and fidelity were therefore operationalised pragmatically using weekly self-report items and Qualtrics survey timestamps. Participants were not required to return completed worksheets or diaries, as these materials were intended for personal use. Objective platform analytics originally planned in the protocol, such as page hits, time-on-page, or download activity, were not retrievable at the participant level during implementation. While feasible within real-world constraints, this approach limits the precision of engagement measurement and may under- or over-estimate true intervention exposure.

Third, attrition was substantial (35.6% overall) and differential between arms (intervention 44.8% vs control 26.7%). Differential dropout introduces potential attrition bias and reduces the effective sample for per-protocol analyses. This pattern is commonly observed in unguided digital interventions (Eysenbach, 2005) and may reflect limited interactive support within the online format. However, attrition may also be associated with symptom burden, motivation, or fluctuating disease status, which could influence outcome trajectories.

An additional limitation relates to the handling of missing outcome data in the context of this attrition. The intention-to-treat analysis employed last observation carried forward (LOCF) to impute missing endpoint values. While LOCF preserves randomisation and offers a pragmatic solution in small pilot trials, it assumes that participants' outcomes would have

remained stable after their last recorded measurement. This assumption may be particularly problematic in Parkinson's disease, where fatigue, mood, and functional performance are characterised by intra-individual variability and motor fluctuations. LOCF may therefore underestimate true variability, obscure deterioration, or artificially stabilise outcomes that would otherwise have changed. Moreover, given the differential attrition between study arms, missingness may not have been random and may have been associated with engagement levels or perceived intervention benefit, increasing the risk of biased estimates. Efficacy findings should therefore be interpreted cautiously as exploratory. Future adequately powered trials should consider more robust missing-data approaches, such as multiple imputation or mixed-effects modelling, to better account for uncertainty and within-person change.

Fourth, eligibility criteria and Parkinson's diagnosis were self-reported online. No clinician verification, cognitive screening, or formal assessment of digital literacy was conducted. While these pragmatic choices facilitated recruitment and enhanced scalability, they may have biased the sample towards more digitally confident, English-proficient individuals and limit external validity, particularly for older adults with lower digital skills.

Fifth, Parkinsonian medication use and medication changes were not systematically monitored or controlled during the study period. Given the known influence of dopaminergic fluctuations on fatigue, mood, and activity levels, medication variability may have confounded outcome trajectories.

Sixth, the Canadian Occupational Performance Measure (COPM) was completed independently online rather than administered in its standard therapist-facilitated semi-structured format (Law et al., 1990). Although structured written instructions and explicit 1–10 scale anchors were provided, the absence of therapist probing may have reduced goal specificity and increased variability in scale interpretation. The COPM relies on guided

clarification to ensure occupations are defined precisely and that rating anchors are applied consistently. Its adaptation for independent online completion therefore introduces potential measurement error, and findings should be interpreted as exploratory feasibility indicators rather than definitive evidence of occupational performance change.

Seventh, safety monitoring relied on passive self-report at follow-up and may not have captured minor adverse events or transient difficulties occurring during the intervention period.

Finally, the qualitative component relied on anonymous weekly open-text responses that were not linked to participant identifiers. While anonymity may have facilitated candid feedback and reduced participation burden, it limited the ability to assess participant-level thematic distribution or longitudinal narrative development across modules.

Where possible, these limitations have been reported transparently and used to inform the design of a future definitive randomised controlled trial. Specifically, a subsequent trial should: (i) secure individual-level objective engagement metrics or embed alternative objective usage measures; (ii) incorporate light-touch human support to reduce attrition; (iii) implement structured prospective safety monitoring; (iv) monitor medication changes; (v) include brief digital literacy screening; and (vi) use more robust missing-data methods than LOCF.

4.6 Implications and next steps

A fully powered randomised controlled trial should use fatigue self-efficacy as the primary outcome, reflecting patient priorities and the most responsive measure in this pilot. Power

calculations based on the pilot effect size for fatigue self-efficacy were conducted using G*Power version 3.1 (Faul et al., 2009). Assuming a two-tailed significance level of $\alpha = 0.05$ and statistical power of 80% ($1-\beta = 0.80$), the estimated sample size for a definitive trial would be approximately 474 participants after accounting for anticipated attrition.

Recruitment should aim for more diverse populations and include embedded strategies to improve retention (human support, tech help). Extended follow-up (6–12 months) would enable assessment of sustainability and cost-effectiveness. Clinically, findings do not yet justify routine adoption of ReFresh, but the programme appears safe, acceptable and promising for promoting fatigue self-management if adapted to address engagement and inclusion barriers.

4.7 Conclusion

This pilot randomised controlled trial evaluated the feasibility, acceptability, and preliminary efficacy of the ReFresh online fatigue management programme for PwP disease. Recruitment was highly successful, with 118 participants randomised, demonstrating both the willingness of PwP to engage with fatigue-focused research and the value of patient advocacy networks in supporting study enrolment. The intervention was safe, no adverse events were reported, and satisfaction ratings indicated strong acceptability of the programme content.

The trial also revealed important limitations and challenges. Retention was modest, with a withdrawal rate of 35.6%, higher in the intervention group than in the control group. These patterns mirrored findings from other digital health interventions and reflected barriers such as digital literacy, competing demands, and the absence of structured support. While no statistically significant changes were observed in fatigue severity, the intervention produced a significant improvement in fatigue self-efficacy, a finding reinforced by lay advisor feedback that prioritised the ability to manage fatigue as a more meaningful outcome than symptom reduction. Small improvements in occupational performance and mood were also observed, though the study was underpowered to detect clinically significant effects across secondary measures.

Taken together, the findings suggest that ReFresh has the potential to be a scalable and cost-effective intervention for enhancing self-management of fatigue in Parkinson's disease, particularly if integrated with structured support mechanisms to improve adherence and accessibility. The trial also demonstrated the feasibility of adapting an intervention originally developed for multiple sclerosis and delivering it effectively in a Parkinson's population.

This chapter builds on the preceding systematic and scoping reviews, which highlighted the paucity of robust evidence for non-pharmacological fatigue interventions in Parkinson's disease, and provides a feasibility evaluation that informs the design of a future fully powered RCT. It adds to the evidence suggesting that fatigue self-efficacy may be a more meaningful, patient-centred primary outcome than fatigue severity alone.

The following reflective chapter provides a concise account of the researcher's positionality, use of generative AI, and methodological accommodations, enabling readers to interpret the subsequent synthesis with explicit awareness of how reflexivity shaped analytical choices. The final discussion then synthesises the thesis findings, considers implications for clinical practice and policy, and sets out concrete recommendations for a definitive trial — notably prioritising fatigue self-efficacy, improving retention and digital inclusion, and extending follow-up with an embedded economic evaluation.

Chapter 5: A Reflective Journey – Researching with Multiple Sclerosis

This chapter provides a critical reflection on the research process, drawing on the 5R reflective framework (Reporting, Responding, Relating, Reasoning, and Reconstructing). It considers how my identity as a researcher living with multiple sclerosis shaped the design, conduct, and interpretation of the work, and reflects on the challenges and opportunities encountered throughout the PhD. Particular attention is given to methodological learning, the experience of navigating ethical complexities, and the influence of patient and public involvement. The chapter concludes by discussing how this journey has shaped my professional identity and prepared me for future research and academic practice.

5.1 Introduction

This chapter reflects on my journey as a PhD researcher living with Multiple Sclerosis (MS). It is not simply a description of my research, but an honest reflection on how life, health, and academic ambition became closely intertwined over the course of this doctorate. I started my PhD with a clear goal: to address the often overlooked issue of fatigue in Parkinson's disease through evidence based, non-pharmacological approaches. What I didn't fully expect was how much my own lived experience with a long term condition would influence the work itself, the way I navigated challenges, and the kind of researcher I have grown into.

From the beginning, I knew this journey would not be straightforward. MS is unpredictable; some days I can think clearly and work steadily, while on others, fatigue and brain fog push my concentration to its limits. Yet, these same challenges have taught me to plan carefully, pace myself, and understand that productivity is not about rushing; it's about persistence. My supervisors have been central to this journey, guiding the academic work while also supporting me as a person.

This PhD has been far more than an academic project; it has been a personal journey of adaptation, resilience, and vision. It has unfolded alongside major life events, under the shadow of a chronic health condition, and with the guidance of supervisors whose support went well beyond the usual academic role. It has shaped my skills not only as a researcher, but as a disabled scholar, an occupational therapist, and an advocate for inclusive and meaningful change.

In structuring this reflection, I adopted the 5R Reflective Framework (Bain et al., 2002), which progresses through five stages: *Reporting* (describing the experience), *Responding* (expressing emotional reactions), *Relating* (connecting to prior knowledge or experience), *Reasoning* (examining underlying factors and relationships), and *Reconstructing* (drawing

conclusions and planning for future action). This framework provided a scaffold that allowed me to move beyond description, integrating personal and professional perspectives in a way that revealed the deeper learning from my PhD journey.

These reflections are not separate from my research; they are an integral part of it. The decisions I made, the methods I used, and the way I interpreted my findings cannot be separated from the context in which they were made; a context shaped by my lived experience of MS, my commitment to amplifying patient voices, my background as an occupational therapist, and my determination to turn research into practical improvements in health care in Saudi Arabia.

5.2 Reporting – What Happened

When I began this PhD, my research focus was already clear: I wanted to explore non pharmacological strategies for managing fatigue in Parkinson's disease. This came directly from my background in occupational therapy and my awareness that fatigue, although common and disabling, is often overlooked in both research and clinical practice.

My doctoral work unfolded through three main components: a systematic review, a scoping review, and a pilot randomised controlled trial (RCT) of the ReFresh online fatigue management programme.

Each part brought its own milestones. The systematic review confirmed that only a small number of intervention types had been tested specifically for Parkinson's related fatigue. Exercise based programmes showed the most consistent benefits, while other approaches produced mixed or inconclusive results. The scoping review broadened the view to fatigue

management in other neurodegenerative conditions, revealing a wider range of strategies and reinforcing the idea that some of these could be adapted for people with Parkinson's.

The pilot RCT was both the most challenging and the most rewarding stage. It tested the feasibility and acceptability of ReFresh; an online adaptation of the FACETS fatigue management programme originally developed for people with Multiple Sclerosis. Running this as an online trial was especially relevant at a time when remote healthcare delivery was becoming increasingly important. Managing recruitment, supporting participant retention, and measuring outcomes all required careful planning; and at times, creative problem solving when unexpected issues arose.

5.2.1 Entering the PhD

I began my PhD in October 2022 at the University of East Anglia (UEA) while on a scholarship from King Saud University (KSU), where I am a lecturer in occupational therapy. From the start, the focus was clear: fatigue in Parkinson's disease; a symptom that can impact quality of life as much as, and sometimes more than, the condition's better known motor symptoms, yet receives far less attention.

The work developed into three linked studies:

- A systematic review of non-pharmacological interventions for fatigue in Parkinson's disease.
- A scoping review extending the focus to fatigue management in other neurodegenerative diseases.
- A pilot RCT of ReFresh, adapted from the FACETS fatigue management programme for people with Multiple Sclerosis.

5.2.2 Living with MS

Since being diagnosed in 2017, MS has been a constant presence in my personal and professional life. It brings with it fluctuating fatigue, and episodes of brain fog. Symptoms meant I had to think differently about how to structure my PhD work from the very beginning. While my research explored fatigue in others, I was also living with my own, creating a unique dual perspective. I could approach the topic as both an occupational therapist and as someone managing the same symptom in daily life.

My treatment, Rituximab, is not available in the UK, so I travelled back to Saudi Arabia regularly for infusions. These trips were built into my research schedule, often becoming natural points for reflection and recalibration. I treated recovery days as non-negotiable; an approach to pacing that shaped both my wellbeing and my thinking about programme design.

5.2.3 Life Events During the PhD

Life did not pause for my PhD. In my second year, my marriage ended, forcing me to rebuild my sense of stability and routine. Around the same time, my mother was diagnosed with Hodgkin's lymphoma. Supporting her through diagnosis and treatment was one of the most difficult periods of my life. Yet, it also clarified my priorities. Her recovery, with only routine check-ups now required every six months, brought relief and renewed focus to my work.

5.2.4 Supervisory Team

The sustainability and direction of my PhD were shaped significantly by my supervisory team:

- **Dr Katherine Deane**: My primary supervisor has conducted much research in occupational therapy (although she is a biologist by training), has a career shaped by

her own lived experience of disability. Her combination of academic rigour, empathy, and personal insight created a supportive and enabling environment throughout my PhD. She respected my health needs without compromising the quality of my work, and her understanding of disability informed research design aligned deeply with my own values. She introduced monthly viva preparation sessions, providing questions in advance and structuring them to suit my energy levels. Katherine's own career journey; from laboratory based immunology to disability focused health research; inspired me to see disability as a source of insight rather than limitation. Her words, *"You've achieved just the same on schedule as all your non disabled colleagues. You should be proud of that"* stayed with me during moments of doubt.

- **Dr Jane Hibberd**; An occupational therapist with over 15 years of clinical experience before moving into higher education as a lecturer in occupational therapy. She offered concise, targeted feedback that helped sharpen my arguments and ensure my work remained grounded in practical relevance.
- **Ana Aragon**; An occupational therapist who joined the supervisory team in my first year, bringing valuable clinical insight. Her sudden passing on 9 August 2023 was a profound personal and professional loss.

5.2.5 Key Milestones

Several moments stand out in my research journey:

- Completing the systematic review and realising how little high quality evidence exists for managing fatigue in Parkinson's.

- Mapping the wider evidence base through the scoping review, confirming the value of adapting FACETS for Parkinson's disease.
- Launching the co-produced ReFresh pilot RCT and managing the realities of online delivery and participant retention.

These milestones were achieved not through a straight, uninterrupted path, but through alternating periods of intense work and deliberate rest, with flexibility and adaptation guiding the process.

5.3 Responding – Emotional and Professional Reactions

5.3.1 Living and Researching with Fatigue

From the outset, I knew that my experience of MS would influence how I worked. Cognitive fatigue could turn a short reading session into a slow, deliberate process. There were days when I would return to the same paragraph several times before its meaning settled in my mind. Physical fatigue meant that some days were about making small, steady gains rather than big leaps forward.

In the beginning, I saw this slower pace as a disadvantage; a sign that I was falling behind. Over time, and with the encouragement of my supervisors, I began to view it differently. Careful, measured work has its own strengths. As Dr Katherine once told me, *"Slow and steady wins the race."* I learned to accept that my timeline was not a weakness but simply a different way of working; one that still produced work of depth and quality.

5.3.2 Balancing Health, Life, and Research

Balancing the demands of a PhD with the unpredictability of MS meant constantly prioritising and adjusting. I applied the same occupational therapy principles I had once used with patients; pacing, energy conservation, and environmental adaptation; to my own life. This meant scheduling writing sessions for my higher energy times, breaking tasks into smaller, manageable parts, and treating rest as a legitimate and necessary part of productivity.

Life events — my divorce and my mother's illness — were significant emotional challenges that, at times, forced me to step back. My mother's diagnosis and treatment journey reinforced the importance of research that addresses real-world health needs. My divorce, while unrelated to my research focus, tested my resilience and ability to maintain momentum during personal upheaval.

5.3.3 Mentorship and Supervisory Support

The support of my supervisory team was central to my ability to keep moving forward. Dr Katherine's approach was always person centred; she treated my health considerations as part of the project, not as obstacles to work around. The monthly viva preparation sessions she introduced; with questions sent in advance and rehearsals tailored to my energy levels; became one of the most valuable aspects of my preparation. Her reassurance that disability should never be seen as diminishing the quality of my work helped me reset my own expectations of myself.

Dr Jane's feedback was concise but transformative, helping me clarify my thinking and ensuring that my work remained relevant and practical. Ana's input in the first year, before

her passing, gave me early confidence that my research direction was sound and worth pursuing.

Working with Ana Aragon (1960–2023) at the outset of my doctoral journey reshaped how I conceptualised fatigue and participation in Parkinson's disease. Her teaching emphasised clear, accessible communication with people with Parkinson's and a rigorous linkage between symptom management and everyday occupation. Even in a short supervisory period, her feedback influenced my methodological choices: to privilege patient-centred outcomes, to be precise about construct boundaries (fatigue versus sleepiness and apathy), and to ensure that intervention content translated into meaningful changes in daily activities. Ana's unexpected passing in August 2023 was personally difficult; professionally, it reinforced my resolve to carry forward the values she modelled—compassion, clarity and practical relevance. This thesis, particularly its focus on non-pharmacological strategies aligned with participation goals, is one way I honour that legacy.

5.3.4 Ethical Learning

One of the most challenging moments came during the outcome prioritisation stage of the ReFresh trial. A short survey, intended only for the lay advisory group, was accidentally sent to all trial participants. Although the survey was anonymous and low risk, it fell outside the approved protocol.

My immediate instinct was to report it. I contacted my supervisors, and together we informed the University's Ethics and Data Protection teams. The deviation was recorded, and data from none lay participants was excluded from analysis. A revised survey was then sent only to the intended group.

It was not an easy experience, but it became one of the most important learning points of my PhD. I came to understand that ethical integrity is not about avoiding every mistake; it is about being transparent, taking responsibility, and ensuring that the right steps are taken to protect participants and uphold research standards.

Analytical consequence; I treated the deviation as a governance stress-test: excluded off-protocol data, added a two-person release gate for surveys, and created a post-trial communications checklist. This strengthens auditability and shapes how I report feasibility and data integrity in Chapter Four (Pilot RCT).

5.4 Relating – Positioning Myself as a Disabled Researcher

Throughout this journey, my lived experience with Multiple Sclerosis (MS) has given me a unique vantage point for understanding fatigue in Parkinson's disease. While I am careful not to assume that one condition's experience directly mirrors another, the underlying reality of managing a chronic, invisible symptom resonated deeply with the participants I sought to serve through my research. This connection strengthened my empathy and influenced both the design of the intervention and the practicalities of the study procedures.

When adapting the ReFresh programme from the FACETS model, I gave particular attention to pacing strategies, the emotional impact of fatigue, and the importance of self-efficacy; not merely symptom reduction. These decisions were not abstract theoretical choices; they were shaped by my own experience of living with fluctuating energy levels and the need for tools that integrate into real life rather than idealised clinical settings.

This sense of connection extended to my supervisory team. With Dr Katherine Deane having done much occupational therapy research and Dr Jane Hibberd being an occupational therapist, we shared a common professional language and philosophy. Their understanding of client centred practice meant they immediately valued the patient voice in my research design. Ana Aragon, before her passing, reinforced this approach, consistently reminding me that the people we serve are the ultimate measure of success. Her influence remains embedded in this project, from its emphasis on accessibility to its focus on practical applicability.

The relationships I built during this PhD went beyond my supervisors. Lay advisors; people living with Parkinson's; played a pivotal role in shaping the research. Their feedback guided the adaptation of materials and often reshaped my thinking about which outcomes truly matter. Involving them from the outset, listening to their priorities, and at times adjusting direction based on their input was both humbling and enriching.

Living with MS while researching fatigue created a constant interplay between my personal experience and my academic focus. I was never a detached observer; I was both the researcher and, in some respects, part of the community I was studying. This dual perspective was not a bias to be controlled, but a source of insight that enhanced the relevance and authenticity of my work.

Early in my PhD, this interplay between my lived experience and academic work was tested when I failed my probationary review on the first attempt. The panel's concerns about my justification for the chosen review designs and the clarity of my analytical approach required me to pause, reassess, and rebuild. Revisiting my methods with my supervisors' guidance and incorporating frameworks such as Munn et al. (2018) and the MRC Complex Intervention Framework (Skivington et al., 2021), not only addressed their feedback but also strengthened

the foundation of my research. While humbling at the time, this experience ultimately improved my methodological rigour, sharpened my ability to defend my decisions, and gave me greater resilience for the rest of the doctoral journey.

The Social Model of Disability (Oliver, 1990) helped me frame my challenges not simply because of MS itself, but as reflections of the systems and environments in which I worked. Fatigue was not just a symptom; it became more disabling when academic expectations, timelines, or institutional structures failed to accommodate it. This perspective encouraged me to design my studies with flexibility in mind, ensuring that participation in the ReFresh trial did not impose unrealistic time or energy demands on people with Parkinson's.

The Affirmation Model of Disability (Swain & French, 2000) offered another important perspective: disability is not something to be "overcome," but a valued part of my identity and scholarly contribution. I chose not to hide my MS from colleagues, supervisors, or participants. Instead, I was open about it; and this openness often encouraged others to share their own health experiences. This fostered a culture of trust in community meetings, advisory sessions, and informal conversations.

Engagement with the Parkinson's UK community further reinforced this approach. These meetings were never simply recruitment opportunities; they were spaces to listen, understand the lived experience of people with Parkinson's, and see first-hand the diverse ways fatigue affects daily life. Conversations from these meetings influenced both the content of the ReFresh programme and my broader thinking on how health interventions should be co designed and delivered.

By positioning myself as both a healthcare professional and a disabled person, I came to understand that research can be more than the generation of data; it can also be an act of

representation. This work was guided by the belief that the voices of those most affected should not be a late stage addition to research, but an integral part of it from the very beginning.

While the Social Model of Disability shaped my understanding of the systemic barriers that make living with MS more challenging, the Affirmation Model of Disability gave me a framework for embracing my disability as a valued part of my identity and scholarly contribution. The affirmation model resists narratives of personal tragedy or deficit, instead recognising disability as a source of pride, community belonging, and unique perspective.

This lens became increasingly relevant during my PhD. Living with MS did not simply run alongside my research on fatigue in Parkinson's disease; it actively informed it. My own experience of fluctuating energy levels, cognitive fatigue, and the need for adaptive strategies made me more attuned to the realities of those I was studying. I was not an outsider peering in; I shared common ground with my participants, which shaped how I designed the ReFresh programme, how I framed outcomes, and how I interpreted attrition or variations in engagement.

Applying the affirmation model meant rejecting the idea that my MS diminished the quality or value of my research. On the contrary, it enriched it; providing insight into pacing, accessibility, and the emotional dimensions of fatigue that might otherwise have been overlooked. It also encouraged openness about my condition, with both colleagues and participants. Rather than concealing my disability to appear more "professional," I found that disclosure often invited others to share their own health experiences, fostering trust and mutual understanding.

This theoretical framing also aligned with my commitment to co production. Just as I valued my lived experience as a legitimate and vital source of knowledge, I recognised that the same was true for my lay advisors with Parkinson's. Their voices were not supplementary; they were central to shaping intervention content, delivery, and evaluation. In this way, the affirmation model underpinned both the spirit and the practice of my research; transforming what some might see as a personal limitation into a professional strength that will continue to guide my future work.

5.5 Reasoning – Making Sense of the Journey

5.5.1 Lived Experience as a Lens for Interpretation

One of the most valuable outcomes of this PhD has been recognising how my lived experience shaped the way I designed, conducted, and interpreted my research. Living with MS allowed me to connect with certain patterns in the data; particularly around participant retention and engagement in the ReFresh trial.

When participants withdrew from the study, I did not automatically frame it as "non-compliance" or "lack of motivation." From personal experience, I understood that stepping back can sometimes be an act of self-care. This perspective influenced how I reported attrition in the trial findings. Rather than treating it solely as a limitation, I saw it as a signal that interventions need to be flexible enough to accommodate fluctuating energy levels, competing priorities, and unexpected health challenges.

5.5.2 Methodological Adaptations and Parallels

The move from the original in person FACETS model to an online adaptation for Parkinson's disease mirrored my own strategies for living with fatigue. Just as I break my own workload into smaller, more manageable parts, ReFresh was designed with shorter modules, downloadable resources, and multiple pathways for engagement. This was not only a practical choice for participants but also reflected an ethos of accessibility shaped by lived experience.

My personal fatigue management strategies also informed the pacing of programme delivery. For example, spacing out the release of content was influenced by my understanding of cognitive fatigue cycles. What may seem like a small scheduling decision was, in fact, a direct application of disability informed knowledge into research design.

5.5.3 Ethical Reflexivity

The outcome prioritisation survey protocol deviation; when a survey intended for lay advisors was mistakenly sent to all participants; became one of the defining ethical lessons of my PhD. While the incident was low risk, it was a stark reminder that governance is not a static checklist but a continuous, active process.

By acting immediately, informing my supervisors, and reporting the issue to the relevant University committees, I was able to turn a potentially negative moment into a constructive one. It led to clearer post-trial communication protocols, which I plan to embed in all future research.

5.5.4 Defining Success Beyond Metrics

This PhD has also challenged me to reconsider what success looks like in research. Traditional indicators such as recruitment numbers or statistical significance are important, but they are not the only measures of value. An intervention can be meaningful even if its immediate statistical impact is modest; especially if it enhances self-efficacy, empowers participants, or sparks new conversations that lead to longer term change.

For me, the greatest achievement of the ReFresh trial was not just the data it generated but the discussions it encouraged: about fatigue, self-management, and the need to design interventions that work within the realities of people's lives.

Looking back, my decision making was shaped by a balance between academic rigour, ethical responsibility, and lived experience. At every stage, I weighed the scientific ideal against feasibility and participant burden. For example, when designing the pilot RCT, I recognised the need for robust outcome measures but also knew; from both literature and personal experience; that excessive questionnaires can be exhausting for people already living with fatigue. This led me to select tools that could capture meaningful data without overburdening participants.

Another example was the decision to distinguish between two key concepts: adherence, defined as weekly module completion, and engagement, defined as participant reported satisfaction. This distinction reflected the understanding that participation is not only about attendance but also about meaningful interaction with the programme. Lay advisors supported this view, noting that someone could "show up" without truly engaging, and that engagement was often more closely linked to outcomes.

The ethical decision making process was tested again during the survey deviation. Although the survey content was low risk and anonymous, the fact that it fell outside the approved protocol meant the data could not be included in publications. It was a sobering reminder that good intentions cannot replace strict adherence to ethical approval; and that maintaining integrity sometimes requires setting aside potentially valuable data to protect trust and uphold standards.

5.6 Reconstructing – Carrying It Forward

This PhD is not the conclusion of my story; it is the start of a much larger one. The work I have undertaken, the lessons I have absorbed, and the networks I have built form the foundations for the next chapter of my career and advocacy. The past three years have reconstructed my understanding of what it means to be both a researcher and a person living with disability.

When I began, I thought primarily in terms of outputs; published papers, completed trials, measurable results. I finish with a deeper appreciation for the process itself: the collaborations that change a project's direction for the better, the problem solving that happens in moments of uncertainty, and the insights that emerge not from control, but from adaptation.

5.6.1 Commitment to Inclusive Research Design

I will embed inclusivity into every stage of research, from the earliest scoping to final dissemination. This means designing studies that are accessible not only in terms of physical participation, but also in how they accommodate fluctuating energy levels, cognitive load,

and diverse life circumstances. Co production will not be an afterthought or a symbolic gesture; it will be an organising principle that shapes the research from day one.

5.6.2 Supervisory and Institutional Advocacy

The adjustments my supervisors made for me; such as monthly viva preparation meetings with advance questions; transformed my experience and performance. I want to advocate for these types of reasonable adjustments to become standard practice for disabled postgraduate researchers across institutions. This is not special treatment; it is equitable treatment that allows talent to thrive without unnecessary barriers.

5.6.3 Ethical Reflexivity and Contingency Planning

Future trials I lead will include clear contingency plans for potential deviations, alongside robust post-trial communication protocols. The ReFresh survey incident taught me that ethical oversight is not a "one off" approval, but a continuous, active process requiring openness, flexibility, and an ability to respond promptly when issues arise.

5.6.4 Disability Advocacy as a Scholar

I intend to integrate disability awareness and Universal Design for Learning principles into occupational therapy education, both at King Saud University and through professional development courses. My aim is for the next generation of therapists to see inclusivity not as an optional extra, but as an essential part of best practice.

5.6.5 Knowledge Translation into the Saudi Context

The outputs of this PhD will not remain confined to the pages of a thesis.

In addition to clinical programme development, this PhD has also shaped my interest in interdisciplinary rehabilitation innovation. Occupational therapy frequently identifies practical barriers to participation that could be addressed through simple assistive technologies. During the course of this research, I became increasingly interested in how low-cost assistive solutions, including 3D printed devices, could complement fatigue management and support independence for people with neurological conditions. While the ReFresh intervention itself focuses on behavioural fatigue management rather than device development, the broader insights from this research reinforce the importance of translating clinical needs into practical solutions. Collaboration between occupational therapy and engineering disciplines therefore represents a logical next step for implementing the principles explored in this thesis, particularly in contexts where locally produced assistive technologies may increase accessibility and reduce cost barriers.

I have concrete plans to adapt and implement them in Saudi Arabia:

- An Arabic, culturally adapted ReFresh programme for Parkinson's disease and other neurological conditions.
- School based occupational therapy integration models that align with both international best practice and the Saudi education framework.
- Interdisciplinary collaborations between occupational therapy and engineering programmes to develop assistive technologies, including low-cost 3D printed solutions that address functional barriers identified through clinical practice.
- National clinical guidelines for fatigue management in rehabilitation.
- Embedding co production frameworks into national health research policy.

These initiatives directly support Saudi Arabia's Vision 2030 goals for healthcare quality, innovation, and inclusivity (Kingdom of Saudi Arabia, 2016)..

5.6.6 Using Technology for Accessibility

During times of cognitive fatigue, I used tools such as AI to rephrase and structure my own words; never to replace my thinking, but to support my expression when energy was low. I plan to continue exploring how technology can level the playing field for disabled researchers without compromising academic integrity.

5.6.7 A Fully Powered RCT and Beyond

One of my immediate post PhD goals is to conduct a fully powered RCT of the ReFresh programme. The pilot findings, combined with lay advisor feedback, provide a clear blueprint for refining the intervention and securing funding for a larger trial. This next step is about more than academic output; it is about equipping people living with fatigue with practical tools to reclaim their energy and agency.

This reconstruction is visible in my broader vision for the future. My work on fatigue management for Parkinson's disease is not an isolated project; it forms part of a larger commitment to improving rehabilitation services in Saudi Arabia. The ideas that have emerged during this PhD; from online delivery models to patient co creation; are ones I will carry forward, adapting them to the cultural and healthcare context of my home country.

I also see my role differently now. I am not simply an academic producing knowledge; I am a bridge between lived experience and evidence based practice. My MS is not a limitation in this role; it is a lens that sharpens my focus on what truly matters to patients and to the therapists who support them.

5.7 Conclusion – Momentum, Not Closure

Completing this PhD has been one of the most challenging and defining experiences of my life. It has tested my endurance, sharpened my thinking, and reminded me that research is not just an intellectual pursuit, but a deeply human one.

I began this journey with a clear academic aim: to explore and expand the evidence base for managing fatigue in neurodegenerative diseases. Along the way, it became far more than an academic project. It became a mirror; reflecting my identity as a disabled researcher and showing me, how personal experience can enrich, guide, and deepen scholarly work.

The achievements in these pages; from the systematic and scoping reviews to the design and delivery of the ReFresh pilot trial; are the result of persistence, adaptability, and a refusal to let my health set the boundaries of my ambition. I have produced a body of work that I believe will make a practical difference, both in my home country and beyond, while navigating life events and a chronic illness that could easily have derailed the process.

I leave this PhD not with a sense of finality, but with the certainty that the work is only just beginning. The questions raised, the networks built, and the initiatives planned are stepping stones to the next phase; one where I aim to translate research into real world change.

Above all, I carry forward the understanding that momentum matters more than speed. As my supervisors often reminded me, *"slow and steady wins the race."* It is a truth I will carry into every future project. Science is, after all, a team game, and the most meaningful contributions come from those who combine rigour with compassion.

This thesis is the product of that combination. It stands as proof of what is possible when persistence meets purpose; and it is my commitment that the work will continue, guided by the same principles that brought me here: inclusivity, integrity, and impact.

5.8 Additional Reflections

There were many moments during this PhD when life and research collided. Some were uplifting; like witnessing lay advisor feedback directly shape the programme content and seeing those changes resonate with participants. Others were more difficult; working through fatigue flare ups while racing against deadlines, or processing grief after the sudden loss of Ana Aragon. Yet, every one of these moments has added depth to this thesis and shaped the researcher I have become.

My supervisors' words remain a constant touchstone. Dr Katherine Deane's reminder that *"science is not done solo. Science is always teamwork"* has become almost a mantra for me. This PhD was never just my work; it was built with the input, encouragement, and belief of many others. Dr Jane Hibberd's calm, steady guidance ensured that ambition never ran ahead of feasibility, and Ana's legacy remains deeply embedded in the patient centred heart of this research.

Perhaps the most important reflection is that success in a PhD is not defined only by publications or viva outcomes. It is also defined by who you become in the process. I began this journey as an occupational therapist determined to address a specific clinical gap. I finish it as a researcher who has navigated complex ethical challenges, balanced health and productivity, built meaningful international collaborations, and learned that resilience is as vital to scholarship as knowledge itself.

Through this reflective process, I have identified both personal and professional growth, highlighting the ways in which lived experience, resilience, and adaptability have strengthened the research and its outcomes. These insights also emphasise the importance of reflexivity in disability research. The next chapter brings together the empirical and reflective findings of the thesis to present an integrated discussion and conclusion.

Chapter 6: General Discussion and Conclusion

This final chapter synthesises the findings of the thesis, integrating insights from the systematic review, scoping review, and pilot RCT. It begins by summarising the key contributions to knowledge regarding non-pharmacological management of fatigue in neurodegenerative diseases, with a focus on Parkinson's disease. It then evaluates the methodological and theoretical implications of the work, including strengths and limitations, before considering directions for future research. The chapter concludes by outlining the clinical and policy implications of the findings and reflecting on the overall contribution of the thesis to occupational therapy and neurorehabilitation.

6.1 Overview of Thesis Findings

This thesis has examined the feasibility, acceptability, and preliminary effectiveness of non-pharmacological fatigue management strategies for people with Parkinson's disease (PwP). Across three interlinked studies—a systematic review, a scoping review, and a pilot randomised controlled trial (RCT)—the research provides a coherent body of evidence demonstrating both the challenges and opportunities in this under-researched field.

The systematic review (Chapter 2) identified only five randomised trials of fatigue management interventions for PwP, indicating a striking paucity of evidence. The few available studies were heterogeneous in their design, intervention content, and outcome measures, which limited the strength of conclusions.

The subsequent scoping review (Chapter 3) extended the focus to other neurodegenerative conditions and identified a broader range of non-pharmacological approaches to fatigue management, including occupational therapy, cognitive-behavioural therapy (CBT), and exercise-based interventions. This review confirmed that fatigue is a cross-cutting challenge across conditions and highlighted both the promise and the fragmentation of the current evidence base.

The pilot RCT (Chapter 4) evaluated ReFresh, an online fatigue management programme adapted from FACETS (developed originally for multiple sclerosis). The study demonstrated feasibility of recruitment and acceptability of the intervention, with participants reporting high satisfaction scores and a statistically significant improvement in fatigue self-efficacy. However, high attrition rates and modest effects on fatigue severity underscored the need for refinements in intervention delivery and support strategies.

Taken together, these studies contribute to knowledge in three critical ways:

1. They confirm the scarcity of high-quality trials of fatigue interventions in Parkinson's.
2. They establish the feasibility and acceptability of adapting established fatigue management programmes to this population.
3. They highlight self-efficacy—rather than fatigue severity—as a promising and meaningful outcome for future research.

6.2 Methodological Reflections

6.2.1 Fatigue Measures

This thesis has underscored the methodological challenges of assessing fatigue in PwP. While validated scales exist (e.g., the Parkinson's Fatigue Scale [PFS] and the Modified Fatigue Impact Scale [MFIS]), there is limited consensus on their interpretability, particularly in terms of minimally clinically important differences (MCIDs). The MFIS, for example, has an established MCID in Parkinson's (13.8 points) but produced minimal change in this study, while the PFS lacks an agreed MCID altogether.

By contrast, fatigue measurement in stroke has achieved stronger consensus and standardisation (English et al., 2023). This discrepancy reflects the relative neglect of fatigue in Parkinson's research and complicates the interpretation of intervention outcomes. Future research would benefit from efforts to harmonise fatigue measurement, including cross-condition initiatives to refine instruments and establish clinically meaningful thresholds.

6.2.2 Self-Efficacy as an Outcome

In contrast to fatigue severity, fatigue self-efficacy (MS-FSE) demonstrated a statistically significant between-group difference in the ReFresh trial (mean difference +6.72, 95% CI

1.68 to 11.76, Cohen's d = 0.48). This aligns with participant feedback and lay advisor prioritisation, both of which emphasised the ability to manage fatigue as more meaningful than reducing its occurrence. Behavioural fatigue management interventions such as ReFresh focus on strategies including pacing, energy conservation, and cognitive reframing, which are designed to enhance coping and perceived control rather than directly reduce symptom severity.

Taken together, the findings of this thesis suggest that fatigue self-efficacy may represent a more appropriate primary outcome than fatigue severity in trials evaluating behavioural fatigue management interventions for people with Parkinson's disease. While reductions in fatigue severity were not observed in this pilot study, the moderate improvement in fatigue self-efficacy indicates that participants developed greater confidence in managing fatigue within daily life. Future trials should therefore prioritise fatigue self-efficacy as the primary outcome while continuing to monitor fatigue severity as a secondary outcome.

These findings also highlight the importance of distinguishing between different dimensions of fatigue. Fatigue severity reflects the intensity or frequency of the symptom itself, whereas fatigue impact captures the extent to which fatigue interferes with daily functioning. Fatigue self-efficacy, by contrast, reflects an individual's confidence in their ability to manage fatigue and maintain engagement in meaningful activities. Behavioural fatigue management programmes such as ReFresh are primarily designed to enhance coping strategies and adaptive behaviour rather than directly reduce the underlying symptom. Consequently, improvements in self-efficacy may occur before measurable changes in fatigue severity become apparent. Conceptually, this suggests that fatigue self-efficacy may act as an intermediary mechanism through which behavioural interventions influence functional outcomes, supporting continued participation even when fatigue itself remains present.

Future trials should therefore examine whether changes in fatigue self-efficacy mediate improvements in participation and daily functioning.

6.3 Implications for Occupational Therapy

The findings reinforce the distinctive role of occupational therapists in addressing fatigue. The ReFresh programme incorporated occupational therapy principles such as pacing, energy conservation, and engagement in meaningful occupations, which resonated strongly with participants. The observed improvements in self-efficacy and occupational performance highlight the value of occupational therapy approaches in supporting PwP to adapt to fatigue, even when symptom reduction is limited.

Interpreting the findings through the lens of the International Classification of Functioning, Disability and Health (ICF) provides an additional perspective on their clinical significance. Within the ICF framework, fatigue in Parkinson's disease can be understood not only as a health-related impairment but also as a factor that contributes to activity limitations (for example, difficulties in sustaining exercise, self-care tasks, or mobility) and participation restrictions (such as reduced involvement in work, family life, or community roles). The ReFresh programme, by emphasising coping strategies and self-management, therefore, has implications that extend beyond symptom reduction, supporting functional independence and broader social engagement. This interpretation situates the trial findings within an internationally recognised rehabilitation framework and underscores the value of addressing fatigue in ways that enhance both activity and participation (World Health Organization, 2001).

Importantly, occupational therapy's strengths lie in enabling participation and function in daily life despite persistent symptoms. This thesis therefore contributes to growing recognition that occupational therapy is well placed to lead in the design, delivery, and evaluation of fatigue interventions in long-term conditions.

6.4 Policy and Professional Context

Recent developments in the UK health policy landscape reinforce the relevance of this thesis. In July 2025, the UK Government announced enhanced support for people with Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS), with a focus on improving access to care, reducing stigma, and strengthening research investment (OT News, 2025). Crucially, occupational therapists were explicitly recognised as central to fatigue management, particularly in pacing, planning, and supporting return to or retention in work.

In parallel, specialist occupational therapy-led services for ME/CFS have demonstrated measurable impact. Kim et al, (2022) describe embedding occupational therapy within a fatigue management service in Scotland, where OTs supported patients with pacing, task simplification, and goal-based interventions. Their evaluation highlighted the positive effects on employability, education, and daily function.

These policy and practice developments underscore that fatigue management is becoming a priority area for health systems and that occupational therapists are increasingly positioned as leaders in this domain. The findings of this thesis, though situated within Parkinson's disease, clearly align with these wider professional trajectories and strengthen the rationale for further development of occupational therapy-led fatigue services.

6.5 Implications for Future Research

This pilot trial suggests several priorities for future research:

- Development of hybrid models that combine digital accessibility with structured human support to improve retention.
- Refinement and standardisation of fatigue outcome measures in Parkinson's.
- Larger, adequately powered RCTs to evaluate clinical and cost-effectiveness.
- Economic evaluations to assess the value of scalable fatigue management interventions.
- Exploration of implementation pathways, including partnerships with charities such as Parkinson's UK for long-term programme hosting.

Further, cross-condition comparisons—drawing from ME/CFS, multiple sclerosis, and stroke—should inform the development of unified fatigue management frameworks.

6.6 Conclusion

This thesis provides the first comprehensive evaluation of non-pharmacological fatigue management for people with Parkinson's, integrating evidence synthesis and empirical testing. The research demonstrates that while statistically or clinically meaningful reductions in fatigue severity were not observed in this pilot study, the findings demonstrate a moderate between-group effect on fatigue self-efficacy and suggest potential benefits in occupational coping strategies. These results support the role of behavioural fatigue management interventions in strengthening individuals' capacity to manage fatigue within daily life.

The high withdrawal rates highlight the importance of integrating human support into digital programmes, while the broader policy context signals a timely opportunity for occupational therapists to assert leadership in fatigue management across long-term conditions.

Collectively, the findings of this thesis suggest that behavioural fatigue management interventions for people with Parkinson's disease may exert their primary effects by strengthening fatigue self-efficacy rather than directly reducing fatigue severity, highlighting the importance of targeting adaptive coping and participation as key outcomes in occupational therapy-led interventions.

In conclusion, the ReFresh pilot trial, situated within a programme of evidence synthesis, offers both methodological insights and practical implications. Fatigue self-efficacy has emerged as a central outcome, reflecting the lived priorities of people with Parkinson's. With further refinement and investment, occupational therapy-led digital interventions such as ReFresh could form a cornerstone of equitable, scalable fatigue management strategies, not only for Parkinson's but across multiple long-term conditions.

Glossary of Terms

Term	Definition
ADherence (trial definition)	Operationalised in the trial as weekly module completion; used to distinguish adherence from engagement in process evaluation.
ADL — Activities of Daily Living	Everyday self-care tasks (e.g. dressing, bathing) referred to when discussing occupational performance and participation in the thesis.
AE — Adverse Event	Any unfavourable or unintended sign, symptom, or illness occurring during the study, whether related to the intervention (defined in the Adverse Event Monitoring protocol).
AE/SAE monitoring and reporting procedure	Protocol describing how adverse events are logged, escalated and reported to supervisory and ethics oversight bodies.
ALS — Amyotrophic Lateral Sclerosis	A neurodegenerative condition listed among comparative conditions in the reviews.
AMED — Allied and Complementary Medicine Database	One of the bibliographic databases searched in the systematic and scoping reviews.
Anonymisation (participant IDs)	Process assigning unique participant IDs at consent with separate encrypted linkage file held by the lead researcher.
CBT — Cognitive Behavioural Therapy	A structured psychological approach targeting thoughts, behaviours and coping; used as a component in fatigue self-management programmes discussed in the thesis.
CFQ — Chalder Fatigue Questionnaire	A fatigue measurement tool referenced in the systematic/scoping review tables.
CI — Confidence Interval	Statistical term used in reporting effect estimates and trial results.
CINAHL — Cumulative Index to Nursing and Allied Health Literature	Database used in literature searches for the reviews.
CIS-20R — Checklist Individual Strength, Revised	A fatigue instrument appearing in the review summary of measurement tools.
CONSORT — Consolidated Standards of Reporting Trials	Reporting guideline used to report the pilot RCT; CONSORT diagram appears in Chapter 4.
COPM change threshold	A two-point change on COPM often used as a common threshold for clinically meaningful change in occupational performance and satisfaction.
COPM — Canadian Occupational Performance Measure	A client-centred occupational therapy outcome measure used in the pilot trial to capture performance and satisfaction in meaningful activities.
COPM — Canadian Occupational Performance Measure (duplicate note)	Client-centred measure used in the pilot trial to capture occupational performance and satisfaction (listed for clarity).

Data Management Plan (DMP)	Documented procedures for data handling, storage, anonymisation, access rights and retention used in the ReFresh pilot.
Deviations and oversight	Governance processes described for reporting deviations from approved plans; thesis states no deviations occurred.
EDSS — Expanded Disability Status Scale	Clinical scale referenced in review tables.
ELEVIDA	Named example of a self-guided online fatigue programme referenced in the thesis.
Engagement (trial definition)	Participant-reported satisfaction and meaningful interaction with the programme, distinct from adherence.
EQ-5D — EuroQol Five-Dimension Scale	A generic health-related quality-of-life instrument listed among outcome measures.
FACETS	Fatigue: Applying Cognitive behavioural and Energy-effectiveness Techniques to lifeStyle — a manualised programme developed for multiple sclerosis; ReFresh was adapted from FACETS.
FIS / MFIS — Fatigue Impact Scale / Modified Fatigue Impact Scale	Instruments measuring the impact of fatigue across domains; MFIS and short forms (MFIS-5) are used or discussed in the thesis.
FM+ — Fatigue Self-Management plus Physical Activity	Intervention category name used in review tables and intervention descriptions.
FSMC — Fatigue Scale for Motor and Cognitive Functions	A fatigue scale listed among measurement instruments in the reviews.
FSS — Fatigue Severity Scale	A unidimensional measure of fatigue severity referenced in the thesis evidence tables.
GDS-15 / GDS — Geriatric Depression Scale	Depression screening instrument used and reported in trial outcomes.
Glossary of Terms	An alphabetised list of specialised terms and definitions provided to help readers interpret concepts used in the thesis.
H&Y — Hoehn and Yahr	A Parkinson's disease staging scale referenced to describe participant disease severity.
HD — Huntington's Disease	A neurodegenerative disorder included among conditions discussed for comparative purposes.
HPA — Hypothalamic–Pituitary–Adrenal (axis)	A neuroendocrine stress-response system discussed as a possible biological contributor to fatigue.
HRA / IRAS	Health Research Authority / Integrated Research Application System — governance platforms referenced in the ethics appendices.
HRV — Heart Rate Variability	A physiological metric mentioned in measurement/tool lists.
iCBT — Internet-based Cognitive Behavioural Therapy	A delivery modality of CBT used in online programmes and discussed in the thesis.
ICF — International Classification of Functioning, Disability and Health	WHO framework used in the thesis to conceptualise impairment, activity limitation and participation.

ISRCTN registration	Public trial registration identifier for the ReFresh pilot (ISRCTN62114944) reported in the thesis.
ISRCTN trial registration (duplicate note)	Public registration identifier for the ReFresh pilot (ISRCTN62114944) — repeated here for completeness.
ITT — Intention-to-treat	An analysis strategy including all randomised participants in the groups to which they were allocated regardless of adherence; used for primary analyses.
JBI — Joanna Briggs Institute	Methodological resource and guidance referenced among evidence-synthesis tools.
Lay advisor / Lay adviser	People with lived experience of Parkinson's who contributed to co-design, review of materials and outcome prioritisation for ReFresh.
Lexicon: list of abbreviations	A front-matter list providing full forms of acronyms used in the thesis.
Logic model	Programme-theory diagram used to specify ReFresh components and pathways (provided in the appendices).
MA — Meta-analysis	Analytic approach used in the systematic review where pooling of comparable studies was appropriate.
MCID — Minimal Clinically Important Difference	Smallest change in an outcome that patients perceive as important; discussed when interpreting clinical meaning of trial effects.
MEDLINE / MeSH	Database and controlled vocabulary terms used in the literature searches.
MFIS-5 — Modified Fatigue Impact Scale (5 items)	Short form of MFIS referenced among outcome measures.
MND — Motor Neuron Disease	Condition included among neurodegenerative diseases in scoping comparisons.
MRC — Medical Research Council (complex interventions guidance)	Framework referenced for developing and evaluating complex interventions.
MS — Multiple Sclerosis	A neurological condition whose fatigue programmes and measures inform adaptation to Parkinson's in this thesis.
MS-FSE — Multiple Sclerosis Fatigue Self-Efficacy Scale	Self-efficacy measure used as an outcome in the pilot trial.
MSA — Multiple System Atrophy	Neurodegenerative disorder listed among comparative conditions.
NMA — Network Meta-analysis	Advanced analytic approach listed in methodological abbreviations.
NMS — Non-Motor Symptoms	Non-motor manifestations of PD (e.g., fatigue, sleep disturbance, mood), used to contextualise research focus.
NRCT — Non-randomised Controlled Trial	Trial design category appearing in evidence tables.
OSF — Open Science Framework	Platform noted for protocol or data deposition.

Participant Information Sheet (PIS) and Consent Form	Participant-facing documents reviewed and revised with lay advisor input; versions described in appendices.
PAS — Parkinson Anxiety Scale	Anxiety instrument used in the trial and reported in results.
PBA — Person-Based Approach	An intervention development approach prioritising user perspectives and iterative adaptation; informed ReFresh design.
PCC — Population, Concept, Context	Scoping review eligibility framework used in Chapter 3.
PD — Parkinson's Disease	The target condition for the thesis research.
PDDS — Patient Determined Disease Steps	Scale listed in abbreviations and used to describe participant characteristics in some included studies.
PDQ-39 — Parkinson's Disease Questionnaire (39 items)	Quality-of-life measure used and reported in the trial and compared to MCID thresholds.
PFS / PFS-16 — Parkinson's Fatigue Scale (16 items)	PD-specific fatigue self-report instrument referenced in measurement sections and evidence tables.
PFS / PFS-16 — Parkinson's Fatigue Scale (16 items)	PD-specific fatigue self-report instrument referenced in measurement sections and evidence tables.
Platform usability issues	Examples of participant difficulties using the platform recorded in logs and resolved via support; used to inform feasibility/acceptability.
PP — Per-protocol	Analysis of participants who adhered to the intervention protocol; used as a sensitivity analysis.
PPI — Patient and Public Involvement	Active involvement of patients/public in co-design, trial processes and dissemination (lay advisors).
PRISMA / PRISMA-ScR	Reporting checklists followed for the systematic review and scoping review respectively; included as appendices.
PSQI — Pittsburgh Sleep Quality Index	Sleep quality instrument used in the trial and reported in results.
PSQI — Pittsburgh Sleep Quality Index (duplicate note)	Sleep quality instrument used in the trial and reported in results.
QOL — Quality of Life	Conceptual outcome domain; PDQ-39 used as QOL instrument.
Qualtrics (UEA enterprise licence)	Survey platform used to collect quantitative data; stored on GDPR-compliant servers.
Qualtrics (UEA enterprise licence) (duplicate note)	Survey platform used to collect quantitative data; stored on GDPR-compliant servers.
RCT — Randomised Controlled Trial	Study design of the pilot ReFresh trial; CONSORT reporting and registration details are provided.
ReFresh — Rebalancing Fatigue & Enhancing Self-Help	Name of the 6-week online fatigue-management programme adapted from FACETS and piloted in Chapter 4; module structure and TIDieR provided in appendices.
Registration number / candidate number	The student registration number used in administrative records (place on title or submission documents as required).

RoB2 — Cochrane Risk of Bias 2 tool	Tool used to appraise risk of bias in randomised trials included in the systematic review.
SAE — Serious Adverse Event	An adverse event that results in death, is life-threatening, requires or prolongs hospitalisation, or results in significant disability — defined in the safety monitoring appendix.
Satisfaction surveys (free-text boxes)	Surveys including open-text responses used to collect qualitative feedback weekly and at endpoint.
Self-efficacy (fatigue self-efficacy)	Participant's belief in their ability to manage fatigue; measured using MS-FSE and discussed as a key outcome.
TFA — Theoretical Framework of Acceptability	Seven-component framework (affective attitude, burden, perceived effectiveness, ethicality, intervention coherence, opportunity costs, self-efficacy) used to analyse acceptability.
TIDieR — Template for Intervention Description and Replication	Checklist used to describe the ReFresh intervention to aid replication and reporting.
Trial adverse event log	Study-specific log where AEs and SAEs are recorded and categorised as per the safety protocol.
Trial registration / ISRCTN	Identifier and public registration details for the pilot trial (ISRCTN62114944).
UEA Ethics reference (ETH2324-0159)	Ethics approval identifier and conditions referenced in the ethics appendix.
UEA OneDrive (encrypted storage)	Institutional storage used to hold identifiable materials with restricted access as described in the DMP.
Universal Design for Learning (UDL)	An inclusive education principle discussed as part of proposed OT education adaptations.
WHO ICF — International Classification of Functioning, Disability and Health	Framework used to interpret how fatigue affects impairment, activity and participation.

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Yesavage, J.A., Brink, T.L., Rose, T.L., Lum, O., Huang, V., Adey, M. & Leirer, V.O. (1982) 'Development and validation of a geriatric depression screening scale: a preliminary report', Journal of Psychiatric Research, 17(1), pp.37–49. https://doi.org/10.1016/0022-3956(82)90033-4

Zhang, M., Fan, C., Ma, L., Wang, H., Zu, Z., Yang, L., Chen, F., Wei, W. & Li, X. (2024) 'Assessing the effectiveness of internet-based interventions for mental health outcomes: an umbrella review', General Psychiatry, 37(4), e101355. https://doi.org/10.1136/gpsych-2023-101355

Appendices

Chapter 2 Appendices

Appendix 2.A. PRISMA 2020 Checklist (Systematic Review, Chapter 2)

This checklist corresponds to the systematic review reported in Chapter 2 (Non-Pharmacological Interventions for Managing Fatigue in Parkinson's Disease). Searches were run to 01 Oct 2024; protocol registration PROSPERO CRD42023394180. Each checklist item maps to the chapter/section where it is reported.

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Results section
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	Results section
Study characteristics	17	Cite each included study and present its characteristics.	Results section

Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Results section
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Results section
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	Results section
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	Results section
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	Results section
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	Results section
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	Results section
DISCUSSION			

Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	Discussion section
	23b	Discuss any limitations of the evidence included in the review.	Discussion section
	23c	Discuss any limitations of the review processes used.	Discussion section
	23d	Discuss implications of the results for practice, policy, and future research.	Discussion section
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	Abstract section
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	Abstract section
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	No amendments made
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	In the Abstract section and acknowledgment
Competing interests	26	Declare any competing interests of review authors.	Under acknowledgment
Availability of data, code	27	Report which of the following are publicly available and where they can be found template data collection forms; data	Data available on request

and other materials		extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

For more information, visit: http://www.prisma-statement.org/

Appendix 2.B. MEDLINE Search Strategy

This appendix contains the full MEDLINE (Ovid) search strategy used to identify relevant studies from database inception to February 2023. The strategy combined MeSH terms and free-text keywords relating to Parkinson's disease, fatigue, and randomised controlled trials.

Ovid MEDLINE(R) ALL <1946 to February 13,2023>

1 Parkinson$.tw. 139073

2 exp Parkinson Disease/ 80106

3 or/1-2 147118

4 energy limitation.tw. 185

5 energy restriction.tw. 1837

6 fatigue.tw. 118229

7 or/4-6 120236

8 randomized controlled trial.pt. 586723

9 controlled clinical trial.pt. 95190

10 randomized.ab. 592773

11 placebo.ab. 235694

12 randomly.ab. 401982

13 trial.ab. 635772

14 groups.ab. 2476224

15 or/8-14 3552353

16 and/3,7,15 286

Limits applied:

- English language
- Database inception – 13 February 2023

- Full-text availability
- Randomised controlled trials only

Appendix 2.C. Table 1. RoB2 Detailed Assessments

This appendix presents the domain-level risk of bias assessments for each included trial, conducted with the Cochrane RoB2 tool (Sterne et al., 2019). Summary results are shown in Table 1 of the main text, while detailed domain-level justifications are provided here for transparency.

Risk of bias assessments for included RCTs, presented across the five domains of the Cochrane Risk of Bias 2 tool (Sterne et al., 2019).

Study	**Randomisation (D1)**	**Deviations (D2)**	**Missing Data (D3)**	**Measurement (D4)**	**Reporting (D5)**	**Overall Risk**
Kluger et al. (2016)	Low	Low	Low	Low	Low	Low
Kong et al. (2018)	Low	Low	Low	Low	Low	Low
Abasi et al. (2020)	Some concerns	Some concerns	Low	Some concerns	Low	Some concerns
Ribas et al. (2017)	Some concerns	Some concerns	Low	Some concerns	Low	Some concerns

Wu et al. (2021)	Some concerns	Some concerns	Low	Some concerns	Low	Some concerns

Narrative Justifications by Study

- **Kluger et al. (2016):** Overall risk of bias was judged low. Randomisation procedures were adequately reported, allocation concealment was maintained, and blinding of participants, clinicians, and assessors was achieved using sham acupuncture. Attrition was minimal and balanced across groups, and all prespecified outcomes were reported.
- **Kong et al. (2018):** Risk of bias was low across domains. Randomisation was clearly described, allocation was concealed, and the use of sham acupuncture minimised performance bias. Outcomes were assessed using validated scales, with no evidence of selective reporting.
- **Abasi et al. (2020):** Some concerns were identified. The randomisation process was insufficiently described, and blinding was not feasible given the exercise-based nature of the intervention. While missing data were minimal, fatigue was self-reported without assessor blinding. No concerns were noted regarding selective outcome reporting.
- **Ribas et al. (2017):** Risk of bias raised some concerns, particularly due to limited reporting on random sequence generation and the inability to blind participants in an exergaming intervention. Fatigue outcomes were self-reported, further limiting robustness. Attrition rates were low, and outcomes corresponded to stated objectives.

- **Wu et al. (2021):** Some concerns were identified. Randomisation was mentioned but allocation concealment was unclear. The home-based intervention precluded participant blinding, and outcomes relied exclusively on self-report. Missing data were minimal and adequately documented, and no concerns regarding selective reporting were noted.

Appendix 2.D GRADE Evidence Profiles

GRADE Evidence Profiles - Detailed Domain Ratings

1. Fatigue severity (post-intervention) - Exercise vs control

Effect estimate: SMD −1.34 (−2.24 to −0.44) across 3 small RCTs (Abasi et al., Ribas et al., Wu et al.).

Overall GRADE certainty: LOW

Domain	Judgement and rationale
Risk of bias	Downgrade 1 level - 'Some concerns' across all 3 exercise trials (RoB2). Key issues: lack of participant blinding (behavioural interventions), reliance on self-reported fatigue outcomes, and incomplete reporting of allocation concealment details in some trials.
Inconsistency	Downgrade 1 level - Serious heterogeneity ($I^2 \approx 89\%$). Substantial differences in intervention modality (vestibular rehab, exergaming, home-based aerobic/resistance), dosing, and comparator types.
Indirectness	No downgrade - Direct evidence: PD populations and fatigue-specific outcomes were assessed.
Imprecision	Serious concern - Small total sample across trials and wide CI. The pooled CI excludes no effect but spans from moderate to very large effects; imprecision noted but not taken as an additional downgrade beyond the two above in the overall rating.
Publication bias	Undetected / not formally assessed - Too few trials to draw conclusions about small-study effects.

Summary of downgrading: Downgraded 1 level for risk of bias and 1 level for inconsistency → overall LOW certainty. Imprecision and reporting limitations are discussed and would support further research.

2. Fatigue severity (post-intervention) - Acupuncture vs sham

Effect estimate: SMD 0.17 (−0.13 to 0.51) across 2 sham-controlled RCTs (Kluger et al., Kong et al.).

Overall GRADE certainty: MODERATE

Domain	Judgement and rationale
Risk of bias	No downgrade - Both trials used credible sham controls and implemented blinding where feasible; overall RoB judged low.
Inconsistency	No downgrade - Results were consistent (no important benefit detected across trials).
Indirectness	No downgrade - Direct PD populations and direct assessment of fatigue.
Imprecision	Downgrade 1 level - CI includes plausible small benefit to small harm; total sample size modest so results are imprecise.
Publication bias	Undetected / not formally assessed - limited number of trials.

Summary of downgrading: Downgraded 1 level for imprecision → overall MODERATE certainty that acupuncture yields little or no effect on fatigue in PD.

3. Quality of life (PDQ-39) - Exercise vs control

Effect estimate: Narrative synthesis (no pooled estimate) - no clear between-group effect reported in included trials.

Overall GRADE certainty: VERY LOW

Domain	Judgement and rationale
Risk of bias	Downgrade 1 level - Some concerns due to unblinded interventions and self-reported QoL.
Inconsistency	Downgrade 1 level - Mixed directions of effect, inconsistent reporting; no pooled estimate possible.
Indirectness	Downgrade 1 level - QoL (PDQ-39) is a distal outcome influenced by multiple non-targeted domains; indirect relative to primary fatigue target.
Imprecision	Downgrade 1 level - small samples and wide or unreported confidence intervals; underpowered analyses.
Publication bias	Undetected / unclear.

Summary of downgrading: Multiple downgrades across domains → overall VERY LOW certainty.

4. Sleep quality (PSQI) - Exercise vs control

Effect estimate: Narrative synthesis (no pooled estimate) - negligible change reported.

Overall GRADE certainty: VERY LOW

Domain	Judgement and rationale
Risk of bias	Downgrade 1 level - Some concerns: lack of blinding and reliance on self-report.
Inconsistency	Downgrade 1 level - Different directions/sizes across studies; no meta-analysis possible.
Indirectness	Downgrade 1 level - Sleep is not the direct target of many interventions; PSQI has uncertain responsiveness in PD for intervention effects.
Imprecision	Downgrade 1 level - small sample sizes and few reported estimates.
Publication bias	Undetected / unclear.

Summary of downgrading: Multiple downgrades across domains → overall VERY LOW certainty.

5. Adverse events (AEs) - Exercise or acupuncture vs control/sham

Effect estimate: AEs were infrequently and inconsistently reported; no serious AEs were clearly attributed to the interventions in the included RCTs.

Overall GRADE certainty: VERY LOW

Domain	Judgement and rationale
Risk of bias	Downgrade 1 level - Passive or inconsistent AE collection; incomplete reporting.
Inconsistency	Not assessable - sparse data and few events.
Indirectness	Downgrade 1 level - AEs were not a primary outcome and ascertainment methods varied across trials.
Imprecision	Downgrade 1 level - Few events and small samples; wide uncertainty.
Publication bias	Possible - under-reporting of AEs in small trials is a concern.

Summary of downgrading: Multiple downgrades → overall VERY LOW certainty about AE estimates; recommend systematic AE collection in future trials.

Footnotes

• Effect sizes, heterogeneity (I^2), and RoB judgements referenced above are taken from Chapter 2 of the thesis (see meta-analysis results and Table 2.1).

• Where narrative syntheses were used (QoL, PSQI, AEs), certainty assessments reflect small samples, inconsistent reporting, and indirectness relative to the primary fatigue target.

• GRADE judgments require subjective, transparent choices. The downgrades applied here are defensible given the trial-level data in Chapter 2, but other reviewers might choose alternative downgrading decisions; providing these domain-level rationales increases transparency for examiners and readers.

Summary of findings: Exercise versus control for PD-related fatigue
Patients/Population: Adults with idiopathic Parkinson's disease in outpatient or rehabilitation settings
Setting: Taiwan, Iran, Brazil (as reported in trials)
Intervention: Exercise programmes (vestibular rehabilitation; exergaming; supervised home aerobic and resistance training; typically 30-60 minutes, 2-3 times per week for 8-12 weeks)
Comparison: Usual care, conventional physiotherapy, or minimal intervention

Outcome (time point)	Effect (95% CI)	No. of participants (studies)	Certainty (GRADE)	Comments
Fatigue severity (post-intervention; various fatigue scales)	SMD -1.34 (-2.24 to -0.44)	142 (3 RCTs)	Low	Serious risk of bias and serious inconsistency (notes 1-2).
Quality of life (post-intervention; PDQ-39 or PDQ-8)	No pooled estimate; narrative: no clear between-group effect	118 (2 RCTs)	Very low	Imprecision, instrument inconsistency, indirectness (note 3).
Sleep quality (post-intervention; PSQI)	No pooled estimate; negligible change	98 (1 RCT)	Very low	Single small study; indirectness (note 4).
Adverse events	Infrequently and inconsistently reported; no serious AEs attributed	142 (3 RCTs)	Very low	Sparse and unsystematic AE capture (note 5).

Notes:
1) Risk of bias: all three exercise trials had 'some concerns' (unblinded behavioural interventions; self-reported fatigue; incomplete concealment reporting). Downgraded 1 level.
2) Inconsistency: substantial heterogeneity across modalities and comparators (I^2 about 89 percent). Downgraded 1 level.
3) QoL: small samples, mixed instruments (PDQ-39 in Ribas 2017; PDQ-8 in Wu 2021), and inconsistent reporting; indirect relative to the fatigue target. Downgraded 3 levels overall.
4) Sleep: single study with small N; sleep not directly targeted by interventions. Downgraded 3 levels.
5) Adverse events: sparse and inconsistent ascertainment; very imprecise estimates. Downgraded 3 levels.

Summary of findings: Acupuncture versus sham for PD-related fatigue
Patients/Population: Adults with idiopathic Parkinson's disease
Setting: USA and Singapore (as reported in trials)
Intervention: Acupuncture (10-12 sessions over 5-6 weeks)
Comparison: Credible sham acupuncture (non-penetrating or toothpick devices)

Outcome (time point)	**Effect (95% CI)**	**No. of participants (studies)**	**Certainty (GRADE)**	**Comments**
Fatigue severity (post-intervention; MFIS or MFI)	SMD 0.17 (-0.13 to 0.51)	128 (2 RCTs)	Moderate	Downgraded for imprecision; otherwise, low risk of bias due to credible shams.
Adverse events	Infrequently reported; no serious AEs attributed	128 (2 RCTs)	Very low	Sparse reporting and imprecision.

Notes:
1) Imprecision: confidence interval spans small benefit to small harm; total sample modest. Downgraded 1 level.
2) Risk of bias: both trials used credible sham controls with blinding where feasible; overall risk of bias low.
3) Adverse events: limited reporting with few events; high imprecision.

GRADE Evidence Profiles
The following evidence profiles present domain-level GRADE judgements by outcome for each main comparison.

Evidence profile: Exercise versus control

Outcome	No. of participants (studies)	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty (GRADE)	Effect / result
Fatigue severity (post)	142 (3 RCTs)	Randomised trials	Serious - some concerns in all 3 trials	Serious - I^2 approx 89 percent	Not serious - direct PD and fatigue outcomes	Not serious - CI excludes no effect but wide; noted	Undetected - too few trials to assess	Low	SMD -1.34 (95 percent CI -2.24 to -0.44)
Quality of life (post)	118 (2 RCTs)	Randomised trials	Serious - some concerns	Serious - mixed instruments and directions	Serious - QoL distal to fatigue target	Serious - small samples, wide or unreported CIs	Undetected/unclear	Very low	No pooled estimate; narrative: no clear between-group effect
Sleep quality (post)	98 (1 RCT)	Randomised trial	Serious - some concerns	Not applicable - single study	Serious - sleep not directly targeted	Very serious - single small study; imprecise	Undetected/unclear	Very low	No pooled estimate; negligible change
Adverse events	142 (3 RCTs)	Randomised trials	Serious - passive/unsystematic AE capture	Not assessable - few events	Serious - AE not primary, varied	Very serious - few events,	Possible - under-reporting likely	Very low	Infrequently reported; no serious AEs clearl

					ascertainment	small N			y attributed

Evidence profile: Acupuncture versus sham

Outcome	**No. of participants (studies)**	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall certainty (GRADE)**	**Effect / result**
Fatigue severity (post)	128 (2 RCTs)	Randomised trials	Not serious - low overall risk due to credible shams	Not serious - consistent direction	Not serious - direct PD and fatigue outcomes	Serious - CI includes small benefit to small harm	Undetected - too few trials to assess	Moderate	SMD 0.17 (95 percent CI -0.13 to 0.51)
Adverse events	128 (2 RCTs)	Randomised trials	Serious - limited, unsystematic AE reporting	Not assessable - few events	Serious - AE not primary outcome	Very serious - few events, small N	Possible - under-reporting cannot be excluded	Very low	Infrequently reported; no serious AEs clearly attributed

Chapter 3 Scoping Review Appendices

Appendix 3.A: Search Strategy

1. Databases Searched:
    - MEDLINE (via PubMed)
    - Cochrane Library
    - CINAHL
    - AMED
    - PsychINFO
2. Search Strings:

Concept 1: Fatigue Management

("Fatigue" OR "Fatigue management" OR "fatigue intervention" OR "fatigue treatment" OR "fatigue therapy")

Concept 2: Neurodegenerative Diseases

("Neurodegenerative diseases" OR "neurological disorders" OR "multiple sclerosis" OR "Parkinson's disease" OR "Huntington's disease" OR "motor neuron disease" OR "progressive supranuclear palsy" OR "ataxia" OR "multiple system atrophy")

Concept 3: Program Evaluation

("Program evaluation" OR "intervention effectiveness" OR "treatment outcomes" OR "outcome assessment" OR "quality of life" OR "patient outcomes")

Concept 4: Non-Pharmacological Interventions

("Non-pharmacological" OR "non-drug" OR "non-medical" OR "psychosocial" OR "behavio*ral" OR "physical activity" OR "exercise therapy" OR "occupational therapy" OR "cognitive behavio*ral therapy" OR "CBT" OR "mindfulness" OR "yoga" OR "acupuncture" OR "acupressure" OR "light therapy" OR "vestibular rehabilitation" OR "physical therapy" OR "rehabilitation" OR "energy conservation" OR "self-management" OR "education" OR "psychological" OR "ACT" OR "acceptance and commitment therapy" OR "IPT" OR "interpersonal therapy" OR "self*help")

3. Date Range:

2006-2024

4. Language Limits:

English and Arabic

5. Additional Notes:

- The search strategy was adapted for each database to account for different indexing terms (MeSH, subject headings, etc.) and interface functionalities.
- Wild cards were used to account for variations in spelling and hyphenation of search terms.

- The reference lists of all included studies and relevant reviews and opinion pieces were screened to identify additional relevant studies.

Appendix 3.B: PRISMA-ScR Checklist (chapter 3 scoping review)

This checklist relates to the Scoping Review reported in Chapter 3. Searches were run to 15 Feb 2025; protocol registered on OSF (DOI: 10.17605/OSF.IO/MJEYP; osf.io/r38sh). Locations are given by chapter/section labels (and figure/table numbers) rather than page numbers.

SECTION	ITEM	PRISMA-ScR CHECKLIST ITEM	REPORTED ON PAGE #
TITLE			
Title	1	Identify the report as a scoping review.	Title and abstract
ABSTRACT			
Structured summary	2	Provide a structured summary that includes (as applicable): background, objectives, eligibility criteria, sources of evidence, charting methods, results, and conclusions that relate to the review questions and objectives.	Abstract
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known. Explain why the review questions/objectives lend themselves to a scoping review approach.	Introduction – rational
Objectives	4	Provide an explicit statement of the questions and objectives being addressed with reference to their key	Aims and objectives

SECTION	ITEM	PRISMA-ScR CHECKLIST ITEM	REPORTED ON PAGE #
		elements (e.g., population or participants, concepts, and context) or other relevant key elements used to conceptualize the review questions and/or objectives.	
METHODS			
Protocol and registration	5	Indicate whether a review protocol exists; state if and where it can be accessed (e.g., a Web address); and if available, provide registration information, including the registration number.	Methods – protocol and registration
Eligibility criteria	6	Specify characteristics of the sources of evidence used as eligibility criteria (e.g., years considered, language, and publication status), and provide a rationale.	Methods – eligibility criteria
Information sources*	7	Describe all information sources in the search (e.g., databases with dates of coverage and contact with authors to identify additional sources), as well as the date the most recent search was executed.	Methods– Information sources and dates

SECTION	ITEM	PRISMA-ScR CHECKLIST ITEM	REPORTED ON PAGE #
Search	8	Present the full electronic search strategy for at least 1 database, including any limits used, such that it could be repeated.	Appendix 3.A – Scoping review search strategy
Selection of sources of evidence†	9	State the process for selecting sources of evidence (i.e., screening and eligibility) included in the scoping review.	Ch3 §3.3.4 Methods—Selection of sources; Fig 3.1 PRISMA-ScR flow
Data charting process‡	10	Describe the methods of charting data from the included sources of evidence (e.g., calibrated forms or forms that have been tested by the team before their use, and whether data charting was done independently or in duplicate) and any processes for obtaining and confirming data from investigators.	Methods—Data charting
Data items	11	List and define all variables for which data were sought and any assumptions and simplifications made.	Methods—Data items
Critical appraisal of individual	12	If done, provide a rationale for conducting a critical appraisal of included sources of evidence; describe	Not Applicable

SECTION	ITEM	PRISMA-ScR CHECKLIST ITEM	REPORTED ON PAGE #
sources of evidence§		the methods used and how this information was used in any data synthesis (if appropriate).	
Synthesis of results	13	Describe the methods of handling and summarizing the data that were charted.	Methods—Synthesis/Mapping
RESULTS			
Selection of sources of evidence	14	Give numbers of sources of evidence screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally using a flow diagram.	Results—Study selection; Fig 3.1 PRISMA-ScR flow
Characteristics of sources of evidence	15	For each source of evidence, present characteristics for which data were charted and provide the citations.	Results—Characteristics; Table 3.1
Critical appraisal within sources of evidence	16	If done, present data on critical appraisal of included sources of evidence (see item 12).	Not applicable
Results of individual sources of evidence	17	For each included source of evidence, present the relevant data that were charted that relate to the review questions and objectives.	Results – individual study summaries

SECTION	ITEM	PRISMA-ScR CHECKLIST ITEM	REPORTED ON PAGE #
Synthesis of results	18	Summarize and/or present the charting results as they relate to the review questions and objectives.	Results – synthesis
DISCUSSION			
Summary of evidence	19	Summarize the main results (including an overview of concepts, themes, and types of evidence available), link to the review questions and objectives, and consider the relevance to key groups.	Discussion – summary of evidence
Limitations	20	Discuss the limitations of the scoping review process.	Discussion – limitation
Conclusions	21	Provide a general interpretation of the results with respect to the review questions and objectives, as well as potential implications and/or next steps.	Conclusions
FUNDING			
Funding	22	Describe sources of funding for the included sources of evidence, as well as sources of funding for the scoping review. Describe the role of the funders of the scoping review.	Funding and declaration

Appendix 3.C: DETAILED SEARCH STRING

DATABASE	WITH CONCEPT 3	SEARCH RESULTS #	WITHOUT CONCEPT 3	SEARCH RESULTS #
PUBMED	("Fatigue" OR "Fatigue management" OR "fatigue intervention" OR "fatigue treatment" OR "fatigue therapy") AND ("Neurodegenerative diseases" OR "neurological disorders" OR "multiple sclerosis" OR "Parkinson's disease" OR "Huntington's disease" OR "motor neuron disease" OR "progressive supranuclear palsy" OR "ataxia" OR "multiple system atrophy") AND ("Program evaluation" OR "intervention effectiveness" OR "treatment outcomes" OR "outcome assessment" OR	1222	("Fatigue" OR "Fatigue management" OR "fatigue intervention" OR "fatigue treatment" OR "fatigue therapy") AND ("Neurodegenerative diseases" OR "neurological disorders" OR "multiple sclerosis" OR "Parkinson's disease" OR "Huntington's disease" OR "motor neuron disease" OR "progressive supranuclear palsy" OR "ataxia" OR "multiple system atrophy") AND ("Non-pharmacological" OR "non-drug" OR "non-medical" OR "psychosocial" OR "behavio*ral" OR "physical	2865

	"quality of life" OR "patient outcomes") AND ("Non-pharmacological" OR "non-drug" OR "non-medical" OR "psychosocial" OR "behavio*ral" OR "physical activity" OR "exercise therapy" OR "occupational therapy" OR "cognitive behavio*ral therapy" OR "CBT" OR "mindfulness" OR "yoga" OR "acupuncture" OR "acupressure" OR "light therapy" OR "vestibular rehabilitation" OR "physical therapy" OR "rehabilitation" OR "energy conservation" OR "self-management" OR "education" OR "psychological" OR "ACT" OR "acceptance and commitment therapy" OR "IPT" OR "interpersonal therapy" OR "self*help")		activity" OR "exercise therapy" OR "occupational therapy" OR "cognitive behavio*ral therapy" OR "CBT" OR "mindfulness" OR "yoga" OR "acupuncture" OR "acupressure" OR "light therapy" OR "vestibular rehabilitation" OR "physical therapy" OR "rehabilitation" OR "energy conservation" OR "self-management" OR "education" OR "psychological" OR "ACT" OR "acceptance and commitment therapy" OR "IPT" OR "interpersonal therapy" OR "self*help")	
COCHRANE	("Fatigue" OR "Fatigue management" OR "fatigue intervention" OR "fatigue	18	("Program evaluation" OR "intervention effectiveness" OR "treatment outcomes" OR	3624

	treatment" OR "fatigue therapy") AND ("Neurodegenerative diseases" OR "neurological disorders" OR "multiple sclerosis" OR "Parkinson's disease" OR "Huntington's disease" OR "motor neuron disease" OR "progressive supranuclear palsy" OR "ataxia" OR "multiple system atrophy") AND ("Program evaluation" OR "intervention effectiveness" OR "treatment outcomes" OR "outcome assessment" OR "quality of life" OR "patient outcomes") AND ("Non-pharmacological" OR "non-drug" OR "non-medical" OR "psychosocial" OR "behavio NEXT ral" OR "physical activity" OR "exercise therapy" OR "occupational therapy" OR "cognitive behavio NEXT ral therapy" OR "CBT"		"outcome assessment" OR "quality of life" OR "patient outcomes")	

	OR "mindfulness" OR "yoga" OR "acupuncture" OR "acupressure" OR "light therapy" OR "vestibular rehabilitation" OR "physical therapy" OR "rehabilitation" OR "energy conservation" OR "self-management" OR "education" OR "psychological" OR "ACT" OR "acceptance and commitment therapy" OR "IPT" OR "interpersonal therapy" OR "self NEXT help")			
PsyINFO	("Fatigue" OR "Fatigue management" OR "fatigue intervention" OR "fatigue treatment" OR "fatigue therapy") AND ("Neurodegenerative diseases" OR "neurological disorders" OR "multiple sclerosis" OR "Parkinson's disease" OR "Huntington's disease" OR "motor neuron disease" OR "progressive supranuclear	676	("Fatigue" OR "Fatigue management" OR "fatigue intervention" OR "fatigue treatment" OR "fatigue therapy") AND ("Neurodegenerative diseases" OR "neurological disorders" OR "multiple sclerosis" OR "Parkinson's disease" OR "Huntington's disease" OR "motor neuron disease" OR "progressive supranuclear	1852

	palsy" OR "ataxia" OR "multiple system atrophy") AND ("Program evaluation" OR "intervention effectiveness" OR "treatment outcomes" OR "outcome assessment" OR "quality of life" OR "patient outcomes") AND ("Non-pharmacological" OR "non-drug" OR "non-medical" OR "psychosocial" OR "behavio*ral" OR "physical activity" OR "exercise therapy" OR "occupational therapy" OR "cognitive behavio*ral therapy" OR "CBT" OR "mindfulness" OR "yoga" OR "acupuncture" OR "acupressure" OR "light therapy" OR "vestibular rehabilitation" OR "physical therapy" OR "rehabilitation" OR "energy conservation" OR "self-management" OR "education" OR "psychological"		palsy" OR "ataxia" OR "multiple system atrophy") AND ("Non-pharmacological" OR "non-drug" OR "non-medical" OR "psychosocial" OR "behavio*ral" OR "physical activity" OR "exercise therapy" OR "occupational therapy" OR "cognitive behavio*ral therapy" OR "CBT" OR "mindfulness" OR "yoga" OR "acupuncture" OR "acupressure" OR "light therapy" OR "vestibular rehabilitation" OR "physical therapy" OR "rehabilitation" OR "energy conservation" OR "self-management" OR "education" OR "psychological" OR "ACT" OR "acceptance and commitment therapy" OR "IPT" OR "interpersonal therapy" OR "self*help")	

	OR "ACT" OR "acceptance and commitment therapy" OR "IPT" OR "interpersonal therapy" OR "self*help")			
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	("Non-pharmacological" OR "non-drug" OR "non-medical" OR "psychosocial" OR "behavio*ral" OR "physical activity" OR "exercise therapy" OR "occupational therapy" OR "cognitive behavio*ral therapy" OR "CBT" OR "mindfulness" OR "yoga" OR "acupuncture" OR "acupressure" OR "light therapy" OR "vestibular rehabilitation" OR "physical therapy" OR "rehabilitation" OR "energy conservation" OR "self-management" OR "education" OR "psychological" OR "ACT" OR "acceptance and commitment therapy" OR "IPT" OR "interpersonal therapy" OR "self*help")		"cognitive behavio*ral therapy" OR "CBT" OR "mindfulness" OR "yoga" OR "acupuncture" OR "acupressure" OR "light therapy" OR "vestibular rehabilitation" OR "physical therapy" OR "rehabilitation" OR "energy conservation" OR "self-management" OR "education" OR "psychological" OR "ACT" OR "acceptance and commitment therapy" OR "IPT" OR "interpersonal therapy" OR "self*help")	
AMED	("Fatigue" OR "Fatigue management" OR "fatigue intervention" OR "fatigue treatment" OR "fatigue therapy") AND	80	("Fatigue" OR "Fatigue management" OR "fatigue intervention" OR "fatigue treatment" OR "fatigue therapy") AND	262

	("Neurodegenerative diseases" OR "neurological disorders" OR "multiple sclerosis" OR "Parkinson's disease" OR "Huntington's disease" OR "motor neuron disease" OR "progressive supranuclear palsy" OR "ataxia" OR "multiple system atrophy") AND ("Program evaluation" OR "intervention effectiveness" OR "treatment outcomes" OR "outcome assessment" OR "quality of life" OR "patient outcomes") AND ("Non-pharmacological" OR "non-drug" OR "non-medical" OR "psychosocial" OR "behavio*ral" OR "physical activity" OR "exercise therapy" OR "occupational therapy" OR "cognitive behavio*ral therapy" OR "CBT" OR "mindfulness" OR "yoga" OR "acupuncture"		("Neurodegenerative diseases" OR "neurological disorders" OR "multiple sclerosis" OR "Parkinson's disease" OR "Huntington's disease" OR "motor neuron disease" OR "progressive supranuclear palsy" OR "ataxia" OR "multiple system atrophy") AND ("Non-pharmacological" OR "non-drug" OR "non-medical" OR "psychosocial" OR "behavio*ral" OR "physical activity" OR "exercise therapy" OR "occupational therapy" OR "cognitive behavio*ral therapy" OR "CBT" OR "mindfulness" OR "yoga" OR "acupuncture" OR "acupressure" OR "light therapy" OR "vestibular rehabilitation" OR "physical therapy" OR "rehabilitation" OR "energy conservation" OR "self-management" OR "education"	

	OR "acupressure" OR "light therapy" OR "vestibular rehabilitation" OR "physical therapy" OR "rehabilitation" OR "energy conservation" OR "self-management" OR "education" OR "psychological" OR "ACT" OR "acceptance and commitment therapy" OR "IPT" OR "interpersonal therapy" OR "self*help")		OR "psychological" OR "ACT" OR "acceptance and commitment therapy" OR "IPT" OR "interpersonal therapy" OR "self*help")	

Appendix 3.D: JBI Scoping Review Checklist

Joanna Briggs Institute Scoping Review Critical Appraisal Checklist

Section	Checklist Item	Reported on Page #
Title	1. The title should clearly specify that the study is a scoping review.	Title & Abstract
Introduction	2. Clearly identify and explain the research question/objective being addressed.	Aim and objectives
	3. Describe the rationale for conducting the scoping review.	Introduction/rationale
Objectives	4. Clearly state the objectives of the scoping review.	Aims and objectives
Inclusion Criteria	5. Specify and justify the inclusion criteria for participants, concepts, context, and study types.	Methods – eligibility criteria
Methods	6. Provide details on the scoping review framework or methodology followed (e.g., Arksey & O'Malley).	Methods – overview and framework
	7. Include a detailed search strategy with databases and date ranges.	Methods– Information sources and search strategy
	8. Clearly describe the process for source selection, including screening and eligibility.	Methods – selection of sources of evidence

	9. Detail the data extraction/charting process, including how variables and themes were identified.	Methods –Data charging
	10. Indicate whether the methods were pilot tested and describe any adjustments.	Not explicitly reported
Data Presentation	11. Present findings in a clear and structured way using tables, charts, or narratives.	Results – overview
Discussion	12. Summarise the results in relation to the objectives and research question.	Discussion – summary of evidence
	13. Discuss gaps in the literature and opportunities for future research.	Discussion – gaps and Implications
	14. Include a clear statement of the study's implications for practice, policy, or research.	Discussion – implications
Conclusions	15. Provide a summary of the key findings.	Conclusions
Funding and Conflicts	16. Disclose any funding sources or conflicts of interest.	Funding and declarations

Chapter 4 – Pilot RCT Appendices

Appendix 4.A: ReFresh programme: module and session breakdown

ReFresh Programme Content and Structure

The full program is available on UEA's web pages. The introductory page at https://www.uea.ac.uk/groups-and-centres/projects/fatigue-management-in-parkinson-s, was separated from the remaining description of the ReFresh program so as participants could be randomly allocated to see it or not at https://www.uea.ac.uk/groups-and-centres/projects/fatigue-management-in-parkinson-s/refresh-study-getting-started.

This outlines the six-week ReFresh programme curriculum, including session objectives, key activities, learning outcomes, and associated exercise recommendations. Participants were encouraged to complete one module per week and engage in at least three 30-minute sessions of exercise weekly, aligned with Parkinson's UK exercise guidelines.

Week	Module Title	Key Topics Covered	Format
Week 1	Understanding Fatigue in Parkinson's	Fatigue triggers, symptom patterns, difference between fatigue and fatigability	Video + worksheet
Week 2	Energy Conservation Strategies	"Do, Delay, Delegate, Ditch" framework, pacing strategies	Video + interactive exercise

Week 3	Cognitive-Behavioural Approaches	Managing fatigue-related thoughts, stress reduction, addressing poor attitudes toward invisible symptoms	CBT-based reflection task + motivational interviewing tools
Week 4	Physical Activity & Movement	Gentle movement strategies, role of exercise in fatigue management	Demonstration videos (Tai Chi, guided walking) + Parkinson's UK exercise resources
Week 5	Sleep Hygiene and Restorative Techniques	Sleep disturbances in PD, relaxation strategies, good sleep hygiene	Interactive self-assessment + strategies for night-time mobility
Week 6	Maintaining Long-Term Gains	Personalised fatigue management plan, goal-setting, summary of previous content	Goal tracker + review session

Delivery Format

- Online, self-paced structure
- Downloadable PDFs for all modules
- Interactive self-assessments
- Optional printed materials for accessibility

- Progress tracking features for participant engagement

Exercise Component

Participants were encouraged to engage in at least three 30-minute sessions per week of exercises that challenge balance, as this has been shown to benefit fatigue management in PD (Abasi, 2020; Ribas, 2017). Exercise recommendations included:

- Low intensity: *Qigong with Suzanne* (YouTube link)

- Mid-intensity: *Dynamic balance exercises with Bev* (YouTube link) & *Balance exercises with Mary* (YouTube link)

- High intensity: *Vigorous aerobics to music with Andy* (YouTube link)

- Vestibular rehabilitation exercises (Video under development, based on Abasi, 2020)

- WiiFit games that challenge balance (Table Tilt, Tilt City, Penguin Slide, Soccer Heading, Basic Run, Obstacle Course, Basic Step) (Ribas, 2017)

Appendix 4.B: CONSORT 2010 checklist (Chapter 4 Pilot RCT)

CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No[a]
Title and abstract			
	1a	Identification as a randomised trial in the title	Title
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	Abstract/sum
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	Introduction – background and rational
	2b	Specific objectives or hypotheses	

Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	Methods – trial design
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	Not applicable

Participants	4a	Eligibility criteria for participants	Methods – participants: Eligibility criteria
	4b	Settings and locations where the data were collected	Methods – setting and locations
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were administered	Methods – interventions
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	Methods – outcomes
	6b	Any changes to trial outcomes after the trial commenced, with reasons	Not applicable
Sample size	7a	How sample size was determined	Methods – sample size
	7b	When applicable, explanation of any interim analyses and stopping guidelines	Not applicable

Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	Methods – random sequence generation
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	Methods – type of randomisation/restrictions
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	Methods – allocation concealment mechanism

Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	Methods – implementation
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	Not applicable
	11b	If relevant, description of the similarity of interventions	Not applicable
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	Methods – statistical methods
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	
Results			
Participant flow (a diagram is strongly	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	Results – participant flow figure 4.1

recommended)	13b	For each group, losses and exclusions after randomisation, together with reasons	Results – participant to flow
Recruitment	14a	Dates defining the periods of recruitment and follow-up	Methods – recruitment Results – follow up
	14b	Why the trial ended or was stopped	Methods
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	Results – baseline characteristic table 4.1
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	Results – number analysed
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	Results – outcomes and estimates

	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	Not applicable
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	Results
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	Adverse events
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	Discussion – limitations
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	Discussion – generalisability
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	Discussion – interpretation
Other information			

Registrati on	23	Registration number and name of trial registry	Chapter 4 front matter
Protocol	24	Where the full trial protocol can be accessed, if available	Noted in chapter 4 header
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	Funding and support/decl arations

Citation: Schulz KF, Altman DG, Moher D, for the CONSORT Group. CONSORT 2010 Statement: updated guidelines for reporting parallel group randomised trials. BMC Medicine. 2010;8:18.

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up-to-date references relevant to this checklist, see www.consort-statement.org.

Appendix 4.C: Data Management Plan

This outlines the procedures for data handling, storage, anonymisation, and access rights implemented throughout the ReFresh pilot RCT. These processes comply with the UK General Data Protection Regulation (UK GDPR), the Data Protection Act 2018, and the University of East Anglia (UEA) data management policies.

1. Data Storage

All quantitative and qualitative data collected through the study were securely stored on password-protected and encrypted systems approved by UEA:

- Online survey responses (baseline, weekly, and endpoint) were collected via Qualtrics (UEA enterprise licence), with data stored on UK-based, GDPR-compliant servers.
- COPM and open-text responses were stored on encrypted UEA OneDrive folders restricted to authorised research personnel.
- Data backups were maintained on UEA's secure research drive, compliant with institutional IT and research integrity standards.

2. Anonymisation

- Each participant was assigned a unique numerical ID at the point of consent. All data files were labelled using these anonymised IDs.
- No names, contact details, or identifiable information were included in analytical datasets.

- A separate encrypted file linking participant names to ID numbers was held securely by the lead researcher (Sarah Alageel) and not shared with the supervisory team or third parties.

3. Access Rights

- Access to raw data was restricted to the principal researcher (Sarah Alageel) and primary supervisor (Dr Katherine Deane).

- Supervisors were provided only with fully anonymised datasets for review and discussion.

- Lay advisors and external stakeholders were not granted access to any raw data.

4. Data Sharing and Retention

- Data will be retained securely for 10 years after study completion, in accordance with UEA policy on research data retention.

- Anonymised datasets may be shared with future researchers upon request, subject to approval by UEA's research governance office and a formal data-sharing agreement.

- Identifiable data (including consent forms) will not be shared or published.

5. Deviations and Oversight

- No deviations from the approved data management plan submitted to the UEA Ethics Committee (reference ETH2324-0159) occurred during the study.

- All procedures were overseen by the supervisory team and supported by the UEA Research Data Management Service.

Appendix 4.D: Ethics Approval and Trial Registration

UEA Ethics Approval Letter (Ref: ETH2324-0159)

University of East Anglia

Faculty of Medicine and Health Sciences Research Ethics Subcommittee (FMH S-REC)

Date: 15 April 2024

Application ID: ETH2324-0159

Study Title: *Pilot RCT Protocol – ReFresh Study: Rehabilitation for Fatigue in people with Parkinson's*

Applicant: Miss Sarah Alageel

Dear Sarah,

Your application was considered on 15th April 2024 by the FMH S-REC.

The decision is: approved.

You are therefore able to start your project subject to any other necessary approvals being given.

If your study involves NHS staff and facilities, you will require Health Research Authority (HRA) governance approval before you can start this project (even though you do not require NHS-REC ethics approval). Please consult the HRA webpage about the application required, which is submitted through the IRAS system.

This approval will expire on **1st January 2025**.

Please note that your project is granted ethics approval only for the length of time identified above. Any extension to a project must obtain renewed ethics approval from the FMH S-REC before continuing.

It is a requirement of this ethics approval that you should report any adverse events which occur during your project to the FMH S-REC as soon as possible. An adverse event is one which was not anticipated in the research design, and which could potentially cause risk or harm to the participants or the researcher, or which reveals potential risks in the treatment under evaluation. For research involving animals, it may be the unintended death of an animal after trapping or carrying out a procedure.

Any amendments to your submitted project in terms of design, sample, data collection, focus etc. should be notified to the FMH S-REC. If the amendments are substantial, a new application may be required.

Approval by the FMH S-REC does not mean your study is compliant with the UK General Data Protection Regulation (UK GDPR) and the Data Protection Act 2018. If you need guidance on how to make your study UK GDPR compliant, please consult UEA's Data Protection team.

Trial registration and basic results summary are publicly available on ISRCTN https://www.isrctn.com/ISRCTN62114944

Appendix 4.E: Lay Advisor Involvement Summary

Overview

Patient and Public Involvement (PPI) was a core component of the ReFresh pilot randomised controlled trial (RCT). A total of **eleven** lay advisors with Parkinson's disease (PwP) were involved throughout the study, recruited through Parkinson's UK Research Support Network. Their input significantly shaped the design, delivery, and evaluation of the intervention.

Recruitment and Onboarding

Lay advisors were initially recruited in the early stages of the project. Eligibility was based on lived experience of Parkinson's, interest in fatigue-related issues, and willingness to participate in virtual meetings. An initial cohort of nine advisors—all white men—were onboarded through a lay-friendly orientation session explaining the trial's objectives, design, and advisory roles. To enhance representation and inclusivity, two additional female advisors were subsequently recruited in collaboration with Parkinson's UK, bringing the total to eleven.

Meetings and Contributions Advisors attended regular meetings (approximately every two months) via Zoom. These sessions provided a platform for discussion, feedback, and collaborative decision-making. Contributions included:

- Reviewing and revising the participant-facing materials (Participant Information Sheet, Consent Form, weekly surveys).
- Providing feedback on content clarity, relevance, and accessibility of the ReFresh programme modules.

- Suggesting modifications for digital usability (e.g., larger fonts, simplified language, increased visual support).

- Selecting patient-centred outcomes and helping prioritise between fatigue severity and fatigue self-efficacy for future trials.

- Reviewing preliminary findings and suggesting dissemination approaches.

Impact on Study Design and Delivery The lay advisors directly influenced the following aspects:

- *Language and Tone*: Modules were edited to reflect more accessible, conversational language.

- *Cultural Sensitivity and Inclusivity*: The advisors highlighted content that might not be relevant or accessible to diverse populations and helped tailor the presentation accordingly.

- *Outcome Prioritisation*: Their input informed the survey sent to lay advisers at the end of the trial to determine whether fatigue severity or self-efficacy should be the primary outcome in a future full RCT.

- *Feedback Mechanisms*: Suggestions were incorporated into the satisfaction surveys, with added free-text boxes for more nuanced feedback.

Reflection and Future Involvement Advisors expressed appreciation for being involved as partners rather than passive participants. They noted that the experience was empowering and valued their voices being taken seriously. Plans are underway to continue their involvement

in the planning of a future full-scale RCT, including reviewing new iterations of the ReFresh content and advising on wider dissemination strategies.

Conclusion The ReFresh trial exemplifies how lay involvement can meaningfully shape the relevance, delivery, and future directions of digital health interventions. Ongoing collaboration with lay advisors remains central to ensuring that future trials are aligned with the lived experiences and priorities of people with Parkinson's disease.

Appendix 4.F: Lay Advisor Outcome Prioritisation Survey Format

Introduction

Thank you for continuing to support our research. We are now reviewing the results from the pilot study of the ReFresh online fatigue management programme for people with Parkinson's.

The aim of this study was to explore whether the ReFresh programme could help reduce the impact of fatigue or improve how people manage their fatigue in daily life. The study was a pilot randomised controlled trial (RCT), meaning it was designed to test feasibility and give us early insight; but it was **not large enough** to confirm with certainty whether differences between the intervention and control groups were due to the programme or just by chance.

We used two key fatigue measures:

1. Fatigue Impact (MFIS): This measures how much fatigue affects someone's daily activities (e.g. concentration, physical tasks, social life). Participants who completed ReFresh showed improvement (i.e. less fatigue), but this result **was not statistically significant**; meaning it could be due to chance.

2. Fatigue Self-Efficacy (MS-FSE): This measures how confident someone feels in managing their fatigue. In this case, ReFresh participants also improved; and the improvement **was statistically significant**, meaning it's more likely to reflect a real effect of the programme.

In planning a future full-scale trial, we would like **your opinion** on what the most important outcome should be. In other words:

How should we decide if the programme works?

---

1. Which of these outcomes do you think is more important as a measure of whether the programme worked?

- ☐ Reduction in fatigue
- ☐ Improved ability to manage fatigue

---

2. Which of these do you personally feel the ReFresh programme is more likely to help with?

- ☐ Reduction in fatigue
- ☐ Improved ability to manage fatigue

---

3. Please explain why you made your choices above:

[Free text response]

---

4. Is there anything else you'd like to tell us about your experience with fatigue or fatigue management, or about what outcomes matter most to you?

[Free text response]

Appendix 4.G: Lay Advisor Survey Responses

Q2. Which outcome is more important	Q3. Which outcome is	Q5. Why did you make your choices?	Q6. Additional comments about

as a measure of whether the programme worked?	ReFresh more likely to help with?		fatigue/fatigue management
Improved ability to manage fatigue	Improved ability to manage fatigue	By improving the ability to manage, gives the patient overall control. This will vary harder to achieve.	It's hard to manage it as it can be a sudden thing, so strategy is important as is staying generally...
Improved ability to manage fatigue	Improved ability to manage fatigue	Fatigue is a given, management is necessary.	—
Improved ability to manage fatigue	Improved ability to manage fatigue	I think the improved ability to manage fatigue will result in a reduction in fatigue.	Successful management of fatigue is more easily attainable.
Improved ability to manage fatigue	Improved ability to manage fatigue	Reducing fatigue is not treatable due to the further deterioration of the disease but managing it is...	I want to be able to manage fatigue so that it doesn't take over my life and makes it easier to live...
Improved ability to manage fatigue	Improved ability to manage fatigue	An improved ability to manage fatigue should lead to a reduction in fatigue that can be sustained by...	Managing fatigue can help with enabling other therapies to be undertaken with greater effect.
Reduction in fatigue	Reduction in fatigue	I try and manage fatigue now, but it's not always possible so if I can reduce fatigue I'll stop, so ...	I expect it really comes down to a bit of both, if I can manage it better, it will probably improve ...
Improved ability to manage fatigue	Improved ability to manage fatigue	May always experience fatigue, need to self-manage it.	Increase of capacity most important. Sleep quality important. Very complex with Parkinson's.

Appendix 4.H: Participant Information Sheet (PIS)

This document outlines the study purpose, participant eligibility, procedures, potential risks, and benefits. It also includes details on data confidentiality, voluntary participation, and withdrawal procedures.

Key Sections Included:

- Introduction to the study (Rationale for research and what participation entails)
- Eligibility criteria (Inclusion and exclusion criteria)
- Study procedures and timeline (Detailed breakdown of participation expectations)
- Data handling and privacy protection (GDPR compliance, anonymisation procedures)
- Potential risks and benefits (Addressing digital fatigue, cognitive effort, and learning benefits)
- Contact information for inquiries or concerns (Study team and ethics committee)

ReFresh Online Fatigue Management Program

INFORMATION ABOUT PARTICIPATION IN THE REFRESH ONLINE FATIGUE MANAGEMENT PROGRAM

Introduction

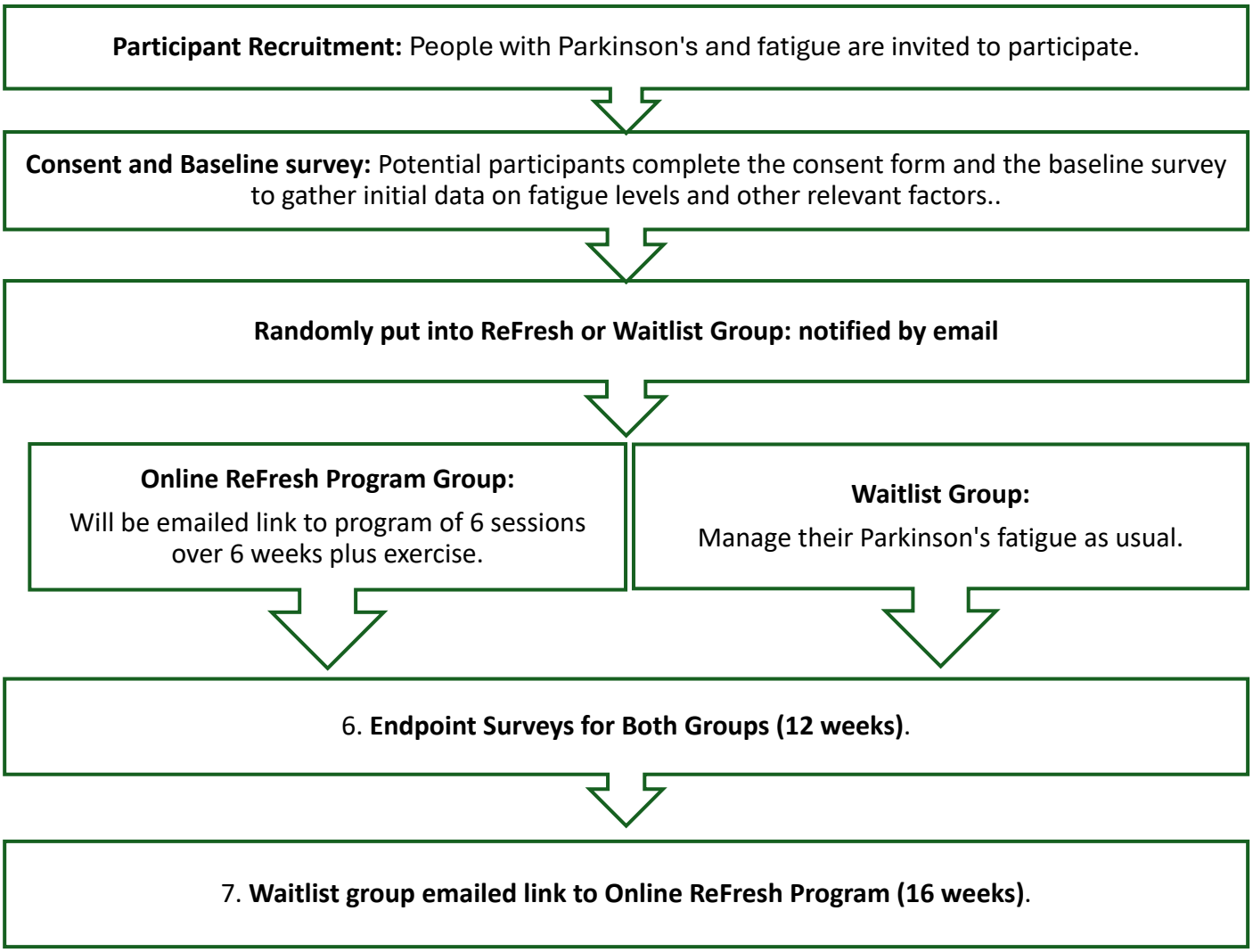
This project, part of Sarah Alageel's PhD studentship, aims to address the significant fatigue experienced by individuals with Parkinson's disease, impacting their quality of life and activity levels. Fatigue management programs have been successful in other health conditions.

You are invited to participate in this research project to assess whether an online program might help people with Parkinson’s better manage fatigue. The study compares those who complete the online ReFresh fatigue management program with a waitlisted group.

To join, you must be over 18, reside in England, and have a diagnosis of idiopathic Parkinson's disease (the most common Parkinson's disease diagnosis (idiopathic means of unknown cause)). Please note exclusion criteria apply, such as Parkinson's plus diseases. Participants should not volunteer to participate if their clinical team advises them against exercise.

This pilot study, involving 40 participants, will examine the program's practicality. While not allowing us to make a definite conclusion as to the effectiveness of the fatigue management program, this project will inform the design of future research and tell us how large these need to be.

What will happen to me if I take part?



You can participate in this online research project entirely from the comfort of your home. At the start of the research project, you will be asked to agree to take part in the ReFresh study and complete a baseline survey covering various aspects of your life, including your Parkinson's condition, experiences of fatigue, daily activities, and overall quality of life. This survey should take approximately 30 minutes to complete.

After completing the baseline survey, participants will be randomly assigned (by chance) to either the ReFresh program or the waitlist group. A computer program conducts this random assignment tosses a virtual coin to see which group any individual will be in.

This allows us to be sure that the two groups are as similar as possible, strengthening the project's statistical robustness. You will receive an email notification of your group assignment. If you are in the ReFresh program group, you will receive a web link to access the online program. Conversely, if you are in the waitlist group, you will be asked to continue managing your Parkinson's until the 12-week follow-up survey.

Participants in the ReFresh program group will engage in six online sessions spread over six weeks, each lasting about 30 minutes, with an additional 30-60 minutes allocated for homework tasks, including exercises. Feedback on each week's content will be collected through short surveys. After the initial 12-week period, both groups will complete a follow-up survey.

At the end of the 16-week study period, the waitlist group will receive a link to access the online ReFresh program. Participation is optional, and uptake will not be recorded.

All surveys are designed to allow participants to stop partway through and continue later. If you prefer to complete surveys on paper, please contact Sarah Alageel at s.alageel@uea.ac.uk, and we will arrange for them to be sent to you. We hope this will help manage any fatigue you experience when completing the surveys.

The study will compare the results of the participants who undertake the ReFresh program and those who do not. The waitlist group allows us to observe the normal variability of fatigue and then see if the ReFresh program makes a substantial difference in fatigue levels compared to this.

Are there any risks for me?

As part of the ReFresh online program, we encourage all participants to exercise for approximately 30 minutes three times a week. To support this, we will provide links to online videos of exercise programs led by physiotherapists and recommend other types of exercise.

It is important to note that these are recommendations, and your level of exercise will be measured as part of the study. If you have any concerns about participating in the exercise, especially if you have another health condition that may increase risk, such as lung or heart disease, we strongly advise you to consult your GP or clinical team to determine what level of exercise is appropriate for you. If you cannot undertake any exercise, this research project is unsuitable for you.

Additionally, we want to emphasise the importance of being careful when exercising, as some people with Parkinson's are prone to falling easily. Therefore, we recommend informing a family member or friend that you are participating in this research project. We suggest clearing a generous space around you if you are exercising at home and keeping a phone nearby in case of a fall. The endpoint survey will ask about falls and any consequences of them.

We will also ask you to reflect on how you cope mentally and physically with fatigue and your Parkinson's. We understand that thinking about your Parkinson's symptoms and how you cope with them can sometimes be distressing. If you would benefit from talking to someone about your mental health and well-being, we highly recommend accessing the services provided by the mental health charity MIND: (https://www.mind.org.uk/information-support/).

For support related to Parkinson's disease, we recommend contacting Parkinson's UK: (https://www.parkinsons.org.uk/information-and-support/support-you).

You can reach them through their free, confidential helpline at 0808 800 0303 (Monday to Friday, 9 am to 6 pm, and 10 am to 2 pm on Saturdays) or by emailing helo@parkinsons.org.uk.

Access Arrangements

We believe that research should be accessible to everyone, regardless of disability. Our surveys meet online accessibility standards and are compatible with screen readers. You are welcome to ask for assistance from family members or caregivers to complete the surveys.

If you prefer a paper copy of the survey, please contact Sarah Alageel at s.alageel@uea.ac.uk, and we will promptly send you a paper copy in either standard or large font size, along with a stamped addressed envelope for your convenience in returning it to us.

We are committed to accommodating any other accessibility requirements you may have for the surveys or participation in the ReFresh program. Please don't hesitate to contact Sarah Alageel (s.alageel@uea.ac.uk), and we will do our best to accommodate your needs.

Can I stop?

Your participation in the research study is entirely voluntary, and you can withdraw at any point up to and including the endpoint (12-week) survey. If you decide to cancel, contact Sarah Alageel at s.alageel@uea.ac.uk, and we will promptly delete your data from the project. After the endpoint survey at 12 weeks is completed and submitted, the data cannot be removed from our study.

We understand that completing surveys can sometimes be challenging, so we want to assure you that you can pause completing them partway through and resume later.

Ethics Approval

This research has undergone a thorough review by a Research Ethics Committee at the University of East Anglia to protect your safety, rights, well-being, and dignity. The Faculty of Medicine and Health Sciences Research Ethics Subcommittee (FMHS-REC) approved this study under reference ETH2324-0159.

Complaints or concerns

If you have any complaints or concerns about the research project, please don't hesitate to contact us:

1. Contact my Primary Supervisor, Dr. Katherine Deane, via email at k.deane@uea.ac.uk or by post to the School of Health Sciences, University of East Anglia, Norwich, NR4 7TJ.
2. If you prefer to escalate your concerns or complaints to someone independent from the study, please contact the Head of the School of Health Sciences, Prof Kenda Crozier, at k.crozier@uea.ac.uk.

Data Management

Ensuring the security and confidentiality of your data is of the utmost importance to us.

- Paper copies of surveys and consent forms will be securely destroyed once the data is transferred to the Qualtrics platform.
- The data will be stored on a secure UEA server, and the original data will be deleted from the Qualtrics platform by 01/01/2025.
- Participant contact details will only be accessible to the project team and deleted after the data collection period ends (i.e., by 01/11/2024). After this point all data will be anonymised.
- All project data will be deleted from the UEA shared drive ten years after the end of the project (by 31st September 2034).
- Only anonymised data will be shared externally, such as in reports and publications.
- Our data management practices adhere to the Data Protection Act 2018 (DPA 2018), the UK General Data Protection Regulations (UK GDPR), and the University of East Anglia's Research Data Management Policy.

As required by data protection legislation, here are some additional details:

- The data controller is the University of East Anglia.
- For further information, contact the University's Data Protection Officer at

dataprotection@uea.ac.uk.

- You can learn more about your data protection rights at the Information Commissioner's Office (ICO).
- If you have any concerns about how your data has been used, please contact the University's Data Protection Officer at dataprotection@uea.ac.uk in the first instance.

Queries

For any questions or concerns about the research project, please do not hesitate to contact Sarah Alageel at s.alageel@uea.ac.uk or by post to the School of Health Sciences, University of East Anglia, Norwich, NR4 7TJ.

This information sheet was last updated on 10/04/2024.

To download a copy of this information sheet, please click here:

https://www.uea.ac.uk/web/groups-and-centres/projects/fatigue-management-in-parkinson-s

What are you consenting to?

Participating in this study is entirely voluntary, and you are not obliged to participate. Your participation will not impact your current or future relationships with the researchers or anyone else at the University of East Anglia.

By providing consent to be involved in this project, you are confirming the following:

	Tick to agree
I understand what I have read in the information sheet	
I agree to take part in the ReFresh research project	
I agree to fill in the surveys at the start and end of the project	
I agree to the use of my personal information as described	
I have downloaded a copy of the Participant Information Sheet to keep	

Your Name:

Your Signature:

Your Email address:

Date:

Thank you for considering participation in our research project.

Appendix 4.I: Baseline and endpoint questionnaires (full instruments)

The following validated instruments were used to assess participant-reported outcomes before and after the intervention:

Primary Fatigue Measures:

1. Parkinson's Fatigue Scale (PFS)
2. Modified Fatigue Impact Scale (MFIS)

Secondary Outcomes:

3. Self-Efficacy for Fatigue Management (MS-FSE)
4. Quality of Life (PDQ-39)
5. Sleep Quality (Pittsburgh Sleep Quality Index – PSQI)
6. Depression (Geriatric Depression Scale – GDS-5)
7. Anxiety (Parkinson's Anxiety Scale – PAS)
8. Occupational Performance (Canadian Occupational Performance Measure – COPM)

Baseline Survey – All participants

Start of Block: Section 1: Participant Information

ReFresh Online Fatigue Management Program

INFORMATION ABOUT PARTICIPATION IN THE REFRESH ONLINE FATIGUE MANAGEMENT PROGRAM

Introduction

This project, part of Sarah Alageel's PhD studentship, aims to address the significant fatigue experienced by some people with Parkinson's disease, impacting their quality of life and activity levels. Similar fatigue management programs have been successful in other health conditions.

You are invited to take part in this research project to assess whether an online program might help people with Parkinson's better manage fatigue. The study compares those who complete the online ReFresh fatigue management program with a waitlisted group.

To join, you must be over 18, reside in England, and have a diagnosis of idiopathic Parkinson's disease (the most common Parkinson's disease diagnosis (idiopathic means of unknown cause)). You cannot take part if you have been diagnosed with any of the Parkinson's plus diseases (vascular Parkinsonism, progressive supranuclear palsy, multiple system atrophy, or Lewy body dementia). However, you can have other diseases, e.g., high

blood pressure, arthritis, or cancer. You should not volunteer to take part if your clinical team has advised you to not do any exercise.

This pilot study, involving 40 participants, will examine the program's practicality. While not allowing us to make a definite conclusion as to the effectiveness of the fatigue management program, this project will inform the design of future research projects and tell us how many people we will need to recruit for them.

What will happen to me if I take part?

You can take part in this online research project entirely from the comfort of your home. At the start of the research project, you will be asked to agree to take part in the ReFresh study and complete a baseline survey covering various aspects of your life, including your Parkinson's condition, experiences of fatigue, daily activities, and overall quality of life. This survey should take approximately 30 minutes to complete.

After completing the baseline survey, you will be randomly assigned (by chance) to either the ReFresh program or the waitlist group. A computer program conducts this random assignment by tossing a virtual coin to see which group any individual will be in. This allows us to be sure that the two groups are as similar as possible, strengthening the project's statistical robustness. You will receive an email notification of your group assignment. If you are in the ReFresh program group, you will receive a web link to access the online program. Conversely, if you are in the waitlist group, you will be asked to continue managing your Parkinson’s until the 12-week follow-up survey.

People in the ReFresh program group will engage in six online sessions spread over six

weeks, each lasting about 30 minutes, with an additional 30-60 minutes allocated for homework tasks, including exercises. Feedback on each week's content will be collected through short surveys (approx. 5 minutes). After the initial 12-week period, both groups will complete a follow-up survey (approx. 30 minutes).

At the end of the 16-week study period, the waitlist group will receive a link to access the online ReFresh program. Whether you access the program or not is up to you, and uptake will not be recorded. All surveys are designed to allow you to stop partway through and continue at another time. We hope this will help manage any fatigue you experience when completing the surveys. If you prefer to complete surveys on paper, please contact Sarah Alageel at s.alageel@uea.ac.uk, and we will arrange for them to be sent to you.

The study will compare the results of those who undertake the ReFresh program against the results of those who do not. The waitlist group allows us to observe the normal variability of fatigue and then see if the ReFresh program makes a substantial difference in fatigue levels compared to this.

Are there any risks for me?

As part of the ReFresh online program, we encourage you to exercise for approximately 30 minutes three times a week. To support this, we will provide links to online videos of exercise programs led by physiotherapists and make recommendations about other types of exercise. It is important to note that these are just recommendations, and your actual level of exercise will be measured as part of the study. If you have any concerns about taking part in the exercises, especially if you have another health condition that may increase risk, such as lung or heart disease, we strongly advise you to consult your GP or clinical team to

determine what level of exercise is appropriate for you. If you cannot undertake any exercise, this research project is unsuitable for you.

Additionally, we want to emphasise the importance of being careful when exercising, as some people with Parkinson's are prone to falling easily. Therefore, we recommend telling a family member or friend that you are taking part in this research project. We suggest clearing a generous space around you if you are exercising at home and keeping a phone nearby in case of a fall. The endpoint survey will ask about falls and any consequences of them. We will also ask you to reflect on how you cope mentally and physically with fatigue and your Parkinson's. We understand that thinking about your Parkinson's symptoms and how you cope with them can sometimes be distressing. If you would benefit from talking to someone about your mental health and wellbeing, we highly recommend accessing the services provided by the mental health charity MIND: (https://www.mind.org.uk/information-support/).

For support related to Parkinson's disease, we recommend contacting Parkinson's UK: (https://www.parkinsons.org.uk/information-and-support/support-you). You can reach them through their free, confidential helpline at 0808 800 0303 (Monday to Friday, 9 am to 6 pm, and 10 am to 2 pm on Saturdays) or by emailing hello@parkinsons.org.uk.

Access Arrangements

We believe that research should be accessible to everyone, regardless of disability. Our surveys meet online accessibility standards and are compatible with screen readers. You are welcome to ask for assistance from family members or caregivers to complete the surveys.

If you prefer a paper copy of the survey, please contact Sarah Alageel at s.alageel@uea.ac.uk, and we will promptly send you a paper copy in either standard or large font size, along with a

stamped addressed envelope for your convenience in returning it to us. We are committed to accommodating any other accessibility requirements you may have for the surveys or participation in the ReFresh program. Please don't hesitate to contact Sarah Alageel (s.alageel@uea.ac.uk), and we will do our best to accommodate your needs.

Can I stop?

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- Our data management practices adhere to the Data Protection Act 2018 (DPA 2018), the UK General Data Protection Regulations (UK GDPR), and the University of East Anglia's Research Data Management Policy.

In addition to the specific information provided above about why your personal data is required and how it will be used, there is also some general information which needs to be provided for you:

- The data controller is the University of East Anglia.
- For further information, contact the University's Data Protection Officer at dataprotection@uea.ac.uk.

- You can learn more about your data protection rights at the Information Commissioner's Office (ICO).
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This information sheet was last updated on 10/04/2024.

To download a copy of this information sheet, please click here: https://www.uea.ac.uk/web/groups-and-centres/projects/fatigue-management-in-parkinson-s

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What are you consenting to?

Being in this study is completely voluntary and you do not have to take part. Your decision whether to participate will not affect your current or future relationship with the researchers or anyone else at the University of East Anglia now or in the future.

By giving consent to take part in this project you are telling us that:

	Click to agree (22)
I understand what I have read in the information sheet. (1)	○
I agree to take part in the ReFresh research project. (14)	○
I agree to fill in the surveys at the start and end of the project. (15)	○
I agree to the use of my personal information as described. (16)	○
I have downloaded a copy of the Participant Information Sheet to keep. (17)	○

Page Break

Now we just need to check you are eligible to take part in our research study. Please tick to confirm your agreement with all the following eligibility criteria.

	Click to agree (1)
I am over 18 years old (1)	○
I live in England (6)	○
I have idiopathic Parkinson's disease (4)	○
I DO NOT have vascular Parkinsonism, progressive supranuclear palsy, multiple system atrophy, or Lewy body dementia (5)	○
I can do exercise (7)	○

Page Break

Thank you for agreeing to take part in the ReFresh research study. We anticipate it will take approximately 30 minutes to complete this baseline survey. Some questions may appear similar or duplicated, this is because we are trying to identify the best measure to use, please be patient with us and answer every question. Your responses are invaluable in helping us better understand your experiences and needs.

Your Name

_____

Your email address

_____

Date

_____

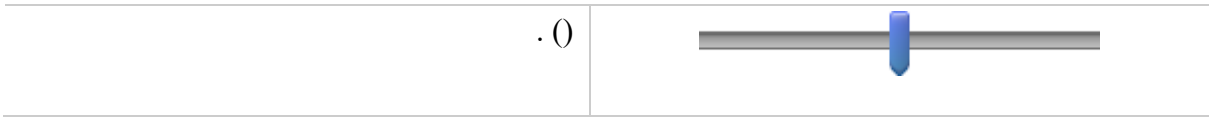
End of Block: Section 1: Participant Information

Start of Block: Section 2: Fatigue Assessment

Next, we need to ask several questions about fatigue. We are unsure what aspects of fatigue are best to measure so there is some duplication of questions as we narrow down the best scales to use.

On a scale from 1 to 10, with 1 being no fatigue and 10 being severe fatigue, how would you rate your current level of fatigue?

1 2 3 4 5 6 7 8 9 10



End of Block: Section 2: Fatigue Assessment

Start of Block: Modified Fatigue Impact Scale - MFIS

Following is a list of statements that describe how fatigue may affect a person. Fatigue is a feeling of physical tiredness and lack of energy that many people experience from time to time.

Please read each statement carefully and then circle the one number that best indicates how

often fatigue has affected you in this way during the past 4 weeks.

Because of my fatigue during the past 4 weeks....

	Never (11)	Rarely (12)	Sometimes (13)	Often (14)	Almost Always (15)
1. I have been less alert. (1)	○	○	○	○	○
2. I have had difficulty paying attention for long periods of time. (2)	○	○	○	○	○
3. I have been unable to think clearly. (28)	○	○	○	○	○
4. I have been clumsy and uncoordinated. (30)	○	○	○	○	○
5. I have been forgetful. (31)	○	○	○	○	○
6. I have had to pace myself in my physical activities. (29)	○	○	○	○	○

7. I have been less motivated to do anything that requires physical effort. (32)	○	○	○	○	○
8. I have been less motivated to participate in social activities. (5)	○	○	○	○	○
9. I have been limited in my ability to do things away from home. (6)	○	○	○	○	○
10. I have had trouble maintaining physical effort for long periods. (7)	○	○	○	○	○

11. I have had difficulty making decisions. (8)	○	○	○	○	○
12. I have been less motivated to do anything that requires thinking. (9)	○	○	○	○	○
13. my muscles have felt weak. (10)	○	○	○	○	○
14. I have been physically uncomfortable. (11)	○	○	○	○	○
15. I have had trouble finishing tasks that require thinking. (12)	○	○	○	○	○

16. I have had difficulty organizing my thoughts when doing things at home or at work. (13)	○	○	○	○	○
17. I have been less able to complete tasks that require physical effort. (14)	○	○	○	○	○
18. My thinking has been slowed down. (15)	○	○	○	○	○
19. I have had trouble concentrating. (16)	○	○	○	○	○

20. I have limited my physical activities. (17)	○	○	○	○	○
21. I have needed to rest more often or for longer periods (18)	○	○	○	○	○

End of Block: Modified Fatigue Impact Scale - MFIS

Start of Block: Parkinson's Disease Fatigue Scale (PFS-16)

Below are a series of statements about fatigue and the impact that it can have. How well do the statements describe your own feelings and experiences over the past four weeks? Read

each statement and decide how much you agree or disagree with it. Then tick the appropriate box.

	Strongly disagree (6)	Disagree (7)	Do not agree nor disagree (8)	Agree (9)	Strongly agree (10)
1. I have to rest during the dayh (1)	○	○	○	○	○
2. My life is restricted by fatigue (5)	○	○	○	○	○
3. I get tired more quickly than other people I know (6)	○	○	○	○	○
4. Fatigue is one of my three worst symptoms (7)	○	○	○	○	○
5. I feel completely exhausted (8)	○	○	○	○	○

6. Fatigue makes me reluctant to socialise (9)	○	○	○	○	○
7. It takes me longer to get things done because of fatigue (10)	○	○	○	○	○
8. I have a feeling of heaviness (20)	○	○	○	○	○
9. If I wasn't so tired I could do more things (12)	○	○	○	○	○
10. Everything I do is an effort (13)	○	○	○	○	○

11. I feel tired for much of the time (14)	○	○	○	○	○
12. I feel totally drained (15)	○	○	○	○	○
13. Fatigue makes it difficult for me to cope with everyday activities (16)	○	○	○	○	○
14. I feel tired even when I haven't done anything (18)	○	○	○	○	○

15. Because of fatigue I do less in my day than I would like (23)	○	○	○	○	○
16. I get so tired I want to lie down wherever I am (24)	○	○	○	○	○

End of Block: Parkinson's Disease Fatigue Scale (PFS-16)

Start of Block: Fatigue self efficacy

Below is a list of statements about how certain people feel about how they manage their fatigue.

Please rank each statement from 0-100 with 0 being very uncertain and 100 being very certain.

	very uncertain	moderately certain	very certain

	0 10 20 30 40 50 60 70 80 90 100
1. How certain are you that you can control your fatigue? ()	
2. How certain are you that you can regulate your activity so as to be active without aggravating your fatigue? ()	
3. How certain are you that you can manage your fatigue so that you can do the things you enjoy doing? ()	
4. How certain are you that you can deal with the frustration of fatigue? ()	
5. How certain are you that you can deal with the uncertainty of fatigue? ()	
6. How certain are you that you can decrease your fatigue quite a bit? ()	
7. How certain are you that you can continue most of your daily activities? ()	
8. How certain are you that you can keep your fatigue from interfering with your time spent with friends or family? ()	

End of Block: Fatigue self efficacy

Start of Block: Open ended impact of fatigue

How would you describe the impact of fatigue on your daily life?

_____

_____

_____

_____

_____

End of Block: Open ended impact of fatigue

Start of Block: SLEEP

Fatigue and sleep are obviously closely linked, so we will now ask a number of questions about your sleep.

The following questions relate to your usual sleep habits during the past four weeks only. Your answers should indicate the most accurate reply for the majority of days and nights in the past four weeks.

During the past month, when have you usually gone to bed at night? USUAL BED TIME

_____

2. During the past month, how long (in minutes) has it usually take you to fall asleep each night? NUMBER OF MINUTES

_____

3. During the past month, when have you usually gotten up in the morning? USUAL GETTING UP TIME

_____

4. During the past month, how many hours of actual sleep did you get at night? (This may be different than the number of hours you spend in bed.) HOURS OF SLEEP PER NIGHT

_____

For each of the remaining questions, check the one best response.

Please answer all questions.

During the past four weeks, how often have you had trouble sleeping because you...

	Not during the past four weeks (1)	Less than once a week (2)	Once or twice a week (3)	Three or more times a week (4)
Cannot get to sleep within 30 minutes (4)	○	○	○	○
Wake up in the middle of the night or early morning (5)	○	○	○	○
Have to get up to use the bathroom (6)	○	○	○	○
Cannot breathe comfortably (7)	○	○	○	○
Cough or snore loudly (8)	○	○	○	○
Feel too cold (9)	○	○	○	○
Feel too hot (10)	○	○	○	○

Had bad dreams (11)	○	○	○	○
Have pain (12)	○	○	○	○
Other reason(s). Please describe: (13)	○	○	○	○

(If relevant) please describe other reason(s) for having trouble sleeping in last four weeks

_____

During the past four weeks, how would you rate your sleep quality overall?

- ○ Very good (16)
- ○ Fairly good (17)
- ○ Fairly Bad (18)
- ○ Very bad (19)

During the past four weeks, how often have you taken medicine (prescribed or "over the counter") to help you sleep?

- ○ Not during the past month (1)
- ○ Less than once a week (2)
- ○ Once or twice a week (3)
- ○ Three or more times a week (4)

During the past four weeks, how often have you had trouble staying awake while driving, eating meals, or engaging in social activity?

- ○ Not during the past month (1)
- ○ Less than once a week (2)
- ○ Once or twice a week (3)
- ○ Three or more times a week (4)

During the past four weeks, how much of a problem has it been for you to keep up enough enthusiasm to get things done?

- ○ No problem at all (1)
- ○ Only a very slight problem (2)
- ○ Somewhat of a problem (3)
- ○ A very big problem (4)

Do you have a bed partner or roommate?

- ○ No bed partner or roommate (1)
- ○ Partner/roommate in other room (2)
- ○ Partner in same room, but not same bed (3)
- ○ Partner in same bed (4)

Display This Question:

If Do you have a bed partner or roommate? = Partner/roommate in other room

Or Do you have a bed partner or roommate? = Partner in same room, but not same bed

Or Do you have a bed partner or roommate? = Partner in same bed

If you have a roommate or bed partner, ask him/her how often in the past month you have had...

	Not during the past four weeks (1)	Less than once a week (2)	Once or twice a week (3)	Three or more times a week (4)
Loud snoring (8)	○	○	○	○
Long pauses between breaths while asleep (9)	○	○	○	○
Legs twitching or jerking while you sleep (10)	○	○	○	○
Episodes of disorientation or confusion during sleep (11)	○	○	○	○
Other restlessness while you sleep (12)	○	○	○	○

End of Block: SLEEP

Start of Block: THE GERIATRIC DEPRESSION SCALE-15 (GDS-15)

We know there are a number of factors that can affect feelings of fatigue, such as mood and stress. We need to know your experiences of these in the last 4 weeks

	Yes (1)	No (9)
1. Are you basically satisfied with your life? (1)	○	○
2. Have you dropped many of your activities or interests? (17)	○	○
3. Do you feel that your life is empty? (18)	○	○
4. Do you often feel bored? (19)	○	○
5. Are you in good spirits most of the time? (20)	○	○
6. Are you afraid that something bad is going to happen to you? (21)	○	○
7. Do you feel happy most of the time? (22)	○	○
8. Do you often feel helpless? (23)	○	○
9. Do you prefer to stay at home, rather than going out and doing new things? (24)	○	○

10. Do you feel you have more problems with your memory than most? (31)	○	○
11. Do you think it is wonderful to be alive? (32)	○	○
12. Do you feel pretty worthless the way you are now (27)	○	○
13. Do you feel full of energy? (28)	○	○
14. Do you feel that your situation is hopeless? (29)	○	○
15. Do you think that most people are better off than you are? (30)	○	○

End of Block: THE GERIATRIC DEPRESSION SCALE-15 (GDS-15)

Start of Block: The Parkinson Anxiety Scale (PAS)

a. Persistent Anxiety.

Please mark one circle for each item below.

In the past four weeks, to what extent did you experience the following symptoms?

	Not at all, or never (1)	Very mild or rarely (2)	Mild or sometimes (3)	Moderate or often (4)	Severe or (nearly) always (5)
Feeling anxious or nervous (4)	○	○	○	○	○
Feeling tense or stressed (5)	○	○	○	○	○
Being unable to relax (6)	○	○	○	○	○
Excessive worrying about everyday matters (16)	○	○	○	○	○
Fear of something bad, or even the worst, happening (17)	○	○	○	○	○

b. Episodic anxiety.

Please mark one circle for each item below.

In the past four weeks, did you experience episodes of the following symptoms?

	Never (1)	Rarely (2)	Sometimes (3)	Often (4)	Nearly always (5)
Panic or intense fear (4)	○	○	○	○	○
Shortness of breath (5)	○	○	○	○	○
Heart palpitations or heart beating fast (not related to physical effort or activity) (6)	○	○	○	○	○
Fear of losing control (7)	○	○	○	○	○

c. Avoidance behaviour

Please mark one circle for each item below.

In the past four weeks, to what extent did you fear or avoid the following situations?

	Never (1)	Rarely (2)	Sometimes (3)	Often (4)	Nearly always (5)
Social situations (where one may be observed or evaluated by others, such as speaking in public or talking to unknown people) (4)	○	○	○	○	○

Public settings (situations from which it may be difficult or embarrassing to escape, such as queues or lines, crowds, bridges or public transport) (6)	○	○	○	○	○

Specific objects or situations (such as flying, heights, spiders or other animals, needles or blood) (9)	○	○	○	○	○

End of Block: The Parkinson Anxiety Scale (PAS)

Start of Block: PDQ39

We also need to know the impact your Parkinson's has on your quality of life.

Due to having Parkinson's disease, how often during the last four weeks have you…

*Please **tick one circle** for each question*

	Never (1)	Occasionally (2)	Sometimes (3)	Often (4)	Always or Cannot do it at all (5)
1. Had difficulty doing the leisure activities which you would like to do? (1)	○	○	○	○	○
2. Had difficulty looking after your home, e.g. DIY, housework, cooking? (3)	○	○	○	○	○
3. Had difficulty carrying bags of shopping? (5)	○	○	○	○	○
4. Had problems walking half a mile? (6)	○	○	○	○	○
5. Had problems walking 100 yards? (7)	○	○	○	○	○

6. Had problems getting around the house as easily as you would like? (8)	○	○	○	○	○
7. Had difficulty getting around in public? (9)	○	○	○	○	○
8. Needed someone else to accompany you when you went out? (10)	○	○	○	○	○
9. Felt frightened or worried about falling over in public? (11)	○	○	○	○	○

10. Been confined to the house more than you would like? (12)	○	○	○	○	○
11. Had difficulty washing yourself? (13)	○	○	○	○	○
12. Had difficulty dressing yourself? (14)	○	○	○	○	○
13. Had problems doing up buttons or shoe laces? (15)	○	○	○	○	○
14. Had problems writing clearly? (42)	○	○	○	○	○

15. Had difficulty cutting up your food? (17)	○	○	○	○	○
16. Had difficulty holding a drink without spilling it? (18)	○	○	○	○	○
17. Felt depressed? (19)	○	○	○	○	○
18. Felt isolated and lonely? (20)	○	○	○	○	○
19. Felt weepy or tearful? (21)	○	○	○	○	○
20. Felt angry or bitter? (22)	○	○	○	○	○
21. Felt anxious? (23)	○	○	○	○	○

22. Felt worried about your future? (24)	○	○	○	○	○
23. Felt you had to conceal your Parkinson's from people? (25)	○	○	○	○	○
24. Avoided situations which involve eating or drinking in public? (26)	○	○	○	○	○
25. Felt embarrassed in public due to having Parkinson's disease? (27)	○	○	○	○	○
26. Felt worried by other people's reaction to you? (28)	○	○	○	○	○

27. Had problems with your close personal relationships? (29)	○	○	○	○	○
28. Lacked support in the ways you need from your spouse or partner? If you do not have a spouse, skip this statement. (30)	○	○	○	○	○
29. Lacked support in the ways you need from your family or close friends? (43)	○	○	○	○	○

30. Unexpectedly fallen asleep during the day? (44)	○	○	○	○	○
31. Had problems with your concentration, e.g. when reading or watching TV? (33)	○	○	○	○	○
32. Felt your memory was bad? (45)	○	○	○	○	○
33. Had distressing dreams or hallucinations? (35)	○	○	○	○	○
34. Had difficulty with your speech? (36)	○	○	○	○	○

35. Felt unable to communicate with people properly? (37)	○	○	○	○	○
36. Felt ignored by people? (38)	○	○	○	○	○
37. Had painful muscle cramps or spasms? (39)	○	○	○	○	○
38. Had aches and pains in your joints or body? (40)	○	○	○	○	○
39. Felt unpleasantly hot or cold? (46)	○	○	○	○	○

Exercise can impact on feelings of fatigue. We are interested in exercise that you have done for at least 15 minutes at a single time point.

During the last week how much time on the average do you do the following kinds of exercise during your free time. Write on each line the approximate number of minutes total for all types of that level of exercise per week.

☐ STRENUOUS EXERCISE. An activity that results in the heart beating rapidly, you will sweat, and a conversation generally cannot be maintained uninterrupted.e.g. running, jogging, football, squash, vigorous swimming, vigorous long distance bicycling (1) _____

☐ MODERATE EXERCISE. An activity that causes breathing to be heavier but is able to be conducted whilst maintaining a conversation uninterrupted e.g. fast walking, tennis, easy bicycling, badminton, easy swimming, dancing (2)

_____

☐ LIGHT EXERCISE. An activity that does not cause a noticeable change in breathing rate e.g. yoga, fishing, bowling, golf, easy walking (4)

_____

Page Break

People with Parkinson's are at higher risk of falling, so we need to keep a particular eye on this. Thinking of the last four weeks have you experienced any of the following?

Display This Choice:

If People with Parkinson's are at higher risk of falling, so we need to keep a particular eye on thi... = c) Did a fall or near fall result in an injury? [Yes]

	Yes (1)	No (9)
a) A near fall (any incident where you may have fallen, but didn't come to rest on the ground)? (1)	○	○
b) A fall (an incident that resulted in your unintentionally coming to rest on the ground)? (17)	○	○
c) Did a fall or near fall result in an injury? (18)	○	○
Display This Choice: If People with Parkinson's are at higher risk of falling, so we need to keep a particular eye on thi... = c) Did a fall or near fall result in an injury? [Yes]		
d) Did the injury require you to spend at least one night in hospital? (34)	○	○

Page Break

Next some questions about you and your health so we can characterise who has taken part in our research.

What is your ethnic group? Please select all the options that best describe your ethnicity or background E.g. you could select Black African and White British if this best reflects your identity.

- [ ] Asian / Asian British (1)
- [ ] White (3)
- [ ] Black / African / Caribbean / Black British (12)
- [ ] Arab (11)
- [ ] Hispanic / Latina (10)
- [ ] Any other ethnic group (9)

What is your religion or strongly held belief, if any?

- [ ] No religion (1)
- [ ] Buddhist (2)
- [ ] Christian (3)
- [ ] Hindu (4)
- [ ] Jewish (5)
- [ ] Muslim (6)
- [ ] Sikh (7)
- [ ] Spiritual (8)
- [ ] Any other religion or belief (9)
- [ ] Prefer not to say (10)

Which of the following best describes your gender?

- ○ Man (1)
- ○ Non-binary (2)
- ○ Woman (3)
- ○ Prefer to self-describe (4)
- ○ Prefer not to say (5)

Do you identify as trans?

- ○ No (18)
- ○ Prefer not to say (19)
- ○ Yes (20)

Which of the following best describes your sexual orientation?

- ○ Asexual (1)
- ○ Bi/bisexual (2)
- ○ Gay man (3)
- ○ Gay woman/lesbian (4)
- ○ Queer (5)
- ○ Straight/heterosexual (6)
- ○ Pansexual (7)
- ○ I identify in another way (8)
- ○ Prefer not to say (9)

Do you have any caring responsibilities? (tick all that apply)

- [ ] None (1)
- [ ] Primary carer of a child or children (under 18) (2)
- [ ] Joint primary carer of a child or children (under 18) (3)
- [ ] Primary carer of a disabled child or children (4)
- [ ] Joint primary carer of a disabled child or chidren (5)
- [ ] Primary carer or assistant for a disabled adult (18 years or over) (13)
- [ ] Joint primary carer or assistant for a disabled adult (18 years or over) (14)
- [ ] Primary carer or assistant for an older person or people (65 and over) (16)
- [ ] Joint primary carer or assistant for an older person or people (65 and over) (18)
- [ ] Secondary carer (another person carries out the main caring role) (20)
- [ ] I have caring responsibilities but prefer not to specify what these are (22)
- [ ] Prefer not to say (25)

What was the occupation of your main household earner when you were about aged 14?

○ Modern professional & traditional professional occupations such as: teacher, nurse, physiotherapist, social worker, musician, police officer (sergeant or above), software

designer, accountant, solicitor, medical practitioner,scientist, civil / mechanical engineer. (1)

○ Senior, middle or junior managers or administrators such as: finance manager, chief executive, large business owner, office manager, retail manager, bank manager, restaurant manager, warehouse manager. (10)

○ Clerical and intermediate occupations such as: secretary, personal assistant, call centre agent, clerical worker, nursery nurse. (11)

○ Technical and craft occupations such as: motor mechanic, plumber, printer, electrician, gardener, train driver. (12)

○ Routine, semi-routine manual and service occupations such as: postal worker, machine operative, security guard, caretaker, farm worker, catering assistant, sales assistant, HGV driver, cleaner, porter, packer, labourer, waiter/waitress, bar staff. (13)

○ Long-term unemployed (claimed Jobseeker's Allowance or earlier unemployment benefit for more than a year). (14)

○ Small business owners who employed less than 25 people such as: corner shop owners, small plumbing companies, retail shop owner, single restaurant or cafe owner, taxi owner, garage owner. (15)

○ Other such as: retired, this question does not apply to me, I don't know. (16)

○ I prefer not to say. (17)

What type of school did you attend for the majority of your time between the ages of 11 - 16?

- ○ A state-run or state-funded school in the UK - Nonselective (1)
- ○ A state-run or state-funded school in the UK - Selective on academic, faith or other ground (2)
- ○ Independent or fee-paying school in the UK - where I received a means tested bursary covering 90% or more of the total cost of attending throughout my time there (3)
- ○ Independent or fee-paying school in the UK (4)
- ○ A state-run or state-funded school outside the UK - Non-selective (5)
- ○ A state-run or state-funded school outside the UK - Selective on academic, faith or other ground (6)
- ○ Independent or fee-paying school outside the UK - where I received a means tested bursary covering 90% or more of the total cost of attending throughout my time there (7)
- ○ Independent or fee-paying school outside the UK (8)
- ○ I don't know. (9)
- ○ Prefer not to say (10)

If you finished school after 1980, were you eligible for free school meals at any point during your school years?

- ○ Yes (1)
- ○ No (2)
- ○ Not applicable (finished school before 1980 or went to school overseas) (3)
- ○ I don't know (6)
- ○ I prefer not to say (5)

Do you consider yourself to have a disability or long-term condition? (such as dyslexia, diabetes, arthritis, a heart condition, or a mental health condition)

- ○ Yes (21)
- ○ No (22)
- ○ Prefer not to say (23)

Do you experience barriers or limitations in your day-to-day activities related to any health conditions (including mental health), physical, sensory or cognitive differences?

- ○ Yes – substantial barriers or limitations (18)
- ○ Yes – some/small barriers or limitations (19)
- ○ No (20)

Display This Question:

If Do you experience barriers or limitations in your day-to-day activities related to any health con... = Yes – substantial barriers or limitations

Or Do you experience barriers or limitations in your day-to-day activities related to any health con... = Yes – some/small barriers or limitations

Please describe what type of barriers or limitations do you face? Please describe these in whatever way works for you, some examples are included below. Please do not include any identifying information.

For example, these might include:

• Attitudinal barriers e.g. discriminatory attitudes; negative or incorrect assumptions

• Physical barriers e.g. no step free access to buildings; physical expectations of participating

• Travel or transportation barriers e.g. lack of accessible transport and accommodation

• Communications barriers e.g. lack of information in different accessible formats; lack of BSL interpretation

• Organisational barriers e.g. length of time and when meetings are scheduled limits participation

• Social barriers e.g. expectations in social interactions

_____

How long have you been diagnosed with Parkinson's disease?

_____

Please list any other health conditions you have been diagnosed with

_____

_____

_____

_____

_____

Please list all the medications you are currently taking.

For each medication, provide the following details:

1. Medication Name

2. Dosage (e.g., milligrams or micrograms)

3. Frequency (e.g., daily, twice a day, as needed)

e.g. Levodopa 95mg 3 times a day

e.g. Rotigotine transdermal patch 4mg/24 hours

_____

_____

_____

_____

_____

Have you received any previous treatment or interventions for fatigue related to Parkinson's disease?

- ○ Yes (1)
- ○ No (2)

Display This Question:

If Have you received any previous treatment or interventions for fatigue related to Parkinson's dise... = Yes

Please describe any previous treatment or interventions for fatigue related to Parkinson's disease, and whether you believe they helped.

_____

End of Block: PDQ39

Appendix 4.J: Weekly participant feedback items & weekly survey instrument

Framing and items. Acceptability was framed using the Theoretical Framework of Acceptability (TFA) and operationalised via six brief post-module items (5-point Likert: Strongly agree=5 to Strongly disagree=1) covering: (1) overall satisfaction, (2) resource usefulness, (3) ease of applying advice, (4) engagement, (5) clarity, and (6) relevance; each week also included a free-text box. Items were developed using the Person-Based Approach (PBA); minor wording/examples were iteratively refined in response to weekly comments while preserving core intervention ingredients (Sekhon, Cartwright & Francis, 2017; Yardley et al., 2015).

Table 4.J1. Pooled responses across all weeks (% of response occasions; n=149)

Percentages are weighted by each week's response count. Scores are on a 5-point scale (5=Strongly agree … 1=Strongly disagree). See Table J2 for week-by-week Ns.

Feedback Statement	Strongly Agree	Somewhat Agree	Neither Agree nor Disagree	Somewhat Disagree	Strongly Disagree	Average Score (/5)
1. Overall, I was satisfied with this week's programme	52%	36%	8%	2%	2%	4.28
2. The additional resources (documents/links) were useful	50%	37%	7%	4%	2%	4.27
3. I found it easy to apply this week's advice to my fatigue management	37%	36%	8%	5%	4%	4.07
4. I engaged well with this week's content	36%	37%	13%	9%	2%	4.00
5. The information was	50%	37%	8%	5%	0%	4.32

clear and easy to understand						
6. This week's content was relevant to me	50%	36%	16%	8%	2%	4.10

Note. "Average Score (/5)" is the weighted mean across response occasions. Percentages may not total 100% due to rounding.

Higher scores indicate more positive feedback.

Table 4.J2. Weekly descriptive statistics for acceptability items (by week and item)

Columns show per-item N, response counts, mean, and SD. Per-item Ns can differ slightly within a week due to occasional missing responses.

Week	Weekly N (responses)	Item	N	Strongly agree	Somewhat agree	Neither agree nor disagree	Somewhat disagree	Strongly disagree	Mean	SD
Week 1	34	1. Content relevant	34	18	12	3	1	0	4.38	0.78
	34	2. Information clear	33	14	13	4	2	0	4.18	0.88
	34	3. Engaged well	33	8	18	6	1	0	4	0.75
	34	4. Easy to apply advice	34	4	17	8	4	1	3.56	0.96
	34	5. Additional resources useful	34	8	15	9	1	1	3.82	0.94
	34	6. Overall satisfied	34	7	19	7	0	1	3.91	0.83
Week 2	31	1. Content relevant	31	15	12	2	2	0	4.29	0.86
	31	2. Information clear	29	16	10	3	0	0	4.45	0.69
	31	3. Engaged well	31	11	12	1	5	2	3.81	1.28
	31	4. Easy to apply advice	30	7	11	5	6	1	3.57	1.17
	31	5. Additional resources useful	30	4	17	7	1	1	3.73	0.87

	31	6. Overall satisfied	31	12	14	0	5	0	4.06	1.03
Week 3	27	1. Content relevant	27	9	12	4	2	0	4.04	0.9
	27	2. Information clear	27	8	14	5	0	0	4.11	0.7
	27	3. Engaged well	27	10	9	7	1	0	4.04	0.9
	27	4. Easy to apply advice	27	2	17	4	4	0	3.63	0.84
	27	5. Additional resources useful	26	5	9	11	1	0	3.69	0.84
	27	6. Overall satisfied	26	8	12	5	1	0	4.04	0.82
Week 4	18	1. Content relevant	18	7	9	2	0	0	4.28	0.67
	18	2. Information clear	18	11	4	3	0	0	4.44	0.78
	18	3. Engaged well	17	5	8	3	1	0	4	0.87
	18	4. Easy to apply advice	18	2	10	2	4	0	3.56	0.98
	18	5. Additional resources useful	18	5	7	6	0	0	3.94	0.8
	18	6. Overall satisfied	18	6	6	5	1	0	3.94	0.94
Week 5	22	1. Content relevant	22	14	7	1	0	0	4.59	0.59
	22	2. Information clear	22	12	10	0	0	0	4.55	0.51

	22	3. Engaged well	22	11	8	1	2	0	4.27	0.94
	22	4. Easy to apply advice	22	4	10	3	5	0	3.59	1.05
	22	5. Additional resources useful	22	6	9	7	0	0	3.95	0.79
	22	6. Overall satisfied	22	8	13	1	0	0	4.32	0.57
Week 6	14	1. Content relevant	14	8	5	1	0	0	4.5	0.65
	14	2. Information clear	14	6	8	0	0	0	4.43	0.51
	14	3. Engaged well	14	5	8	1	0	0	4.29	0.61
	14	4. Easy to apply advice	14	3	8	1	2	0	3.86	0.95
	14	5. Additional resources useful	14	1	9	3	1	0	3.71	0.73
	14	6. Overall satisfied	14	5	7	1	1	0	4.14	0.86

Weekly Ns (responses): Week 1=35, Week 2=31, Week 3=28, Week 4=19, Week 5=22, Week 6=14; *Total response occasions* = 149.

Example per-item N variation: Week 3, Item 5 N=26.

Appendix 4.K: Summary Table of Primary and Secondary Outcomes (Per Protocol analysis)

Per-protocol definition and adherence measurement

The per-protocol (PP) sample comprises participants who reported accessing ≥4 of the 6 ReFresh modules, operationalised using participant self-report within the weekly feedback surveys and corroborated by Qualtrics survey timestamps where available. Participants were not required to return completed diaries or worksheets, as these materials were intended for personal use during the programme. The platform did not allow extraction of participant-level analytics such as module access logs or download activity. The PP numbers are: Intervention PP n = 32; Control PP n = 21. (See Methods section 4.2.5 and Appendix 4.N–4.O for the TIDieR and logic model.)

Measure	Group	Baseline Mean (SD)	Endpoint Mean (SD)	Change Mean (SD)	P-value (Intervention vs. Control)
Fatigue Measures					
PFS	Intervention	55.52 (13.61)	47.57 (16.65)	-7.95 (11.15)	0.097
	Control	57.14 (14.59)	55.05 (14.49)	-2.09 (18.60)	
MFIS	Intervention	36.74 (14.63)	34.74 (21.85)	-2.00 (18.72)	0.23
	Control	40.94 (14.06)	41.22 (16.44)	0.28 (10.80)	
Quality of Life					
PDQ	Intervention	23.29 (12.60)	33.08 (24.52)	9.79 (21.01)	0.88

	Control	29.31 (16.26)	34.14 (28.78)	4.83 (22.13)	
Participation and Activities					
PAS	Intervention	24.50 (9.53)	24.38 (9.54)	-0.13 (5.68)	0.67
	Control	24.75 (9.61)	25.36 (7.70)	0.61 (7.56)	
Mood					
GDS	Intervention	3.87 (2.99)	3.70 (4.30)	-0.17 (2.73)	0.05
	Control	5.11 (3.57)	5.94 (4.20)	0.83 (2.48)	
Sleep					
PSQI	Intervention	9.64 (2.93)	9.00 (3.16)	-0.64 (1.68)	0.13
	Control	10.94 (3.36)	10.35 (3.13)	-0.58 (1.82)	
Self-Efficacy					
MS-FSE	Intervention	3.67 (2.10)	66.42 (18.57)	62.76 (19.40)	0.0012
	Control	12.43 (6.20)	47.60 (22.13)	35.17 (24.29)	

Appendix 4.L: Adverse Event Monitoring and Safety Protocol

Definitions

An *adverse event (AE)* was defined as any unfavourable or unintended sign, symptom, or illness that occurred during the study, regardless of whether it was considered related to the intervention.

A *serious adverse event (SAE)* was defined as any adverse event that resulted in death, was life-threatening, required hospitalisation or prolongation of existing hospitalisation, or resulted in significant disability or incapacity.

Monitoring and Reporting Procedure

Participants were informed at the outset that they could report any concerns or issues at any point via email or during routine check-ins. All reported issues were reviewed by the trial coordinator (Sarah Alageel), who determined whether the concern met the threshold for an AE or SAE. If there were any potential SAEs, these would have been escalated immediately to the supervisory team and reported to the UEA FMH Ethics Committee (Ref: ETH2324-0159).

Documentation

A log was maintained to record any reported events. This log included the date of report, nature of concern, participant code, and any action taken.

Findings

No serious adverse events (SAEs) were reported during the course of the ReFresh pilot study. One participant reported difficulty using the platform during Week 2, which was resolved with additional support and was not classified as an AE.

Appendix 4.M: Adverse Event Report Regarding Outcome Prioritisation Survey

Ethics Reference: ETH2324-0159

Date of Incident: 07 April 2025

Description of the incident:

On 7 April 2025, a supplementary survey was emailed to all participants of the ReFresh pilot trial, asking them to indicate whether they felt fatigue severity or fatigue self-efficacy was a more meaningful outcome for future research. The intent was to gather lay perspectives to aid in interpreting the pilot findings and planning a future full RCT design.

However, this communication was outside the scope of the original ethical approval (ETH2324-0159), which did not include consent for further participant contact after trial completion. Although the survey was anonymous, did not collect personal or sensitive data, and was closely aligned with the original research aims, contacting the broader participant group represents a deviation from the approved protocol**.**

Parties affected:

113 individuals who previously participated in the ReFresh trial (intervention and waitlist control groups) received the follow-up email. The survey was entirely anonymous, and no identifiable or sensitive data were collected. No participant expressed concern or distress, and several offered thoughtful and positive responses. No harm was reported.

The 9 lay advisors involved in programme co-design were also contacted separately, as recontact was previously approved for them.

Action taken and oversight:

The issue was identified at supervision on 15 April 2025 and immediately reported to FMH Ethics and the UEA Data Protection team. The survey was closed on the same day.

- Ethics: The ethics chair/committee noted the breach and advised submitting an Adverse Event report in Ethics Monitor and not using the survey data in analyses or publications unless and until further ethical approval is granted.
- Data protection: The Data Protection team did not deem this a significant personal-data breach, as the communication fell within participants' expected research-related contact (i.e., not marketing or unrelated purposes) and no identifiable/sensitive data were collected.

Current status

An Adverse Event report has been filed. The survey data are quarantined and excluded from all analyses and dissemination; they will only be used if subsequent ethical approval is obtained.

Appendix 4.N: TIDieR Checklist for the ReFresh Online Fatigue Management Program

TIDieR checklist adapted from Hoffmann et al. (2014). This checklist records the core, replicable elements of ReFresh as described in the trial protocol (UEA Ref 45033, and module materials (Sessions 1–6).

Brief name

ReFresh — an online, CBT-informed fatigue self-management programme with balance/combined exercise options for people with Parkinson's.

Why (rationale, theory, goals)

Targets multidimensional Parkinson's fatigue by addressing cognitive–behavioural drivers (beliefs, pacing, sleep routines) and physical deconditioning/balance. Theory of change: improving self-efficacy, behavioural activation, and energy allocation reduces fatigue impact and/or improves fatigue self-management. Digital delivery increases access while minimising clinician time.

What (materials)

• Web modules (n = 6) with concise text, slides and PD-relevant examples.

• Printable worksheets: activity/fatigue diary; rest–activity–sleep planner; SMART goal sheet; unhelpful-thoughts diary; thought-challenge sheet; 'Keeping on Track' planner.

• Curated exercise video links (Parkinson's UK physiotherapist-led content) plus a one-page home-exercise safety sheet.

• Participant emails (study schedule, module prompts) and online brief acceptability items post-module.

What (procedures)

Orientation → six weekly self-guided modules pairing short content (≈30 minutes) with a practical task/homework (≈30–60 minutes):

• Module 1: Education on PD fatigue; start diary.

• Module 2: Planned rest/relaxation (diaphragmatic breathing) and sleep hygiene (rest–activity–sleep planner).

• Module 3: Pacing and energy-budgeting; set SMART goals.

• Module 4: Stress response and CBT model; unhelpful-thoughts diary.

• Module 5: Thought-challenging practice and belief ratings.

• Module 6: Review, maintenance ('Keeping on Track') and relapse-prevention.

Exercise is recommended throughout (participant-chosen modality, safety guidance provided). Brief post-module acceptability questions administered online.

Who provided (expertise)

Programme authored by the research team (PhD lead with supervisory team) and refined with PPI (PwP) feedback. Exercise content signposted to Parkinson's UK physiotherapist materials. Delivery is primarily self-guided; the research team provides light-touch onboarding and technical/support queries by email if needed. No routine live therapeutic sessions are planned.

How (modes of delivery)

Individual, asynchronous online delivery via a UEA-hosted web platform. Materials are downloadable/printable for offline use. Participant contact is via emails and online survey prompts; optional ad-hoc email support from the team for onboarding or technical issues.

Where (locations, infrastructure)

Participant homes or any private internet-enabled location. Platform hosted on UEA webpages; outcomes collected via the online survey platform (Qualtrics). Home exercise guidance includes safety checks (clear space, phone nearby, falls risk advice).

When & how much (dose / schedule / intensity)

Programme length: 6 weeks. Modules: 6 modules (1 per week). Module time: ~30 minutes core content + ~30–60 minutes homework/practice. Exercise recommendation: ≥30 minutes per session, ideally 3×/week; progression tailored to ability and safety.

Tailoring (personalisation / titration)

Personalisation via diaries, SMART goals and graded activity plans; exercise type/intensity chosen to match ability, balance confidence and comorbidities. Content is chunked to reduce cognitive load. Optional carer involvement and printable materials offered for accessibility.

Modifications (changes during the study)

Pre-launch refinements informed by PPI: emphasised commitment language, added brief safety/clarity notes for vivid dreams concerns, improved device accessibility and simplified participant information; encouraged clearer exercise guidance. No protocol-documented content changes occurred during the pilot trial.

How well — planned (fidelity/adherence monitoring)

Fidelity: standardised web content archived (appendix). Adherence monitoring: platform analytics (log-ins, pages viewed, time-on-page, downloads), counts of task/diary completion. Per-protocol completion defined as accessing ≥4 of 6 modules; primary analyses use Intention-to-Treat. Brief post-module acceptability items (TFA domains) to inform iterative refinement.

How well — actual (to be reported)

The trial protocol pre-specified platform analytics (page hits/time-on-page) as a planned fidelity/adherence source. In practice, the live web platform did not provide reliable, individual-level analytics for logins or time-on-page during the implementation period. Therefore adherence and fidelity reported in this thesis are based on: (a) weekly participant self-report items asking which module(s) were accessed (see Appendix 4.J), (b) submitted diaries/worksheets (uploaded or returned as hard copy), (c) counts of resource download requests recorded by the study team, and (d) Qualtrics survey timestamps to corroborate timing of assessments. The pre-specified per-protocol threshold (accessing ≥4/6 modules) was operationalised using participant self-report corroborated by diaries where available. This limitation is discussed in the Methods and Limitations sections.

Source / supporting documents: ReFresh protocol and module materials (UEA Ref 45033), Statistical Analysis Plan (SAP), and session files (Session 1–6).

Appendix 4.O: ReFresh Logic Model

Adapted from: W.K. Kellogg Foundation (2004) and CDC guidance on logic models. Programme specification and causal pathways aligned with MRC complex intervention

guidance (Skivington et al., 2021). See Appendix 4.N for a TIDieR specification. Sources: ReFresh protocol (UEA Ref 45033); ReFresh module materials (Sessions 1–6).

ReFresh Online Fatigue Management Program for People with Parkinson's (PwP) — summary of inputs, activities, mechanisms, outputs and outcomes.

Logic flow: Context & Inputs → Activities/Components → Mechanisms of Action → Proximal Outputs → Outcomes → Implementation & Equity

Context & Need

Fatigue is a prevalent, disabling non-motor symptom in Parkinson's. Evidence supports CBT/energy-conservation and structured exercise; PD-specific trials are scarce. Online delivery increases access and reduces clinic burden.

Inputs

Protocol and SAP (UEA Ref 45033); 6-module session materials; UEA web platform & Qualtrics surveys; links to Parkinson's UK physiotherapist-led videos; research team (PhD lead, supervisors, statistician); PPI feedback informing pre-launch refinements; ethics and approvals.

Activities / Components (core)

Weekly self-guided modules (~30 minutes core content + homework) over 6 weeks:

• Module 1: education on Parkinson's fatigue; start fatigue/activity diary.

• Module 2: planned rest & relaxation (diaphragmatic breathing); sleep hygiene; rest–activity–sleep planner.

• Module 3: pacing/energy budgeting toolbox; lifestyle factors; set SMART goals.

• Module 4: stress response & CBT model; unhelpful-thoughts diary.

• Module 5: challenging unhelpful thoughts; belief ratings; thought-challenge sheet.

• Module 6: review progress; maintenance plan ('Keeping on Track').

Exercise recommended throughout (participant-chosen modalities). Engagement supports: study emails and brief post-module acceptability items.

Mechanisms of Action

increase self-efficacy and behavioural activation; decrease unhelpful fatigue beliefs; improve pacing/energy allocation and sleep routines; and improve balance/conditioning via regular exercise. Improved intervention coherence is expected to support adherence.

Proximal Outputs

Module access and completion (web analytics); completed diaries/planners/SMART goals; initiation of exercise; post-module acceptability ratings (relevance, usefulness, pace, duration) and free-text feedback.

Outcomes (Clinical)

Primary: reduced fatigue severity and fatigue impact. Secondary: improved participation and role functioning, improved sleep quality, and improved mood/anxiety using PD-appropriate measures.

Outcomes (Feasibility & Fidelity)

Recruitment and retention; adherence (Per-Protocol defined as accessing ≥4/6 modules); completeness of diaries and surveys; safety of home exercise; uniform delivery via standardised web content.

Assumptions, Risks & Equity

Assumptions: participants have basic digital access; home exercise is feasible with guidance; behavioural and exercise components are complementary. Risks and mitigations: cognitive/motor load → chunked content and clear stepwise instructions; falls risk → home-safety guidance and safety checks; digital barriers → simple pages and printable worksheets;

adherence concerns → SMART goals and weekly cadence. Equity considerations: home-based delivery, screen-reader compatibility, and low-cost exercise options.

Appendix 4.P — Email templates

1. Emails for Allocation Decisions:

For Participants in ReFresh Arm:
Subject: Allocation Decision: You are in the ReFresh Arm

Dear ……

Congratulations! We are pleased to inform you that you have been allocated to the ReFresh arm of our study. Thank you for your participation and commitment. Engaging fully with the program and completing the homework requested is critically important to allow us to make a fair assessment of the program.

Please find the link to access the ReFresh program below:

Link

We will be in touch with you in 12 weeks to provide you with the endpoint survey link and further instructions. Completing the surveys requested is critically important to allow us to properly assess the ReFresh program.

Should you have any questions or require further assistance, please do not hesitate to contact us.

Best regards,

For Participants in Waitlist Group:
Subject: Allocation Decision: You are in the Waitlist Group

Dear ……..

Congratulations! We are pleased to inform you that you have been allocated to the T the waitlist group. Thank you for your participation and commitment. Being a part of the waitlist group allows us to compare your results against the group that get immediate access to the ReFresh program. In a disease as variable as Parkinson's this is critical to allow us to determine if any differences are "real" and useful,

We will be in touch with you in 12 weeks to provide you with the endpoint survey link and further instructions. Completing the surveys requested is critically important to allow us to properly assess the ReFresh program.

We will then be in touch with you in 16 weeks where we will provide your with the link to the ReFresh online program. Your participation at this point will not be recorded.

If you have any questions or concerns, please feel free to reach out to us.

Best regards,

---

2. COPM Result Emails:

Subject: COPM Survey Results
Dear …….

We are pleased to share with you the results of your personal activity survey (Canadian Occupational Performance Measure (COPM)).

[COPM Results]

You will need this with you when you complete the 12 week endpoint assessment as we will ask you to rate yourself against your personal activities at that time point as well. If you would like to discuss your results or require further clarification, please do not hesitate to contact us.

Best regards,

---

3. Emails for 12-Week Endpoint Survey and Reminder:

For 12-Week Endpoint Survey:
Subject: Endpoint Survey: 12-Week Follow-Up

Dear ……

It's time for the 12-week follow-up survey as part of our study. Your input is invaluable to us, and we appreciate your continued participation. All of this data is critical to our understanding of the ReFresh program.

Please click on the link below to complete the survey:

[Survey Link]

Thank you for your time and contribution.

Best regards,

For Reminder:
Subject: Reminder: 12-Week Endpoint Survey

Dear ……..

We hope this email finds you well. Just a friendly reminder to complete the 12-week endpoint survey if you haven't already done so.

Your feedback is crucial to our study, and we greatly appreciate your participation.

Please click on the link below to access the survey:

[Survey Link]

Thank you for your cooperation.

Best regards,

---

4. Emails for 16-Week Waitlist Group to Access ReFresh Program:

Subject: Access to ReFresh Program: 16-Week Waitlist Group

Dear ……

We are pleased to inform you that you now have access to the ReFresh program as part of the 16-week waitlist group.

Please find the link to access the program below:

[Link]

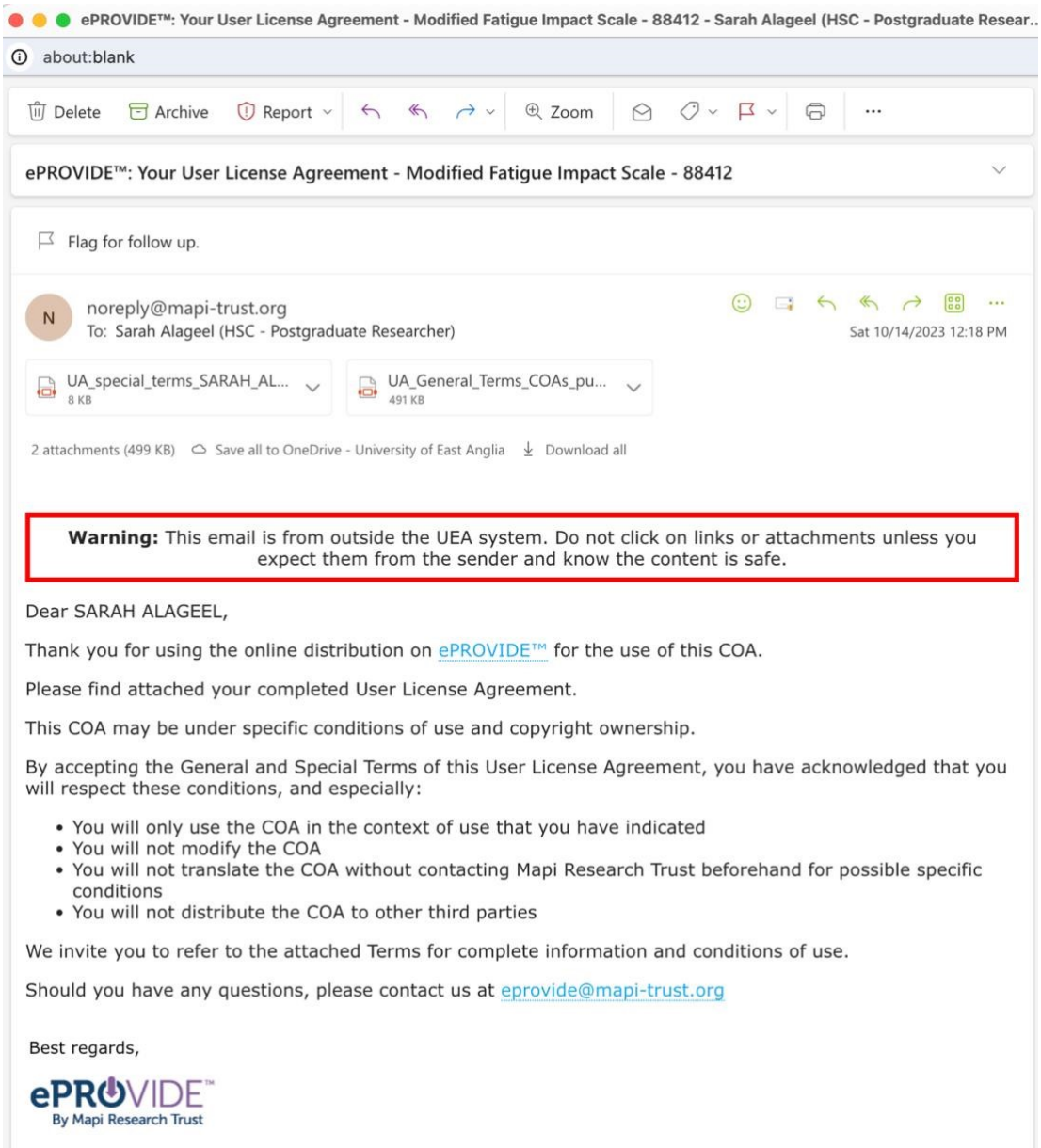
Should you have any questions or need assistance, please feel free to reach out to us.

Best regards,

Appendix 4.Q — Outcome measure permissions granted

Several outcome measures will be used, and consent for their use has been obtained where required:

1. Modified Fatigue Impact Scale (MFIS)



ePROVIDE™: Your User License Agreement - Modified Fatigue Impact Scale - 88412 - Sarah Alageel (HSC - Postgraduate Resear..

about:blank

Delete Archive Report Zoom ...

ePROVIDE™: Your User License Agreement - Modified Fatigue Impact Scale - 88412

Flag for follow up.

N noreply@mapi-trust.org
To: Sarah Alageel (HSC - Postgraduate Researcher)
Sat 10/14/2023 12:18 PM

UA_special_terms_SARAH_AL... 8 KB
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2 attachments (499 KB) Save all to OneDrive - University of East Anglia Download all

Warning: This email is from outside the UEA system. Do not click on links or attachments unless you expect them from the sender and know the content is safe.

Dear SARAH ALAGEEL,

Thank you for using the online distribution on ePROVIDE™ for the use of this COA.

Please find attached your completed User License Agreement.

This COA may be under specific conditions of use and copyright ownership.

By accepting the General and Special Terms of this User License Agreement, you have acknowledged that you will respect these conditions, and especially:

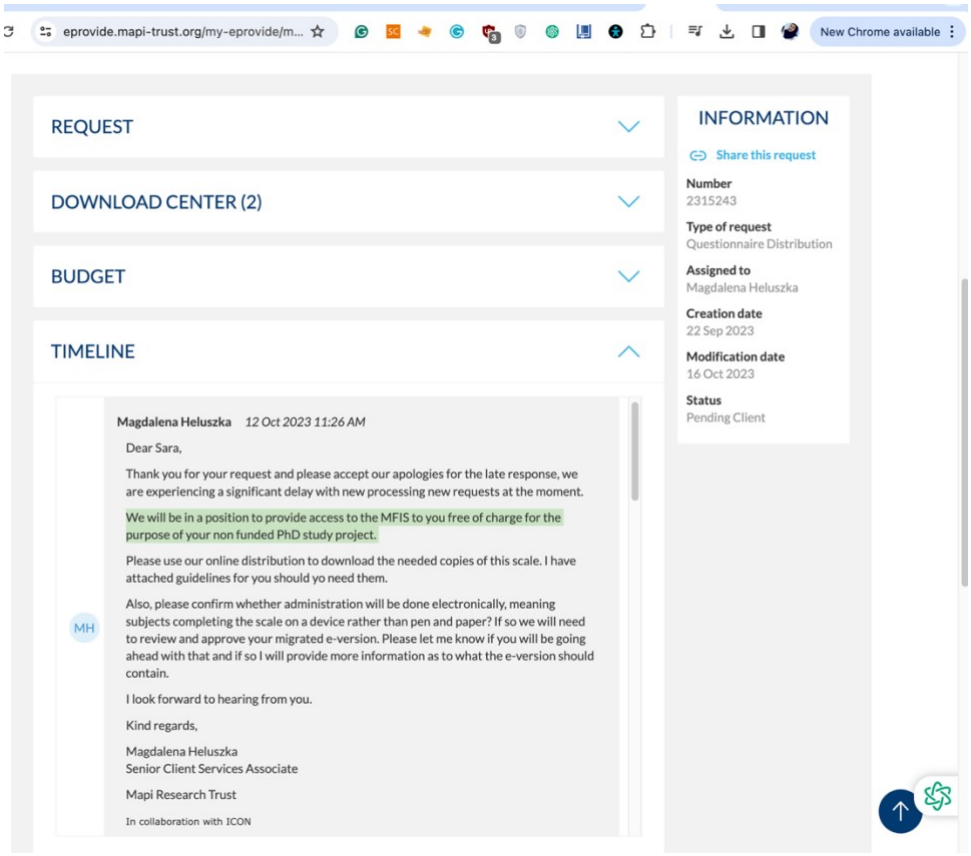
- You will only use the COA in the context of use that you have indicated
- You will not modify the COA
- You will not translate the COA without contacting Mapi Research Trust beforehand for possible specific conditions
- You will not distribute the COA to other third parties

We invite you to refer to the attached Terms for complete information and conditions of use.

Should you have any questions, please contact us at eprovide@mapi-trust.org

Best regards,

ePROVIDE™ By Mapi Research Trust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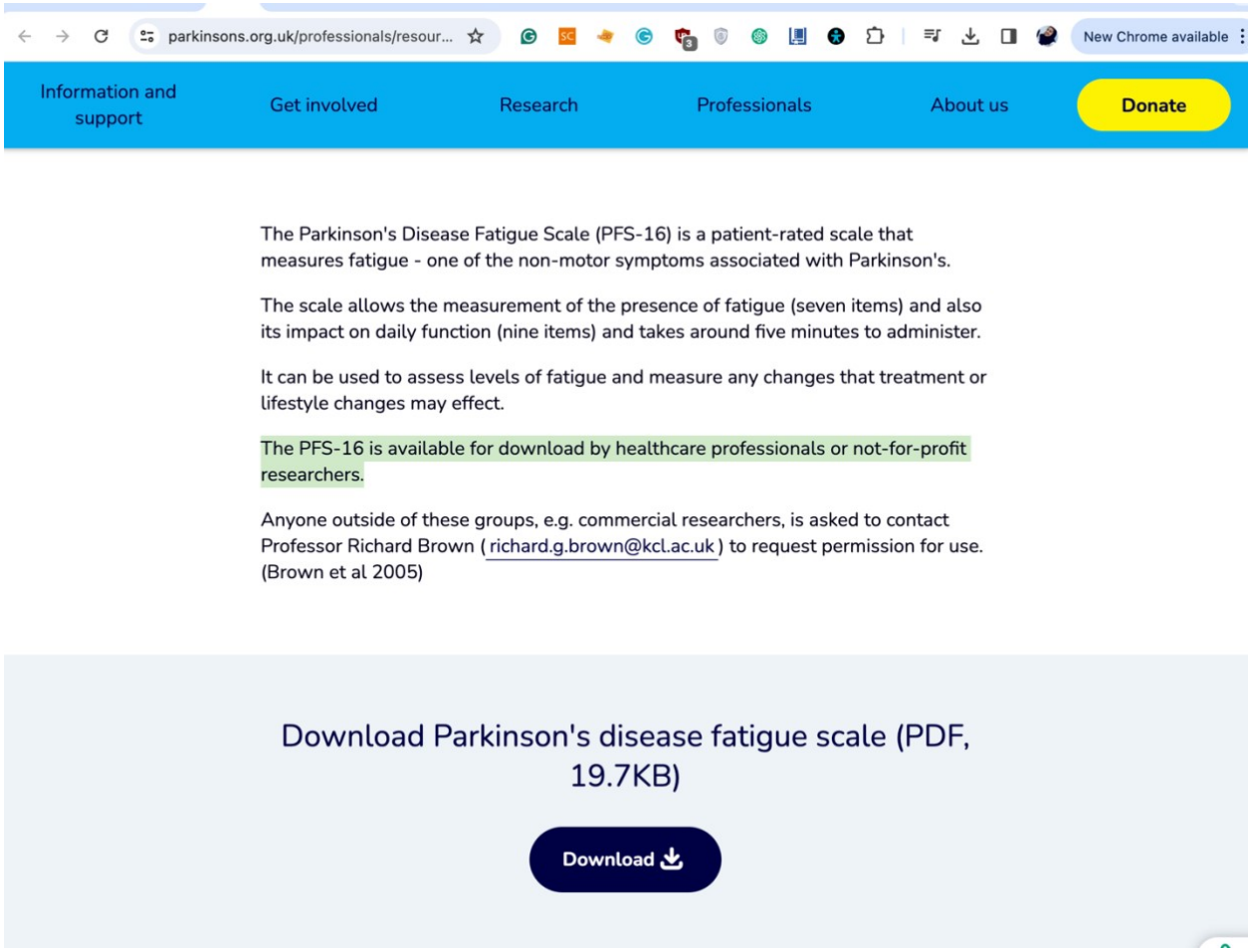
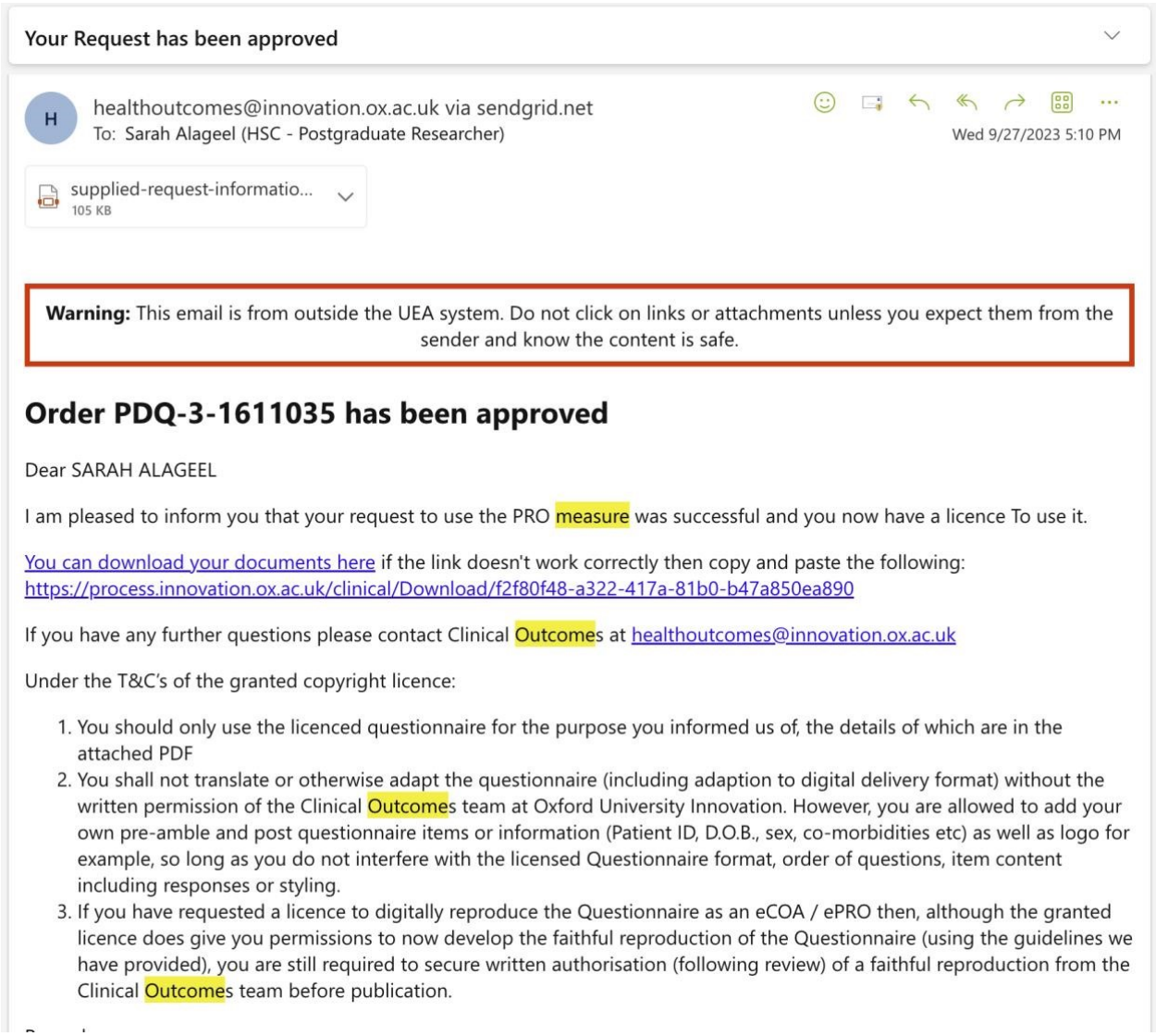
Questionnaire Distribution
Assigned to
Magdalena Heluszka
Creation date
22 Sep 2023
Modification date
16 Oct 2023
Status
Pending Client
Magdalena Heluszka 12 Oct 2023 11:26 AM
Dear Sara,
Thank you for your request and please accept our apologies for the late response, we are experiencing a significant delay with new processing new requests at the moment.
We will be in a position to provide access to the MFIS to you free of charge for the purpose of your non funded PhD study project.
Please use our online distribution to download the needed copies of this scale. I have attached guidelines for you should yo need them.
MH
Also, please confirm whether administration will be done electronically, meaning subjects completing the scale on a device rather than pen and paper? If so we will need to review and approve your migrated e-version. Please let me know if you will be going ahead with that and if so I will provide more information as to what the e-version should contain.
I look forward to hearing from you.
Kind regards,
Magdalena Heluszka
Senior Client Services Associate
Mapi Research Trust
In collaboration with ICON

2. Parkinson's Fatigue Scale (PFS)



3. Parkinson's disease Questionnaire - 39 (PDQ-39)



Your Request has been approved

H healthoutcomes@innovation.ox.ac.uk via sendgrid.net
To: Sarah Alageel (HSC - Postgraduate Researcher)
Wed 9/27/2023 5:10 PM

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105 KB

Warning: This email is from outside the UEA system. Do not click on links or attachments unless you expect them from the sender and know the content is safe.

Order PDQ-3-1611035 has been approved

Dear SARAH ALAGEEL

I am pleased to inform you that your request to use the PRO measure was successful and you now have a licence To use it.

You can download your documents here if the link doesn't work correctly then copy and paste the following:
https://process.innovation.ox.ac.uk/clinical/Download/f2f80f48-a322-417a-81b0-b47a850ea890

If you have any further questions please contact Clinical Outcomes at healthoutcomes@innovation.ox.ac.uk

Under the T&C's of the granted copyright licence:

1. You should only use the licenced questionnaire for the purpose you informed us of, the details of which are in the attached PDF
2. You shall not translate or otherwise adapt the questionnaire (including adaption to digital delivery format) without the written permission of the Clinical Outcomes team at Oxford University Innovation. However, you are allowed to add your own pre-amble and post questionnaire items or information (Patient ID, D.O.B., sex, co-morbidities etc) as well as logo for example, so long as you do not interfere with the licensed Questionnaire format, order of questions, item content including responses or styling.
3. If you have requested a licence to digitally reproduce the Questionnaire as an eCOA / ePRO then, although the granted licence does give you permissions to now develop the faithful reproduction of the Questionnaire (using the guidelines we have provided), you are still required to secure written authorisation (following review) of a faithful reproduction from the Clinical Outcomes team before publication.

4. The Parkinson Anxiety Scale (PAS)

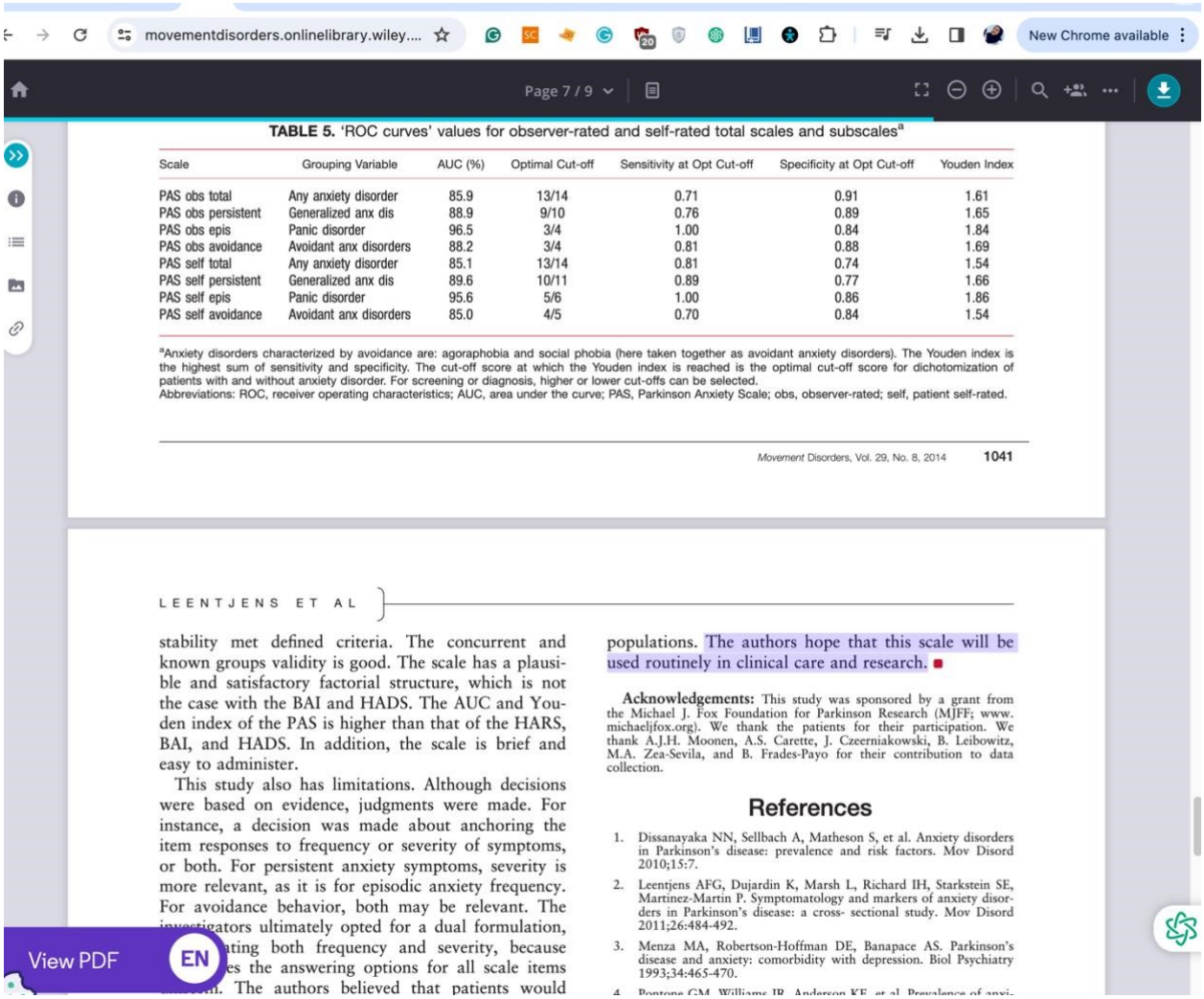


TABLE 5. 'ROC curves' values for observer-rated and self-rated total scales and subscales[a]

Scale	Grouping Variable	AUC (%)	Optimal Cut-off	Sensitivity at Opt Cut-off	Specificity at Opt Cut-off	Youden Index
PAS obs total	Any anxiety disorder	85.9	13/14	0.71	0.91	1.61
PAS obs persistent	Generalized anx dis	88.9	9/10	0.76	0.89	1.65
PAS obs epis	Panic disorder	96.5	3/4	1.00	0.84	1.84
PAS obs avoidance	Avoidant anx disorders	88.2	3/4	0.81	0.88	1.69
PAS self total	Any anxiety disorder	85.1	13/14	0.81	0.74	1.54
PAS self persistent	Generalized anx dis	89.6	10/11	0.89	0.77	1.66
PAS self epis	Panic disorder	95.6	5/6	1.00	0.86	1.86
PAS self avoidance	Avoidant anx disorders	85.0	4/5	0.70	0.84	1.54

[a]Anxiety disorders characterized by avoidance are: agoraphobia and social phobia (here taken together as avoidant anxiety disorders). The Youden index is the highest sum of sensitivity and specificity. The cut-off score at which the Youden index is reached is the optimal cut-off score for dichotomization of patients with and without anxiety disorder. For screening or diagnosis, higher or lower cut-offs can be selected.
Abbreviations: ROC, receiver operating characteristics; AUC, area under the curve; PAS, Parkinson Anxiety Scale; obs, observer-rated; self, patient self-rated.

stability met defined criteria. The concurrent and known groups validity is good. The scale has a plausible and satisfactory factorial structure, which is not the case with the BAI and HADS. The AUC and Youden index of the PAS is higher than that of the HARS, BAI, and HADS. In addition, the scale is brief and easy to administer.

This study also has limitations. Although decisions were based on evidence, judgments were made. For instance, a decision was made about anchoring the item responses to frequency or severity of symptoms, or both. For persistent anxiety symptoms, severity is more relevant, as it is for episodic anxiety frequency. For avoidance behavior, both may be relevant. The investigators ultimately opted for a dual formulation, rating both frequency and severity, because es the answering options for all scale items . The authors believed that patients would

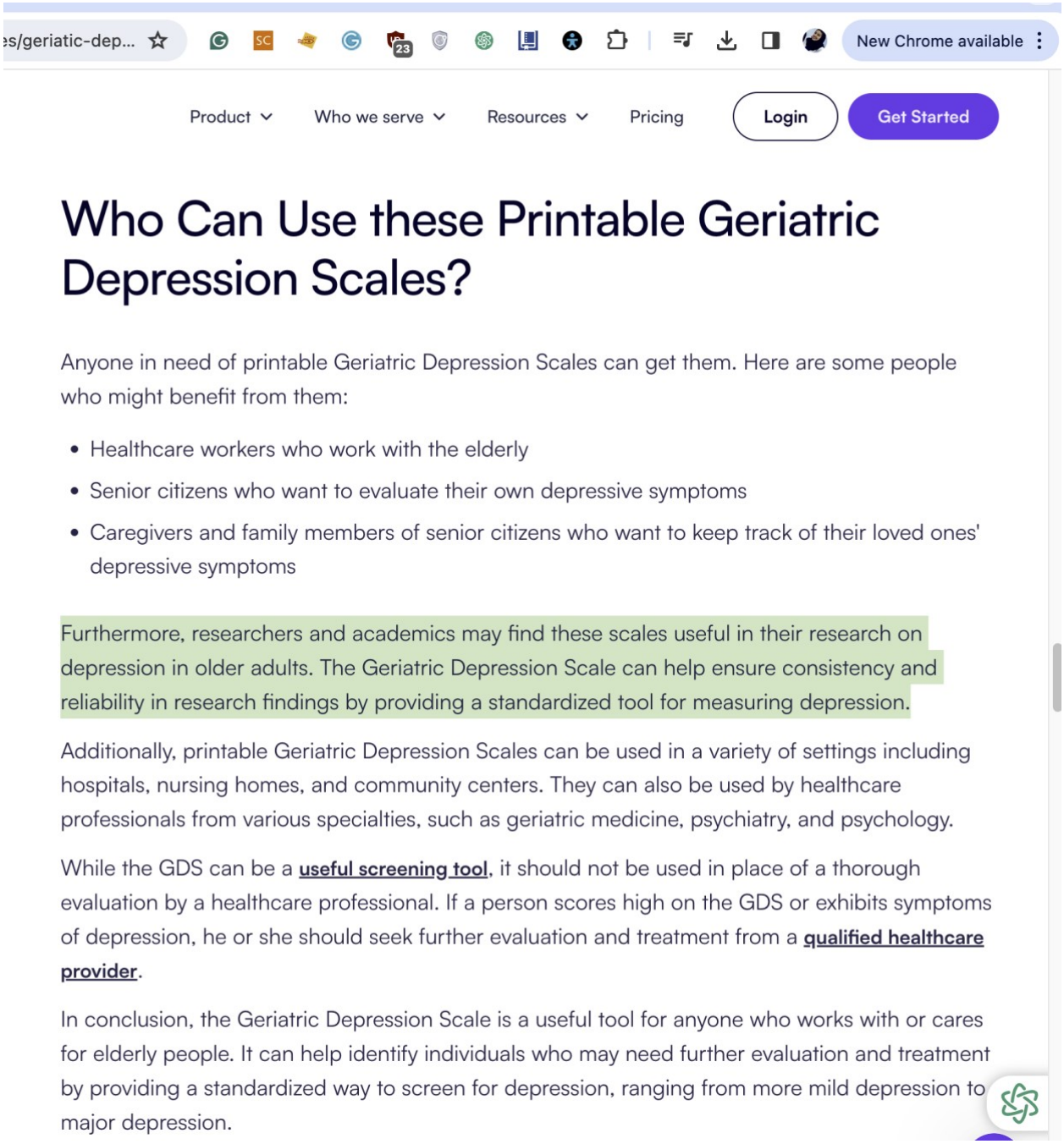
populations. The authors hope that this scale will be used routinely in clinical care and research.

Acknowledgements: This study was sponsored by a grant from the Michael J. Fox Foundation for Parkinson Research (MJFF; www.michaeljfox.org). We thank the patients for their participation. We thank A.J.H. Moonen, A.S. Carette, J. Czeerniakowski, B. Leibowitz, M.A. Zea-Sevila, and B. Frades-Payo for their contribution to data collection.

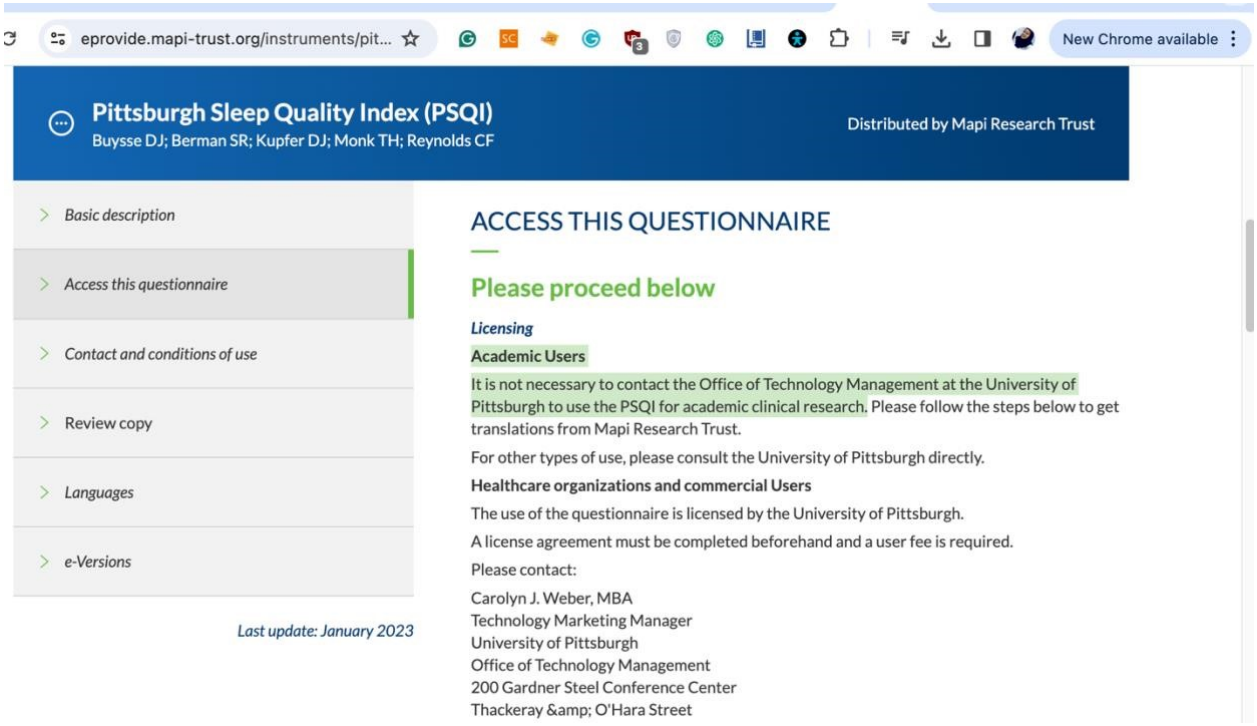
References

1. Dissanayaka NN, Sellbach A, Matheson S, et al. Anxiety disorders in Parkinson's disease: prevalence and risk factors. Mov Disord 2010;15:7.
2. Leentjens AFG, Dujardin K, Marsh L, Richard IH, Starkstein SE, Martinez-Martin P. Symptomatology and markers of anxiety disorders in Parkinson's disease: a cross- sectional study. Mov Disord 2011;26:484-492.
3. Menza MA, Robertson-Hoffman DE, Banapace AS. Parkinson's disease and anxiety: comorbidity with depression. Biol Psychiatry 1993;34:465-470.
4. Pontone GM, Williams JR, Anderson KE, et al. Prevalence of anxi-

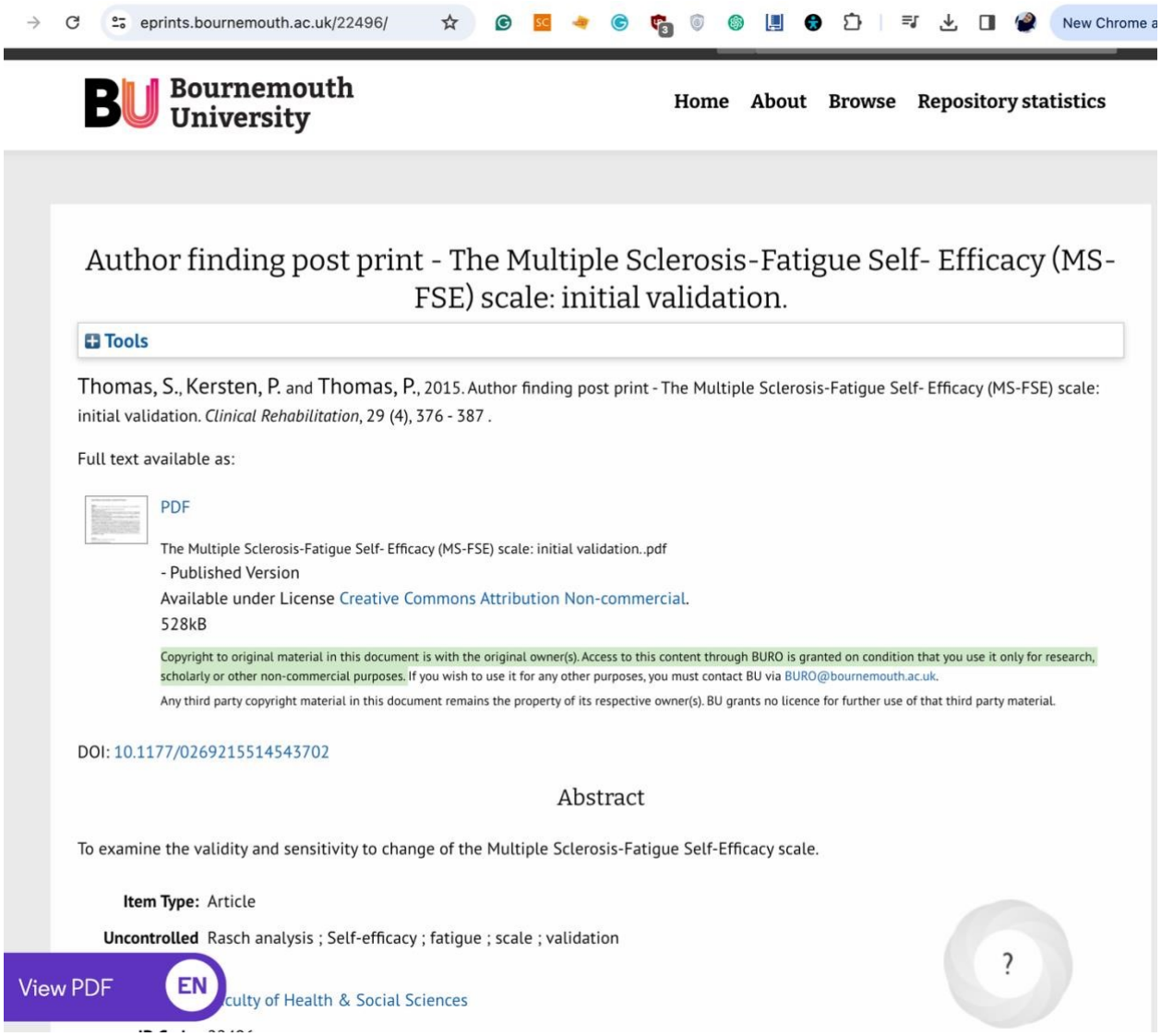
5. The Geriatric Depression Scale-15 (GDS-15)



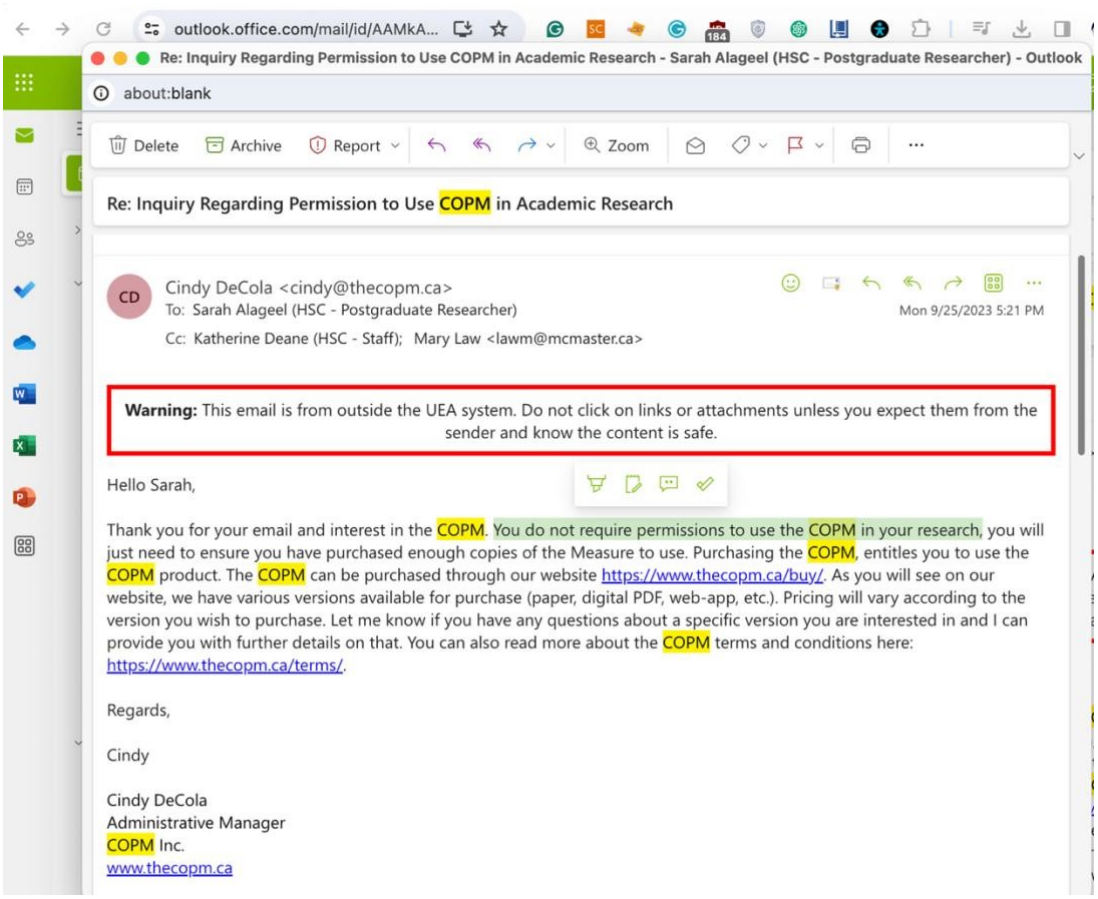
6. Pittsburgh Sleep Quality Index (PSQI)

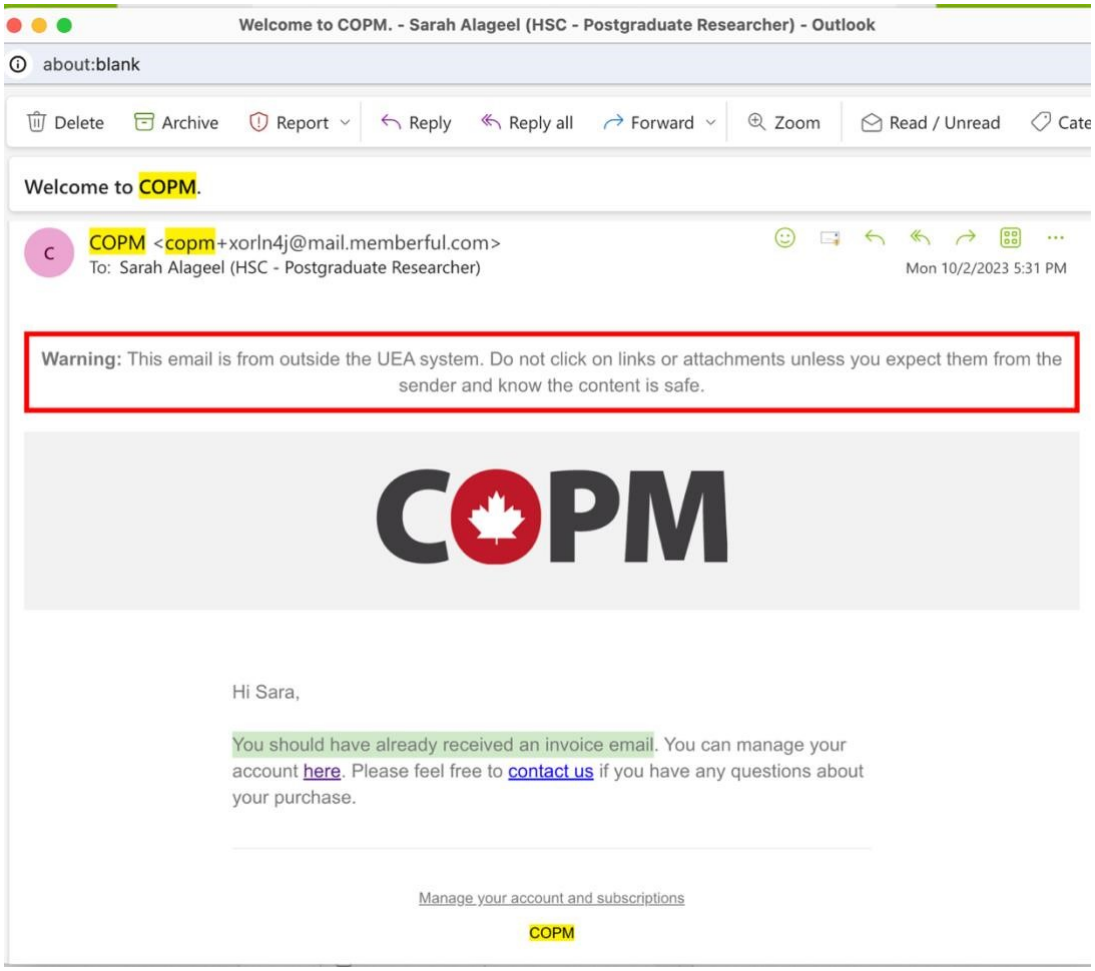


7.The Multiple Sclerosis-Fatigue Self– Efficacy (MS-FSE) scale



8. Canadian Occupational Performance Measure (COPM)




Welcome to COPM. - Sarah Alageel (HSC - Postgraduate Researcher) - Outlook
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Delete
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To: Sarah Alageel (HSC - Postgraduate Researcher)
Mon 10/2/2023 5:31 PM
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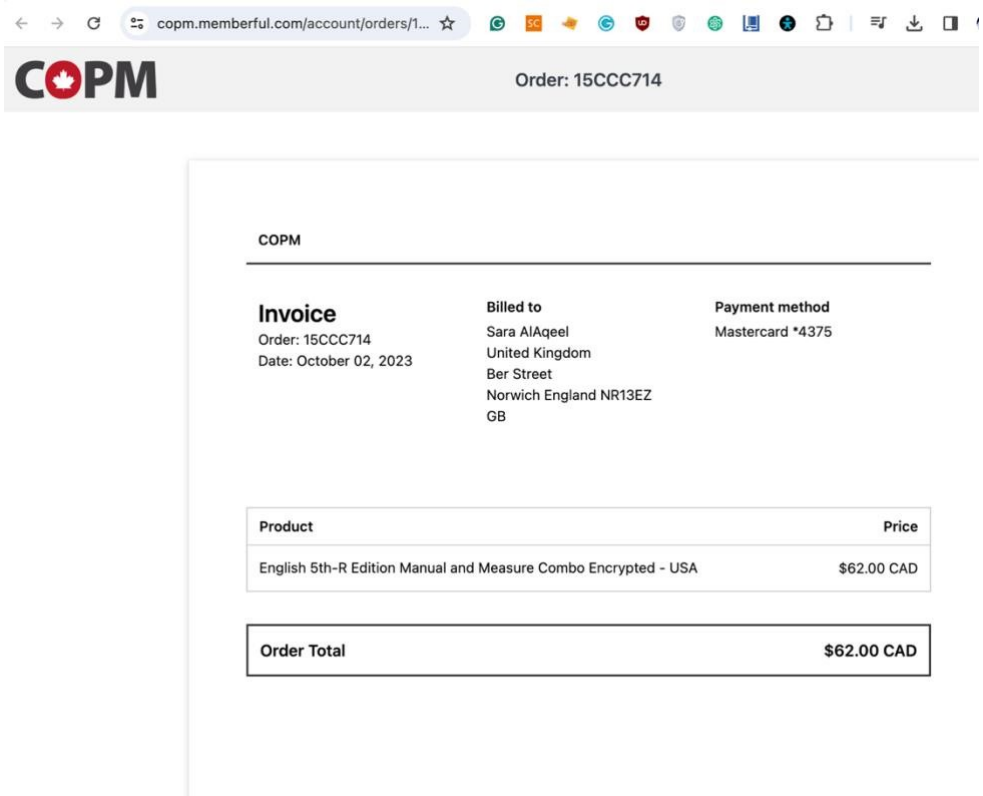
COPM
Hi Sara,
You should have already received an invoice email. You can manage your account here. Please feel free to contact us if you have any questions about your purchase.
Manage your account and subscriptions
COPM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Date: October 02, 2023
Billed to
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United Kingdom
Ber Street
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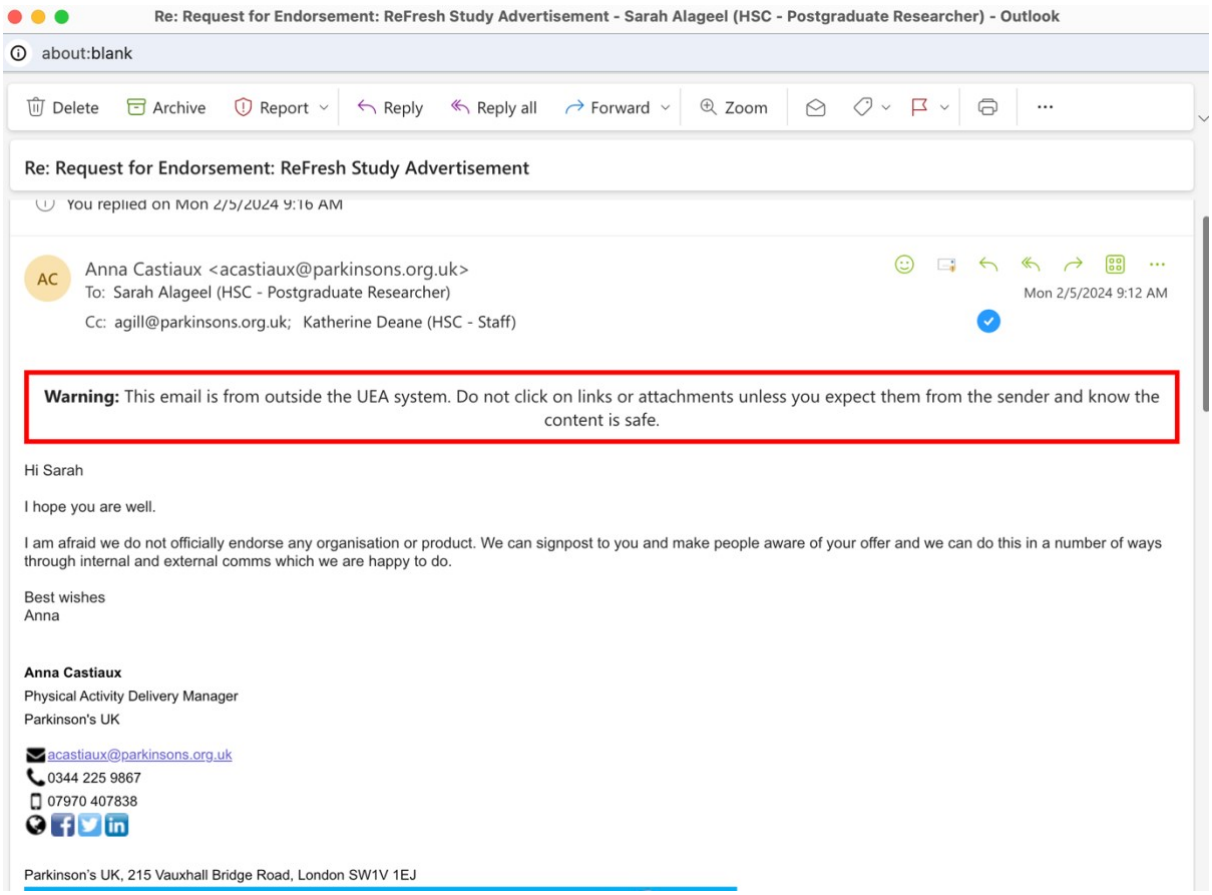
Appendix 4.R — Advertising approvals and adverts

1. Parkinson's UK approval



Re: Request for Endorsement: ReFresh Study Advertisement - Sarah Alageel (HSC - Postgraduate Researcher) - Outlook

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Re: Request for Endorsement: ReFresh Study Advertisement

You replied on Mon 2/5/2024 9:16 AM

AC

Anna Castiaux <acastiaux@parkinsons.org.uk>
To: Sarah Alageel (HSC - Postgraduate Researcher)
Cc: agill@parkinsons.org.uk; Katherine Deane (HSC - Staff)

Mon 2/5/2024 9:12 AM

Warning: This email is from outside the UEA system. Do not click on links or attachments unless you expect them from the sender and know the content is safe.

Hi Sarah

I hope you are well.

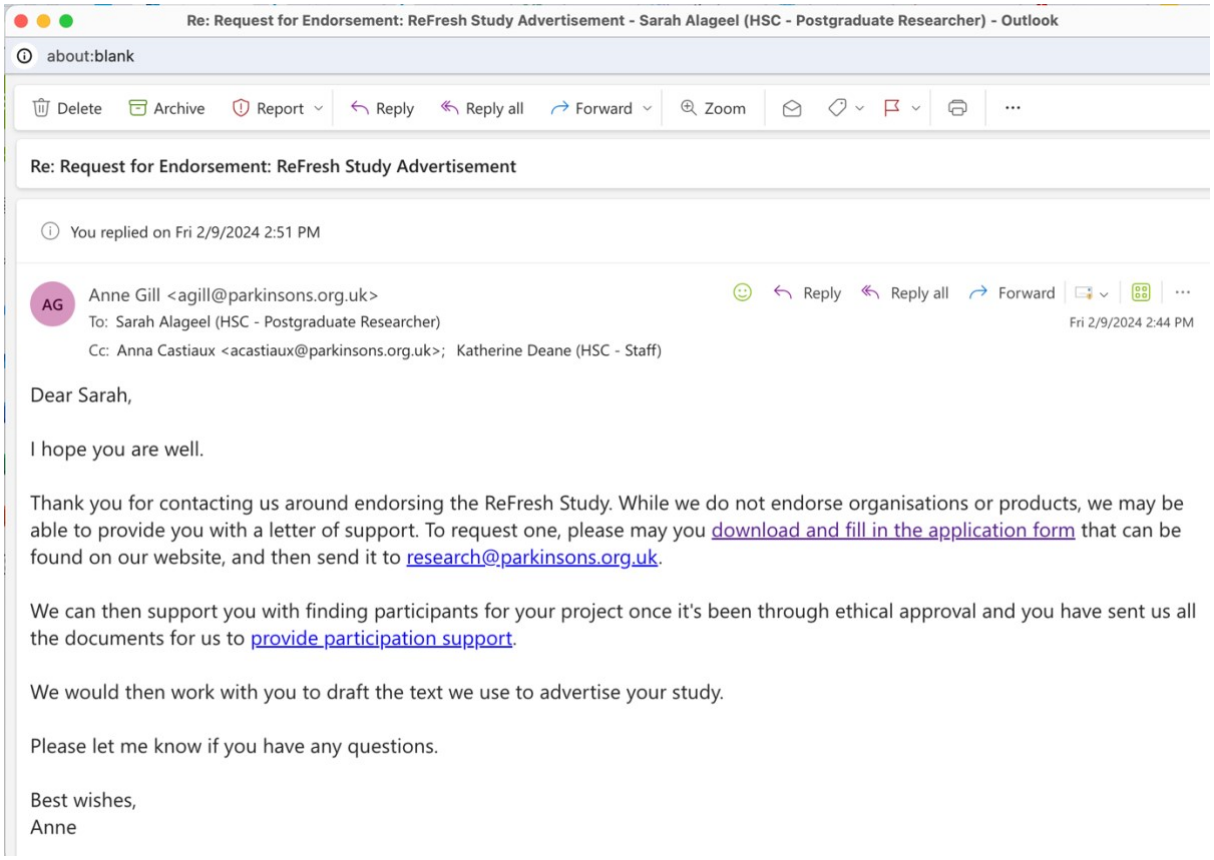
I am afraid we do not officially endorse any organisation or product. We can signpost to you and make people aware of your offer and we can do this in a number of ways through internal and external comms which we are happy to do.

Best wishes
Anna

Anna Castiaux
Physical Activity Delivery Manager
Parkinson's UK

acastiaux@parkinsons.org.uk
0344 225 9867
07970 407838

Parkinson's UK, 215 Vauxhall Bridge Road, London SW1V 1EJ



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Re: Request for Endorsement: ReFresh Study Advertisement

You replied on Fri 2/9/2024 2:51 PM

AG

Anne Gill <agill@parkinsons.org.uk>

To: Sarah Alageel (HSC - Postgraduate Researcher)

Cc: Anna Castiaux <acastiaux@parkinsons.org.uk>; Katherine Deane (HSC - Staff)

Reply Reply all Forward

Fri 2/9/2024 2:44 PM

Dear Sarah,

I hope you are well.

Thank you for contacting us around endorsing the ReFresh Study. While we do not endorse organisations or products, we may be able to provide you with a letter of support. To request one, please may you download and fill in the application form that can be found on our website, and then send it to research@parkinsons.org.uk.

We can then support you with finding participants for your project once it's been through ethical approval and you have sent us all the documents for us to provide participation support.

We would then work with you to draft the text we use to advertise your study.

Please let me know if you have any questions.

Best wishes,
Anne