Measuring the Effects of Nurse-Practitioner (NP)-Led Care on Depression and Anxiety Levels in People with Multiple Sclerosis: A Study Protocol for a Randomized Controlled Trial

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Study protocol

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Abstract

Background

Canada has one of the highest rates of multiple sclerosis (MS) in the world. Treatments and supports for people with MS (PwMS) have become increasingly complex, requiring individualized and adaptive care. Specialized NPs provide advanced skills to those with complex medical conditions, with potential to enhance the health, functioning and quality of life for PwMS. This study aims to determine the effect of Nurse Practitioners (NPs) on depression and anxiety levels in PwMS.

Methods

We will perform a parallel randomized controlled trial. PwMS who are followed by general private-practice neurologists will be randomly assigned to the intervention group (NP-led care) or the 'usual care' control group (general neurologist or family physician and registered nurse support). In the intervention group, the NP will assess and provide care to the MS patient and their caregiver at a baseline visit, with 3-month and 6-month follow-up visits. PwMS in the control group will receive usual care provided by their community neurologists or family physicians with the standard assistance provided by registered nurses experienced in MS care. The primary outcome will be the difference in change in the patient's anxiety and depression scores as measured by the validated Hospital Anxiety and Depression Scale (HADS) questionnaire at 3 months. Secondary outcomes will include difference in change in HADS at 6 months; Modified Fatigue Impact Scale scores (MSIF) at 3 and 6 months; EQ-5D scores at 3 and 6 months; caregiver health-related quality of life in MS measures (CAREQOL-MS) at 3 and 6 months; number of visits and phone calls to health-care professionals recorded by patient, and satisfaction with NP-led care vs usual care measured by the validated Consultant Satisfaction Questionnaire.

Discussion

Findings from this study will contribute to exploring benefits of advanced nursing practitioner interventions for PwMS followed by general neurologists and family physicians in a community setting. It will provide evidence of the benefits of NP-led care for PwMS and offer an alternative healthcare resource for management of MS.

Trial Registration:

Retrospectively registered June 26, 2020 at ClinicalTrials.gov (Unique protocol ID:Pro00069595);url: https://register.clinicaltrials.gov/prs/app/action/SelectProtocol?sid=S0009VEL&selectaction=Edit&uid=U00053N2&ts=4&cx=5oyfdk

Protocol version:

January 2017, version 1

Background

Multiple sclerosis (MS) is the leading cause of non-traumatic disability in young adults.[1,2] It is most commonly diagnosed in people between the ages of 20 to 50, causing visible and invisible disability that limits functioning, and usually progressing over time. Canada has one of the highest prevalence of MS in the world,[1,2] with Alberta having the highest rate of MS in Canada (340/100,000 population).[3] Since MS onset most often occurs in early adulthood, persisting and progressing throughout their lives, it becomes important for healthcare systems to address and adapt to their individual needs, and to keep people with MS (PwMS) as functional as possible.

The global approach to treating and supporting PwMS has become multidisciplinary, multi-pronged, and increasingly complex, as MS impacts a person's physical, psychological, and social well-being.[4] There is strong evidence that PwMS prefer multidisciplinary care,[5] similarly viewed as essential by international MS experts.[6,7] Since every individual's experience of having MS is unique, the education, treatments (symptomatic and disease modifying therapies), and counseling provided should be tailored and personalized, adapting as their MS advances.[5] The resources (e.g., education, counselling, support, care etc.) provided to PwMS should also evolve and change as a person's MS progresses and their needs change.[8] However, despite this recognition for multidisciplinary and personalized care, healthcare for PwMS in the 21st century has not advanced. Multiple studies have reported a number of unmet care needs for PwMS: these areas include healthcare delivery,[8–10] education, counseling, psychological support,[11,12] and in support provided to their informal caregivers.[12–14] In 2020, a study of over 1000 PwMS found a correlation between those that had a high level of unmet health and social care needs and lower health-related quality of life.[15] They also identified all the domains of the EQ5D-3L were important in measuring quality of life for PwMS.

Private-practice, community general neurologists and family physicians provide care to approximately 2000 PwMS outside of a tertiary multidisciplinary clinic setting with a wide catchment area extending across Central and Northern Alberta, Northern BC, Saskatchewan, and Northwest Territories. It is challenging for general neurologists and family physicians to balance care of PwMS with the pressures of busy office practices in a fee-for-service setting. Thus, it is important to look at look at ways to enhance care of PwMS through multi-disciplinary teams containing MS specialized nurses, especially nurse practitioners who practice with increased autonomy and expertise.

A 2020 integrative review identified three key themes required of the role for MS specialised nurses: (1) longitudinal care co-coordinator; (2) care provider; and (3) expert resource.[16] In an audit questionnaire conducted in 2013, 83% of PwMS indicated that they preferred contacting the MS specialized nurse

above other health professionals as they felt the MS nurse understood their specific condition better.[17] It has been suggested nurse practitioners (NP's) with their expertise in chronic disease management are well-placed to provide comprehensive care to PwMS.[18,19] In addition, having NPs to enhance the multidisciplinary team could potentially provide healthcare cost-savings: in the United States, NP-led care was reported to be cost-saving of 11–29% in comparison to physician-led care.[20,21]

There have been only a handful of randomized controlled trials comparing NP-led care vs usual care for people with chronic diseases. Broderick et al, published in 2014, demonstrated clear benefits of NP involvement in managing people with chronic pain, reporting better pain control, coping, and use of pain medication by those receiving NP-led care.[22] Another trial reported better outcomes for people with Parkinson's disease randomized to a NP multidisciplinary team vs usual care provided by a general neurologist.[23]

This randomized control trial study design will follow a protocol which studied the impact of NP-led care for people with atrial fibrillation and was designed by Smigorowsky et al .[24]

Our research question is to evaluate whether care by a nurse practitioner is as impactful to PwMS, as their usual medical care involving a community neurologist and/or family physician in addition to a registered nurse.

This study aims to evaluate the effects of NP-led care for PwMS on their depression and anxiety levels at 3 months, 6 months, and 12 months compared to 'usual care' (community neurologists' care or family physician and MS registered nurses). It also aims to measure quality of life for PwMS and their caregivers, fatigue levels, number of outpatient healthcare visits and phone calls, and to measure patients' satisfaction of the care provided in both groups. We hypothesize that PwMS whose care is managed by an NP would have less depression and anxiety (as measured by the Hospital Anxiety and Depression Scale – HADS) at 3 months.[25–28]

Methods

This study has been designed as a prospective parallel randomized controlled trial with two equal-sized groups (see Figure 1). We used the SPRINT reporting guidelines; please see the appendix for the SPRINT checklist.[29] Figure 1 outlines the study protocol procedure and Table 1 provides the study timeline, as per SPIRIT guidelines.[29] Participants will be randomized to either nurse practitioner-led care (NP-led care arm) as the intervention arm of the study over a 6 month period vs their usual medical care comprising the control arm (usual care arm), consisting of their community neurologist and/or family physician and registered nurse (RN).

Study Setting

The RCT will be conducted in a distributed, outreach model, in the offices of seven community neurologists who follow PwMS as a part of their general neurology private practices, with the NP based in the multi-disciplinary, tertiary MS Clinic at the University of Alberta Hospital, Canada. The NP will provide outreach support to the community neurologists' offices, seeing patients within their private office settings, based on referral from community neurologists. Family physicians will be able to refer their PwMS directly to the NP, if they are not followed by any neurologist, through the already established MS clinic referral process.

Population (Inclusion/Exclusion Criteria)

All adult PwMS who are thought to potentially benefit from NP involvement in their care will be referred to the NP by community neurologists or family physicians and assessed for eligibility and informed consent. Informal caregivers (defined as a partner or close friend who provides for, and/or supports the PwMS) will also be approached to participate in the study. Informal caregivers for PwMS as defined above will be approached to be involved in the study, after the PwMS they care for enrolls in the study and nominates for the inclusion of their caregiver into the study. Consent will be obtained by the software application the PwMS uses to access the study; this will be followed up by the NP and/or neurologist on the first visit.

PwMS will be invited to participate in the study if they are >/= 18 years of age, are diagnosed with MS as per the clinical 2010 McDonald criteria,[30] are followed by a private-practice general neurologist and/or family physician, willing to provide informed consent, have the ability to complete questionnaires on their own or with assistance (either by computer or paper copy), be able to attend outpatient visits with the NP, are English-speaking, and who are experiencing disability from their MS with an Expanded Disability Status Scale (EDSS) between 3.0 to 8.5 or a Patient Determined Disease Steps (PDSS) >/= 2.[31,32] PwMS will be excluded from this study if they are younger than 18 years of age, have an EDSS of less than 3.0 or PDDS less than 2, have a diagnosis of a central nervous system inflammatory disorder other than MS, are unable to provide informed consent, and/or are unable to attend visits with the NP in person, or by telehealth.

Recruitment

Recruitment will be conducted using two methods, as participants will be recruited from various community neurologists' offices and family physicians' practices in Northern Alberta. There are seven community neurologists who have volunteered to participate in recruiting of PwMS through their practices and iPads will be placed in their office waiting rooms. The neurologists will mention the study to their patients. If a PwMS expresses interest in participating in the study, an iPad containing the study information will be provided to them. Potential participants using the iPad will complete the EQ5D questionnaire and are then given an interpretation of their score. They will be encouraged to discuss their score with their neurologist and invited to self-register for the study, if they indicated they would be interested in potentially exploring alternate ways of healthcare delivery to optimize their health and MS

management. If the patient opts to self-register, they will be provided with the participant information sheet on the iPad and invited to complete the informed consent form. The signed informed consent form will be electronically sent to the study team where they will assess the patient with the eligibility inclusion/exclusion criteria. Those who meet the eligibility criteria will be randomized to the intervention or control arms as per this study protocol.

Those PwMS who are followed primarily by a family physician, outside of a neurologist, can be referred by their family physician directly to the NP via the established tertiary MS Clinic fax system. These referrals will be screened by the NP and one of the researchers (PS, a MS specialist neurologist). Those who meet the eligibility inclusion criteria will be invited to take part in the study. If the patient consents to the study, they will be randomized to either the intervention or control arm as per this study protocol. If the patient is randomized to the control arm, the family physician will be informed that the referral for the NP would be scheduled for after study conclusion: 6 months after the date of referral. Family physicians will be given the additional opportunity of referring the patient to a community neurologist or a NP outside of the study if they feel that the patient cannot wait six months for MS specialized care. If the family physician opts for more urgent patient assessment, these patients will be excluded from being involved in the study.

Caregivers will be approached and invited to participate in the study, if the PwMS indicates a caregiver and contact information through their participant consent process. At the end of the informed consent, the PwMS will be asked whether they have a caregiver (with our definition for this study provided). If the participant answers 'yes they have a caregiver', they will be invited to provide the caregivers' name, email address and/or physical address. A separate informed consent will then be sent to the caregiver by email or by mail, outlining their involvement in the study and seeking their informed consent. Date of first enrolment was July 28, 2017 and our recruitment was completed as of March 29, 2019.

Data Collection

Participants may withdraw from the study at any time without effect to their care. They will be informed they will not receive any incentive for participation and the risks are not beyond the day-to-day risks. After the participants have provided informed consent, they will be invited to complete the questionnaires. PwMS will be asked to complete the Hospital Anxiety and Depression Scale (HADS),[25] Euro Quality of Life Measurement (EQ5D),[33] Modified Fatigue Impact Scale (MSIF),[34,35] at specific timepoints (baseline, 3 months, 6 months, and 12 months); their caregivers (where applicable) will be asked to complete the Caregiver Health-Related Quality of Life in MS (CAREQOL-MS) questionnaire at the same timepoints.[36] These questionnaires will take approximately 10 to 15 minutes to complete at each time point. Participants will be asked to keep a participant diary submitted at the same time points, recording the number of outpatient visits and phone calls to their neurologists, family physicians, registered nurses, pharmacists, physiotherapists, occupational therapists, and other allied health professionals (such as massage therapists, chiropractors, dieticians etc.). Alberta has a linked provincial system where all emergency visits and inpatient admissions are recorded. This database will be searched for any

emergency visits and inpatient admissions for the 6-month period that the participants are involved in the study.

Participants' satisfaction with the level of care provided to them will be measured at 6 months at the conclusion of their NP care using the validated Consultant Satisfaction Questionnaire (CSQ).[24,37] The CSQ consists of 18 Likert scale questions, ranging from 1= strongly disagree to 5 = strongly agree, with the higher score indicating a higher level of patient satisfaction.

Randomization and Blinding

This is an interventional study with parallel groups, done through block randomization (variable block sizes) 1:1, using centralized secure website to: 1. Intervention Group (NP-led care) and 2. Control Group (Usual care – community neurologist/family physician and registered nurse (RN), in a non-inferiority framework. The EPICORE Centre will randomize consented patients who meet eligibility inclusion and exclusion criteria on a 1:1 ratio using a centralized secure website. Block randomization (using variable block sizes) will be used to ensure there are equal participants in the intervention and control arms and to further conceal allocation. Participants will be enrolled into the study by the community neurologist's office (e.g., registered nurse, nurse practitioner or neurologist). Participants will register themselves through filling out an iPad questionnaire in the waiting room of community neurologists' offices, indicating whether they wish to participate in the study or not. The participants, after providing informed consent, will be randomized by the independent EPICORE research team to either the intervention group of NP-led care or the control group of standard care provided by community neurologist and registered nurse. After participants have provided informed consent, the EPICORE research team will use a centralised website to randomize the patients to either the intervention or control group and then the NP and/or community neurologist will provide the intervention. Participants will be randomized to either the intervention group of NP-led care or the control group of standard care provided by community neurologist and registered nurse. Due to the nature of the intervention, blinding of the providers or patients will not be possible. However, the statistician will be blinded as to which group represents the intervention and control.

Individuals who will perform the interventions:

The nurse practitioner will deliver care to those participants randomized to the NP-led care arm during the 6 months of study duration in addition to participants' regular healthcare providers, while the participants' regular community neurologists and family physicians in addition to their registered nurses will deliver care to those participants in the usual care arm.

Intervention Arm (NP-led care arm):

Participants randomized to the intervention group will be contacted by the NP to be scheduled for an appointment with the NP within 4 to 6 weeks from the date of the referral. The NP consultation will include patient history, physical examination, symptomatic management strategies as appropriate (e.g.,

bladder and bowel management strategies, fatigue management, depression, anxiety, spasticity etc.), discussion of mental and physical health resources for symptomatic treatment, support, physical and mental health resources to optimize functioning (e.g., home care or physical/occupational therapy referral), and quality of life interventions. The NP will follow up with the patient either in person, by phone, or by videoconferencing at 3 months, at 6 months, and again at 12 months. The NP will be accessing the electronic medical record offered by Alberta Health Services[38] to maintain charting consistency in diagnostic testing, appointments, and communications.[38] During the visits, the NP will check the completion of study questionnaires at the appropriate timepoints, and ask the participant +/- caregiver about the completion of questionnaires. If the NP feels that he/she needs help in managing a participant, he/she will refer the participant back to the community neurologist and/or family physician in charge of the participant at any time throughout the study.

Control Arm (Usual care arm):

PwMS who are randomized to the usual care arm (community neurologist or family physician and registered nurses) will be contacted by the NP to be scheduled for an NP appointment at 6 months after study conclusion. Thus, every PwMS is given the opportunity to access NP care after their involvement in the study has concluded. During the 6-month period, patients randomized to the control group will receive usual care from community neurologists or family physicians and MS registered nurses. The care will be delivered according to standard practices, and follow-up visits will be conducted according to the various clinical practices of the neurologists' or family physicians' clinics. For those in the usual care arm, the EPICORE research team will contact the participant +/- caregiver about the completion of questionnaires at the appropriate timepoints. The participant diary will be collected by the NP when the participant in the usual care arm has finished the study, and is offered a follow-up visit with the NP outside of the study. If family physicians wish to have more urgent patient assessments, they will be offered the additional opportunity of referring the patient to a community neurologist or a NP outside of the study if they feel that the patient cannot wait six months for MS specialized care; these patients will also be excluded from being involved in the study.

Participants are able to initiate contact with their usual community neurologist and/or family physician in either arm of the study, throughout the study as they need. Participants will continue to be followed by their family physicians and regular community neurologists during the study, in either arm. For those in the NP-led care arm, they will receive additional care by the NP during the 6 months of the study duration.

Outcomes

The primary outcome will be the difference in change in the Hospital Anxiety & Depressional Score (HADS): depression score (HADS-D) and HADS anxiety score (HADS-A) between intervention and control groups at 3 months.[25] Mood disorders are commonly experienced by PwMS, significantly affecting quality of life,[25] amenable to identification and treatment through the chronic disease management model entrenched within a nurse practitioner's approach to patient care.

Secondary outcomes include difference in change in: (a) HADS-D and HADS-A scores at 6 months; (b) European Quality of Life Score (EQ5D) at 3 and 6 months,[33] a scale used by Alberta Health Services to measure impact of healthcare delivery models; (c) Modified Fatigue Impact Scale (MFIS) score at 3 and 6 months,[35] a severely disabling symptom commonly experienced by those living with MS; (d) Caregiver Health Related Quality of Life (CAREQOL-MS), a caregiver quality of life questionnaire for those informal caregivers helping PwMS who can experience burden and lack of support, at 3 months and 6 months,[36] participant diary of outpatient healthcare interactions during the study period and provincial database search for inpatient/emergency admissions, to see if the intervention of a NP decreases other costs of healthcare providers in the care of PwMS; in addition to (e) a Consultant Satisfaction Questionnaire (CSQ) at 6 months,[37] to see if participants perceive NP-led care to be equivalent to that provided by their usual care (community neurologist, family physician and registered nurse.

A longer-term follow-up will be conducted at 12 months to evaluate the long-term differences of the six-month intervention in change of the patient-reported outcome measures (HADS, MFIS, EQ5D, and CAREQOL-MS). By then, all participants would have seen the NP, and the goal of the late follow-up would be to see if there was (1) long-term impact of the 6 month NP intervention (from those in the original intervention group), and (2) to check the larger patient number impact of the NP intervention upon those within the control group.

If participants score very low or severe on their scales around anxiety, depression, fatigue, quality of life and/or their caregivers score as very low on their questionnaire, their community neurologist and/or family physician will be contacted to see the participant on an urgent basis.

Sample size & power analysis

Honarmand and Feinstein (2009),[39] validated the use of HADS in PwMS [Baseline scores and standard deviation (SD)]. Using the validation information in the study by Honarmand and Feinstein and the following assumptions of 80% power and a two-sided alpha of 0.05, a total sample size of 200 (100 in each group) will be required to detect 1.5 difference[40] between the intervention and the control groups. The same size has been calculated for both HADS-A and HADS-D. This study will use the sample size calculated for HADS-A, as it required a larger sample size and to ensure there will be sufficient power for both HADS-A and HADS-D. This sample size will be inflated to 220 to account for possible dropouts, losses to follow-up, and withdrawals of consent.

Feasibility

We investigated the feasibility of this intervention by searching community neurologists' electronic medical record databases to identify the number of PwMS typically followed by each of the seven neurologists. The number of PwMS in these practices do fluctuate over time (movement of PwMS in and out of the province, referral to another neurologist, or loss to follow-up etc.). There were greater than 2000 PwMS followed by community neurologists as of January 2017. There is also an established NP practice

in the tertiary MS clinic at the University of Alberta, seeing more than 400 PwMS per year. Thus, we have determined that we will be able to recruit the required 200 PwMS for the study.

Preliminary Screening

Prior to conducting statistical analysis, preliminary screening will be conducted using SAS 9.4 software (SAS Institute Inc, Cary, NC, USA) to ensure that all the enrolled patients meet the eligibility inclusion and exclusion criteria and confirm the participants provide informed consent.

Statistical Analysis

Data analysis will be performed using the computer R 3.4.0 software (Vienna, Austria; https://www.R-project.org/) and SAS 9.4 software (SAS Institute Inc. Cary, NC, USA). Patient demographic and clinical characteristics will be analyzed using descriptive statistics.

The primary outcome of difference in change of HADS-D and HADS-A from baseline to 3 months between the intervention and control, will be tested using an Independent T-test. The last observation will be carried forward in the case of missing data. Secondary outcomes will be analysed using the same methods as described below. The CSQ will be treated as continuous variables with an overall satisfaction score as a sum of the sub-scales for each question in the CSQ.

Categorical variables will be reported using frequency and percentage and continuous variables will be reported using mean (SD) or median [Interquartile range (IQR)] as appropriate. Univariable analysis will be conducted to determine if there is a statistical significance between the outcomes (e.g., baseline to three months and six months, respectively). Chi-square and Independent T-tests will be used for the univariate analysis, or where appropriate the non-parametric tests (Fishers test and Wilcoxon rank test). ANOVA and generalized linear models will be used to test for overall differences between the intervention and control at the different timepoints and variances amongst the variables by group and timepoints. Post-hoc Tukey HSD (Honestly Significant Difference) Test will be performed afterwards with adjustments made using the Bonferroni method. All test assumptions will be checked during the data analysis process. Statistical significance will be set at p values less than 0.05.

Validity and Reliability

The questionnaires used in the study (EQ5D, HADS, MFIS, and CAREQOL-MS) have been tested for validity and reliability in studies involving PwMS. Three papers report total HADS scores in PwMS and were considered in the study design of this study.[25,27,28] The EQ5D quality of life measure is commonly used in the MS population,[33] and the MFIS is a standard measurement of fatigue in PwMS.[35,41] The CAREQOL-MS, a caregiver quality of life survey for those caring for PwMS is also commonly used in this patient population.[36,42] Satisfaction with healthcare provider care will be measured by the overall mean score of the CSQ completed at the 6 month follow-up visit. The CSQ is a self-administered tool with 18 questions, it measures 3 factors of the healthcare provider interaction: (1) professional aspects; (2) depth

of patient relationship with provider; and (3) perceived length of consultation. The higher the score indicates a higher level of patient satisfaction.[24,37]

To reduce possible biases in the study, we will use objective measures to examine the effects of NP-led care in comparison to standard care. It is important that all participants are offered an opportunity to see a NP either within 4 weeks for the intervention arm vs at 6 months for the control arm. Thus, those participants randomized to the control arm will be provided with an appointment with the NP at 6 months. Then, 12-month follow-up of all participants will be conducted, to see if the timing of intervention makes a difference over the long-term.

Ethical considerations

The research protocol was reviewed and approved by the Health Research Ethics Board of the University of Alberta (approval number Pro00069595), initially on March 30, 2017, with protocol modification to version 2 approved on Jan 11, 2018. PwMS will be able to be referred to the NP by community neurologists and family physicians outside of participating in the study if they decline to participate in the study.

Funding

Funding was obtained through the University Hospital Foundation (Pro00069595), and partially matched by the Strategy for Patient-Oriented Research, Canadian Institutes of Health Research)

Data security and storage

Electronic data will be collected and stored using the RedCap secure website, housed behind the Faculty of Medicine and Dentistry firewall and secure server. Data will be stored under secure conditions for 10 years at EPICORE Centre, in accordance with EPICORE Centre's standard operating procedures. The questionnaires and consent forms will be completed electronically by the participants, participants will be offered paper copies if required. Electronic files will be kept on a secure server (Faculty of Medicine and Dentistry firewall) with password protection. Access will be limited to directly involved personnel. Paper copies will be kept in locked cabinets within the EPICORE Centre as according to their standard operating procedures.

A master list of participant name and personal health care number with associated research number, will be kept in a separate locked cabinet. Once secondary outcome blinded analysis has been completed, it will be destroyed. The research patient data will also be kept in a separate locked cabinet. Both of these cabinets are located in a locked room with limited access to research personnel only. Electronic files will be kept on a secure server (Faculty of Medicine and Dentistry firewall) with password protection. Access will be limited to those directly involved in this study (e.g., statistician, research assistant, and database manager). The electronic data information will be deleted after the 7-year post study completion requirement has been completed.

Data Monitoring

There will be an interim analysis completed after the 3-month follow up has been completed. The study involves PwMS completing validated surveys of their depression and anxiety scores which will be reviewed routinely by the NP and neurologist. If a PwMS depression and anxiety score falls drastically, the NP or neurologist will follow-up with the patient and provide any necessary care or referral. Quality assurance of the data will be performed by the data entry researcher and the project manager for the trial. Any and all amendments will be communicated to all investigators, research ethics office, and the participants. The study investigators will make the final decision to terminate the trial if needed. Since this a smaller, single centre study, we do not have plans for independent audit of trial conduct.

Electronic data will be collected and stored using the RedCap secure website which is housed behind the Faculty of Medicine and Dentistry firewall and secure server. Paper copies will be kept in locked cabinets within the EPICORE Centre as according to their standard operating procedures. Participants will be sent a reminder by the EPICORE team to complete the questionnaires at baseline, 3 months, 6 months, and at 12 months to encourage participants to complete follow-up visits. The first or last observation will be carried through to account for any missing data during the data analysis.

Confidentiality

Initially, identifying information will be collected to allow the research assistant to look for data required to assess for secondary outcome information (i.e., admission to hospital and/or emergency visits, MS relapse, infection or adverse events from medication). Participants will be offered to complete the questionnaires via secure internet website, however, some may prefer a paper copy in which case the participant's full address and phone number may be required for participants that opt for paper questionnaires to be mailed to them for follow-ups. Therefore, depending on patient preference, we will collect the email or postal addresses for reminders to be sent to fill out the questionnaires.

Patients will complete diaries of phone calls and visits to GP, neurologist, emergencies, HealthLink, and other healthcare professionals (such as physiotherapists, occupational therapists, pharmacists, dieticians, homecare, social workers, etc.). This information will be deidentified once collected.

Identifying information will be removed once the above data are obtained. Charts will be reviewed weekly to ensure all data are complete and all identifying information will be removed by a research assistant and coded with only a research number. A master list coordinating research numbers and patient's healthcare number will be kept separate from patient data in a separate locked cabinet which will be retained until the end of the study. At the conclusion of the study, this list will be destroyed.

Dissemination

This randomized control trial will be published once data analysis has been completed and all investigators will be invited to contribute to the manuscript. A copy of the publication and findings will be provided to the participants. At this time, there are no plans or arrangements for data sharing. We plan to

disseminate the results at the European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS) conference.

Discussion

This study will evaluate the effects of an NP-led care intervention on depression and anxiety levels in PwMS and their informal caregivers. The evidence gained from this study will provide information on how NPs can enhance the care and potentially resolve the identified unmet needs for PwMS when introduced as part of a multidisciplinary team approach for general neurologists working in a distributed community setting.

To our knowledge, there have been no studies examining the intervention of NP-led care provided to PwMS in a prospective, randomized and controlled clinical trial. Findings of this study will contribute to ways in which the multidisciplinary care for PwMS and their caregivers could be enhanced by the addition of a specialized NP. This study has the potential to provide an additional healthcare service available to PwMS to assist them in managing their complex disease and to aid community neurologist practices in care delivery to PwMS outside of tertiary MS clinic settings.

Limitations

There are study limitations inherent within the process of inviting PwMS to participate in a study looking at alternate ways of delivering care through a NP. This study preferentially selects for individuals who are open to having an NP provide care to them. Additionally, participants are not blinded as to whether they will be in the intervention arm vs the control arm. We will try to address that bias by offering NP visits to every participant in the study – either within 4 to 6 weeks for the intervention arm, or for those in the control arm at 6 months once the study concludes. An additional limitation might be that the NP may initiate appointments and/or phone calls with participants in the intervention arm beyond the three visits outlined in the study protocol where deemed clinically appropriate. We have limited participants to those who speak English and who can attend visits with the NP. This may limit the generalizability of the results with those who live in more rural areas, and those who primarily speak different languages. Finally, we will be relying on participants self-reported data to complete patient diaries to record their outpatient interactions with the healthcare system (e.g. family physician and neurologist visits and phone calls) and to complete the questionnaires which could be susceptible to subjective bias.

Trial Status

The trial was retrospectively registered June 26, 2020 at ClinicalTrials.gov (Unique protocol ID: Pro00069595). Recruitment and enrollment have been completed (initiated May 2017, completed Nov 2019) but the data collection for the 12-month follow-up is being completed and then final data quality assurance and analysis will be underway.

Abbreviations

PwMS – person/people with MS; MS – multiple sclerosis; NP – nurse practitioner; EDSS - Expanded Disability Status Scale; EQ5D – European Quality of Life Scale; PDSS - Patient Determined Disease Steps; MFIS - Modified Fatigue Impact Scale; HADS-A - Hospital Anxiety and Depression Scale, Anxiety score; HADS-D - Hospital Anxiety and Depression Scale, Depression score; CSQ - Consultation Satisfaction Questionnaire

Declarations

1. **Ethics Approval and consent to participate**

The research protocol was reviewed and approved by the Health Research Ethics Board of the University of Alberta (approval number Pro00069595). Written, informed consent to participate will be obtained from all participants. Please see appendix for ethics approval documents and consent forms.

2. **Consent for publication**

Not applicable

3. **Availability of data and materials**

Only the investigators will have access to the final trial dataset.

4. **Competing interests**
5. Smyth has received grant support through CIHR and the MS Society of Canada and is a co-investigator in a study funded by an unrestricted research grant from Biogen pharmaceuticals. She has consulted on advisory boards for Novartis Pharmaceuticals, Roche Canada, Biogen Idec Pharmaceuticals, Alexion Pharmaceuticals, Alberta Blue Cross and the Short Term Exceptional Drug Therapy Program for Alberta Health Services.
6. Watson has no conflicts of interest to declare
7. Tsuyuki has done consulting for Emergent BioSolutions, Shoppers Drug Mart and has received investigator-initiated research grants from Sanofi, Merck, AstraZeneca, and Pfizer.
8. **Funding**

This study is funded by the University Hospital Foundation at the University of Alberta (RES0013590), partially matched funds from the Strategy for Patient-Oriented Research (SPOR) through Alberta Innovates and CIHR. See Appendix for letter from funder.

6. **Authors' contributions, roles, and responsibilities**

Penelope Smyth (Department of Medicine, University of Alberta) filled the role of co-principal investigator, creating the study protocol, ethics submission, lead author on paper.

Kaitlyn Watson (EPICORE Centre, Department of Medicine, University of Alberta) aided in study protocol, organizing database information, ethics re-submission with study extension, and contributed greatly to writing the paper.

Ross Tsuyuki (Department of Pharmacology, and EPICORE Centre, Department of Medicine, University of Alberta) was co-principal investigator on the study, creating the study protocol, oversaw creation of the database and contributed to writing the paper.

7. **Funders -** University Hospital Foundation at the University of Alberta (RES0013590) and the Strategy for Patient-Oriented Research (SPOR) through Alberta Innovates/CIHR, were not involved in any of the following study activities; in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication.
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Tables

Table 1: Study Timeline

Timepoint	T_1	T_2	T_3	T_4	T_5	T_6	T_7	T_8	T_9
Enrollment	X	X							
Eligibility Screen EQ5D	X	X							
Informed Consent	X	X							
Allocation		X							
Baseline Questionnaires HADS MFIS EQ5D CAREQOL- MS			X						
3-month follow-up Questionnaires HADS MFIS EQ5D CAREQOL- MS				X					
6-month follow-up Questionnaires HADS MFIS EQ5D CAREQOL- MS CSQ					X				
12-month follow-up Questionnaires HADS MFIS EQ5D CAREQOL- MS						X			
Quality Assurance							X		
Data Analysis								X	
Results									X

*Timepoints in 3-month increments; see abbreviations for list of validated questionnaires provided at baseline, 3-month, 6-month, and 12 month follow-ups.

Figures

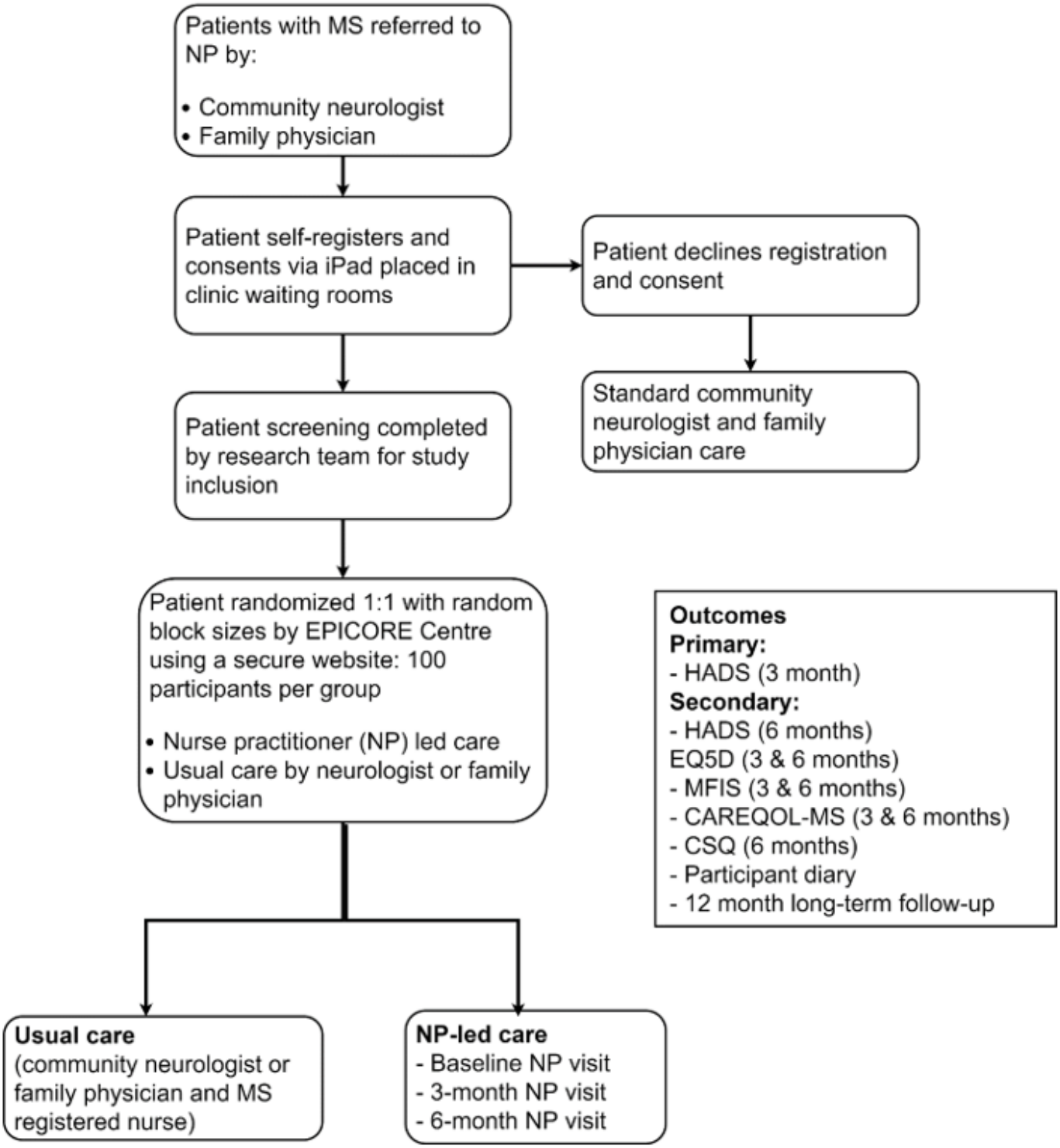

Figure 1

Study protocol procedure and flow

Supplementary Files

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- StudyConsents.pdf