The Leeds Teaching Hospitals NHS Trust

FULL TITLE OF THE STUDY

Preventing job loss using Acceptance and Commitment Therapy in Vocational Rehabilitation

SHORT STUDY TITLE

MS-PROACTIVE

PROTOCOL VERSION NUMBER AND DATE

Version 2.0, 06/07/2020

RESEARCH REFERENCE NUMBERS

IRAS Number: 279736

FUNDERS Number: Award Ref 119

This protocol has regard for the HRA guidance and order of content

The Leeds Teaching Hospitals NHS Trust

DECLARATION

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the study in compliance with the approved protocol and will adhere to the principles outlined in the Declaration of Helsinki, the Sponsor's SOPs, and other regulatory requirement.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the investigation.

I also confirm that I will make the findings of the study publically available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the study will be given; and that any discrepancies from the study as planned in this protocol will be explained.

Chief Investigator:

Name: (please print):

Helen Ford Date: 06/07/2020

For and on behalf of the Study Sponsor:

Name (please print):

Anne Gowing Date: 06/07/2020

Position: Research Governance Manager, R&I Department, Research & Innovation Centre, St James's University Hospital, Beckett Street, Leeds

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Funder	MS Society MS National Centre 372 Edgware Road London NW2 6 ND Registered Charity Number: 1139257
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ABBREVIATIONS

ACT	Acceptance and Commitment Therapy
COMPACT	Comprehensive assessment of Acceptance and Commitment Therapy processes
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
IRAS	Integrated research application system
MS	Multiple Sclerosis
MSIS-29	Multiple Sclerosis Impact Scale (29 items)
MS-WIS	Multiple Sclerosis Work Instability Scale
NFI-MS	Neurological Fatigue Index for Multiple Sclerosis
NHS	National Health Services
PwMS	People with multiple sclerosis
READY(for MS)	Resilience for Adults Everyday
REC	Research and ethics committee
R&D	Research and development
SUS	System useability scale
USE-MS	Uni-dimensional Self-efficacy Scale for Multiple Sclerosis

STUDY SUMMARY

Study Title	Preventing job loss using Acceptance and Commitment Therapy in Vocational Rehabilitation
Internal ref. no. (or short title)	MS-PROACTIVE
Study Design	Randomised external pilot trial
Study Participants	Patients with multiple sclerosis
Planned Size of Sample (if applicable)	92
Follow up duration (if applicable)	6 months
Planned Study Period	24 months
Research Question/Aim(s)	1. To adapt the READY for MS Acceptance and Commitment Therapy programme to a digital format for use in the UK. 2. To assess the efficacy of using web-based ACT versus standard care in a randomised pilot study

FUNDING AND SUPPORT IN KIND

FUNDER(S) (Names and contact details of ALL organisations providing funding and/or support in kind for this study)	**FINANCIAL AND NON FINANCIAL SUPPORT GIVEN**
MS Society MS National Centre 372 Edgware Road London NW2 6ND	Total: £149,950,25 Salaries: £111,480.25 Non-salaries: £38,470.00
Leeds Teaching Hospitals NHS Trust Beckett St, Leeds LS9 7TF University College London	Study site, provision of premises for study participant visits and assessments Study site, provision of premises for study participant visits and assessments

ROLE OF STUDY SPONSOR AND FUNDER

The study sponsor is the Leeds Teaching Hospitals NHS Trust and it will provide premises for carrying out study specific activity that involves patients. The outpatient clinic rooms and rooms at the clinical research facility will be used for the study assessments and visits. As the NHS trust is the sponsor for the study, the NHS indemnity scheme will cover the study specific activity that takes place on trust premises. The sponsor has no role in the development or design of the protocol, but will have reviewed the protocol and provided its approval prior to any study specific activity commences. The outcomes of the study will be made known to the sponsor and the sponsor will be acknowledged in any publications arising from the study.

The funder is the MS Society. The outcomes of the study will be made known to the funder and the funder will be acknowledged in any publications arising from the study. Terms and conditions…

ROLES AND RESPONSIBILITIES OF STUDY MANAGEMENT COMMITEES/GROUPS & INDIVIDUALS

Members and individual roles of the trial management group

The trial management group will consist of the following individual and specific roles:

CI: Ford: Clinical Lead trial design, execution, leadership working with Co-Is; strategic links with MS Society, MS Clinical Trials Network and NIHR CRN for operational efficient delivery.

Co-Is:

Pavitt: Trial methodologist, MS Triallist, PPIE

Pakenham: Developer of READY for MS. Adaptation and implementation of the READY for MS web-based ACT programme in the UK setting

Thompson: Director of Learning, Lecturer and BPS Registered Coaching Psychologist at the Centre for Sustainable Working Life, Birkbeck UoL. Expertise in occupational health psychology, adaptation of ACT intervention and lead for process evaluation.

Horton: Director of Leeds Psychometric Laboratory for Health Sciences. Expertise in Rasch Analysis, psychometrics, scale development and scale validation

Pepper: PPI, CEO and Co-Founder of Shift.ms the social network for PwMS. Leading a Comic Relief project on MS and Work.

Brownlee: Consultant Neurologist, MS clinical trials expertise, PI for LondonHenshall: Senior Occupational Therapist, MS rehabilitation expertise

General responsibilities of the trial management group

The TMG in this study will also have the following general responsibilities:

- Attend TMG meetings and advise on availability for future TMG meetings
- Input into and comment on the protocol
- Develop strategies to encourage recruitment and address any issues with recruitment
- Be involved in the day-to-day running of the study by supporting the Chief Investigator
- Provide clinical or other expert guidance on clinical and practical queries and interpretation of data collected
- Provide responses to any issues or concerns raised by the chief investigator or the external ethics committees
- Input into the development of the statistical analysis plan
- Input into the interpretation and writing up of the study results

- Presentation of the study results at scientific meetings and in written publications

Schedule of meetings of the trial management group

The TMG will meet formally on a quarterly basis during the course of the study to monitor progress, completion of appropriate assessment and troubleshoot any issues raised during the study, either by participants or other members of the TMG. The agenda of these meetings and timetable will be driven by the chief investigator. It is anticipated the chief investigator will meeting with individual members of the TMG more frequently as required. The patient representative will not be needed to attend all the TMG meetings, but will be invited to meet with the TMG on a six monthly basis to provide input on the progress of the study and future direction. The TMG meetings will be minuted and a record kept in the study file.

We will convene a Trial Steering Committee (TSC) who will meet formally in Year 1 and Year 2 of the study. Any significant concerns from the Trial Management Group will be escalated to the TSC. The TSC will receive the minutes from the TMG and a formal report of the progress of the study.

PROTOCOL CONTRIBUTORS

The protocol for the study has been developed by the chief investigator and co-investigators with advice from lay reviewers and the MS Society Grant Review Panel. The initial proposed study plan was submitted to the MS Society Research Network for advice on the application development. We received detailed reviews from five lay reviewers on developing the project plan. Based on the reviews we developed the proposal by adjusting the time frame of questionnaires, providing more detail on the content and length of on-line sessions, included MS nurse support and provided further information about previous testing of READY for MS in Australia and Italy. The revised proposal was then submitted to the MS Society Grant Round. The project received external peer and lay reviews. The final protocol has included advice and recommendations from the Grant Review Panel prior to confirmation of MS Society funding.

PLAIN ENGLISH SUMMARY

Up to 80% of people with MS (PwMS) leave employment within ten years of MS onset. Complex personal and workplace factors influence job loss. Self-efficacy has been highlighted as a key factor in job retention for PwMS.

An Acceptance and Commitment therapy (ACT) course called 'READY for MS' has been developed in Australia. ACT has been shown to improve self-efficacy. This trial aims to adapt and measure the feasibility of using an online version of this course in the NHS.

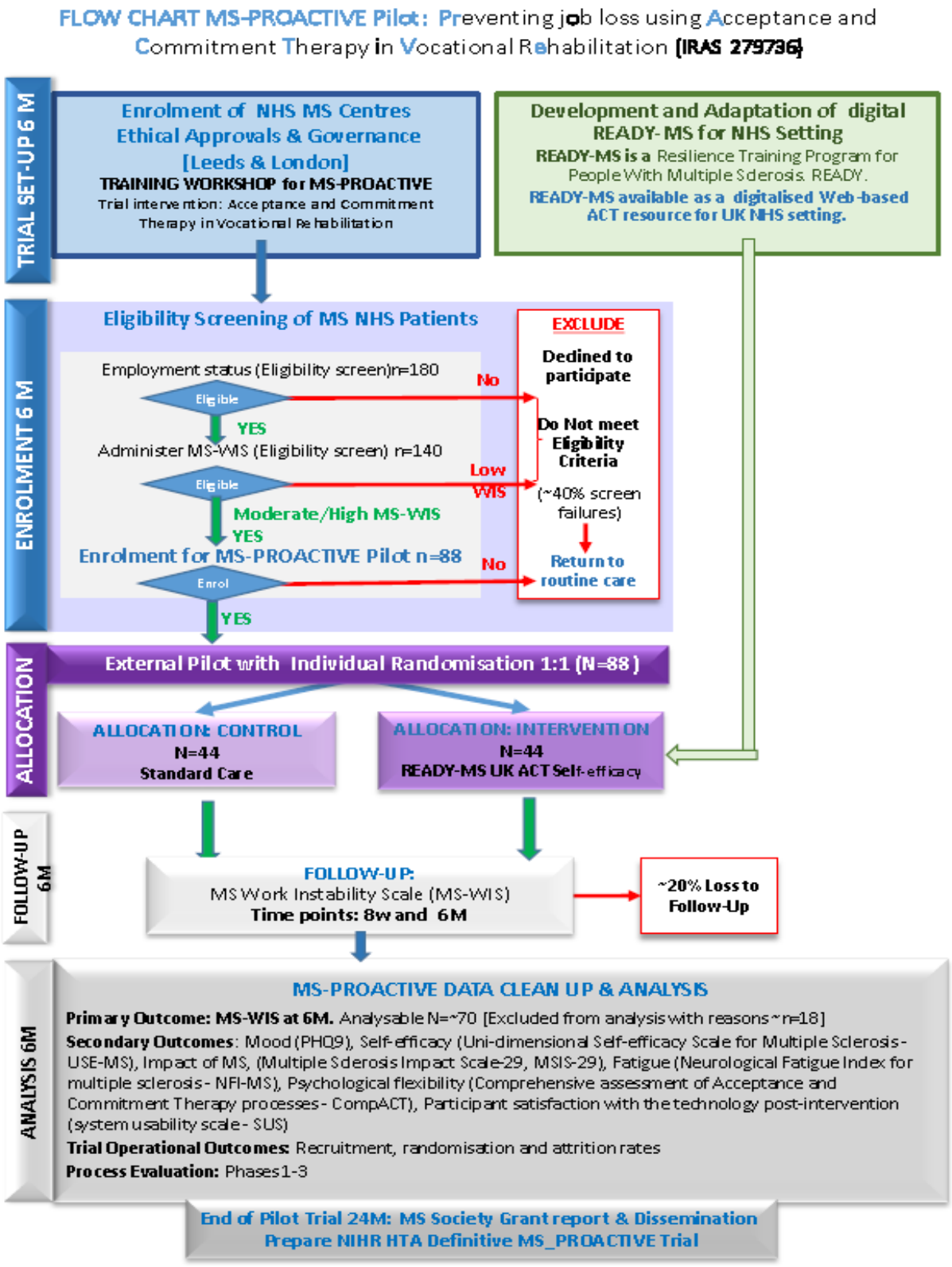
Researchers will work with a digital company and the developer of READY for MS to develop an online version. This will then be tested by four people with MS. Based on their detailed feedback the online version will be adapted. We will then recruit and randomise 88 PwMS in Leeds and London who are at potential risk of job loss. Participants in the active treatment group will use the online treatment and standard care from their local MS teams; the control group will receive standard care.

Participants will be asked to complete questionnaires at the start of the study (baseline), 8 weeks and 6 months. The questionnaires will measure work, self-efficacy, mood, quality of life, fatigue and the impact of MS. The questionnaire data will be analysed to test the effectiveness of the treatment.

We also want to find out how the use of the online treatment works in practice. This is known as process evaluation and will help with any future use of the online READY for MS sessions. Four PwMS in each centre will be asked to consent to be interviewed before they start doing the course, at 12 weeks and at 6 months. This qualitative interview data will be evaluated to understand the experience of the participants using READY for MS.

This pilot trial may lead to a larger randomised control trial and application to the wider UK population. This cost-effective treatment could help PwMS improve self-efficacy in and beyond employment.

STUDY FLOW CHART



STUDY GANTT CHART

See Appendix

The Leeds Teaching Hospitals NHS Trust

STUDY PROTOCOL

1 BACKGROUND AND RATIONALE

Multiple sclerosis (MS) is the commonest acquired disabling neurological disease affecting young adults. MS affects approximately 120,000 people in the UK and 2.5M globally. The onset of MS is typically, in working age adults between 20 and 40 years of age. It is common for people's working life to be adversely affected with 50%–80% of people with multiple sclerosis (PwMS) losing employment by 10 years after disease onset. The Multiple Sclerosis International Federation Survey on MS and Employment found that almost half of the people leaving the workforce did so within three years of diagnosis (MSIF 2010). 75% of PwMS in a Work Foundation study reported that their condition had impacted their employment and career opportunities (Bevan, Zheltoukova & McGee, 2011). More than half of PwMS who are not in paid employment would ideally like to be in work (Wetherly & McIntosh, 2016).

Most people with MS in the UK are in full-time education or employment at the time of diagnosis. People with MS struggle to continue working and a higher percentage of people with MS are unemployed than in the rest of the population (Sweetland, Howse & Playford, 2012). Estimates of work retention vary in the UK, USA and Europe with between 20 and 30% remaining employed 5-17 years after diagnosis. The unpredictable nature of MS causes problems for people with MS and their employers. Many MS symptoms are 'invisible' making it difficult for employers to understand. The employer burden is significant in terms of absenteeism and disability costs. People with MS and their employers are not always sure how to implement effective accommodations, particularly if these relate to mental health (Frndak et al., 2015). Lack of knowledge or timeliness in implementing effective accommodations can create barriers to continued employment (Nevala, Pehkonen, Koskela, Ruusuvuori & Anttila, 2015). Employers are less likely to grant accommodations that involve schedule adjustments or expensive devices (Rumrill, Fraser & Johnson, 2013). The economic impact of loss of employment has huge implications for people with MS, their families and society. Women with MS are more

likely to withdraw from the workforce and this may be linked to taking on additional responsibilities at home. One of the NHS 5 year forward (2014) aims was to help develop and support new workplace incentives to promote employee health and cut sickness-related unemployment. Sickness absence related costs to employers and taxpayers have been estimated at £22 billion a year. Emerging evidence suggests that well targeted health support can help keep people in work thus improving their wellbeing and preserving their livelihoods. Different factors have been described as predicting which PwMS may develop problems at work, including gender, socio-economic status, age, MS symptoms, psychological and emotional factors, workplace variables and disability benefits. However, the reasons for actual job loss often involve complex interactions between these different variables. The level of reported physical disability does not explain the high rate of unemployment. Self-efficacy and negotiating workplace accommodations have been consistently highlighted as key factors for job retention for PwMS. (Gist & Mitchell, 1992; Wilski & Tasiemski, 2016). PwMS who have higher levels of self-efficacy are less likely to need to reduce their working hours within the first year following diagnosis (Jongen, Wesnes & van Geel, 2014).

Work instability (WI) precedes job loss and describes the extent of any mismatch between functional (in) capacity and work demands at a point in time. When WI is present the individual is vulnerable to job loss, and this is the time at which vocational rehabilitation is of greatest preventive importance. A measure of work instability was first developed in rheumatoid arthritis and a robust MS-specific scale, the Multiple Sclerosis Work Instability Scale (MS-WIS) has been generated with PwMS (McFadden et al., 2012). The MS-WIS provides clinical teams the means to screen PwMS to facilitate early, appropriate referral for vocational rehabilitation intervention (evidence for VR). In our study of employed PwMS, high baseline risk on the MS-WIS and low levels of self-efficacy were the key variables associated with actual job loss (Ford, Wicks, Stroud & Tennant, 2019).

There is a need for early intervention for employed PwMS to prevent job loss. Improved self-management has been linked to maintained employment (Bishop, Frain, Rumrill & Rymond, 2009). Developing skills in self-

efficacy can enable PwMS to cope with discrimination, to solve problems systematically, request accommodations, negotiate solutions and effectively communicate in the work place (Roessler & Rumrill, 1994). Self-efficacy was identified as being the missing link between MS and employment (Rumrill,2009).

Acceptance and commitment therapy (ACT) offers a meaningful early intervention in this context. A 'third-wave' cognitive behavioural therapy, ACT utilises empirically supported therapeutic processes including a combination of acceptance, mindfulness, values and traditional behaviour change techniques. These processes cultivate psychological flexibility, the cornerstone of mental and physical health and resilience, and reduce experiential avoidance, a core pathological process whereby behaviours are rigidly guided by thoughts, feelings, and other psychological experiences, rather than one's values (that which would be meaningful) or direct contingencies (that which would be effective). Six interrelated and interdependent processes are identified as contributing to psychological flexibility: [1] acceptance (willingly allowing all experiences to take place), [2] cognitive defusion (the ability to distance oneself from cognitions), [3] contact with the present (non- judgemental awareness of the present moment), [4] values (defining what is important to an individual), [5] committed action (acting in accordance with those values), and [6] self-as-context (flexible perspective-taking) (Hayes, Luoma, Bond, Masuda, & Lillis, 2006). According to the ACT model, an individuals' attempts to eliminate or resist unpleasant internal experiences e.g. thoughts, emotions and sensations, can paradoxically increase distress and inhibit the ability to lead a meaningful life (McCracken, 1998). ACT interventions seek to encourage more flexible responses that enable a richer life (Hayes, Strosahl, & Wilson, 2012).

By reducing psychological inflexibility, ACT can treat a very broad range of psychological problems. Accordingly, more than 100 randomized controlled trials (RCTS) (Hooper & Larsson, 2015) have found ACT to be effective and, in turn, it is considered a trans-diagnostic model, appropriate to addressing the challenges encountered in a range of conditions, including chronic illnesses, and contexts, including the workplace. Given the myriad of difficulties that PwMS may face at work, the generic trans-diagnostic nature of the ACT processes are particularly helpful.

ACT interventions can improve physical wellbeing and quality of life and reduce anxiety and depression in PwMS (Hill et al., 2017; Nordin & Rorsman, 2012; Sheppard, Forsyth, Hickling & Bianchi, 2010). ACT has also been shown to be effective in addressing the particular challenges of (non-disabled) employees in the workplace (Burton, Pakenham & Brown, 2010; Lloyd, Bond & Flaxman, 2017; Hayes, Strosahl & Wilson, 2012). ACT has been shown to improve self-efficacy and resilience in both chronic conditions (Khashouei, Ghorbani & Tabatabaei, 2017; Lappalainen et al., 2014) and the workplace (Burton, Pakenham & Brown, 2010) indicating a key opportunity to apply ACT for purposes of vocational rehabilitation. However, capitalising on the potential applications of ACT in this context - at the intersection of heath and work, and to prevent job loss in PwMS - has been under-utilised. We address this gap through development and adaptation of an online ACT intervention.

REsilience for Adults EverydaY (READY) is an ACT training programme developed in Australia which has been tailored to specific contexts (Burton, Pakenham & Brown, 2010). READY has been shown to improve resilience, role functioning and quality of life (QoL) in a non-clinical workplace sample and in people with a range of chronic illnesses including MS (Burton et al., 2010; Pakenham, Mawdsley, Brown & Burton, 2018) The READY programme tailored for MS demonstrated improvement in resilience, quality of life, depression, stress, and protective factors in PwMS (Pakenham et al., 2018). A RCT of the READY programme for MS showed that the participants receiving READY reported significantly better mental health, QoL and less distress compared to relaxation therapy participants (Giovannetti et al., 2019). ACT self-management programs are often conducted in group settings (Hill et al., 2017). However, this presents challenges in terms of access equity and immediacy of support. Remote interventions are increasingly being suggested as an effective, non-threatening, and less resource intensive method for vocational rehabilitation for PwMS (Dorstyn et al., 2017). A series of RCTs has evaluated the efficacy of ACT in web-based self-help formats with positive outcomes in patients with depression and chronic pain (Lappalainen et al., 2014) (Trompetter, Bohlmeijer, Veehof & Schreurs, 2015). Viskovich & Pakenham (2018) have developed and evaluated a digital READY ACT programme for promoting

mental health in students called YOLO. The digital READY for MS Programme is based on the READY for MS group programme. It will adapt some elements of the YOLO web-based ACT programme. The research team will assess the feasibility of this programme to address the specific challenges of MS and the workplace in the UK.

Effective job retention interventions need to be flexible and easily accessible for employed people. Our PwMS advisors favour an intervention to improve self-efficacy that is convenient (i.e. does not require additional leave from work, ideally web-based, brief and flexible) and empowers them to take control and manage their own situation. They favoured signposting from their MS clinical team where their MS condition is managed and where there is greater understanding and familiarity with access to support networks rather than their GPs. Use of the digital READY ACT intervention would increase fidelity, enable wide and rapid dissemination and could be supported by the wider clinical team (e.g. telephone support by MS nurses) providing a likely practical and cost-effective method for addressing barriers to engagement such as lack of time, immobility, inconvenience or perceived stigma. PwMS have consistently reported they wanted to be more informed and involved with their own care and one of the MS Society's Top 10 priorities is 'How can people with MS be best supported to self- manage their condition?' This research is important because there is a potentially effective and cost-effective intervention for PwMS which can be adapted and tested for use in the UK.

2 RESEARCH QUESTION/AIM(S)

There is a type of treatment which improves self-efficacy and resilience called 'Acceptance and Commitment Therapy'. A type of ACT has been developed in Australia specifically for PwMS called 'READY for MS'.

Our aims are:

- To develop a new digital online version of READY for MS that can be used on a computer without PwMS having to go to hospital or a clinic to see a psychologist.
- To test whether this works in a small pilot study with PwMS in the NHS.
- In the longer term we want to see whether READY for MS can help PwMS stay in work.

2.1 Objectives

- To develop and adapt the READY for MS web-based Acceptance and Commitment Therapy programme for use in the UK.
- To assess the efficacy of using web-based ACT versus standard care in a randomised study.
- To use MS-PROACTIVE to provide the key underpinning data to support the delivery of a definite trial externally funded via the NIHR HTA programme.

2.2 Outcomes

- Primary Outcome: MS Work Instability Scale (MS WIS) at 6 months after randomisation: 22-item, self-administered scale measuring work instability.
- Secondary outcomes: Health related quality of Life (EQ-5D, SF-12), mood (HADS), self-efficacy (Uni-dimensional Self-efficacy Scale for Multiple Sclerosis - USE-MS), impact of MS (Multiple Sclerosis Impact Scale-29, MSIS-29), fatigue (Neurological Fatigue Index for multiple sclerosis - NFI-MS), psychological flexibility (Comprehensive assessment of Acceptance and Commitment Therapy processes -

CompPACT), participant satisfaction with the technology post-intervention (system usability scale - SUS).

3 STUDY DESIGN and METHODS of DATA COLLECTION AND DATA ANALYSIS

DESIGN: This is an external pilot trial. The main purpose is to assess the efficacy of the new online version of READY for MS. The process evaluation will assess the methods of recruitment, randomisation and follow up for a future full trial. The trial is a two centre, two-arm individual patient randomised control trial. We plan to recruit people with a confirmed diagnosis of MS in paid employment attending regional outpatient MS clinics in Leeds and London. The planned follow up is 6 months post-intervention.

SETTING: Recruitment from outpatient MS clinics in 2 regional NHS MS centres. The intervention will be self-managed flexibly in the home setting.

CENTRES: Leeds Teaching Hospitals NHS Trust (CI HF) and Queen Square MS centre, University College London (Co-I WB).

TRAINING: We will hold a training workshop on 'READY for MS' in Leeds for the investigators and the MS Specialist Nurses from the two recruiting centres.

RANDOMISATION: 1:1 by patient. Randomisation will be managed by an independent statistician.

INTERVENTION: The intervention to be tested is the digital version of the READY for MS group programme (Pakenham et al., 2018) adapted for the UK setting. This will be used with standard care with a written information leaflet about employment and MS 'Work and MS: An employee's guide' (MS Society, 2015).

The group version of READY for MS has been successfully implemented with Australian and Italian PwMS. Implementation in Italy only required minor language adjustments in the translation of content into Italian, but otherwise no other changes were necessary (Pakenham, personal communication). The digital version of the READY for MS Program will consist of 7 weekly modules and a booster session module delivered five weeks after the 7th module. The 7 modules are as follows: Introduction to the READY Resilience Model, Mindfulness, Defusion, Self-as-context, Acceptance, Values and Meaningful Action, and Review and Future Planning. Each

module will be of approximately 30 minutes duration. The modules will consist of engaging animated presentations, guided experiential exercises, video clips, audio files and written exercises. The digital program will be accompanied by a digital copy of the READY Participant Workbook which consists of two parts: written content for each module and the READY Personal Plan. The READY Personal Plan is an important resource as it contains reflection exercises and directed home practice tasks that are undertaken during and between modules.

The adaptation phase will comprise an iterative process of user testing and content development to tailor 'READY for MS' to a UK workplace context. This will involve drawing on relevant principles of experience based co-design (Chisholm, Holttum & Springham, 2018) and digital user experience (UX) testing methodologies to assess user ‘ journeys' and relevance for self-guided therapeutic application in a range of UK workplace settings. READY for MS will be initially reviewed by the project team for its alignment with research objectives and outcomes, and any immediate changes made. 4 people PwMS (representative of genders, ages and educational level) will then be recruited to experientially review the digital program in terms of its suitability for a UK workplace context. The feedback of 2 employers will also be sought to enhance the co-design process. Participants’ feedback will be considered by the research team and program modifications implemented accordingly for a final round of review. In particular, we will consider how the workbook, reflection exercises and directed home practice tasks can be tailored further to represent challenges typical to PwMS in UK workplaces. This process of user testing will also allow consideration of the form and nature of support provided by MS Specialist nurses to support therapeutic engagement.

There is a risk of a high rate of attrition with on-line psychological treatment. The MS Nurses will receive training in the READY programme and will provide planned telephone support at 2-3 weeks post-randomisation. Adherence and completion of the programme will be measured.

CONTROL: Standard care with a written information leaflet about employment and MS ‘Work and MS:

An employee's guide' (MS Society, 2015).

PRIMARY OUTCOMES: MS Work Instability Scale (MS WIS) at 6 months after randomisation: 22-item, self-administered scale measuring work instability.

SECONDARY OUTCOMES: Health related quality of Life (EQ-5D, SF-12), mood (PHQ9), self-efficacy (Uni-dimensional Self efficacy Scale for Multiple Sclerosis - USE-MS), impact of MS, (Multiple Sclerosis Impact Scale-29, MSIS-29), fatigue (Neurological Fatigue Index for multiple sclerosis - NFI-MS), psychological flexibility (Comprehensive assessment of Acceptance and Commitment Therapy processes - CompPACT), participant satisfaction with the technology post-intervention (system usability scale - SUS).

PROCESS EVALUATION

The process evaluation will comprise three phases.

3.1 Phase 1

In Phase I, academic and grey literature will be reviewed to identify stakeholders' theories concerning how ACT can be embedded into MS Specialist services and its impacts. In investigating the theoretical basis for work-focussed ACT in this setting, we wish to understand the mechanism through which the intervention might be expected to 'work'. The precise search terms and inclusion and exclusion criteria for the literature review will be determined by the project team, in collaboration with subject-specialist librarians at the University of Leeds and Birkbeck University of London. We will conduct an exhaustive literature search of available health, psychology and social science databases that index research relevant to the topics above. The literature review will be used to inform the development of case studies in Phase 2 by reviewing the mechanisms by which READY for MS may work in this setting and the outcomes it may impact on. Specifically, it will inform development of the interview schedule and more broadly to situate the findings and conclusions of this study in the wider literature.

3.2 Phase 2

In Phase 2, a multi-site case study (n=4 in each site) to test and refine the candidate theories will be conducted. The case studies will include interviews with PwMS (pre-intervention/post-intervention/6 months follow up) and ACT facilitation staff (MS Specialist nurses). Participants/staff will be purposively sampled to provide maximum variation and information-rich cases (Patton, 1990; Mason, 2002).

3.3 Phase 3

In Phase III, 2 consensus workshops of 1 hour each will be conducted with 6-8 participants including PwMS and clinical staff to assess the extent to which the results of Phase II are generalisable and to refine the resulting theories to reflect the experience of a broader range of users and implementing health services.

Overall analysis: the analysis from phases 1 & 2 will be synthesised to determine what works for whom in what circumstances.

FOLLOW UP: Patient reported-outcome measures will be completed at baseline, 8 weeks and 6 months. Email/ telephone reminders will be sent at each time point.

ANALYSIS: The primary outcome will be analysed using a linear mixed model, including assessments at all available time points (baseline, 8 weeks and 6 months) and include as fixed effects: trial arm, time, arm by time interaction and other important baseline covariates with participant treated as a random effect to account for the repeated measures within subjects.

TIMELINE: MS-PROACTIVE duration - 24 months: Adaptation of the intervention and trial setup - 6 months; Recruitment and randomisation - 6 months; RCT follow up - 6M; data analysis & report writing - 6 months.

All personal and patient identifiable data will be processed in accordance with the European Union General Data Protection Regulation (GDPR) and the UK Data Protection Act 2018.

4 STUDY SETTING

4.1 Recruitment

Recruitment to the study will be from outpatient MS clinics or day case units in two regional NHS MS centres: Leeds Teaching Hospitals NHS Trust (CI HF) and Queen Square MS Centre, University College London (Co-I WB).

The outpatients department and day-case units will be the same locations which patients routinely attend for their regular clinical visits and will be a familiar environment for the participants. Potential participants will be given at least 48 hours to consider the study and will then be asked if they wish be enrolled in the study.

4.2 Intervention

The intervention will be self-managed flexibly in the home setting. The primary and secondary outcome measures are questionnaires and can be completed at home.

5 SAMPLE AND RECRUITMENT

5.1 Eligibility Criteria

5.1.1 Inclusion criteria

- Age above 18 years at the time of enrolment into the study
- Participants with a confirmed diagnosis of MS
- Participants are in paid employment including full-time, part-time or self-employed
- Participants must be able to comply with the terms and methods of the protocol
- Study specific written informed consent obtained

5.1.2 Exclusion criteria

- Age below 18 years at the time of enrolment into the study
- Participants who are planning to retire or fully leave employment in the time period of the randomised controlled external pilot trial
- Participants unable to comply with the terms or methods of the protocol, in particular the completion of the online sessions of READY for MS and completion of the questionnaire outcome measures

5.2 Sampling

5.2.1 Size of sample

This study aims to recruit 88 PwMS who are in paid employment and have medium or high work instability to participate in the randomised controlled pilot trial.

The sample size calculations are based on estimating participation and attrition rates and standard deviation of the primary outcome. If we identify 176 eligible subjects, we will be able to estimate a

participation rate of 50% to within a margin of error of ±7% and an attrition rate of 20% to within ±8%

(Hertzog, 2008). Furthermore, an external feasibility study of at least 70 measured subjects will provide robust estimates of the standard deviation of the outcome measure to inform the sample size calculation for the subsequent larger definitive fully powered trial (Teare et al., 2014).

5.2.2 Sampling technique

We aim to recruit people with a confirmed diagnosis of MS in paid employment. We plan to use the MS Work Instability Scale (MS-WIS) as a screening tool to identify subjects with medium or high levels of work instability (WI). In the baseline population from the longitudinal study of 208 PwMS 20.2% had high WI, 37.0% had medium WI and 42.8% had low WI. (Wicks et al., 2016).

5.3 Recruitment

5.3.1 Sample identification

Potential study participants will be approached by the clinical MS teams in person or over the phone. This will include identification by specialist consultant neurologists, neurology trainees working in the MS clinics, MS clinical nurse specialists, MS physiotherapists, occupational therapists and neuropsychologists. All are directly involved in the clinical care of PwMS.

There are a large population of employed PwMS attending the outpatient services and day-case units in both of the recruiting centres. There are 1,080 PwMS registered on the Leeds MS register. As this is a small pilot study, we don't anticipate significant problems in recruitment. The Leeds site has previously recruited 200 employed PwMS to a longitudinal questionnaire study over 3 years with excellent retention rates.

The eligibility criteria of the study will be disseminated to the clinical team, in order for them to be able to identify potential participants for the study. The participants will be informed of the study briefly and if

interested they will be asked if their details can be given to the research team to provide the participant information sheet (PIS) of the study.

We will not use adverts or websites for recruitment purposes. The participants will not receive any financial incentives to participate in the study.

5.3.2 Consent

Consent will be obtained by the lead clinical investigator at each site: this will be the Chief Investigator in Leeds (HF) and the Consultant Neurologist Co-Investigator in London (WB).

Participants will be provided with a written patient information sheet by the research team.

Once potential participants have been identified, the Chief investigator or Co-Investigator will discuss the study with the potential participant and any relatives/carers the participant would like to be made aware. The verbal discussion will include a detailed description of the objectives and schedule of the study as well as what is required of the participant. The investigator will explain the benefits and possible risk of taking part in the study.

During the initial meeting, the investigator will make an assessment of the participant's capacity to consent to take part in the study. The participant's understanding of the study, their role in the study, as well as their ability to retain the information will be assessed. After the potential participant has received all the relevant information on the study and wants to be involved in the study, they will then receive the consent form which will be completed before any study specific activity takes place. The consent form will be countersigned by the chief investigator or the study co-investigator. A copy of the PIS and completed consent form will be retained by the participant and the original copy of the consent form will be filed in the site file.

6 ETHICAL AND REGULATORY CONSIDERATIONS

People with MS lose their jobs much earlier than expected. This can be due to complex factors including psychological factors. Self-efficacy has been found to be a key factor in staying in work.

The aim of this pilot study is to test an online version of a type of Acceptance and Commitment Therapy (ACT) called READY for MS. This has been developed and tested in Australia.

This project meets one of the MS Society's Top 10 James Lind Alliance priorities: How can people with MS be best supported to self-manage their condition?

Recruitment:

We plan to recruit from the outpatient MS clinics at Leeds Teaching Hospitals NHS Trust and University College London. We will explain to PwMS that this is a small study called a pilot trial. They may have no personal benefit at all from taking part in the study. If the study is successful it may lead to a much larger trial of READY for MS.

We have previous experience in Leeds of recruiting over 200 employed PwMS to a previous MS Society funded project grant. This required the completion of questionnaires at 4 time points over 2 years. We had a very impressive response rate at each time point of 96%, 94%, 91% and 88%.

Inclusion and Exclusion criteria:

To be included in the trial people need to have a confirmed diagnosis of MS and currently be in paid employment (full-time, part-time or self-employed). We plan to screen PwMS with a short screening questionnaire called the Work Instability Scale. This measures the level of work instability as no/moderate or high. Work instability measures the potential risk of job loss. Participants with moderate or high work instability will be invited to be randomised in the trial. Those with no work instability will not be included in the

trial. The reason for this is that the trial is measuring work instability as the main outcome with an aim to show improvement.

PwMS who are currently working on a voluntary basis or in an unpaid role will not be eligible for the trial. PwMS who are planning to fully leave work or retire before the end of the trial will be excluded.

Consent

PwMS who are currently employed will be approached by their clinical MS team including the MS Specialist nurses and MS specialist neurologists. The clinical team will introduce the study to the potential participants. Those PwMS who say that they would potentially be interested in the study will be asked if their details can be given to the research team to provide written information about the study for them to consider (the Participant Information Sheet). The consent process will be completed by the research team.

We are recruiting PwMS in paid employment to this study and we anticipate that this study population will have capacity to consent. We don't anticipate that this employed population will have significant cognitive impairment.

Confidentiality

All the investigators in the study will comply with the requirements of the Data Protection Act 2018, and by extension the principles of the GDPR 2018.

All the participants' data will be depersonalised, coded and then stored electronically in password protected files. There will be an encrypted digital copy of the original files kept in separate storage media. The data will be processed and stored for the duration of the study and thereafter for the purposes of any follow-up. Access to the data will be limited to the minimum number of individuals necessary for quality control, audit and analysis.

Conflict of interest

There are no conflicts of interest for the health care professionals who are investigators in this study. Professor Pakenham developed READY for MS. This study is a non-commercial NHS based study.

All the data collected will be held in accordance with the GDPR 2018 regulations and any pertinent clinical information will be relayed to the clinical team looking after the participant with their consent.

6.1 Assessment and management of risk

PwMS who are excluded at screening due to having no work instability may feel disappointed at not being able to participate in the trial. We will explain that the main purpose of the trial is to find out if we can measure an effect on work instability and if they have no work instability to start with then no improvement in this can be measured.

There is a risk that completing the online sessions and workbook of READY for MS may highlight work related problems or other problems related to living with MS. The MS specialist nurses will provide both planned support and flexible support as required including signposting. Any significant issues involving psychological distress will be escalated according to the local pathways of care. This would include informing the GP and appropriate psychological support. READY for MS has been designed to improve resilience and the ability to cope with day to day life challenges. However, we acknowledge that there may be unintended consequences.

The benefit of participating in the study is that this research addresses one of the key priorities of the MS Society in improving self-management of MS. Although this study will not lead to any personal benefit it may lead to a larger trial and potentially an effective treatment in the future.

During the study the participant will be reminded of their right to withdraw from the study at any point, without the need to provide an explanation and the PIS will include the Project Manager's contact details for all queries throughout the duration of the study.

6.2 Research Ethics Committee (REC) and other Regulatory review & reports

Prior to the start of the study a favourable opinion will be sought from the Leeds Teaching Hospitals Trust research ethics committee (REC) and research and development (R&D) department, to ensure the protocol complies with local regulations. The study has also been submitted via the portfolio application form for consideration of support by the National Institute for Health Research Clinical Support Network in England. The study will also be submitted to the Health Research Authority (HRA) via the Integrated Research Application System (IRAS). Subsequently, any substantial amendments that require review by the HRA will then be applied for separately and the Leeds Teaching Hospitals Trust REC will be notified of any amendments to the protocol. Where required the chief investigator will produce an annual report to the Leeds Teaching Hospitals Trust REC. The chief investigator will notify the Leeds Teaching Hospitals Trust REC and NHS HRA upon completion of the study. Within one year after the end of the study or if otherwise specified, the chief investigator will submit a final report with the results to the HRA and Leeds Teaching Hospitals REC.

6.2.1 Regulatory Review & Compliance

Before any patients are recruited into the study, the chief investigator will ensure that appropriate approvals from the local REC and R&D department are in place. The study will also need to have received HRA approval via IRAS. Any subsequent amendments to the protocol will be submitted via IRAS for HRA approval prior to any change in the study parameters. The chief investigator will work with the R&D department at the study site as well as the TMG so they can put the necessary arrangements in place to implement the amendment, to confirm their support for the study as amended. As part of the required clinical standard in conducting research within the NHS, the chief investigator has Good Clinical Practice (GCP) certification.

6.2.2 Amendments

The chief investigator will be responsible for the decision to make any amendments to the protocol after agreement with the co-investigators. For any substantial amendment to the protocol, the chief investigator will submit a valid notice of amendment to the HRA for consideration via IRAS. Amendments will also be notified to the

local Leeds R&D team to assess whether the amendment affects the NHS permission for that site. The protocol version with the amendment will be updated and the most recent version of the protocol will be disseminated to all relevant study personnel. The updated version of the protocol as well as the historical version of the protocol will be filed in the site file.

6.3 Patient & Public Involvement

People with MS (PwMS) have brought their lived experience into the design of MS-PROACTIVE.

Design:

We worked closely with PwMS in the co-development of the MS-Work Instability Scale. This is the primary outcome measure in the MS-PROACTIVE trial.

The 'READY for MS' Acceptance and Commitment Therapy programme was developed by Professor Kenneth Pakenham in Australia to improve resilience and self-efficacy. The programme has been tested by PwMS in Australia and in Italy. Our PwMS advisors favour an intervention to improve self-efficacy that is convenient and empowers them to take control and manage their own situation. PwMS consistently reported they wanted to be more informed and involved with their own care and that MS-PROACTIVE offers opportunities for better health through supported self-care.

We have been working with Shift.ms, the social network for PwMS, who have helped us design the research. Shift.ms were keen for us to use a web-based type of therapy that would be flexible and easy for people who are working to use in their own time.

We submitted the initial plan for this study to the MS Society's Lay Research Network for review and advice on the application development. We received five detailed reviews from Research Network members on developing the project plan. Based on the reviews we have changed the proposal by adjusting the time frame

of the questionnaires, providing more detail on the content and length of sessions and included planned MS Nurse support in addition to the usual flexible support provided.

Four PwMS have provided verbal and written feedback on the Participant Information Sheet. This feedback has been incorporated in the current version.

Management of the research:

The Chief Executive of Shift.ms who has multiple sclerosis is a Co-Investigator for this project and a member of the Trial Management Group. The Trial Steering Committee will have representation from PwMS.

Undertaking the research:

In the first phase of the project four PwMS will be asked to consent to an external feasibility phase of the study. These four participants will trial the online version of READY for MS and advise on any modifications required and their experience of completing the online sessions. They will also advise on any changes required to the workbook. Data from these four participants will not contribute to the main pilot study analysis.

In the pilot study 88 PwMS will be randomised to either completing the online READY for MS sessions and standard care or standard care.

4 of the participants at each site will be asked to consent to be interviewed before doing the course, after completing the course and 6 months later. This is part of the process evaluation to work out how READY for MS works in practice.

Dissemination:

Shift.ms will support co-production of a plain English end of trial paper for trial participants, their families and the wider MS community especially PwMS and their employers.

6.4 Protocol compliance

The chief investigator will be responsible for all the recruitment, data collection and administration of assessments. The study participants will be informed about the protocol during the consent process and one of the consent criteria will be an agreement to adhere to the study protocol. The participants will be asked to make known any changes in their circumstances that might put them outside the eligibility criteria for the trial and they will be asked about this during every study visit. The chief investigator will log any protocol deviations and these will be made known to the TMG and where deemed appropriate, the chief investigator will also inform the local R&D team and REC.

6.5 Data protection and patient confidentiality

All the investigators in the study will comply with the requirements of the Data Protection Act 2018, and by extension the principles of the GDPR 2018 as well. Study specific information will be kept in the study site file including the participant consent forms and assessment sheets, as well as pertinent personal information. The site file will be stored in a secure location, not accessible to the public and other staff not part of the study. All the participants' data will be depersonalised, coded and then stored electronically in password protected files. There will be an encrypted digital copy of the original files kept in separate storage media. The data will be processed and stored for the duration of the study and thereafter for the purposes of any follow-up. Access to the data will be limited to the minimum number of individuals necessary for quality control, audit, and analysis.

7 DISSEMINATION POLICY

The data arising from the study will be owned by the chief investigator and the co-investigators of the study. On completion of the study, the data will be analysed and a final study report will be prepared. The full study report will then be submitted for peer review publication in relevant journals. The funding body and sponsor will be acknowledged within the publication. The findings from the study will be communicated to the

participants via newsletter and local clinical networks. Participants will be able to request copies of any publications resulting from the study and where possible these will be made available. The findings from the study will be presented at local and national or international scientific meetings.

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