Contemporary Clinical Trials 64 (2018) 219–229

Contents lists available at ScienceDirect

Contemporary Clinical Trials

journal homepage: www.elsevier.com/locate/conclintrial

Improving the quality of depression and pain care in multiple sclerosis using collaborative care: The MS-care trial protocol☆

Dawn M. Ehde[a,*], Kevin N. Alschuler[a,b], Mark D. Sullivan[c], Ivan P. Molton[a], Marcia A. Ciol[a], Charles H. Bombardier[a], Mary C. Curran[a], Kevin J. Gertz[a], Annette Wundes[a,b], Jesse R. Fann[a,c]

[a] Department of Rehabilitation Medicine, School of Medicine, University of Washington, 325 9th Ave, Box 359612, Seattle, WA 98104, USA
[b] Department of Neurology, School of Medicine, University of Washington, UW Multiple Sclerosis Center, 1536 N 115th St, McMurray Building Suite 130, Seattle, WA 98133, USA
[c] Department of Psychiatry and Behavioral Sciences, School of Medicine, University of Washington, 1959 NE Pacific Street, Box 356560, Seattle, WA 98195, USA

ARTICLE INFO

Keywords:
Multiple sclerosis
Pain
Depression
Collaborative care
Integrated care

ABSTRACT

Background and objectives: Evidence-based pharmacological and behavioral interventions are often underutilized or inaccessible to persons with multiple sclerosis (MS) who have chronic pain and/or depression. Collaborative care is an evidence-based patient-centered, integrated, system-level approach to improving the quality and outcomes of depression care. We describe the development of and randomized controlled trial testing a novel intervention, *MS Care*, which uses a collaborative care model to improve the care of depression and chronic pain in a MS specialty care setting.

Methods: We describe a 16-week randomized controlled trial comparing the MS Care collaborative care intervention to usual care in an outpatient MS specialty center. Eligible participants with chronic pain of at least moderate intensity (≥ 3/10) and/or major depressive disorder are randomly assigned to MS Care or usual care. MS Care utilizes a care manager to implement and coordinate guideline-based medical and behavioral treatments with the patient, clinic providers, and pain/depression treatment experts. We will compare outcomes at post-treatment and 6-month follow up.

Projected patient outcomes: We hypothesize that participants randomly assigned to MS Care will demonstrate significantly greater control of both pain and depression at post-treatment (primary endpoint) relative to those assigned to usual care. Secondary analyses will examine quality of care, patient satisfaction, adherence to MS care, and quality of life. Study findings will aid patients, clinicians, healthcare system leaders, and policy makers in making decisions about effective care for pain and depression in MS healthcare systems. (PCORI- IH-1304-6379; clinicaltrials.gov: NCT02137044).

This trial is registered at ClinicalTrials.gov, protocol NCT02137044.

1. Introduction

Multiple sclerosis (MS) is the most common cause of acquired neurologic disability in young adults [1]. Because MS is typically diagnosed between the ages of 20 and 50, people live many years managing the physical, cognitive, and psychological aspects of the disease [1]. Chronic pain and major depressive disorder (MDD) are two of the most prevalent problems experienced by MS patients. Nearly 25% of adults with MS have MDD [2] and over 50% experience moderate or severe chronic pain [3–5]. Approximately 20% to 25% of people with MS have both depression and chronic pain [6]. Both are associated with poorer MS outcomes, functioning and health-related quality of life, and greater healthcare utilization [4,7–9].

Depression and chronic pain are often under-treated in MS patients [10], despite the availability of effective treatments [4,5,11,12]. An estimated 50–66% of people with MS and MDD are under-treated [13–16]. Systematic screening alone has not consistently led to adequate treatment [12]. Pain treatments that patients prefer and evidence-based non-pharmacological pain management strategies are seldom used [17]. There is an urgent need to identify ways to improve

Abbreviations: BPI, Brief Pain Inventory; HSCL-20vB, Hopkins Symptom Checklist-20 Version B; MS, Multiple Sclerosis; PHQ-9, Patient Health Questionnaire 9; MS Care, MS Care collaborative care intervention

☆ This work was supported through a Patient-Centered Outcomes Research Institute (PCORI) Award (IH-1304-6379).

* Corresponding author at: University of Washington, Department of Rehabilitation Medicine, Box 359612, Seattle, WA 98104, USA.
E-mail address: ehde@uw.edu (D.M. Ehde).

http://dx.doi.org/10.1016/j.cct.2017.10.001
Received 10 May 2017; Received in revised form 2 October 2017; Accepted 3 October 2017
Available online 05 October 2017
1551-7144/

access to effective pain and depression care.

Successful healthcare delivery models developed in other patient populations provide a template for improving pain and depression care in MS. One highly successful model is collaborative care, a systematic, population-based approach to integrated care [18]. Core components of collaborative care include: [1] care managers who deliver brief evidence-based treatments and coordinate patients, providers, experts, and community resources; [2] registries to facilitate and track information, including outcomes; [3] measurement based treatment to target; and [4] stepped-care in which treatments are intensified as need [19]. Collaborative care has been used to improve healthcare for depression, and more recently, pain, within primary and specialty care settings [20–24]. Collaborative care is a cost-effective method for improving adherence and response to treatment, quality of life, and satisfaction with care for depression, pain, and other chronic conditions such as diabetes [23–27].

Only one small ($N = 83$), non-randomized trial using a collaborative care approach for depression care has been published in MS [28]. The trial emphasized depression screening, referral to a psychiatric nurse care manager, choice of guideline-based antidepressant or problem-solving therapies, outcomes monitoring, and relapse prevention. About a third ($n = 28$) of the subjects participated in the depression management intervention for a median of seven sessions with the care manager. The authors found that the frequency of major depression at 6-months was lower in the intervention group relative to usual care, suggesting that it is worthwhile to conduct more investigation of this approach. Thus far, no studies have evaluated collaborative care focusing on pain in patients with MS.

We sought to develop and test a new intervention, *MS Care*, which utilized collaborative care principles to improve depression and chronic pain care in MS. The purpose of this paper is to describe: [1] the development and structure of the MS Care intervention for improving chronic pain and depression outcomes in patients with MS, and [2] the methodology of the MS Care study, a randomized controlled trial testing the effectiveness of the intervention in outpatients at a specialty MS clinic.

2. Methods

2.1. Stakeholder engagement during study design and implementation

The MS Care study is funded by the Patient-Centered Outcomes Research Institute (PCORI), which encourages active participation of stakeholders throughout all phases of the research enterprise, from study design through dissemination [29]. In the present study, stakeholders include individuals with MS, partners/family members of individuals with MS, MS clinic providers/staff, and representatives from community advocacy groups, including the National MS Society. Stakeholders are involved in all facets of the study, including shaping the study design and intervention to meet the needs of individuals with MS and the MS treatment environment, identifying outcomes of interest to stakeholders, trouble-shooting problems that come up during study implementation, monitoring study progress, and participating in the dissemination of study results.

2.2. Study aims, hypotheses, and design

The study is a single-center two-group randomized (1:1) effectiveness trial comparing two alternative approaches to pain and depression care in which outcome assessors are unaware of intervention allocation. The specific aims and related hypotheses are:

Aim 1. To test the effectiveness of MS Care, a patient-centered collaborative care approach to treating depression and pain in individuals with MS, relative to usual care, in reducing pain and depression at post-treatment (primary endpoint) and at 6-month follow-up.

Hypothesis 1. Compared to those in usual care, patients randomly assigned to MS Care will demonstrate significantly greater control of both pain and depression at post-treatment (primary endpoint) and at 6-month follow-up.

Aim 2. To examine the impact of MS Care on secondary outcomes including quality of depression and pain care, disability, patient satisfaction, adherence to MS care, and quality of life at post-treatment (primary endpoint) and at 6-month follow-up.

Hypothesis 2. Patients randomly assigned to MS Care will show significantly better quality of life, disability, fatigue, adherence to MS Care, patient satisfaction, and quality of care at post-treatment and 6-month follow-up.

We specifically selected a randomized controlled study design to provide Level I evidence per American Academy of Neurology's Evidence Classification Criteria [30]. Furthermore, as there is clinical equipoise, a randomized study is ethically acceptable. As collaborative care is traditionally offered as an enhancement to care, the question of critical importance is whether MS Care improves outcomes above and beyond that which can be achieved with the current model of usual care.

We will report the participant flow and study procedures following the Consolidated Standards of Reporting Trials (CONSORT) guidelines [31]. The trial was registered on ClinicalTrials.gov on April 22, 2014.

2.3. Study setting

A sample of 190–200 participants (to achieve the goal of 160 completers) is being recruited from the UW Medicine Multiple Sclerosis Center at the University of Washington, Seattle, WA. The UW Medicine MS Center is a multidisciplinary center with in-house neurology, rehabilitation medicine, rehabilitation psychology, rehabilitation counseling, infusion, and nursing services, as well as co-located physical therapy, occupational therapy, and speech therapy services.

2.4. Participant eligibility and recruitment procedures

Inclusion and exclusion criteria were selected to maximize the generalizability of the study findings to the population of patients obtaining care at MS specialty centers. *Inclusion criteria* are: patient [1] has definitive diagnosis of MS confirmed by patient's MS physician in the MS Center using McDonald 2010 criteria;[32][2] plans to continue to receive care at the UW Medicine MS Center during the enrollment period to ensure integration of services; [3] has access to and is able to communicate over the telephone to facilitate the telehealth components of the intervention and outcome assessments; [4] reads, speaks and understands English; [5] is 18 years or older; and [6] reports a clinically significant problem in pain or depression, specifically: (a) chronic pain: average pain intensity in the past week of at least moderate severity (defined as a 3 or greater on 0–10 numeric rating scale)[33] and pain of at least six months duration, with pain reportedly present greater than or equal to half of the days in the past six months; or (b) depression: depressive symptoms over the past two weeks in the range of probable major depression on Patient Health Questionnaire-9 (PHQ-9: total score 10 or higher)[34] and endorsement of depressed mood and/or anhedonia (i.e., one of the cardinal symptoms of depression) present more than half the days in the past two weeks.

Exclusion criteria are: [1] presence of a severe psychiatric disorder as evidenced by (a) high suicide risk (i.e., current intent or plan, or thoughts of suicide in the past month with at least one suicide attempt in the past), (b) diagnosis of bipolar disorder with current psychotic features, or (c) symptoms of a current psychotic disorder [35] at the time of screening; [2] severe cognitive impairment, resulting in inability to provide informed consent, defined as two or more errors on

the Six-Item screener;[36][3] self-reported active substance abuse within the past month;[37][4] patient reports a planned major surgery scheduled in the next 10 months; or [5] ongoing psychiatric (> once a month) care of depression provided by a psychiatrist.

Many individuals with MS are prescribed antidepressants and/or analgesics for a variety of reasons, although often at sub-therapeutic doses [16] so patients on antidepressants and/or analgesics are eligible for the study. Women who are pregnant, breast-feeding, or planning pregnancy during the study are eligible to participate given that they can utilize the behavioral treatment components of MS Care. We decided to exclude persons who fail the cognitive screen (an extremely rare event in MS) out of concern that such severe impairment may interfere with their ability to provide informed consent. We also decided to exclude persons who are currently receiving frequent psychiatric care in order to avoid interference with existing medication management of depression, although we anticipate this will not exclude many individuals given that few patients with MS have ready access to psychiatric care. Given that nearly all patients with MS have telephones and speak and read English, very few patients, if any, will be excluded due to these constraints. However, the results will not be generalizable to the subgroup of individuals with MS who do not have access to a phone and/or are not English speaking; future studies of the MS Care approach should adapt the intervention for including patients from such under-represented groups.

Participants are primarily recruited through the UW MS Center's research recruitment system, which asks clinic patients to indicate whether they are interested in being contacted about research opportunities when they check in for clinic appointments. The medical records of consecutive patients who are potentially interested in research are then pre-screened by a research staff member ("staff") to confirm the initial inclusion criterion of an existing MS diagnosis. Those with a confirmed diagnosis of MS are then approached specifically about the MS Care study. In the event that direct contact is not made, staff attempt to reach the patient by telephone outside of the clinic appointment. In addition, clinic healthcare providers may make direct referrals to the study. Individual clinic patients may also self-refer to the study upon reviewing a study brochure or flyer posted in the MS Center. Staff send recruitment letters to patients with upcoming appointments at the UW Medicine MS Center and to patients who do not have scheduled appointments in the immediate future.

Staff ask interested patients with a confirmed MS diagnosis a set of standardized questions and measures to ascertain eligibility based on the inclusion/exclusion criteria using a case report form. The screening may take place either via telephone or in-person during a clinic visit. Average pain intensity (past week) is assessed using an 11-point numeric rating scale, where 0 means "no pain" and 10 means "pain as bad as you can imagine." The 0–10 numeric rating scale has consistently shown its validity as a measure of pain intensity through its strong association with other measures of pain intensity as well as its sensitivity to detect changes in pain associated with pain treatment [38]. The Patient Health Questionnaire–9 (PHQ-9) [34], a nine item measure of depressive symptoms, is used to assess for a probably major depressive episode. A score of 10 or more has high sensitivity and specificity for major depression in MS [39]. To screen for psychiatric exclusion criteria, the MINI Screener [35] is used to determine the presence of high suicide risk (MINI screener module C) or a diagnosis of a current psychotic disorder or bipolar disorder with current psychotic features (MINI Screener section L). The CAGE-AID [37] is used to assess alcohol or psychoactive substance dependence within the past month, and the Six-Item Screener is used to assess for cognitive impairment [36].

Eligible individuals are engaged in informed consent prior to any further study procedures. Staff track the recruitment outcome for patients who are deemed ineligible or opt out of participating prior to completion of the consent process, including reasons for ineligibility or declining participation. In addition, basic demographic information without identification is requested from those patients considered eligible to participate whom decline to enroll; this information will be used to compare them to study participants in order to assess the representativeness of the sample to the clinic population.

2.5. Safety protocols

Although participants with high suicide risk are excluded from the study, we developed a suicide safety protocol for use should any participant exhibit indications of possible self-harm risk during any phase of the study. Staff have been trained to implement the protocol if a participant or potential participant scores as moderate or high risk on the Suicidality module of the MINI [35], endorses 1 or high on the suicide item (item 9) of the Patient Health Questionnaire-9 [34], endorses 1 or higher on item M of the HSCL-20vB, or makes any reference to self-harm or suicidal thoughts at any time during the screening, outcome assessments, or treatment procedures. Upon identification of possible self-harm risk, staff are instructed to use the suicide risk assessment protocol, which assesses risk for self-harm and provides instructions for enacting procedures to assure patient safety based upon their assessed risk.

We track adverse events per UW Human Subjects Division procedures which include monitoring for possible adverse events, managing them, and reporting them to the principal investigator, Human Subjects Division, and study sponsor, as indicated.

2.6. Study intervention: MS care collaborative care intervention

2.6.1. Overview of MS care

The collaborative care intervention, *MS Care*, is a systematic and integrated approach to improving the delivery and utilization of evidence-based treatments for chronic pain and depression in adults with MS. The MS Care intervention was built upon the substantial evidence for the effectiveness of collaborative care in treating depression in primary care [40–43], evidence-based cognitive-behavioral interventions for pain and depression in MS [15,44–46], and pharmacotherapy recommendations for pain and depression specific to MS [5,11]. Studies of collaborative care targeting pain and depression in other medical populations, including primary care [25,47] and cancer [48], also informed our intervention design.

MS Care was designed to include the key principles of effective collaborative care [19], which include:

1. An **integrated patient-centered team care approach** is achieved by re-designing how depression and pain care are organized in the clinic setting. An MS care manager is added to the healthcare team and responsible for providing front-line care. Domain specialists, often not readily available in outpatient settings, are also added to the team to provide pain and depression expertise for a panel of patients. In partnership with the patient, the care manager ensures that patients, their healthcare providers, domain experts, and community resources collaborate together toward a shared care plan built upon the patient's needs and goals.
2. A **population-based approach** is used to track patients systematically using outcomes monitoring for all patients, an electronic case registry, and planned follow up contacts. The semi-automated case registry facilitates information flow, tracks critical clinical information including treatment response, and identifies patients in need of treatment adjustment, intensification, and/or outreach.
3. **Measurement-based treatment to target** (remission) is achieved via the routine use of validated pain and depression outcome measures to guide treatment adjustments and intensification. This facilitates prompt, responsive treatment adjustments and reduces the use of treatments that are not producing improvements.
4. **Evidence-based care** is provided to the patient based upon their goals and needs, including:

a. strategies to engage, educate, and motivate the patient and enhance treatment adherence;
b. brief evidence-based behavioral or physical activity interventions for depression and pain provided by the care manager,
c. guideline-concordant recommendations for optimizing pharmacotherapy for depression and pain; and
d. intensification or adjustment of treatments in patients not responding to initial treatment strategies.

5. **Accountable care** is facilitated by weekly team caseload review and supervision of care managers by pain and depression experts toward achieving patient and population treatment targets.

Built upon these principles of effective collaborative care, the MS Care intervention was designed to enhance the existing comprehensive care found in the typical MS specialty care center. It is built around a care manager who directly interfaces with patients while representing the treatment recommendations of an interdisciplinary team which includes not only the patient's MS providers (including neurologists, physiatrists, nurse practitioners, and nurses) but also specialists, specifically psychologists and psychiatrists with expertise in depression and/or chronic pain. MS Care also places great importance on the patient being an integral team member. The patient is taught their central role in self-managing many aspects of their depression and/or pain and shares decision-making about treatment options. Table 1 describes the specific roles of the MS Care team members.

MS Care also enhances usual care in that it systematizes many aspects of pain and depression care (e.g., weekly treatment response monitoring, weekly review of all patients not responding to treatment) and utilizes technology to support patient tracking, consultation, and outreach efforts. These features cue the team to rapidly intensify or modify care for patients whose pain and depression are not responding to treatment. They also allow the team to quickly identify those who are not adhering to treatment so that efforts to re-engage the patient can be promptly deployed. The care manager provides the critical link for implementing these “rapid response” strategies for delivering evidence-based care. Whereas usual care typically requires pain and depression treatments be delivered in person in a clinic setting, MS Care offers patients the choice of receiving the care management sessions face-to-face in clinic, by telephone, or a combination of the two modalities. For further information on how MS Care compares to and enhances usual care, see Fig. 1.

2.6.2. Outline of MS care sessions and procedures

Once a patient is randomized to MS Care, the MS Care manager contacts that patient to set up a patient-centered assessment and treatment planning session (Session 1), which is followed by up to 11 additional care management sessions over 16 weeks, depending on treatment response and patient preference. These sessions are delivered by the care manager in person or over the phone, based upon patient preference. As MS Care is patient-centered and thus intentionally flexible, each patient's care may vary depending on their individual needs and preferences. What follows is a description of the sessions and care provided.

Session 1: Patient-centered assessment and treatment planning session (45–60 min): Although participants can choose to engage in sessions by telephone or in person, an in person first visit is encouraged if possible to establish rapport. The aims of this session are to foster a therapeutic alliance and develop a preliminary treatment plan based upon a structured clinical assessment. The assessment includes the patient's current pain/depression symptoms, treatment history, current medications, and goals and preferences for depression and pain treatment. The care manager explains the rationale for and parameters of the intervention and collaborates with the patient to develop the overall initial treatment plan, which is reviewed, placed in the electronic medical record, and shared with the other team members.

Care Management Sessions: Each 30–60-minute session starts with a brief assessment in which the care manager administers standardized measures of pain intensity, pain interference, depressive symptoms, and depression interference. The care manager reviews the patient's adherence to pharmacological and non-pharmacological treatments over the past week and collaboratively addresses barriers to adherence, using problem-solving and motivational enhancement strategies. The care manager discusses any new treatment recommendations from the team and educates the patient on the rationale for the changes. Each session includes instruction in and rehearsal of a behavioral self-management skill (e.g., goal-setting, mindfulness meditation, relaxation), which they are encouraged to practice between sessions. Time is also spent reviewing the patient's homework from the past session, including their practice and application of self-management skills for pain and mood. A summary of each session is documented in the electronic medical record, and the patient's scores on the pain and depression measures is recorded in the electronic caseload registry for review in the weekly team caseload review meetings.

The care managers utilize a Care Manager Manual which was developed specifically for MS Care to guide them in delivering collaborative care for pain and depression in the context of MS. The manual provides an outline of the essential elements of a typical care management session. It also includes information about and modules for other components of MS Care. A patient workbook (paper and/or electronic copy) is provided to MS Care participants; the workbook is tailored to each patient based upon their specific symptoms, needs, and treatment plan. The workbook is used to facilitate review of information in session, particularly for those participating by phone, and to facilitate retention of educational content and practice of specific self-management skills outside of the care management sessions.

Collaborative Medical Management: Medication recommendations from the study's expert consultants follow established evidence-based treatment algorithms [5,11]. Optimized medical management may also include recommendations for physical activity, physical therapy, or occupational therapy to address pain or to safely increase physical activity. Recommendations are communicated to the MS providers via their preferred methods (e.g., electronic medical record, in person, secure email or telephone). If medication adjustments are approved, the treating MS physician provides an updated prescription. In occasional complex medication management cases, direct communication between the treating MS physician and the content expert in that domain (e.g., psychiatrist) may occur.

Behavioral Treatment: MS Care incorporates brief evidence-based behavioral treatments into each care management session, including pain and/or depression self-management skill training (based upon cognitive-behavioral therapies), motivational interviewing to promote adherence to care, and education about community resources. The care manager manual has several core modules to guide delivery of the behavioral interventions along with optional modules. Depending on the participant's presenting problem (pain, depression, or both), preferences, and past treatment (if any), the behavioral interventions may include [1] education about pain and depression specific to MS; [2] relaxation skills and/or mindfulness meditation training (as a coping strategy for pain and/or depression); [3] behavioral activation and goal setting (focused on pain/depression self-management); [4] cognitive therapy, including teaching patients to identify, challenge, and modify unhelpful thoughts and replace them with helpful thoughts; [5] energy management strategies to address fatigue that may interfere with goals

Table 1
MS care team members and roles.

MS care team members	Roles
Patient	• Participate in shared decision-making about treatment plan, including goals and preferences for pain and depression care • Implement treatment recommendations, including medications, behavioral strategies, follow up appointments, and other strategies • Complete measures used to assess progress and outcomes • Communicate updates and concerns to the care manager
MS care manager	• Perform initial assessment to inform the treatment plan built around patient's goals and preferences • Initiate treatment plan, consulting with patient and MS providers • Provide weekly care management sessions by phone or in clinic • Provide patient education about pain, depression, treatments, and self-management strategies to address these symptoms • Motivate and engage the patient in treatment and self-management • Provide brief, evidence-based behavioral treatments tailored to patient's needs and goals • Monitor patient's adherence and response to treatment using brief, validated measures of pain and depression • Participate in weekly caseload consultation meetings with consultant team and communicate team's recommendations to patient and MS providers • Coordinate and facilitate treatment adjustments and communication between patient, MS providers, and consulting team • Document each session, including outcome measures, progress, and treatment recommendations, in electronic medical record • Coordinate pain and behavioral health management plan with team, stepping up or adjusting care when clinically indicated • Facilitate referrals to other providers and community resources as needed • Complete a relapse prevention plan with patients to maintain treatment gains
Patient's existing MS and primary care providers	• Provide usual care for MS disease and symptoms • Refer patients to MS Care • Share information with MS Care team as indicated • Act on recommended modifications to the patient's treatment plan • Are welcome to participate in weekly caseload consultations (but not required)
Specialty consultants	
Consulting psychologist with multiple sclerosis expertise	• Participate in weekly caseload review meetings • Provide consultation and guide care by providing expertise in evidence-based treatments, particularly behavioral and rehabilitation interventions for pain and depression • Provide guidance on the neuropsychological and psychosocial aspects of MS and impact on symptoms, functioning, and treatments • Identify patients in need of more specialized consultation or services (e.g., more intensive psychotherapy or other interdisciplinary care) • Support care managers, providing ad hoc consultation • Guide or support care plans for difficult clinical situations (e.g., crisis management) • Provide ongoing training to the care managers and team to enhance provider education, particularly related to brief pain and behavioral health treatments
Consulting psychiatrist	• Participate in weekly caseload review meetings • Provide consultation and guide care by providing expertise in evidence-based psychiatric interventions, including medication recommendations • Identify patients in need of more specialized consultation or services (e.g., more intensive psychiatric evaluation) • Support care managers, providing ad hoc consultation • Guide or support care plans for difficult clinical situations (e.g., crisis management) • Provide ongoing training to the care managers and team to enhance provider education, particularly around psychotropic medications
Consulting medical pain expert	• Participate in weekly caseload review meetings • Provide consultation and guide care by providing expertise in evidence-based pain interventions, including bot medications and physical activity • Identify patients in need of more specialized consultation or services (e.g., more intensive medical evaluation or other multidisciplinary care) • Support care managers, providing ad hoc consultation • Guide or support care plans for difficult clinical situations (e.g., crisis management) • Provide ongoing training to the care managers and team to enhance provider education, particularly around medical pain treatments

such as increased activity; and [6] motivational interviewing to promote adherence to healthcare and goals. The care manager also educates the patient about community resources including those available through the Greater Northwest Chapter of the National MS Society, which has programs, resources, and services available. If the patient is working with a clinic psychologist or a behavioral health provider in the community, the care manager coordinates care with that provider.

Team Caseload Review: The care managers participate in weekly one-hour caseload review meetings with the MS Care domain (pain and depression) experts. The caseload registry is an electronic spreadsheet that lists basic information about each participant and shows their baseline and weekly pain and depression outcomes collected in the care management sessions. This allows the team to quickly review treatment response trends over time. The registry is automated to list participants who are not improving or worsening at the top, with remitted cases at the bottom. Cases who are not improving are reviewed first, followed by new cases and, as time permits, remaining cases. The care manager is responsible for briefly summarizing each participant's treatment goals and progress, and the team discusses the case and may suggest treatment adjustments as indicated. The care manager also communicates any recommendations or changes in care to the patient and MS providers.

Treatment Monitoring/Intensification: In consultation with the supervisors, the care manager offers the participant choices for modified or intensified treatment if the outcome measures indicate that

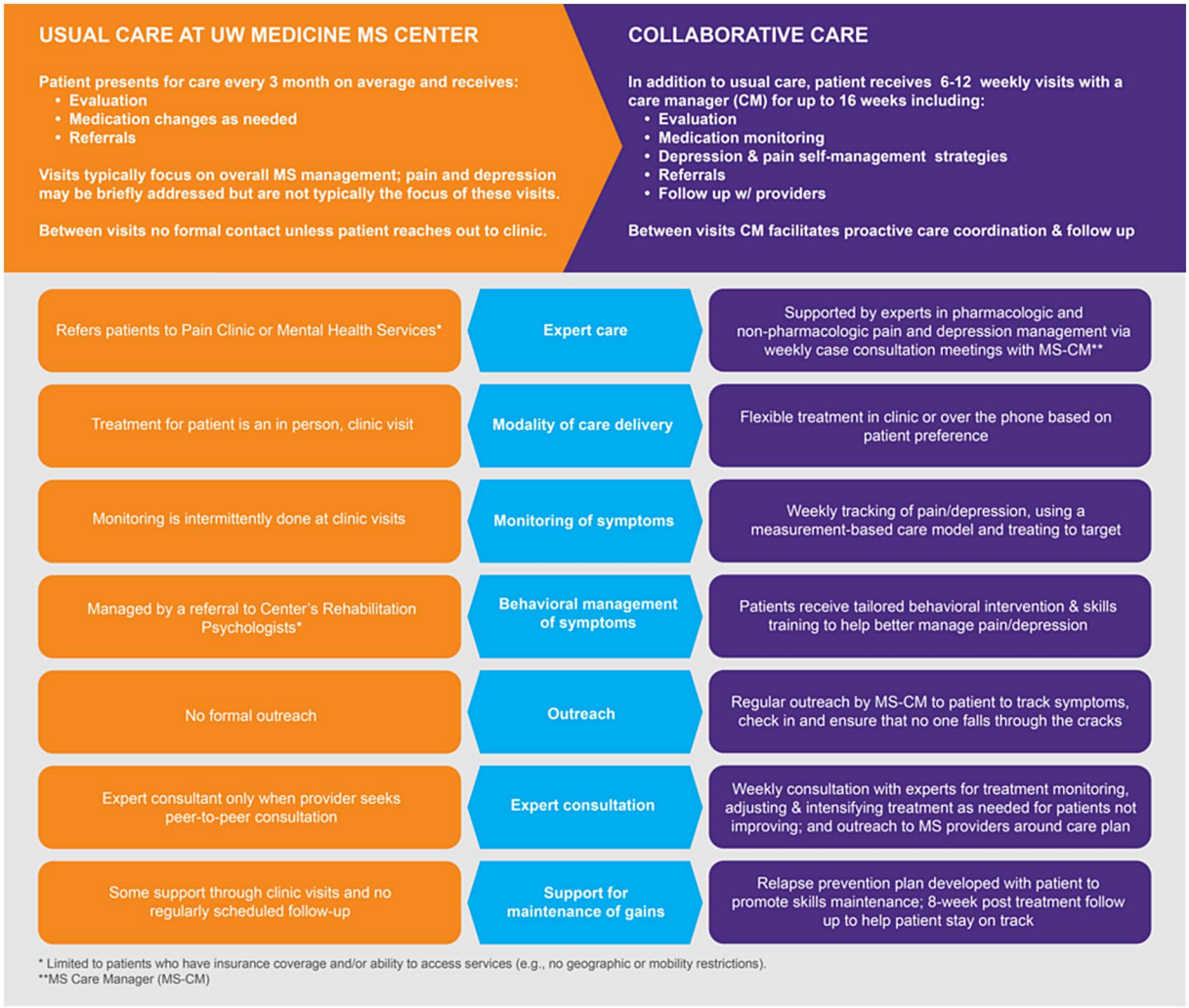

Fig. 1. A comparison of usual care and MS care.

the participant's pain and depression are not in remission or clinically improved. Partial- and non-responders are offered an intensified treatment, which may include combined medical and behavioral interventions, and/or in-person or telephone consultation with the appropriate expert. Care may also include referral to the specialist with expertise in that condition for consultation and/or referral to outside specialists for treatment, depending on the judgment of the MS provider and MS Care team.

Relapse Prevention Plan: Participants who are in remission work with the care manager to come up with a relapse prevention plan based on the successful elements of their treatment, potential relapse triggers, foreseeable barriers to continuation, and a plan for how they will cope with relapse. A copy of the relapse prevention plan is provided to the participant; a summary of this plan and any final recommendations is provided in the electronic medical record. Participants not in remission are referred for further support or treatment if they could benefit from further treatment.

Follow-up Call (week 24). All participants receive a follow-up call from their care manager at 24 weeks to maximize continuation and maintenance of treatment gains. This call includes a review of pain, depressive symptoms, treatment adherence, side effects, and current stressors. They review the patient's implementation of the relapse prevention plan and discuss recommendations for ongoing treatment or self-management strategies. The care manager helps coordinate additional follow up in the clinic or the community if indicated.

2.7. Usual care

Participants assigned to the usual care arm are notified by phone by the care manager regarding their group assignment and are told that they can continue to receive or seek care as they normally would, including at the MS Center. They are informed that we recommend that they speak to their healthcare provider about options that may be available to them for addressing pain and/or depression. They are also provided with a resource list of community and web-based resources for pain, depression, and MS. Participants are reminded of the outcome assessment timeline and the importance of completing the outcome assessments.

As patients of the UW Medicine MS Center, usual care participants receive medical care from a neurologist and/or rehabilitation medicine physician. Additional services available within the MS Center that some patients receive include: rehabilitation psychology, vocational counseling, infusion services, and consultation with an on-site pharmacist. Patients also often receive services that are external to the MS Center. Common services include physical therapy, occupational therapy, speech therapy, and urology. On an individual basis, patients may be prescribed any of a number of other external specialty services of relevance to this study; these may include treatment in a specialty pain center or care provided by an outside psychiatrist. Fig. 1 provides

additional information about usual care in the UW MS Center.

2.8. Care manager training, supervision, and fidelity monitoring

The MS Care study employed two masters-level social workers as care managers. Both care managers had expertise in behavioral interventions and care coordination prior to the study. Formal training in the collaborative care approach, treatment of pain and depression in MS, and study procedures was provided by co-investigators with relevant expertise. Didactic training was provided via lecture, experiential training, and an online training system. Given the breadth of treatment and the unique element of utilizing a treatment model that is tailored to individual participants, the study also included ongoing training via individual and group consultation and supervision on a weekly basis.

Although collaborative care is inherently flexible in its delivery of evidence-based interventions, there are key components considered important to the care management sessions. To assess the care managers' fidelity to these key components, we will audio record care management sessions, which will be assessed through an independent review of randomly selected digital recordings from 10% of all sessions across both care managers.

2.9. Randomization, allocation concealment, and procedures to minimize bias

Participants who complete the pre-treatment assessment are randomly assigned on a 1:1 ratio to receive either MS Care or usual care over a period of 16 weeks. Blocked randomization is stratified by the presence of pain, depression, or both pain and depression (total of 3 groups). A staff member who does not perform outcome assessments manages the random assignment protocol. A care manager is informed of the assignment and initiates treatment scheduling accordingly. Participants assigned to the usual care group are contacted by telephone by a care manager and informed of their assignment. Participants allocated to the MS Care condition are contacted by a care manager to arrange the first treatment session using the IRB-approved telephone script.

In this single-blinded study, study participants, care managers, treating MS physicians, and the expert panel are aware of group assignment but make significant efforts to ensure that staff collecting outcome assessments remain unaware of participants' group assignments. Data collection staff are uninvolved in participants' care and trained on the importance of remaining unaware of group assignment. Staff are instructed to explicitly inform the participants that they (the staff) are to remain unaware of participants' allocation and to stop any participant who begins to discuss information that may lead to disclosure of allocation.

2.10. Data collection procedures and measures

All outcomes are assessed by telephone interview at pre-treatment (baseline), 4-months post-randomization (post-treatment; primary endpoint), and 10-months post-randomization (6-month follow-up). The 4-month post-treatment assessment will allow sufficient time to complete the MS Care intervention for those assigned to it. Participants will be compensated $30 for completion of each outcome assessment plus an additional $40 if all three outcome assessments are completed, for a total of up to $130. A list of the primary and secondary outcome measures, along with their associated time point of administration, is provided in Table 2.

2.10.1. Primary outcome: Control of pain and depression

The primary outcome, control of pain and depression, and the measures used to determine control were chosen because they are considered the gold standards for assessing pain and depression outcomes in clinical and collaborative care research. *Control of pain* is defined as either an average pain intensity score of < 3 in the last week or obtaining a 30% or greater reduction in pain intensity from baseline. Pain intensity will be assessed using the 10-point numerical rating scale for average pain intensity in the past week from the Brief Pain Inventory [49,50]. This measure has been validated in MS samples [51]. The 30% criterion is based on research in MS [52] and on the recommendations of a consensus panel [38] who defined this reduction as a clinically meaningful outcome. *Control of depression* is defined as a reduction of at least 50% depression severity or a score of < 0.5 on the Hopkins Symptom Checklist-20 Version B (HSCL-20vB) [53,54]. The HSCL-20vB is a brief self-report measure of cognitive, emotional and somatic symptoms of depression commonly used in treatment outcome studies. The measure has excellent psychometric properties and is highly sensitive to change, particularly in medical populations. It contains the 13-item depression subscale and 7 additional items that reflect the somatic component of depression, all on a 5-point scale (0 = not at all, 4 = extremely). It has been shown to have high validity and reliability, including in people with MS [55]. The depression control cutoffs are considered clinically significant improvements in depression trials [56].

The primary outcome - control of pain and depression - is a binary variable, scored as positive if the participant meets the criteria for both control of pain and control of depression at the post-treatment assessment. For those who only have one problem (i.e., only have pain *or* depression but not both at time of enrollment), they will automatically meet the control criteria for that domain. For example, if someone is identified as having depression but not pain, they will be defined as having “control of pain”.

2.10.2. Secondary outcomes

A modified version [57] of the Brief Pain Inventory Interference Scale (BPI)[58] will be used to assess pain interference using a 0 “does not interfere” to 10 “completely interferes” numeric rating scale. The modified BPI changed the item “walking ability” to “mobility-ability to get around” to accommodate wheelchair or power mobility users and has been validated for use in the MS population [51]. Self-reported depression severity will be computed from the HSCL-20vB (total score). Depression diagnosis status is being collected via a structured diagnostic assessment, the Major Depressive Episode and Dysthymia modules of the MINI International Neuropsychiatric Interview, which can reliably and validly be administered by trained staff who are not clinicians [35].

Other secondary outcomes are being collected because they were identified by our stakeholders as important outcomes impacted by pain and depression or are outcomes commonly affected by depression and/or pain in the literature. They are listed in Table 2 and include assessment of disability, fatigue, perceived self-efficacy for managing MS, and health-related quality of life. Given that this study is evaluating an intervention changing a system of care, quality of care, satisfaction with care, and healthcare services utilization are also being assessed. We are collecting healthcare services utilization including number of hospitalizations and days hospitalized, number of emergency department and clinic visits as well as information about other types of relevant care including psychotherapy and rehabilitation therapies. Medication use, including use of opioids, antidepressants, and MS disease-modifying medications is assessed via self-report. Patient satisfaction with and perceived improvement from care is assessed at post-treatment and 6-month assessments. For those assigned to MS Care, the care managers track the nature and number of treatment components delivered during treatment (e.g., relaxation training, medication coordination) so that we will be able to describe in detail the treatments delivered as part of the MS Care intervention.

2.10.3. Descriptive measures

Descriptive variables are collected at baseline from the medical

Table 2
Study measures.

Outcome or variable	Measure	Timing
Primary outcomes		
Control of pain	Brief pain inventory 4-item pain intensity scale[a]	Baseline, post-treatment, 6-months
Control of depression	Hopkins symptom checklist-20 version B (HSCL-20vB)[b]	Baseline, post-treatment, 6-months
Pain and depression secondary outcomes		
Pain interference	Brief pain inventory- interference scale[a]	Baseline, post-treatment, 6-months
Quality of depression and pain care	Composite of medical services utilization and medication data	Baseline, post-treatment, 6-months
Depressive disorder diagnosis	Major Depressive Episode & Dysthymia modules of the M.I.N.I. International Neuropsychiatric Interview[c]	Baseline, post-treatment, 6-months
Other secondary outcomes		
Disability	Sheehan disability scale 3-item measure[d]	Baseline, post-treatment, 6-months
Health-related quality of life	EuroQol EQ-5D[e]	Baseline, post-treatment, 6-months
Patient ratings of improvement and satisfaction with care	Patient global impression of change scale & patient global assessment of treatment satisfaction	Post-treatment, 6-months
Fatigue	Patient reported outcomes measurement information system (PROMIS)-fatigue-MS (short-form)[f]	Baseline, post-treatment, 6-months
Medical services utilization	Cornell services index[g]	Baseline, post-treatment, 6-months
Self-Efficacy for managing MS	Self-efficacy scale for multiple sclerosis[h]	Baseline, post-treatment, 6-months
Medication use	Self-report	Baseline, post-treatment, 6-months

[a] Tan, G., Jensen, M. P., Thornby, J. I., & Shanti, B. F. (2004). Validation of the Brief Pain Inventory for chronic nonmalignant pain. J Pain, 5 [2], 133–137.
[b] Walker J, Sharpe M, Kroenke K, and Murray G. (2010). The HSCL-20: One questionnaire, two versions. J Psychosom Res. 68. 313–314.
[c] Linn, E.H., VonKorff, M., Russo, J., et al. (2000). Can depression treatment in primary care reduce disability? A stepped care approach. Arch Fam Med, 9, 1052–1058.
[d] Sheehan, D. V., Lecrubier, Y., Sheehan, K. H., Amorim, P., Janavs, J., Weiller, E., … Dunbar, G. C. (1998). The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. J Clin Psychiatry, 59 Suppl 20, 22–33.
[e] Johnson, J. A., Coons, S. J., Ergo, A., & Szava-Kovats, G. (1998). Valuation of EuroQOL (EQ-5D) health states in an adult US sample. Pharmacoeconomics, 13 [4], 421–433.
[f] Cook, K. F., Bamer, A. M., Roddey, T. S., Kraft, G. H., Kim, J., & Amtmann, D. (2012). A PROMIS fatigue short form for use by individuals who have multiple sclerosis. Qual Life Res, 21 [6], 1021–1030.
[g] Sirey, J. A., Meyers, B. S., Teresi, J. A., Bruce, M. L., Ramirez, M., Raue, P. J., … Holmes, D. (2005). The Cornell Service Index as a measure of health service use. Psychiatr Serv, 56 [12], 1564–1569.
[h] Amtmann, D., Bamer, A. M., Cook, K. F., Askew, R. L., Noonan, V. K., & Brockway, J. A. (2012). University of Washington Self-Efficacy Scale: A New Self-Efficacy Scale for People With Disabilities. Archives of Physical Medicine and Rehabilitation, 93 [10], 1757–1765.

record and interview. They include demographic variables (sex, age, race, ethnicity, education level, employment status, postal zip code, and marital status) and MS variables including date first experienced symptoms believed to be related to MS diagnosis, date of MS diagnosis, course of MS (relapsing-remitting, primary-progressive, secondary-progressive, or progressive-relapsing), and use of disease-modifying medications. We administer a current Expanded Disability Status Scale-self-report, as it is a core measure of MS disease progression in clinical trials [59]. Baseline descriptive measures also include participants' pain and depression histories, including number of pain sites, pain duration, pain type (neuropathic, nociceptive, or mixed/unknown).

Given that 40–65% of adults with MS have mild to moderate cognitive difficulties [60], the Brief Test of Adult Cognition by Telephone (BTACT) is administered by telephone following enrollment but prior to treatment [61,62]. It takes approximately 15–20 min to complete and provides reliable and valid measurement of working memory, episodic memory, reasoning, verbal fluency, and executive function. We will use these measures to assess if treatment effects are moderated by baseline cognitive impairment.

2.11. Statistical power

We intend to enroll 190–200 participants into the MS Care trial. The sample size is based on the proportion of individuals who achieved pain and depression control found in the two, large published studies of collaborative care for pain and depression [47,48]. These studies are similar in design to our study but were conducted in different populations, primary care patients and cancer patients. In these studies, the proportions of individuals with pain control were 0.46 in the intervention group and 0.26 in the control group, while the proportions for major depression were 0.31 for the intervention and 0.52 for the control. Using a test of proportion, with significance level of 0.05, to detect an increase of at least 0.20 in the proportion of pain control in the collaborative care group relatively to the UC group, with a power of 80%, the study requires 90 cases per group. Similarly, for control of depression, the study requires 87 cases per group. We plan to enroll 95–100 cases per group to have sufficient power to detect differences if they exist.

We plan to analyze subgroups based on sex, race, and type of initial symptom (and any other subgroups identified via stakeholder engagement) to assess whether MS Care is more effective in some subgroups than others. We acknowledge that the sample size will be too small to detect anything but a large interaction. These analyses, while important, will be exploratory in nature.

2.12. Statistical analyses

The study analysis plan conforms to the intent-to-treat principle: all randomized cases are included based on their assigned treatment group regardless of actual treatment received. Those not assessed at the end of treatment will be considered missing values. If the missing mechanism is such that it allows for imputation, we will do so according to the

appropriate methods for a binary variable (using multiple imputation) [63]. If it is not possible to use imputation (due to the missing mechanism), the most conservative approach is to consider the missing values as failures, but we will perform additional analyses to assess sensitivity by excluding cases not assessed at the end of treatment, and assuming that only unassessed cases in the collaborative care group were failures.

For the primary analysis, we will compare the proportion of individuals who have control of depression and pain symptoms (separately) between the two groups (collaborative care & usual care) at the end of treatment period (4-month post-randomization). As a secondary analysis, we will use binomial regression with a log link to compare the ratio of the proportion of control of both pain and depression in the collaborative care group to that in the usual care group at the end of the treatment period (the 4-month outcome) while controlling for stratification variables and imbalanced pre-randomization characteristics in addition to assigned treatment. A 2-sided significance level of 0.05 will be used. Additionally, those not assessed at the end of treatment will be considered treatment failures for a conservative analysis if the mechanism of missing values does not allow us to make imputations; otherwise, multiple imputation will be used to estimate the outcome. However, we will perform additional sensitivity analyses by excluding cases not assessed at the end of treatment, assuming only unassessed cases in the collaborative care group were failures to account for missed assessments. We will analyze secondary binary endpoints (at 6-month follow-up) using similar methods. The secondary outcomes for the two groups will be compared at post-treatment (4-months post randomization) and at 6-month follow up by using *t*-test for the variables that can be considered continuous and Fisher test for variables that are categorical.

2.13. Trial status

The UW Human Subjects Division approved the study protocol on January 23, 2014, and participant recruitment began on May 1, 2014. The treatment phase is anticipated to end in September of 2016, with the final outcome assessments planned for Spring of 2017.

3. Discussion and conclusions

This study protocol describes the first application of a collaborative care approach to integrated care of both pain and depression in adults with MS. We are unaware of any other applications of this model for pain and depression in persons with neurologic conditions. The extant literature on collaborative care in primary care settings suggests that collaborative care has considerable potential to improve outcomes and the quality of care in MS patients with pain and depression, common problems of significant impact on patients' quality of life and function. The MS Care trial is a randomized controlled trial designed to test if the integration of MS Care into an existing MS specialty care setting improves the outcomes and quality of care over and above usual care. In addition to providing data about the immediate effects on pain and depression outcomes, the trial will yield data on the maintenance of any effects at 6-months post the conclusion of the collaboration period. The trial will also determine if MS Care improves other outcomes relevant to MS patients and other stakeholders, including fatigue, disability, quality of life, and satisfaction with healthcare.

An important aspect of the MS Care study is its engagement of MS stakeholders. When developing the research proposal, we sought input from a range of stakeholders, including clinic patients, clinic providers (physicians, nurses, nurse practitioners, psychologists, administrative staff, and a pharmacist), and staff from the National MS Society via a series of meetings and semi-structured interviews. Patients with MS shared their perceptions on barriers to adequate depression and pain care, for example: "*Managing MS is confusing…so many things to be compliant with" "I know from my doctor there are treatments (for pain, mood), but it is hard to get connected to them in a way that works for me." "When I was depressed my doctor recommended I see a therapist, but I never followed up-why? It seemed too difficult; I wasn't sure where to start.*" Providers also described barriers to pain and depression care which included geographic barriers, lack of insurance for psychology services, and patient non-adherence or "resistance" to psychosocial care. Patient stakeholders provided suggestions for improving pain and depression care. For example, one said *"It would be better if you could get your care for your pain and depression in one place; right now my care is fractured, all things are separate." Another said, "My counselor is near my home but doesn't know much about MS and doesn't talk to my MS doctor."* All of the patients with MS said that they liked the idea of "*having a team*" look after their depression and pain care, and they believed that MS Care would decrease barriers to care. The MS Care intervention and study were informed by these important stakeholder perspectives. Our stakeholders continue to be active participants in the trial and will assist in interpreting and disseminating study findings.

MS care as provided in MS specialty centers tends to be interdisciplinary, and MS healthcare providers are well aware of the high prevalence of depression and pain in this patient population. Therefore, in this setting we anticipate that usual care is already more comprehensive compared to MS care by solo practitioners in community-based settings. Nonetheless, the MS Care approach offers potential advantages over usual care in both specialty and community settings where individuals with MS are treated. Collaborative care adds the care manager to the MS healthcare team, whose focus is monitoring, tracking, treating, and coordinating depression and pain care. MS teams do not typically have a provider focused solely on depression and pain treatment. The integration of the domain experts into the team is also an advantage of the MS Care model. These specialists provide the patient, care manager, and MS providers with timely, responsive, expert consultation that is typically only available on a referral basis or, for many patients living in rural or underserved regions, not available at all. MS Care also systematizes services such that outcomes are routinely tracked electronically and treatments adjusted according to ongoing outcomes monitoring and treatment protocols. Collaborative care is, by design, highly proactive; it utilizes evidence-based principles and strategies to engage patients in care, build motivation, and reach out to those who may not be adhering to depression or pain care. Treatment is quickly adjusted and, as needed, intensified through the consultation and coordination that comes out of the weekly caseload review meetings. As a result, it may be more difficult for patients to "fall through the cracks" in MS Care.

MS Care was built upon the evidence-based principals and systems of collaborative care that have been effective in primary care settings. However, MS Care also differs from the typical collaborative care approach in its emphasis on telephone-delivery, non-pharmacological pain management interventions, and rehabilitation psychologist involvement. Although other collaborative care interventions have utilized the telephone to some degree, care management sessions typically occur face-to-face in the primary care clinic. In contrast, MS Care offers participants the choice to receive the care management sessions in person in the MS clinic, by telephone, or a combination of the two. Given the geographic, transportation, and mobility barriers often encountered by MS patients when seeking pain and behavioral healthcare, telehealth is increasingly being used to provide healthcare to individuals with MS. Telephone-delivered interventions for MS-related fatigue, chronic pain, depression, and physical activity promotion have been efficacious in treating symptoms and improving outcomes in randomized controlled trials [15,44,64–66]. Telephone delivery does not appear to compromise the establishment of a therapeutic working alliance between therapists and individuals [64,67] and has resulted in high levels of treatment adherence [44,64]. The MS Care study will extend this research to collaborative care and provide important data on patient preferences for receiving in person versus telehealth care.

Given the robust evidence for the use of cognitive-behavioral

strategies in chronic pain management in the general population [68], MS Care emphasizes non-pharmacological pain management. MS Care offers a broader menu of cognitive-behavioral strategies for pain self-management than the few published randomized controlled trials of collaborative care for pain, which were conducted in primary care settings [20,24]. Physical activity goal-setting and counseling are also central to chronic pain management and thus included in MS Care.

The MS Care model also differs from most other collaborative care models in its inclusion of psychologists with expertise in rehabilitation psychology and neuropsychology as domain experts. A psychologist attends the weekly caseload review meetings and provides ongoing consultation to the care manager and other team members about neuropsychological and rehabilitation factors influencing patients' treatment needs and progress. Rehabilitation and neuropsychologists also adapted the MS Care behavioral and educational materials to the needs of patients with MS and provided the care manager in training on the psychosocial and neuropsychological aspects of living with MS.

In conclusion, the MS Care study seeks to build on the strong evidence-base for collaborative care in improving depression and pain outcomes in other populations and increase the potential for benefit to people with MS via several innovations, including: [1] tailoring the intervention to the unique needs of the MS population (e.g., complex symptoms, cognitive dysfunction, varying levels of disability); [2] adapting collaborative care to address pain, depression, or both, thus ensuring relevance to a larger proportion of the MS population; [3] offering the option of telehealth delivery in order to reach MS patients who live in rural areas or are unable to access regularly in-person care; and [4] improving the intervention and relevance using stakeholder engagement. If effective, results of this intervention could be disseminated via professional (e.g., Consortium of MS Centers) and consumer (the National MS Society, the MS Foundation) organizations which have existing mechanisms for rapid dissemination of research findings and publishing clinical practice guidelines in MS. The MS Care intervention and study results may also have relevance to other neurorehabilitation populations, including traumatic brain injury, where pain and depression are common and access to evidence-based pharmacological and non-pharmacological treatments limited.

References

[1] J.A. Stern, L. Sorkin, K. Milton, K. Sperber, Aging with multiple sclerosis, Phys. Med. Rehabil. Clin. N. Am. 21 (2) (2010) 403–417.
[2] R.A. Marrie, S. Reingold, J. Cohen, et al., The incidence and prevalence of psychiatric disorders in multiple sclerosis: a systematic review, Mult. Scler. 21 (3) (2015) 305–317.
[3] D.M. Ehde, T.L. Osborne, M.A. Hanley, M.P. Jensen, G.H. Kraft, The scope and nature of pain in persons with multiple sclerosis, Mult. Scler. 12 (5) (2006) 629–638.
[4] A.B. O'Connor, S.R. Schwid, D.N. Herrmann, J.D. Markman, R.H. Dworkin, Pain associated with multiple sclerosis: systematic review and proposed classification, Pain 137 (1) (2008) 96–111.
[5] D.M. Ehde, A.L. Kratz, J.P. Robinson, M.P. Jensen, Chronic pain, in: M. Finlayson (Ed.), Multiple Sclerosis Rehabilitation: From Impairment to Participation, Taylor & Francis, London, 2013, pp. 199–226.
[6] K.N. Alschuler, D.M. Ehde, M.P. Jensen, The co-occurrence of pain and depression in adults with multiple sclerosis, Rehabil. Psychol. 58 (2) (2013) 217–221.
[7] K.N. Alschuler, M.P. Jensen, D.M. Ehde, The association of depression with pain-related treatment utilization in patients with multiple sclerosis, Pain Med. 13 (12) (2012) 1648–1657.
[8] D.M. Ehde, L.E. Gibbons, L. Chwastiak, C.H. Bombardier, M.D. Sullivan, G.H. Kraft, Chronic pain in a large community sample of persons with multiple sclerosis, Mult. Scler. 9 (6) (2003) 605–611.
[9] A. Feinstein, S. Magalhaes, J.F. Richard, B. Audet, C. Moore, The link between multiple sclerosis and depression, Nat. Rev. Neurol. 10 (9) (2014) 507–517.
[10] S.L. Minden, A. Feinstein, R.C. Kalb, et al., Evidence-based guideline: assessment and management of psychiatric disorders in individuals with MS: report of the Guideline Development Subcommittee of the American Academy of Neurology, Neurology 82 (2) (2014) 174–181.
[11] P. Arnett, A. Ben-Zacharia, R. Benedict, et al., The Goldman Consensus statement on depression in multiple sclerosis, Mult. Scler. 11 (3) (2005) 328–337.
[12] D.C. Mohr, S.L. Hart, L. Julian, E.S. Tasch, Screening for depression among patients with multiple sclerosis: two questions may be enough, Mult. Scler. 13 (2) (2007) 215–219.
[13] A. Feinstein, An examination of suicidal intent in patients with multiple sclerosis, Neurology 59 (2002) 674–678.
[14] D.C. Mohr, S.L. Hart, I. Fonareva, E.S. Tasch, Treatment of depression for patients with multiple sclerosis in neurology clinics, Mult. Scler. 12 (2) (2006) 204–208.
[15] D.C. Mohr, W. Likosky, A. Bertagnolli, et al., Telephone-administered cognitive-behavioral therapy for the treatment of depressive symptoms in multiple sclerosis, J. Consult. Clin. Psychol. 68 (2) (2000) 356–361.
[16] K. Cetin, K.L. Johnson, D.M. Ehde, C.M. Kuehn, D. Amtmann, G.H. Kraft, Antidepressant use in multiple sclerosis: epidemiologic study of a large community sample, Mult. Scler. 13 (8) (2007) 1046–1053.
[17] D.M. Ehde, K.N. Alschuler, T.L. Osborne, M.A. Hanley, M.P. Jensen, G.H. Kraft, Utilization and patients' perceptions of the effectiveness of pain treatments in multiple sclerosis: a cross-sectional survey, Disabil. Health J. 8 (3) (2015) 452–456.
[18] W. Katon, J. Unutzer, K. Wells, L. Jones, Collaborative depression care: history, evolution and ways to enhance dissemination and sustainability, Gen. Hosp. Psychiatry 32 (5) (2010) 456–464.
[19] J.R. Fann, J. Sexton, Collaborative psychosocial oncology care models, in: J.C. Holland, W.S. Breitbart, P.B. Jacobsen, M.J. Loscalzo, R. McCorkle, P.N. Butow (Eds.), Psycho-oncology, 3rd ed., Oxford University Press, London, 2015, pp. 1–16.
[20] S.K. Dobscha, K. Corson, N.A. Perrin, et al., Collaborative care for chronic pain in primary care: a cluster randomized trial, JAMA 301 (12) (2009) 1242–1252.
[21] S. Gilbody, P. Bower, J. Fletcher, D. Richards, A.J. Sutton, Collaborative care for depression: a cumulative metaanalysis and review of longer-term outcomes, Arch. Intern. Med. 166 (2006) 2314–2321.
[22] W. Katon, E.H. Lin, M. Von Korff, et al., Collaborative care for patients with depression and chronic illnesses, N. Engl. J. Med. 363 (27) (2010) 2611–2620.
[23] E. Woltmann, A. Grogan-Kaylor, B. Perron, H. Georges, A.M. Kilbourne, M.S. Bauer, Comparative effectiveness of collaborative chronic care models for mental health conditions across primary, specialty, and behavioral health care settings: systematic review and meta-analysis, Am. J. Psychiatry 169 (8) (2012) 790–804.
[24] K. Kroenke, E.E. Krebs, J. Wu, Z. Yu, N.R. Chumbler, M.J. Bair, Telecare collaborative management of chronic pain in primary care: a randomized clinical trial, JAMA 312 (3) (2014) 240–248.
[25] W. Katon, J. Russo, E.H. Lin, J. Schmittdiel, P. Ciechanowski, E. Ludman, D. Peterson, B. Young, M. Von Korff, Cost-effectiveness of a multi condition collaborative care intervention: a randomized controlled trial, Arch. Gen. Psychiatry 69 (5) (2012) 506–514.
[26] J. Archer, P. Bower, S. Gilbody, et al., Collaborative care for depression and anxiety problems, Cochrane Database Syst. Rev. 10 (2012) CD006525.
[27] M. Panagioti, P. Bower, E. Kontopantelis, et al., Association between chronic physical conditions and the effectiveness of collaborative care for depression: an individual participant data meta-analysis, JAMA Psychiatry 73 (9) (2016) 978–989.
[28] S.B. Patten, S. Newman, M. Becker, C. Riddell, L. Metz, Disease management for depression in an MS clinic, Int. J. Psychiatry Med. 37 (4) (2007) 459–473.
[29] J.V. Selby, L. Forsythe, H.C. Sox, Stakeholder-driven comparative effectiveness research: an update from PCORI, JAMA 314 (21) (2015) 2235–2236.
[30] W. Edlund, G. Gronseth, Y. So, G. Franklin, Clinical practice guidelines process manual, American Academy of Neurology, St. Paul (MN), 2004.
[31] I. Boutron, D. Moher, D.G. Altman, K.F. Schulz, P. Ravaud, Extending the CONSORT statement to randomized trials of nonpharmacologic treatment: explanation and elaboration, Ann. Intern. Med. 148 (4) (2008) 295–309.
[32] C.H. Polman, S.C. Reingold, B. Banwell, et al., Diagnostic criteria for multiple sclerosis: 2010 revisions to the McDonald criteria, Ann. Neurol. 69 (2) (2011) 292–302.
[33] K.N. Alschuler, M.P. Jensen, D.M. Ehde, Defining mild, moderate, and severe pain in persons with multiple sclerosis, Pain Med. 13 (10) (2012) 1358–1365.
[34] K. Kroenke, R.L. Spitzer, J.B. Williams, The PHQ-9: validity of a brief depression severity measure, J. Gen. Intern. Med. 16 (9) (2001) 606–613.
[35] D.V. Sheehan, Y. Lecrubier, K.H. Sheehan, et al., The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10, J. Clin. Psychiatry 59 (Suppl. 20) (1998) 22–33 (quiz 34–57).
[36] C.M. Callahan, F.W. Unverzagt, S.L. Hui, A.J. Perkins, H.C. Hendrie, Six-item screener to identify cognitive impairment among potential subjects for clinical research, Med. Care 40 (9) (2002) 771–781.
[37] R.L. Brown, L.A. Rounds, Conjoint screening questionnaires for alcohol and other drug abuse: criterion validity in a primary care practice, Wis. Med. J. 94 (3) (1995) 135–140.
[38] R.H. Dworkin, D.C. Turk, J.T. Farrar, et al., Core outcome measures for chronic pain clinical trials: IMMPACT recommendations, Pain 113 (1–2) (2005) 9–19.
[39] B. Arroll, F. Goodyear-Smith, S. Crengle, et al., Validation of PHQ-2 and PHQ-9 to screen for major depression in the primary care population, Ann. Fam. Med. 8 (4) (2010) 348–353.
[40] D. Rosenberg, E. Lin, D. Peterson, E. Ludman, M. Von Korff, W. Katon, Integrated medical care management and behavioral risk factor reduction for multicondition patients: behavioral outcomes of the TEAMcare trial, Gen. Hosp. Psychiatry 36 (2) (2014) 129–134.
[41] M. McGregor, E.H. Lin, W.J. Katon, TEAMcare: an integrated multicondition collaborative care program for chronic illnesses and depression, J. Ambul. Care Manag. 34 (2) (2011) 152–162.
[42] W. Katon, E.H. Lin, M. Von Korff, et al., Integrating depression and chronic disease care among patients with diabetes and/or coronary heart disease: the design of the TEAMcare study, Contemp. Clin. Trials 31 (4) (2010) 312–322.
[43] J. Unutzer, W. Katon, C.M. Callahan, et al., Collaborative care management of late-life depression in the primary care setting: a randomized controlled trial, JAMA 288 (22) (2002) 2836–2845.

[44] C.H. Bombardier, D.M. Ehde, L.E. Gibbons, et al., Telephone-based physical activity counseling for major depression in people with multiple sclerosis, J. Consult. Clin. Psychol. 81 (1) (2013) 89–99.
[45] D.M. Ehde, G.H. Kraft, L. Chwastiak, et al., Efficacy of paroxetine in treating major depressive disorder in persons with multiple sclerosis, Gen. Hosp. Psychiatry 30 (1) (2008) 40–48.
[46] M.P. Jensen, D.M. Ehde, K.J. Gertz, et al., Effects of self-hypnosis training and cognitive restructuring on daily pain intensity and catastrophizing in individuals with multiple sclerosis and chronic pain, Int. J. Clin. Exp. Hypn. 59 (1) (2011) 45–63.
[47] K. Kroenke, M.J. Bair, T.M. Damush, et al., Optimized antidepressant therapy and pain self-management in primary care patients with depression and musculoskeletal pain: a randomized controlled trial, JAMA 301 (20) (2009) 2099–2110.
[48] K. Kroenke, D. Theobald, J. Wu, et al., Effect of telecare management on pain and depression in patients with cancer: a randomized trial, JAMA 304 (2) (2010) 163–171.
[49] R.L. Daut, C.S. Cleeland, R.C. Flanery, Development of the Wisconsin Brief Pain Questionnaire to assess pain in cancer and other diseases, Pain 17 (1983) 197–210.
[50] C.S. Cleeland, K.M. Ryan, Pain assessment: global use of the brief pain inventory, Ann. Acad. Med. 23 (2) (1994) 129–138.
[51] D.M. Ehde, K.P. Nitsch, J.P. Smiley, Measurement characteristics and clinical utility of the brief pain inventory-short form for individuals with multiple sclerosis, Rehab. Psychol. 60 (4) (2015) 365–366.
[52] K.N. Alschuler, M.P. Jensen, D.M. Ehde, Defining mild, moderate, and severe pain in persons with multiple sclerosis, Pain Med. 13 (10) (2012) 1358–1365.
[53] L.R. Derogatis, N. Melisaratos, The brief symptom inventory: an introductory report, Psychol. Med. 13 (3) (1983) 595–605.
[54] J. Walker, M. Sharpe, K. Kroenke, G. Murray, The HSCL-20: One questionnaire, two versions, J. Psychosom. Res. 68 (2010) 313–314.
[55] D. Amtmann, A.M. Bamer, K.L. Johnson, et al., A comparison of multiple patient reported outcome measures in identifying major depressive disorder in people with multiple sclerosis, J. Psychosom. Res. 79 (6) (2015) 550–557.
[56] Research. AfHCPa, Depression Guideline Panel. Clinical Practice Guideline Number 5: Depression in Primary Care. Volume 2: Treatment of Major Depression, Vol 93-0551 U.S. Department of Health and Human Services. Agency for Health Care Policy and Research, Rockville (MD), 1993.
[57] T.L. Osborne, K.A. Raichle, M.P. Jensen, D.M. Ehde, G. Kraft, The reliability and validity of pain interference measures in persons with multiple sclerosis, J. Pain Symptom Manag. 32 (3) (2006) 217–229.
[58] G. Tan, M.P. Jensen, J.I. Thornby, B.F. Shanti, Validation of the brief pain inventory for chronic nonmalignant pain, J. Pain 5 (2) (2004) 133–137.
[59] J. Bowen, L. Gibbons, A. Gianas, G.H. Kraft, Self-administered expanded disability status scale with functional system scores correlates well with a physician-administered test, Mult. Scler. 7 (3) (2001) 201–206.
[60] G.C. DeLuca, R.L. Yates, H. Beale, S.A. Morrow, Cognitive impairment in multiple sclerosis: clinical, radiologic and pathologic insights, Brain Pathol. 25 (1) (2015) 79–98.
[61] A.S. Gurnani, S.E. John, B.E. Gavett, Regression-based norms for a bi-factor model for scoring the brief test of adult cognition by telephone (BTACT), Arch. Clin. Neuropsychol. 30 (3) (2015) 280–291.
[62] M.E. Lachman, S. Agrigoroaei, P.A. Tun, S.L. Weaver, Monitoring cognitive functioning: psychometric properties of the brief test of adult cognition by telephone, Assessment 21 (4) (2014) 404–417.
[63] R. Little, D. Rubin, Statistical Analysis With Missing Data, 2nd ed., Wiley-Interscience, Hoboken, NJ, 2002.
[64] D.M. Ehde, J.L. Elzea, A.M. Verrall, L.E. Gibbons, A. Smith, D. Amtmann, Efficacy of a telephone-delivered self-management intervention for persons with multiple sclerosis: a randomized controlled trial with a one-year follow-up, Arch. Phys. Med. Rehabil. (2015).
[65] M. Finlayson, K. Preissner, C. Cho, M. Plow, Randomized trial of a teleconference-delivered fatigue management program for people with multiple sclerosis, Mult. Scler. 17 (9) (2011) 1130–1140.
[66] C.H. Bombardier, M. Cunniffe, R. Wadhwani, L.E. Gibbons, K.D. Blake, G.H. Kraft, The efficacy of telephone counseling for health promotion in people with multiple sclerosis: a randomized controlled trial, Arch. Phys. Med. Rehabil. 89 (10) (2008) 1849–1856.
[67] V. Beckner, L. Vella, I. Howard, D.C. Mohr, Alliance in two telephone-administered treatments: relationship with depression and health outcomes, J. Consult. Clin. Psychol. 75 (3) (2007) 508–512.
[68] D.M. Ehde, T.M. Dillworth, J.A. Turner, Cognitive-behavioral therapy for individuals with chronic pain: efficacy, innovations, and directions for research, Am. Psychol. 69 (2) (2014) 153–166.