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TITLE: MS CATCH: Closing the Gaps in Depression Care for People with MS by Closing the Information Loop

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14. ABSTRACT Depression occurs in over 50% of individuals living with multiple sclerosis (MS) and can be treated using many modalities, yet it remains under-reported by patients, under-ascertained by clinicians, and under-treated. To enhance these behaviors to promote depression care, we engaged multiple stakeholders to design a first-in-kind digital health tool. The tool, MS CATCH, closes the communication loop between patients and clinicians. Between clinical visits, the tool queries patients monthly about mood symptoms, supports patient self-management, and alerts clinicians to worsening mood via their EHR in-basket. Clinicians can also access a MS CATCH dashboard displaying patients' mood scores over the course of their disease, and providing comprehensive management tools (contributing factors, antidepressant pathway, resources in patient's neighborhood). The goal of the current trial is to evaluate the clinical effect and usability of MS CATCH in a real-world clinical setting. Methods and analysis: MS-CATCH is a single site, Phase II randomized, delayed start, trial enrolling 125 adults with MS and mild to moderately severe depression. Arm 1 will receive MS-CATCH for 12 months, and Arm 2 will receive usual care for 6 months, then MS-CATCH for 6 months. Clinicians will be randomized to avoid practice effects. The effectiveness analysis is superiority intent-to-treat comparing					
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1. Introduction

MS CATCH is a closed loop, doctor to patient, mobile application for people with depression and Multiple Sclerosis. People living with Multiple Sclerosis (PwMS) face a higher likelihood of being diagnosed with a depressive disorder than the general population. Though many low-cost screening tools and evidence-based interventions including medications exist, depression in PwMS is under-reported, under-ascertained by clinicians, and under-treated. The goal of the current project was to design a closed-loop tool to improve depression care. It would support regular depression screening, tie into the clinician at the point of care, and support shared decision making and comprehensive follow up. The project involved a development phase, a proof-of-concept pilot clinical validation study, a detailed design phase, and soon, a phase II clinical trial at the UCSF MS clinic.

2. Keywords

Depression; MS; quality of life; bring your own device; mHealth; closed loop; Clinical trial; multiple sclerosis; mobile application; digital health; screening; randomized; intervention

3. Accomplishments

What were the major goals of the project?

The major goal of this project is to address the suboptimal screening and treatment of depression in real-world MS Settings by developing a digital tool, MS CATCH. This tool will aim to close the loop of information flow from patients to clinicians, at the point of care, and back to patients to support patient-centered care. This tool will be tested through a two year long pragmatic clinical trial. The last 6 months of the study will be the evaluation phase.

Aim 1. To refine MS CATCH based on stakeholder engagement and intended user input over 6 months.

This 100% complete. The planned timeline was 0 – 6 months, we completed it at 11 months from project approval.

What was accomplished under these goals?

Aim 1. To refine MS CATCH based on stakeholder engagement and intended user input over 6 months.

The following activities have been completed –

1. All focus group sessions with patients and clinicians have been completed (5 patients, 5 clinicians)
2. All think-aloud sessions with patients have been completed (7 patients)
3. Final tool testing sessions with internal clinicians are 100% complete (5/5 completed)
4. Final tool testing sessions with patients are 100% complete (20/20 completed)
5. Combined think aloud and final tool testing sessions with external clinicians have been completed (5 external clinicians interviewed)
6. During the sessions listed above, feedback on tool likeability, usability and perceived usefulness is being obtained from both clinicians and patients, in addition to a list of features to be modified, and how features map to COM-B principles of behavior change.
7. Meeting with psychiatrist stakeholders to discuss trial details (2/8/23) was performed.
8. Clinical trials.gov posting has been made for trial.
9. Mental health resources (helpline numbers, support groups, websites) have been made accessible for trial participants.
10. The technical team has integrated the patient surveys into the EMR. They have built the clinician messaging and alerts in the EMR.
11. A paper detailing our pilot study results has been submitted to journals. *Appendix 2*
12. A paper detailing the study protocol for aim 2 has been submitted to journals. *Appendix 1*

The following results and outcomes have been realized –

1. On average, patients strongly agreed (4.6/5.0) that it would be useful to have a record of their mood over time, and to have MS CATCH screens available to view after appointments (5.0/5.0)
2. On average, clinicians strongly agreed that MS CATCH is useful (4.4/5.0), easy to use (4.7/5.0), and likeable (4.7/5.0).
3. Qualitative feedback from patients resulted in the addition of key features, including a free text field at the end of both surveys for additional comments (to provide context to their responses), as well as change in frequency of surveys to monthly to reduce burden. Clinician feedback influenced resources for patients and widget design, and workflows for distributing the summary display.

Aim 2. To evaluate effectiveness of MS CATCH vs. usual care on care of depression.

This is in progress. Planned timeline: 6 months – 30 months.
Six clinicians have been enrolled.

Aim 3. To measure “treatment adherence” to MS CATCH over one year of use.

This is in progress. Planned timeline: 6 months – 30 months.
Six clinicians have been enrolled.

What opportunities for training and professional development has the project provided?

Nothing to Report

How were the results disseminated to communities of interest

3 Stakeholder meetings have taken place to provide updates on progress, obtain feedback and strategize next steps in the project. Results of Aim 1 activities were used to inform tool design and refine it. The Aim 1 findings are being disseminated actively (papers submitted to journals).

What do you plan to do during the next reporting period to accomplish the goals?

We are currently in the recruitment phase and actively reaching out to potential participants. Both clinician and patient participants will use the tool and provide feedback on it. We will actively monitor their use of this tool during the clinical visit.

4. Impact

Despite its higher prevalence in people with MS, Depression remains underreported, under evaluated and undertreated. The MS CATCH tool enables patients to report their mood related symptoms at regular intervals (in between clinical visits) and makes these scores available to their clinician to view and follow-up if needed. Through a pilot study, we demonstrated that doing so increases depression screening and reporting in the clinical setting and gives clinicians an opportunity to address an often-ignored comorbidity.

The technological infrastructure that has been built for MS CATCH is highly customizable and can be easily adapted for other outcomes of interest and in non-neurological conditions as well. We have launched another study to monitor falls in patients, utilizing the same data pathways. Hence, we believe this tool could help improve quality of care in other conditions as well.

This tool could have far-reaching impact on society as a whole. It can be used for remote patient monitoring, education, encouraging lifestyle changes to ultimately improve population health. Clinicians can easily monitor thousands of patients without spending countless hours on collecting and tracking

information, enabling them to utilize their time more efficiently. Adding efficiency to the health system would ultimately lead to lowered cost of care for the general population.

5. Changes and problems

- a. Delay in IRB approval – To avoid delays in study approvals, we decided to obtain approval in two stages. Aim 1 related study activities were submitted and approved. Aim 2 and 3 have been submitted and approved.
- b. Due to COVID-19 related restrictions and precautions currently in place, we decided not to conduct focus groups. Thinkaloud sessions were instead conducted remotely via Zoom.
- c. Based on clinician and patient feedback – We changed the frequency of depression questionnaire to monthly instead of biweekly. This ensures there is a balance between clinician burden while maintaining a reasonable frequency of monitoring.

6. Products

1. MS CATCH In-Clinic Tool – Built as a clinical dashboard that launches from the UCSF EMR.
2. MS CATCH Mood Survey Tool – Built as a RedCap tool that surveys patient mood monthly and also visually displays for patients their results. MS CATCH In-Clinic Tool will pull data from this database to display in the EMR.
3. REDCap Study Database: A set of REDCap surveys were created and adopted for the purposes of the study. This database will be used to collect and store patient generated data.
4. Thinkaloud Sessions (audio recording) – These were conducted via Zoom and recorded for transcription purposes.
5. Manuscript #1: MS CATCH Study design and pilot results (under review)
6. Manuscript #2: MS CATCH Trial Design (under review)

7. Participants and other collaborating organizations

Person 1:

Name: Dr. Riley Bove

Project Role: Principal Investigator

Researcher Identifier (e.g. ORCID ID): 0000-0002-2034-8800

Nearest person month worked: 2 months

Contribution to Project: Oversees entire project, manages team members, guides study vision and execution

Person 2: “no change”

Name: Kanishka Koshal

Project Role: Program Manager

Person 3:

Name: Kyra Henderson

Project Role: Research Coordinator

Researcher Identifier (e.g. ORCID ID): 0009-0006-8350-0474

Nearest person month worked: 6 months

Contribution to Project: Aids in participant recruitment, scheduling meetings and project logistics

Person 4:

Name: Jennifer Reihm

Project Role: Plain Language Health Expert

Researcher Identifier (e.g. ORCID ID): x

Nearest person month worked: 3.5 months

Contribution to Project: Aids in participant interviews, language for consent forms, and survey language

Person 5:

Name: Narender Sara

Project Role: Lead Software Engineer

Researcher Identifier (e.g. ORCID ID): 0000-0003-4552-9832

Nearest person month worked: 7 months

Contribution to Project: Plan, build and test software infrastructure for the project, manage technical team

Person 6:

Name: Nicolette Miller

Project Role: Programmer

Researcher Identifier (e.g. ORCID ID): 0000-0001-8987-4908

Nearest person month worked: 7 months

Contribution to Project: Plan, build and test software infrastructure for the project

What other organizations were involved as partners?

The National Multiple Sclerosis Society graciously provided our team access to their database of care organizations and providers which was included in the MS CATCH Map widget. This helps clinicians identify mental health resources in the patients' vicinity.

8. Special reporting requirements

Nothing to Report

9. Appendices

- a. Study protocol manuscript: currently submitted and waiting reviewer comments
- b. Pilot study manuscript: compiling feedback from co-authors prior to submission

BMJ Open

A Pragmatic Phase II Clinical Trial to improve depression care in a real-world cohort of individuals with MS: MS CATCH Study Protocol

Journal:	<i>BMJ Open</i>
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Keywords:	Quality of Life, Clinical Trial, Multiple sclerosis < NEUROLOGY, Depression & mood disorders < PSYCHIATRY

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Note from the Editors: Instructions for reviewers of study protocols

Since launching in 2011, BMJ Open has published study protocols for planned or ongoing research studies. If data collection is complete, we will not consider the manuscript.

Publishing study protocols enables researchers and funding bodies to stay up to date in their fields by providing exposure to research activity that may not otherwise be widely publicised. This can help prevent unnecessary duplication of work and will hopefully enable collaboration. Publishing protocols in full also makes available more information than is currently required by trial registries and increases transparency, making it easier for others (editors, reviewers and readers) to see and understand any deviations from the protocol that occur during the conduct of the study.

The scientific integrity and the credibility of the study data depend substantially on the study design and methodology, which is why the study protocol requires a thorough peer-review.

BMJ Open will consider for publication protocols for any study design, including observational studies and systematic reviews.

Some things to keep in mind when reviewing the study protocol:

- Protocol papers should report planned or ongoing studies. The dates of the study should be included in the manuscript.
- Unfortunately we are unable to customize the reviewer report form for study protocols. As such, some of the items (i.e., those pertaining to results) on the form should be scored as Not Applicable (N/A).
- While some baseline data can be presented, there should be no results or conclusions present in the study protocol.
- For studies that are ongoing, it is generally the case that very few changes can be made to the methodology. As such, requests for revisions are generally clarifications for the rationale or details relating to the methods. If there is a major flaw in the study that would prevent a sound interpretation of the data, we would expect the study protocol to be rejected.

Title

A Pragmatic Phase II Clinical Trial to improve depression care in a real-world cohort of individuals with MS: MS CATCH Study Protocol

Authors

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Author contributions

Henderson: drafted manuscript
Koshal, Wijangco: collected preliminary data, revised manuscript
Reihm: trial design, conducted focus group interviews and interpreted results, revised manuscript
Feinstein, Mangurian, Doyle, Mallory, Guo, Oommen: contributed expertise from their respective fields through stakeholder feedback sessions and other avenues, revised manuscript
Sara, Miller: tool iterative development, revised manuscript
Lazar: created statistical analysis plan, revised manuscript
Bove: trial design, obtained study funding, drafted manuscript

For peer review only

ABSTRACT

Introduction: Depression occurs in over 50% of individuals living with multiple sclerosis (MS) and can be treated using many modalities. Yet it remains: under-reported by patients, under-ascertained by clinicians, and under-treated. To enhance these three behaviors likely to promote evidence-based depression care, we engaged multiple stakeholders to iteratively design a first-in-kind digital health tool. The tool, MS CATCH, closes the communication loop between patients and clinicians. Between clinical visits, the tool queries patients monthly about mood symptoms, supports patient self-management, and alerts clinicians to worsening mood via their EHR in-basket. Clinicians can also access a MS CATCH dashboard displaying patients' mood scores over the course of their disease, and providing comprehensive management tools (contributing factors, antidepressant pathway, resources in patient's neighborhood). The goal of the current trial is to evaluate the clinical effect and usability of MS CATCH in a real-world clinical setting.

Methods and analysis: MS-CATCH is a single site, Phase II randomized, delayed start, trial enrolling 125 adults with MS and mild to moderately severe depression. Arm 1 will receive MS-CATCH for 12 months, and Arm 2 will receive usual care for 6 months, then MS-CATCH for 6 months. Clinicians will be randomized to avoid practice effects. The effectiveness analysis is superiority intent-to-treat comparing MS-CATCH to usual care over 6 months (primary outcome: evidence of screening and treatment; secondary outcome: HADS-D scores). The usability of the intervention will also be evaluated (adoption, adherence, engagement, satisfaction).

Ethics and dissemination: University of California, San Francisco Institutional Review Board (22-36620). The findings of the study are planned to be shared through conferences and publications in a peer-reviewed journal.

Trial registration: NCT05865405

Keywords: depression, quality of life; bring your own device; mHealth; closed loop; Clinical trial; multiple sclerosis.

STRENGTHS AND LIMITATIONS OF THIS STUDY

Strengths

- A novel tool designed with extensive stakeholder engagement to deliver data from patients between visits to the point of care and to alert clinicians of severe depression in real-time
- Numerous resources made available to both patients and clinicians for comprehensive, behaviorally informed depression care in MS.
- A pragmatic trial design enrolling diverse people with MS with mild-moderately severe depression
- One delayed-start arm allowing 6 months of observing and defining “usual care”

Limitations

- Neurologists randomized to delayed start could experience contamination if some patients begin months 6-12 before others

INTRODUCTION

Despite high burden of illness, there is a large depression care gap for patients with Multiple Sclerosis (MS) who experience depression. Depression is prevalent among people with MS (PwMS): PwMS are 2-3 times more likely to be diagnosed with a depressive disorder than the general population, with depression affecting about 50% PwMS over the course of their lifetime.¹ Clinical guidelines for MS care include depression management, for which non-sedating antidepressant drugs, suicidal intent screening, and psychotherapy are all usually recommended.^{2,3} Yet despite the high prevalence of evidence-based screening and treatment modalities - depression in MS remains under-reported, under-evaluated, and under-treated.⁴

Barriers to reporting, evaluating and treating depression are many. To treat depression in the MS neurology clinic, it must be reported by the patient and screened for by the clinician, then it must be comprehensively evaluated to establish patient safety and implement interventions likely to be effective. In clinical settings, stigma may further reduce a patient's comfort with sharing their psychiatric symptoms.^{1,4} Further, the standardized validated tools for depression screening are seldom used to identify depression in MS, reducing the effectiveness of interventions.⁵ Treating depression in PwMS often requires a complex, individualized plan rather than a one size fits all approach. When other contributing MS specific conditions are not fully considered, such as fatigue, cognitive impairment, and urinary retention – these may interfere with the efficacy of treatments tested in non-MS patients and could worsen symptom burden.⁵ In addition, antidepressants are prescribed often at inadequate dose, duration and ineffective mechanism of action.⁶ After the visit, patients may face barriers to following through on treatment plans that they develop with their doctor, such as difficulties with access, insurance, or finding specialists close to home, as well as the many competing demands on their time. Finally, although better integration is associated with improved psychiatric care, integration between psychiatric and nonpsychiatric care in the electronic health record (EHR) is often low.⁷

MS-CATCH (Care technology to Ascertain, Treat, and engage the Community to Heal depression in patients with MS) is a behaviorally informed, digital health, closed-loop-intervention that seeks to overcome some of the aforementioned challenges (**Figure 1**). MS-CATCH was designed using several established principles. The first was an extensive process of human-centered design in all phases of development to refine the overarching infrastructure. To promote sustainability and generalizability, the tool was developed using industry standards, such as REDCap for electronic data capture,⁸ and Substitutable Medical Applications and Reusable Technologies (SMART) on Fast Healthcare Interoperability Resources (FHIR) application programming interfaces (APIs).⁹ Each individual care component and visualization was then developed and refined using extensive stakeholder engagement. Throughout, decisions were made based on how they might promote changes in behaviors likely to improve depression reporting, screening, comprehensive treatment and follow through. For this, the COM-B principles of behavioral change were followed. This extensive, iterative process is described elsewhere¹⁰⁻¹². In its final version, the tool was rated as easily implementable, useful, and valuable to screen for and catch depression and mood related symptoms in MS prior to the worsening health of a patient.

Trial Objectives. The hypothesis tested is if MS-CATCH reduces depressive symptoms in PwMS by closing the communication loop between patients and clinicians. The goal of this single-site pragmatic clinical trial is to evaluate the effectiveness of MS-CATCH that would inform effect size, trial duration and expected 'adherence' for a larger, multicenter trial. Trial outcomes include: behaviors intended to reduce depression, patient-reported depression scores, clinical diagnoses of depression, and adoption of/adherence to the tool.

METHODS AND ANALYSIS

Overall Study Design. MS CATCH is a Phase II 12-month pragmatic clinical treatment trial enrolling diverse PwMS with mild to moderately severe self-reported mood using simple stepped wedge design (Figure 2).

Patient and Public Involvement. Patients were involved in the design of the study as stakeholders.

Setting. The primary clinical setting is the UCSF MS and Neuroinflammation Center, which provides specialized care to over 5,000 adults with MS annually, and has an extensive track record of pivotal trials for MS,^{13 14} remote monitoring^{15,16} and treatment.¹⁷

Participants. MS clinicians and MS patients will be enrolled and sign written electronic informed consent forms. Clinicians will then be randomized 1:1 to Arm 1 or Arm 2 using an automated permuted block randomization scheme to start using MS CATCH.

Intervention. MS CATCH consists of a simple mood reporting tool (patient-facing electronic data capture of PHQ9) that can be accessed via a smartphone, tablet, or web browser. Responses then trigger real-time alerts delivered to the clinician's medical record inbox, who can then access a comprehensive dashboard featuring multimodal risk factors and interventions to be considered, as well as mental health resources, including for patient self-management and a map of clinicians local to the patient (Figure 1).

Design Rationale. Patient participation in the trial will last 12 months, with each participant receiving at least 6 months of the intervention. Randomization will occur by clinician, since (1) it is difficult to blind clinicians to tool use and (2) to prevent "contamination" (i.e., practice changes incurred as a result of using MS CATCH). The 6-month "usual care" period for the delayed start group will allow us to define "usual care" in a consistent way and to appropriately compare MS CATCH to usual care. This is important to do for a real-world clinic, given that the sparse guidelines for mood care in MS⁶ are heterogeneously followed in typical clinical practice.³ The 12-month trial will: (a) inform the feasibility of a larger RCT, and (b) allow us to account for a potential therapeutic lag between the time that interventions are recommended (e.g., consult talk therapist) and a treatment duration sufficient for effect (e.g., identify a therapist in-network, schedule intake, attend 12 weeks of talk therapy) has occurred. Further, (c) we will also be able to compare the effect of 6 vs. 12 months of tool use on depression outcomes, i.e., whether benefits incurred over months 6-12 exceed those over months 0-6 of tool use.

Patient recruitment, enrollment and screening. From the participating neurologists' practices, adult patients with MS – whether relapsing or progressive¹⁸ – with upcoming clinical visits will be pre-screened via chart review. Patients who fulfill the initial study inclusion criteria will be contacted by IRB-approved means (telephone or email). The study is also posted on clinicaltrials.gov. Interested patients will be scheduled for an enrollment visit with the study coordinator either in-person, or via telephone or Zoom (an institutionally-approved, HIPAA-secure, televideo platform^{9,10}). During this visit, they will complete a detailed informed consent (DocuSign, paper upon request) with the study team trained in ethical research conduct. In the rare event that there be concern, a potential participant's capacity will be evaluated using the University of California Brief Assessment of Capacity to Consent (UBACC).^{19,20} Patients who cannot or will not consent will *not be enrolled* as they would be unlikely to be able to adhere to the study protocol and personally respond to PROs. Any participant will be able to discontinue the study at any time.

Inclusion/Exclusion criteria. Once they sign the informed consent, participants will be asked to complete a PHQ-9 questionnaire. This tool is a validated, self-administered survey used in the field of mental health that assists clinicians in objectively assessing the severity of depression. It has sensitivity and specificity values, and is comprised of the 9 criteria that comprise the DSM-IV depressive disorder diagnosis²¹. Given its validity and its brevity, this will be the screening tool to confirm inclusion criteria and monitor patients remotely. Patients with mild (scores: 5-9), moderate (scores: 10-14) or moderately severe (scores: 15-19), depression will be included. Given existing literature,^{22,23} we anticipate that about half of the clinical patients will fall in these categories. Participants with severe depression (i.e., PHQ9 scores 20+) will result in the study team alerting their primary clinician to support safety; they will not be enrolled. Other inclusion/exclusion criteria are presented in Table 1. Patients meeting these criteria will be formally enrolled in the study.

Plans to recruit a diverse research cohort. To ensure demographic representativeness, enrollment will be capped at 65% White non-Hispanic patients to ensure that trial participants reflect the composition of the diverse clinic population (30-35% of whom identify as Black, Hispanic, Asian or “other”), and that the data are generalizable to the experiences of diverse PwMS. Enrollment is expected to be approximately 2:1 to 3:1 female to male, reflecting the clinical MS population. *Language.* The REDCap mood survey can be viewed on the patient’s device in the other major languages spoken by UCSF patients, namely Spanish or Cantonese *Device access.* To reduce the likelihood of excluding participants based on socioeconomic status, participants who do not have a smartphone, laptop, tablet or computer in their homes will be provided with a device and/or wifi card for the duration of the study. In this pragmatic trial there may be differences in patient characteristics reflecting clinicians’ individual practices (these will be included as covariates in the analyses). Inclusion will not be based on ambulatory disability/EDSS; patients will only be excluded if they are not able to use the tool.

Study blinding. In this pragmatic trial, neither patients, clinicians nor patient-facing research coordinators will be blinded to tool use due to the difficulties of blinding, including lack of a comprehensive ‘sham’ tool. To minimize potential for bias, all patient-reported and physician-reported scores will be automated using REDCap to reduce any potential for subjective scoring. Further, the coordinator conducting chart review to extract data (such as depression mention in the clinical note, prescriptions filled, etc.) will be blinded to clinician group assignment. Finally, data analysis will be performed by our statistician who is blinded to treatment assignment until the dataset is locked and analyzed.

Study Procedures. Clinical visits (whether in person or via telemedicine) will occur per usual routine at baseline, 6 months and 12 months. PROs will be collected via REDCap at these timepoints as well as 3M and 9M. Tool use will be monitored over the course of the study. This will include: patient response to prompts to the REDCap mood survey, clinician launching of the MS-CATCH clinician-facing dashboard. After the 12-month visit, an exit interview will be performed and participants will rate the tool. To ensure participant safety, patients with severe HADS-D scores at screening or participants with severe depression or suicidality at any point during the trial will be referred to the study psychiatrist (Dr. Mangurian) for expedited psychiatric care.

Study Measures to be Collected

Baseline covariates from EHR.

Demographics: age, sex, race, ethnicity, employment, education, and zip code to estimate socio-economic status indicators²⁴ and travel distance from clinic.

Clinical: MS history (symptom onset, date of diagnosis, MS type), co-morbidities, medications. Clinical disability measures will include the Expanded Disability Status Scale (EDSS^{25,26} and if not available within the past year, a validated e-PR-EDSS²⁷) and Symbol Digit Modalities Test (SDMT).

Psychiatric history: history of psychiatric and/or substance used disorder diagnoses, history of treatment (psychological and psychotropic medications).

Health literacy: eHealth literacy (eHEALS)²⁸ measures patients’ combined knowledge, comfort, and perceived skills at finding, evaluating and applying electronic health information to health problems.

Patient-reported quantitative *social network assessment* validated in MS (Social network assessment tool.²⁹

Trial Outcomes: Effectiveness

Primary: Intermediary behavioral outcomes (Process of Care). At the baseline, 6 and 12 month visits, the study record will be updated for data regarding mood evaluation and care. Data about care utilization from the UCSF EHR and other institutional medical records will be complemented by the patient exit survey, since some aspects of clinical care (e.g., out of pocket talk therapy) will not necessarily figure in the EHR. Major categories are described in **Table 2**.

Secondary: Mood (collected at baseline and at 3,6,9 and 12 months)

Hospital Anxiety Depression Scale (HADS). The HADS is widely used to assess psychological distress in non-psychiatric patients. It consists of two subscales, measured via 14 items: seven items for the Anxiety subscale (HADS-Anxiety) and seven for the Depression (HADS-Depression) subscale.³⁰ It has been validated for use in MS demonstrated satisfactory psychometric properties in several different populations.² Each item is scored on a response scale with four alternatives ranging between 0 and 3 and a higher score indicates greater anxiety or depression. **Thresholds.** The clinically meaningful HADS-D depression cut-off in MS is ≥ 8.0 .² The minimal clinically important difference (MCID) in HADS D has not been defined in MS but in other chronic conditions ranges 1.5-17.^{31,32} We will use 1.7. Finally, the standard deviation of HADS-D scores in a recent survey of PwMS was 3.7.³³ We will also evaluate other patterns of HADS-D improvement, including categorical (reduction in HADS-depression scale to <8 ; reduction in HADS-depression scale by 2+ points).

Exploratory:

Self-efficacy: Patient self-efficacy at managing a chronic disease will be self-reported at the baseline, 6 month and 12 month visits.³⁴ Clinician self-efficacy at evaluating and managing mood will be evaluated at their enrollment and final patient out, on a 1-5 Likert scale as per.³⁵

Mood. Mini-International Neuropsychiatric Interview (MINI): This is a 15-minute structured assessment of depression that can be administered by a non-clinician. This will be an exploratory endpoint given project focus on the behavioral modifiers of this ultimate clinical outcome (depression).⁴ Changes in PHQ9 will also be evaluated.

Other Patient-Reported Outcomes, Possible contributors to mood/covariates. Fatigue (Modified Fatigue Index³⁶), sleep (Pittsburgh Sleep Quality Index),³⁷⁻³⁹ social engagement (Short form Oxford Participation and Activities Questionnaire⁴⁰) and work participation for employed participants (Impact on Participation and Autonomy⁴¹) will also be collected.

Trial Outcomes: Tool Evaluation.

These use an implementation science framework to evaluate tool adoption, engagement, adherence and satisfaction and are depicted in **Table 3**.

Data collection and storage

Data will be collected through the institutionally secured HIPAA-compliant REDCap portal.⁸ All information relating to patients will be stored behind the UCSF firewall.

Statistical Plan and Data Analysis

The Full Analysis Set (FAS) comprises all doctors to whom trial intervention has been randomly assigned 1:1 to Arm 1 or Arm 2 by block randomization. According to the intent-to-treat principle, doctors will be analyzed according to the intervention arm they were randomized to and strata (Employment Status: Part-Time ($<50\%$). V. Full-Time ($\geq 50\%$)) they have been assigned to during the randomization procedure. The primary behavioral effectiveness outcome is depression screening at 6 months. The following statistical hypotheses will be tested to address the primary objective: $H_0: \theta_1 = 0$ vs. $H_A: \theta_1 \neq 0$ where θ_1 is the difference in proportions between Usual Care and CATCH at 6 months. The primary analysis to test this hypothesis and compare the two treatment arms will use the adjusted chi-square analysis via the Rao-Scott design that adjusts for clustering of doctors via SAS v.9.4 proc surveyfreq stratified by employment status (Full-time v. Part-Time ($<50\%$)). A similar approach will be undertaken examining other effectiveness outcomes: HADS scores, MINI scores, and self efficacy.

We will also use mixed effects linear (for continuous outcomes) and logistic (for dichotomous secondary outcomes) regression analyses. We will flexibly model trajectories by testing whether including quadratic or cubic terms for time (up to 5 visits: baseline, 3 months, 6 months, 9 months,

12 months) or random slopes for individuals improve the model fit and include them if indicated by a significant ($P<0.05$) likelihood ratio test. The overall difference will be assessed using an F-test and post-estimation t-test in SAS v 9.4. Using this approach, we can assess whether intervention improvement occur during different time-periods to assess duration of use of CATCH. We will present the results with and without a multiple testing adjustment when comparing across time-periods. All of the secondary outcomes will be assessed using this mixed modeling approach. We will also adjust for important covariates (e.g, PHQ9 levels, age, sex, EDSS), as well as explore potential interactions between intervention arm and PHQ9, and other covariates. We will also assess the model fit (e.g., residuals) and assess whether transforming the outcomes (e.g., log transformations) provides the best fit. For all results, the estimates and associated 95% confidence intervals will be reported.

We will also use mixed effects linear (for continuous outcomes) and logistic (for dichotomous secondary outcomes) regression analyses. We will flexibly model trajectories by testing whether including quadratic or cubic terms for time (up to 5 visits: baseline, 3 months, 6 months, 9 months, 12 months) or random slopes for individuals improve the model fit and include them if indicated by a significant ($P<0.05$) likelihood ratio test. The overall difference will be assessed using an F-test and post-estimation t-test in SAS v 9.4. Using this approach, we can assess whether intervention improvement occur during different time-periods to assess duration of use of CATCH. We will present the results with and without a multiple testing adjustment when comparing across time-periods. All of the secondary efficacy outcomes will be assessed using this mixed modeling approach. We will also adjust for important covariates (e.g., PHQ9 levels, age, sex, EDSS), as well as explore potential interactions between intervention arm and PHQ9, and other covariates. We will also assess the model fit (e.g., residuals) and assess whether transforming the outcomes (e.g., log transformations) provides the best fit. We will also assess whether the baseline values are subject to confounding by isolating within person changes. The benefit of mixed-effects models is that they produce unbiased estimates even when some individuals have missing observations, adjust for differential loss to follow-up, accommodate irregular time measurements, and account for clustering of individuals, as required in this study. For all results, the estimates and associated 95% confidence intervals will be reported.

To evaluate the tool itself, descriptive statistics (mean, standard deviation, median and inter-quartile range for numeric will be used.

Sample size considerations: 125 patients will be enrolled in each arm to ensure at least 60 patients with PHQ9>5 in each arm who can participate in the trial (i.e., 250 total sign informed consent and 125 total participate), with 50 anticipated completers in each arm (82% retention at 6 months). In our experience, this sample size is ample to identify significant predictors of adherence to a digital health intervention and to ensure reasonable completers should there be unforeseen low study retention.^{15,42} Based on our preliminary data, we expect a small design effect of 1.72 with an intraclass correlation coefficient of 0.45 ($1+0.45*(17-1)$). Using this design effect, our effective sample size is 118, which results in at least 80% statistical power to detect an improvement in our primary outcome, **depression screening**, from 25% in the usual care arm to 50% in the MS CATCH arm at the 6-month visit using a chi-square test assuming a 2-sided a level of 0.05.

For our secondary outcome, change in HADS-D, an effective sample size of 114 (57 per group, assuming design effect of 1.72, see above) will provide approximately 80% statistical power to detect a clinically meaningful difference of 1.7 at 6 months, assuming a change from baseline in HADS-D of 1.7 for Arm 1 (MS CATCH intervention), and no change with usual care (Arm 2), with common standard deviation of 3.2. This sample size calculation was based on a 2-sample independent t-test using Stata 15.1, assuming an alpha level of 0.05. We did not adjust for multiple tests given in the calculation given that HADS-D is a secondary outcome. However, we plan to present results adjusted for multiple testing using the Bonferroni correction to maintain the family-wise alpha level at 0.05.

The detailed *Statistical analysis plan (SAP)* will include details about handling of potential missing data, including consideration of multiple imputation if more than 5% of the data is missing at random. It is possible that the data is not missing at random, but rather missing not at random, and we will explore this possibility. To account for possible effects of crossover and contamination, we will consider performing marginal structural modeling as a sensitivity analysis. Though, given that the primary endpoints of the study occur at 6 months before Arm 2 crosses over to MS CATCH, we do not expect this to be a major limitation. The SAP will follow the guidelines provided by CONSORT.

Ethics and Dissemination

The trial received ethical approval from the University of California, San Francisco (UCSF) Institutional Review Board (22-36620) and is registered to ClinicalTrials.gov (NCT 05865405). Both patient and clinician participants will provide informed consent, either electronically, through a secured online portal, or on paper, prior to study enrollment. Results from the study will only report aggregated deidentified patient information and will be published through peer-reviewed journals and presented in conferences. Deidentified data will be shared with qualified investigators upon reasonable request. Adverse events will be reported through the UCSF IRB.

DISCUSSION

The MS CATCH Phase II trial has innovative design features. It will test a novel, closed-loop method of delivering information about patient function directly to the clinical workflow, enabling a range of evidence-based interventions - as opposed to any specific treatment/intervention. Each element of the tool is designed with input from intended users to promote behaviors likely to improve depression care. The trial will enroll diverse individuals with MS experiencing depression and will anchor interventions within the existing clinical workflow. Finally, this symptom treatment trial is long enough to support adoption of behaviors and titration of treatments likely to be effective. While pilot testing revealed each of these features was determined to likely improve depression care, to our knowledge such an approach has not been taken in MS symptom trials.

One strength of the study is that it avoids a “one-size-fits-all” model for symptom treatment in MS, focusing not on a specific new device (e.g., app or neurostimulation) or medication (e.g., antidepressant), but rather on information flows between patients, clinicians, and depression-relevant resources. This is by design, though does carry the risk that it will not be possible to identify one particular feature that was most effective. A trial design limitation is the difficulty of blinding clinicians. If enrollment is protracted for individual clinicians in Arm 2, then it is possible that contamination could happen if a participant returns for their 6 month MS CATCH visit while the clinician is still seeing participants for their baseline, non-MS CATCH visits. Also, since there is a fairly wide gap between adherence/satisfaction scores in pilot testing and adoption/effectiveness of a tool in the real world, it is difficult to predict the eventual adoption and impact of MS CATCH. A final possible limitation is tool scalability. While the tool does require institutional approvals to launch within the UCSF EHR, the design elements could be readily repurposed using the standard technologies to support other institutions’ requirements.

From a design perspective, it is possible that patients and clinicians who, during the design phase of MS CATCH, wanted to visualize key aspects of the neurological examination (e.g., cognitive test), end up over the course of the study prioritizing instead patients’ reports of social support or their activity levels to determine course of action, and find that the cognitive test was not in practice useful for their treatment recommendations. Modules and data types that are not felt to be useful by at least 50% of users could be de-prioritized in a version for broader dissemination. If there is discrepancy between patient and clinician

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users, separate visualizations could be envisaged in the future. These qualitative insights will inform the need for tool modifications prior to wider dissemination and a controlled trial.

This study hopes that MS CATCH can close the gap in communication and resource distribution to address mood related symptoms and depression in patients with MS will result in better care for this population. This study will serve as guidance for an expansion into a multi-site RCT study and implementation of these protocols into the UCSF MS clinic.

For peer review only

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Table 1. Major inclusion and exclusion criteria for patients

Inclusion criteria	Exclusion criteria
• Diagnosis of MS (relapsing or progressive) by 2017 McDonald Criteria⁴³ • Ages 18 -80 (by going much beyond 80, you run the risk of including cognitively compromised people with another diagnosis) • PHQ9 score of 5-19 • Any MS therapy, or no treatment • California resident to enable clinical telemedicine visits if warranted during the study visit	• Cognitive dexterity or visual impairment (typically defined as corrected acuity less than 20/70) that, in the opinion of the study neurologist (RB), would put the participant at risk or limit their ability to adhere to the study protocol • Inability to provide informed consent • Psychotic disorders: bipolar disorder, schizophrenia, schizoaffective disorder, substance abuse • Another co-morbid CNS diagnosis eg. TBI

Abbreviations: MS: multiple sclerosis; PHQ: Patient Health Questionnaire 9

Table 2: Major categories of care utilization and follow through

Source(s)	Data Type	Target Outcomes
Medical record/ patient survey (q6M) prospectively collected by a data analyst blinded to clinician/ patient randomization	Hospitalization, ER visits, Outpatient Visits Orders: Medication prescriptions and refills, Referrals to psychiatrist, psychotherapist, social worker, neuropsychologist, other behavioral health professional; Other medical services. Non-medical approaches recommended (join support group or club)	
	Behavioral outcomes: EHR neurologist notes: Mood screening, mood evaluation, mood treatments	% visits where mood screening was documented by the clinician in the EHR comprehensive depression evaluation: % depression risk factors evaluated at each patient visit (goal: 80%) preventive care recommendations: % visits in which applicable care was recommended (goal: 80% visits), and the %applicable interventions recommended per visit.
Patient facing tool analytics		Patients: Mood reporting (do patients report mood to their doctor)
Patient exit interview	Behavioral outcomes: referrals completed, prescriptions filled, activity level Missed work, work productivity	Patient follow through: 6M follow-through of mutually agreed upon interventions (e.g., start medication, schedule visit with local therapist) to improve mood, as per ¹⁰

Table 3. Implementation Science-informed framework for evaluating the trial intervention: MS CATCH.

	Patients	Clinicians
Adoption (uptake)	% who respond to the survey during the initial month of study (goal 80%),	% patient-clinician dyads who use the in-visit dashboard at the 6M follow
Primary		
Additional	% approached for the study who initially agreed to “adopt” MS CATCH	% willing to participate in the study
Engagement (sustained use)	% who continued to use the patient-facing tool at least quarterly (goal 60%)	% clinician-patient dyads in Arm 1 who use the in-visit dashboard at the 12M clinical visit (goal 60%).
Adherence	% depression-reporting prompts adhered to per participant on their patient-facing tool (goal 75%)	
	% adhering to >75% depression prompts (goal 75%).	
	trial retention at 3, 6, 9, and 12 months	
Satisfaction	Net Promoter Score ⁴⁴	Net Promoter Score ⁴⁴
	12 item mHealth Satisfaction Questionnaire. ⁴⁵	
	Qualitative (Exit interview, or early exit): patterns of use, barriers to use, and ask for feedback about the tool’s functionality; if applicable, dropout and to elicit any additional qualitative feedback on their depression care.	Qualitative: satisfaction with the tool (also using perceived barriers to use, feedback about the tool’s functionality, and to estimate the overall burden of use of MS CATCH.

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Figure 1. MS-CATCH, a closed-loop depression management tool for use in MS.

Legend. Between clinical visits, at 4-week intervals, participants complete a brief mood survey through the secure UCSF REDCap portal. These surveys are emailed to ensure accessibility from any device at any time. Scores indicating severe mood trigger an alert directly to their physician's EHR in-basket. During the medical encounter or between visits, the physician can access a dashboard via one click on the EHR that displays regarding a participant's current mood status. Clinicians can then open BRIDGE through the EHR to see treatment recommendations, participant health information, contributing risk factors, and resources local to the patient.

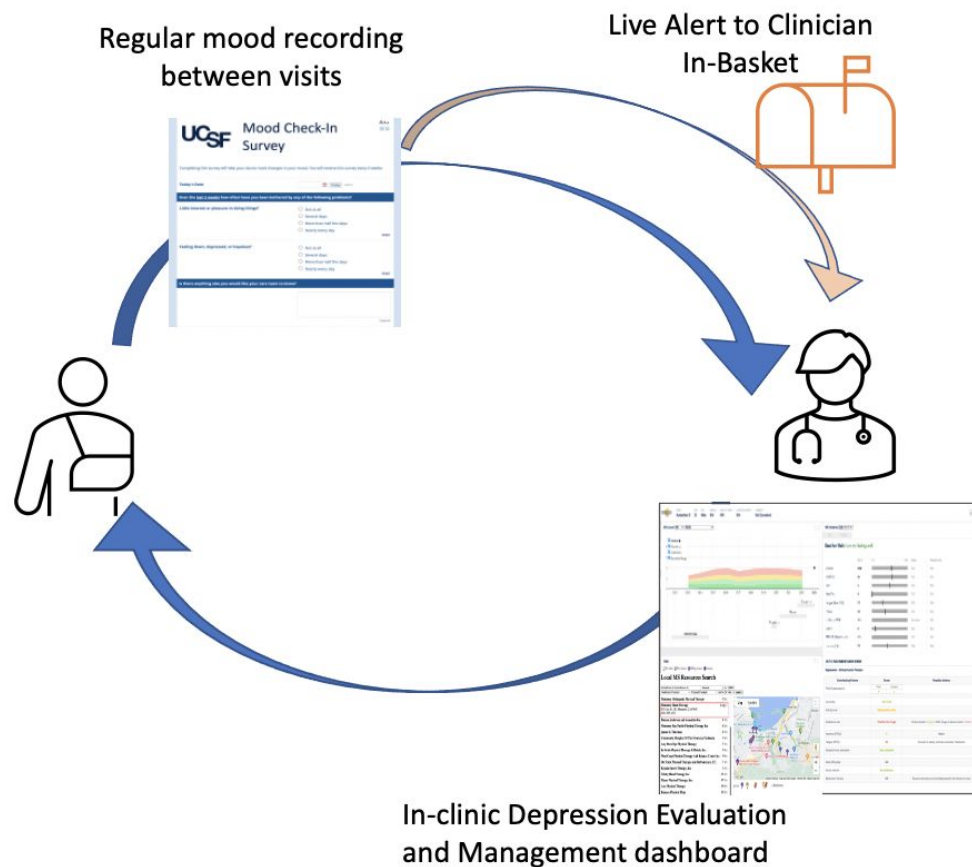
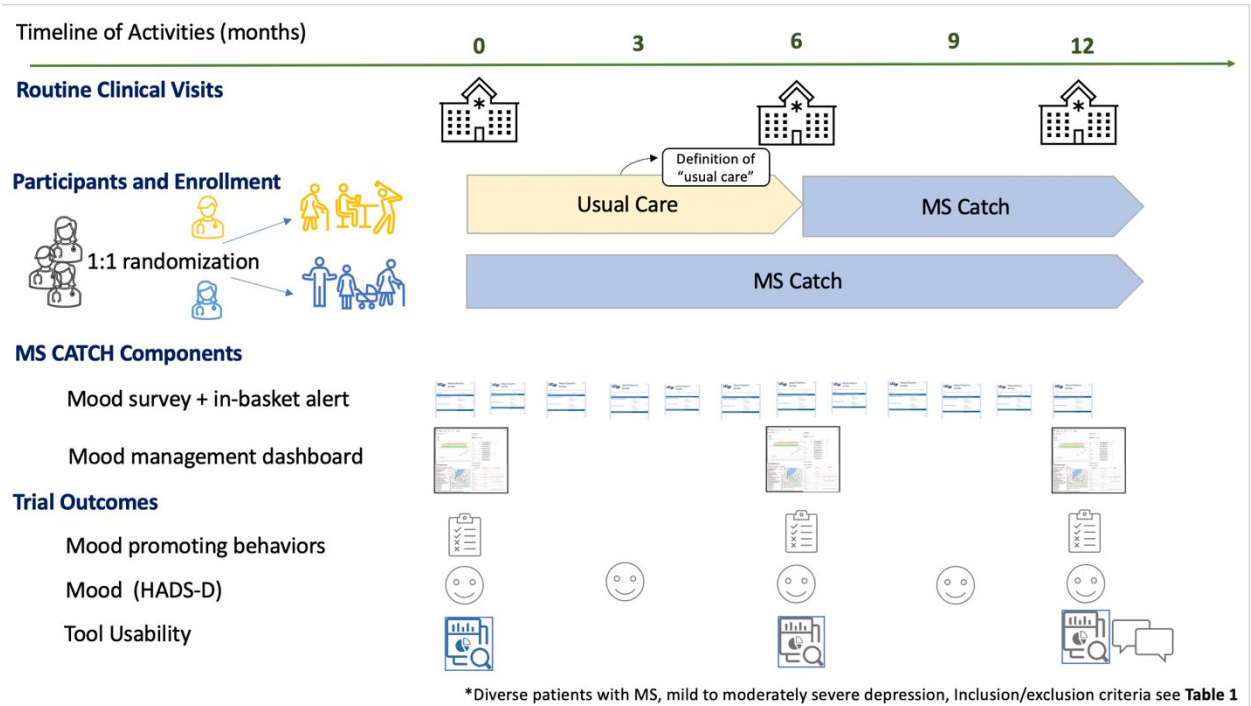


Figure 2. Overview of Trial Design and Outcomes. A 12-month, delayed-start, randomized Phase II clinical trial evaluating the efficacy (behaviors, mood) and usability of a closed loop tool for comprehensive real-time depression care in MS.



Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRIT reporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Gøtzsche PC, Altman DG, Mann H, Berlin J, Dickersin K, Hróbjartsson A, Schulz KF, Parulekar WR, Krleža-Jerić K, Laupacis A, Moher D. SPIRIT 2013 Explanation and Elaboration: Guidance for protocols of clinical trials. BMJ. 2013;346:e7586

		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	3
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	n/a
Protocol version	#3	Date and version identifier	1
Funding	#4	Sources and types of financial, material, and other support	1
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	1

1	Roles and	#5b	Name and contact information for the trial sponsor	1
2	responsibilities:			
3	sponsor contact			
4	information			
5				
6				
7				
8	Roles and	#5c	Role of study sponsor and funders, if any, in study	1
9	responsibilities:		design; collection, management, analysis, and	
10	sponsor and funder		interpretation of data; writing of the report; and the	
11			decision to submit the report for publication, including	
12			whether they will have ultimate authority over any of	
13			these activities	
14				
15				
16				
17	Roles and	#5d	Composition, roles, and responsibilities of the	n/a, no committees
18	responsibilities:		coordinating centre, steering committee, endpoint	
19	committees		adjudication committee, data management team, and	
20			other individuals or groups overseeing the trial, if	
21			applicable (see Item 21a for data monitoring	
22			committee)	
23				
24				
25				
26				
27	Introduction			
28				
29				
30	Background and	#6a	Description of research question and justification for	5
31	rationale		undertaking the trial, including summary of relevant	
32			studies (published and unpublished) examining	
33			benefits and harms for each intervention	
34				
35				
36				
37	Background and	#6b	Explanation for choice of comparators	5
38	rationale: choice of			
39	comparators			
40				
41				
42	Objectives	#7	Specific objectives or hypotheses	5
43				
44	Trial design	#8	Description of trial design including type of trial (eg,	6
45			parallel group, crossover, factorial, single group),	
46			allocation ratio, and framework (eg, superiority,	
47			equivalence, non-inferiority, exploratory)	
48				
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51	Methods:			
52	Participants,			
53	interventions, and			
54	outcomes			
55				
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57				
58	Study setting	#9	Description of study settings (eg, community clinic,	6
59				
60				

		academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	6,7
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	6
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	n/a, no modifications
Interventions: adherence	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	7,8
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	n/a
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	8
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	20 (figure 2)
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	10
Recruitment	#15	Strategies for achieving adequate participant enrolment	6

to reach target sample size

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Methods:
Assignment of
interventions (for
controlled trials)

Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	6, 9, n/a, no blinding between patients, clinicians, nor patient facing research coordinators
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	n/a, no blinding between patients, clinicians, nor patient facing research coordinators
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	6,8
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	6,8, no blinding between patients, clinicians, nor patient facing research coordinators
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	n/a, no blinding between patients, clinicians, nor patient facing research coordinators

Methods: Data
collection,
management, and
analysis

Data collection plan	#18a	Plans for assessment and collection of outcome,	8
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baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol

Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	10
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	9
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	8
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	9
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	9
Methods:			
Monitoring			
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	n/a, no formal DMC

1	Data monitoring:	#21b	Description of any interim analyses and stopping	10
2	interim analysis		guidelines, including who will have access to these	
3			interim results and make the final decision to terminate	
4			the trial	
5				
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8	Harms	#22	Plans for collecting, assessing, reporting, and	10
9			managing solicited and spontaneously reported adverse	
10			events and other unintended effects of trial	
11			interventions or trial conduct	
12				
13				
14	Auditing	#23	Frequency and procedures for auditing trial conduct, if	n/a
15			any, and whether the process will be independent from	
16			investigators and the sponsor	
17				
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20	Ethics and			
21	dissemination			
22				
23				
24	Research ethics	#24	Plans for seeking research ethics committee /	10
25	approval		institutional review board (REC / IRB) approval	
26				
27	Protocol amendments	#25	Plans for communicating important protocol	10
28			modifications (eg, changes to eligibility criteria,	
29			outcomes, analyses) to relevant parties (eg,	
30			investigators, REC / IRBs, trial participants, trial	
31			registries, journals, regulators)	
32				
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35				
36	Consent or assent	#26a	Who will obtain informed consent or assent from	6
37			potential trial participants or authorised surrogates, and	
38			how (see Item 32)	
39				
40				
41	Consent or assent:	#26b	Additional consent provisions for collection and use of	n/a
42	ancillary studies		participant data and biological specimens in ancillary	
43			studies, if applicable	
44				
45				
46	Confidentiality	#27	How personal information about potential and enrolled	9
47			participants will be collected, shared, and maintained	
48			in order to protect confidentiality before, during, and	
49			after the trial	
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52				
53	Declaration of	#28	Financial and other competing interests for principal	1
54	interests		investigators for the overall trial and each study site	
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57	Data access	#29	Statement of who will have access to the final trial	9
58			dataset, and disclosure of contractual agreements that	
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			limit such access for investigators	
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation		n/a
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions		10
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers		n/a
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code		10
Appendices				
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	1, attached in separate document	
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	n/a, no biological specimens	

Notes:

- 5d: n/a, no committees
- 11b: n/a, no modifications
- 13: 20 (figure 2)
- 16a: 6, 9, n/a, no blinding between patients, clinicians, nor patient facing research coordinators
- 16b: n/a, no blinding between patients, clinicians, nor patient facing research coordinators
- 17a: 6,8, no blinding between patients, clinicians, nor patient facing research coordinators
- 17b: n/a, no blinding between patients, clinicians, nor patient facing research coordinators
- 21a: n/a, no formal DMC

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- 32: 1, attached in separate document
- 33: n/a, no biological specimens The SPIRIT Explanation and Elaboration paper is distributed under the terms of the Creative Commons Attribution License CC-BY-NC. This checklist was completed on 04. July 2023 using <https://www.goodreports.org/>, a tool made by the [EQUATOR Network](#) in collaboration with [Penelope.ai](#)

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A Closed-loop Digital Health Tool to Improve Depression Care in Multiple Sclerosis: Iterative Design and Cross-Sectional Pilot RCT Impact on Depression Care

Authors

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Study Funding

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Abstract

Introduction. People living with Multiple Sclerosis (PwMS) face a higher likelihood of being diagnosed with a depressive disorder than the general population. Though many low-cost screening tools and evidence-based interventions including medications exist, depression in PwMS is under-reported, under-ascertained by clinicians, and under-treated. The goal of the current project was to design a closed-loop tool to improve depression care for these patients. It would support regular depression screening, tie into the clinician at the point of care, and support shared decisionmaking and comprehensive follow up. After an initial development phase, the project involved a proof-of-concept pilot randomized clinical trial (RCT) validation phase and a detailed human-centered design (HCD) phase.

Methods and analysis. During an initial development phase, the technological infrastructure of a clinician-facing point-of-care clinical dashboard for MS management (BRIDGE) was leveraged to incorporate features that would support depression screening and comprehensive care (MS CATCH prototype). This linked a patient survey, in-basket messages, and the clinician dashboard. During the Pilot RCT phase, a convenience sample of 50 adults with MS recruited from a single MS Center with PHQ-9 scores of 5-19 (mild to moderately severe depression) were enrolled. During the routine MS visit, their clinicians were either asked vs. not asked, to use MS CATCH to review their scores, and care outcomes were collected. During the HCD phase, MS CATCH components were iteratively modified based on feedback from stakeholders: PwMS, MS clinicians, interprofessional experts.

Results. MS CATCH is a closed-loop tool linking three distinct features designed to support mood reporting and ascertainment, comprehensive evidence-based management, and ultimately clinician and patient self-management behaviors likely to lead to sustained depression relief. In the pilot RCT (n=50 visits), visits in which the clinician was randomized to use MS CATCH had a greater percentage of notes documenting a discussion of depressive symptoms than the visits when MS CATCH was not used (75% vs. 34.6%, $X^2 P= 0.0042$). During the HCD phase, 45 PwMS and clinicians/other experts participated in the design and refinement. The final testing round included 20 PwMS and 10 clinicians including five not affiliated with our health system. Most scoring targets for likeability, usability, including perceived ease of use and perceived effectiveness, were met. Net Promoter Scale was 50 for patients and 40 for clinicians.

Discussion. Created with extensive stakeholder feedback, MS CATCH is a closed-loop system aimed to increase communication about depression between PwMS and their clinicians, and ultimately improve depression care. Pilot findings showed evidence of enhanced communication. Stakeholders also advised on trial design features of a full year-long DOD-funded feasibility and efficacy trial, now underway.

Ethics and dissemination. University of California, San Francisco Institutional Review Board. The pilot RCT is registered under 18-26148 and the HCD process is registered under Aim 1 of the full trial, 22-36620.

Trial registration. The MS CATCH RCT is registered with clinicaltrials.gov: NCT05865405.

Keywords. depression, quality of life; bring your own device; mHealth; closed-loop; Clinical trial; multiple sclerosis.

Introduction

About 50% people with MS (PwMS) have a depressive disorder, and PwMS are 2-3 times more likely to be diagnosed with a depressive disorder than the general population.[1] Yet despite the prevalence of depression in PwMS, the low-cost tools available to screen for depression, and evidence-proven, society-recommended pharmacologic and non-pharmacologic treatment modalities[2] [3] - depression in MS remains under-reported, under-evaluated,[4] and under-treated.[5] The barriers to these clinical goals include time constraints during clinical visits,[6] stigma and discomfort discussing psychiatric symptoms,[7] insufficient antidepressant medication dose, duration or mechanism of action,[8] inadequate attention to other MS symptoms (fatigue, cognitive impairment, urinary retention) that could interfere with mood and worsen symptom burden,[4] as well as patient difficulty following through on treatments due to difficulties with access, insurance, or finding specialists close to home, as well as the many competing demands on their time.

A closed-loop[9, 10] intervention could close these gaps in care and represent a pragmatic approach to addressing the suboptimal treatment of depression in real-world MS settings. Such a tool could support relevant clinical information flow from patients to clinicians at the point of care, and back to patients to support patient-centered care. Such a system would not focus on a specific one size-fits-all treatment or intervention modality (e.g., social intervention) or on a specific proprietary mood app, but rather could support developing a complex plan individualized for each patient's symptoms, goals and capability. To accomplish this, the tool should efficiently deliver patient-reported mood symptoms to clinicians in line with the "5 rights"[11] (right information, to the right person, in the right format, through the right channel, at the right time in the workflow). Further, the tool must promote the behaviors (e.g., reporting, screening, treatment recommendations and follow through with timely refills or referral scheduling) likely to lead to mood improvements. For example, the "Capability, Opportunity, and Motivation" for Behavioral change (COM-B)[12] model, a hub in the center of Michie's Behavioral Change Wheel (BCW),[12] can help inform a patient's intention to engage in a planned behavior, which is considered the best predictor of that behavior.[13, 14] The COM-B approach, and individual intervention functions, have been successfully applied to facilitate behavioral change in PwMS.[15] Finally, this tool should seek to streamline workflows and streamline care within an existing care team (neurologist, nurse, interprofessional staff) and system of care (informatics, care delivery, and payment structure). Once developed, even after extensive multidisciplinary stakeholder input, a digital health solution must be thoroughly socialized within a health system to increase adoption.

Prior studies have shown feasibility of monitoring patient mood longitudinally in PwMS, and good concordance between patient reports and clinical depression.[16] For example, the three-month pilot COACH-MS RCT (NCT03335618, n=21 PwMS),[17] showed that it was feasible, and acceptable, to monitor patients' bothersome symptoms (mood, ambulation, and bladder) and to act on them clinically in near real-time (coaching patients to address these).[17] This intervention showed some preliminary efficacy in supporting behavioral change[12, 15] likely to address depression – including in one case, recognition of and urgent hospitalization for suicidality. A proposed closed-loop[10] intervention could further deliver data on patient function directly to the clinician at the point of care to support effective response.

The current manuscript details a three-phase endeavor designed to develop a comprehensive, closed-loop system for monitoring and thoroughly treating depression to be tested in real-world clinical settings: *MS CATCH* (Care technology to Ascertain, Treat, and engage the Community to Heal depression in PwMS). A prototype was developed. It was then piloted in a clinical setting to obtain preliminary cross-sectional efficacy data on a fundamental premise, namely that visualization of patient mood during the clinical encounter would improve clinical attention to mood during that visit. Having ensured that the tool was satisfactory to patients and clinicians and that its use did indeed improve attention to depression in the pilot study, the tool was then refined using an extensive process of human centered design (HCD[18, 19]).

Methods

Initial technical build.

Members of the primary research team led earlier engagement efforts that informed MS CATCH development, namely, creating the BRIDGE dashboard concept,[20] testing the acceptability of Patient Reported Outcomes (PROs) in a point-of-care MS clinical dashboard (MS NEUROSHARE),[21] and developing a closed-loop

reporting system that collects and synthesizes data at the point of care (MS FIT)[22]. Key learnings were incorporated in the MS CATCH prototype used for the current study, visualized in *Supplementary Figure 1*.

BRIDGE[20].

This is a technologically scalable, institutionally approved, workflow friendly, cross-disease, modular precision medicine platform. BRIDGE launches from within a patient's encounter from the Epic EHR at UCSF using industry standard integration (see *Figure 1* and *Supplementary Table 1*), delivering a seamless experience for clinicians.[20] BRIDGE was designed using an extensive process of Human Centered Design (HCD),[18, 19] and the prototype for MS CATCH (Care technology to Ascertain, Treat, and engage the Community to Heal depression in PwMS) was further refined from this technical scaffolding, with further input from seven different MS clinicians and their patients, for the purposes of depression monitoring and treatment. A patient-facing REDCap survey collects patient mood (PHQ-9) every four weeks, with data visualized both in the MS BRIDGE dashboard as well as triggering a clinician's inbox message for worsening mood. The mechanism by which MS CATCH is postulated to work is by facilitating communication flows likely to support intended users' COM-B behaviors (patient: reporting and follow through; clinician: evaluating and recommending) likely to lead to symptom improvement. With regard to usability, the intended users, i.e., both clinicians and patients, can each access it with one click (*Figure 1*). The tool accesses and visualizes data that are currently available in various disparate sources (EHR, patient diaries, publicly accessible websites), with the substantial innovation that they are presented here in one comprehensive and streamlined format.

MS NEURO-SHARE.

This prototype designed for a collaborating health system integrated a patient-facing PRO app with an EHR-based clinician-facing dashboard. Patient participants cited the perceived value of thinking about and recording information prior to their appointments, noting how it impacted discussions with their clinicians, adding that co-viewing information with the doctor put doctors and patients on the same page and promoted a conversation of equals. Clinicians perceived patients' prospectively collected mood scores as more sensitive, accurate and comprehensive than a patient's recall during the visit, and felt these could improve value and promote clinician engagement.[21]

Proof of Concept Pilot Randomized Controlled Trial

Research Setting and Participants.

Design. Cross-sectional, randomized-controlled pilot study

Setting. The primary clinical setting was the UCSF Center for MS and Neuroinflammation, which specializes in providing care to over 5,000 adults with MS annually, and has an extensive track record of pivotal trials for MS,[23] [24] remote monitoring[25, 26] and treatment.[27]

Participants. MS clinicians were enrolled using a signed electronic consent form. Then, from the participating neurologists' practices, adult patients with an MS diagnosis scheduled for upcoming in-person and video neurology visits were contacted prior to the clinic visit by the study coordinator via email and phone call. Interested patients were scheduled for an enrollment visit whether in-person, or via telephone or Zoom (an institutionally-approved, HIPAA-secure, televideo platform). During this visit, they completed a detailed informed consent via DocuSign. Once patients signed the informed consent, participants were asked to complete a series of PROs including the PHQ-9 scale via a secure REDCap link. This could be accessed on any device with wifi or cellular data capabilities. This validated, self-administered tool assists clinicians in objectively assessing the severity of depression. It has sensitivity and specificity values of 88%, and contains the nine criteria that comprise the DSM-IV depressive disorder diagnosis (see[28]). Patients with scores of five and above (mild depression (5-9), moderate (10-14), moderately severe (15-19), severe (20-27)) met study criteria and were then enrolled in the pilot study. All participants were computer literate. Enrollment was capped at 50 individuals meeting criteria. Full inclusion criteria are summarized in *Supplementary Table 1*.

Study Procedures.

The PRO data obtained from the patient participants populate the BRIDGE dashboard in real-time. Patient visits were randomized 1:1 using a simple randomization scheme in which the clinician was or was not asked by study team to launch BRIDGE during the participant's visit. For those not using BRIDGE, the visit proceeded as a usual clinical visit. Clinicians were reminded to launch BRIDGE via text or email prior to the patient appointment

when applicable, and neither clinician nor patient participant were blinded to the intervention. Patients continued to be recruited until a target $n=50$ had met inclusion criteria and were seen in the clinic. For participants with PHQ-9 scores of 19 or above, even if their clinician was not asked to use BRIDGE, the clinician was informed of their score near the conclusion of the clinic visit to ensure safe treatment of the patient. At the conclusion of the study visit, both clinician and patient feedback about the tool was solicited. During the proof-of-concept pilot, MS CATCH was used once during the visit in real time. For the full RCT, MS CATCH will be utilized by the patient participant monthly.

Trial Outcomes.

Usability: Participant feedback on tool.

At the end of the study visit, patients were asked for feedback on the tool. There were two main prompted questions: “Tell us (with illustrative examples) of what worked well and what didn’t, with regards to BRIDGE, during your appointment.” This question was asked of both patients and clinicians, while “Please explain in detail, why it was or wasn’t useful for you to report your mood symptoms before the visit” was just addressed to the patients. A small set of questions presented on the Likert scale were used to assess likeability and usefulness for patients and clinicians.

Efficacy: Effect of the tool on attention to depression.

At the end of the study, each clinical encounter was reviewed by a team member blinded to treatment assignment, with an eye to whether mood was mentioned in the clinical visit. After review was finished by one team member, another team member audited the report. Any disagreements were reviewed by a third party.

Ethical approvals.

This study was approved by the UCSF Institutional Review Board 18-26148.

MS CATCH Tool Refinement: Stakeholder engagement and intended user input over 6 months

Study Design.

Human-centered design (HCD) is a process that holds at its center the needs of the intended users. During the MS CATCH refinement phase, the overall goal was to finetune and optimize the intervention by partnering with patient and clinician users, and multidisciplinary stakeholders in a sequence of iterative feedback sessions to inform and validate design decisions (*Table 1*). Since to our knowledge, features assembled into the MS CATCH prototype had never before been available at the point of care in a clinically actionable format for depression treatment in MS, it was important to verify that the workflow and displays promoted the COM-B factors,[12] and to simplify the display into the features most likely to drive adoption of the tool and support depression care. To maximize the likelihood that the tool would be adopted and effective, it was evaluated using the Health IT Usability Evaluation Model[29] (Health ITUEM). This model integrates multiple usability theories including the Technology Acceptance Model (TAM) and evaluates both subjective and objective outcomes. While refining the critical data and visualization elements, as well as technological and clinical workflow aspects, the four key variables proposed by Mathews et al[30] for digital health tool validation were examined to determine whether the tool (a) reflects HCD principles, and (b) is likely to engage patients. These factors are: usability, effectiveness, learnability/ease of use, and likeability.

Sequential Methods, with iterative technological modifications.

Over a 9-month period between September and June, sequential activities were conducted as outlined in *Table 1*.

Stakeholder advisory group.

This group was convened and led by members of the primary research team. The primary research team comprised investigators with a track record of collaboration as well as expertise in both scientific and technological aspects of this project, including MS clinical trials (Bove), digital tools to evaluate and treat cognition and mood in MS[17] (Bove, Feinstein), psychiatric care for underserved populations and innovations in treatment of psychiatric conditions in diverse settings (Mangurian),[31-38] implementation science (Mangurian), statistics (Lazar; will generate a formal Statistical Analysis Plan), patient engagement (Bove, Reihm),[19-21] human-centered design (HCD) of digital tools (Reihm, Bove, Sara, Miller)[19-21] and launching an institutionally and technologically sophisticated, scalable, cross-disease platform from the EHR at UCSF (Bove and BRIDGE team). Stakeholders also included a patient champion Dr. Judith Sheridan, patient advocacy group leader Linda

Glassel, NMSS Northern California Chapter President, MS nurse expert Alicia Mallory, RN, social worker Marianne Doyle LISCW and neurologist Dr. Chu-Yueh Guo.

Participants.

MS clinicians and other experts were identified within the UCSF MS clinic and the investigators' broader professional network. Adults with MS were recruited from the UCSF MS Center by the study team. All participants provided informed consent to test the tool and provide preliminary data.

Table 1. The sequence of iterative feedback and human-centered design development leading to tool optimization over 9 months, including activities, participants, and outcomes.

Group	Objectives
Stakeholder Advisory Group	Mtg 1. Study kickoff: refine project goals, inform patient and clinician engagement protocols, and advise on potential clinical, technological or ethical challenges. Mtg 2. Tool ready for Clinical Trial: review the tool optimization and scores (see below) and confirm that the intervention is ready for launch in the trial. Mtg 3. Planned after trial start: review enrollment and early qualitative feedback once clinical trial activated; and develop a roadmap for the transition plan.
Discovery Interviews	Process: Conducted 1:1 interviews with patients and clinicians, separately, via the UCSF Zoom platform and led by members of the primary research team with expertise in engagement and HCD. The sessions were recorded to ensure that all feedback was captured. Goal: To Ideate new features; map all features and data types to COM-B principles with the goal of facilitating behavioral outcomes (reporting, evaluating, treating)[12] likely to support depression reduction. Outcomes: Feedback was used to generate a list of features to be modified (e.g., enhanced, clarified, removed, simplified) by the developer. Clarifying feedback was also elicited on perceived <u>ease of use</u> and <u>usefulness</u> to ensure that only the components most likely to be effective would be used.
Thinkaloud Session	Process: After modifications in response to the discovery interviews, during these 1:1 sessions the tool was launched and tested to further refine and clarify each feature.[39] Here, patients were presented with specific scenarios for entering data into the platform (e.g., using the tool after a difficult life event vs for monitoring during periods of emotional stability) and the way they engaged with the tool was observed. Clinicians were exposed to interactive live demonstrations. Outcomes: Both patients and clinicians were asked to <u>prioritize the individual data types</u> by scoring their " <u>perceived usefulness</u> ," so that only the key drivers of behavioral changes were retained. If any specific data scored low (i.e., not perceived as useful), then they would either be removed/modified in the visualization.
Final Tool Scoring	Process: The final version of MS CATCH was scored by 20 diverse patients with MS and 10 MS clinicians (five from UCSF, five from non-UC, recruited from a larger network of neurologists) using established scales presented in <i>Table 4</i> . Clinicians scored usability with the System Usability Scale (SUS), both patients and clinicians scored usefulness and ease of use (Health ITUES based questions), as well as likeability (a single question and a Net Promoter Score (NPS)).[40, 41] Any domains scoring below target would trigger another round of iterative edits.

Ethical approvals.

Activities during this Phase (HCD phase) were approved by the UCSF IRB (UCSF IRB #22-36620).

Results

Proof of Concept Pilot Randomized Controlled Trial

Participants.

Out of 200 patients contacted, 106 agreed to participate in the study. Of these, 50 (47.2%) met the inclusion criteria of a PHQ-9 > 4; they were cared for by 6 participating physicians. Distribution of PHQ-9 scores was: n=26 mild depression (5-9), n=16 moderate depression (10-14), n=5 moderately severe depression (15-19), and

n=3 severe (20-27). Patients were then randomized to visits where the BRIDGE dashboard was used (n=24), and not used (n=26). All participants were contacted prior to their clinical visit, which occurred between May and December of 2021. This visit is where the MS CATCH intervention was used. The cohort included 40 females (80%) and 10 males, ages 25-75 (mean 50.46, SD 13.0), including individuals with all MS subtypes (32 RRMS, 9 PPMS, 1 PRMS, 6 SPMS, 1 unspecified, 1 MS likely).

Table 2. Demographic information for MS CATCH proof of concept pilot RCT.

Diagnosis (RRMS: N, %)	Sample Size (N)	Age range* (yrs)	Sex (Females: N, %)
32 (64%)	50	25-75 (mean 50.46, SD 13.0)	40 (80%)

Tool Usability.

Mean *likeability* score was 4.3/5 for patients (93% patient participants agreed/strongly agreed that they liked the tool) and 4.4/5 for clinicians (100% clinicians agreed/strongly agreed that they liked the tool).

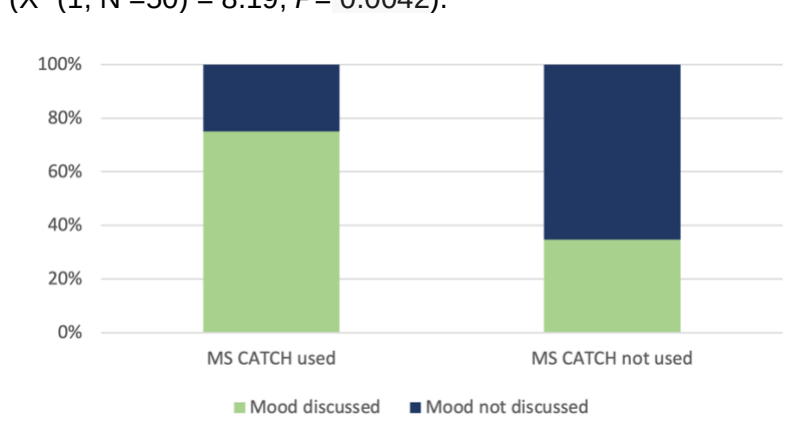
Perceived usefulness: [40, 41] Among clinicians, 100% reported that the tool increased their attention to the patient's mood – *particularly for patients with mild to moderate symptoms* which might otherwise have been missed. Clinicians provided some specific feedback on how to further customize the dashboard, suggesting it would be better to have the categorical components of the PHQ-9 rather than just the raw score (n=3/6).

Among patients, 71.4% reported feeling that it was useful to report their mood related symptoms prior to the visit. In qualitative feedback, many patients reported that filling out the mood survey ahead of time gave them the opportunity to reflect on their own feelings: "It set the tone, upfront, about how I was feeling" ... "It's helpful for me to think about assessing my mood in a structured way" ... "was useful because it made me stop and reflect" "it opened the door to explain how... new MS symptoms are affecting my mood", and so on.

Tool effectiveness.

For the patients with a PHQ-9 score of five or greater, visit notes documented a discussion of depressive symptoms in 75.0% of visits where MS CATCH was used vs. 34.6% of visits where it was not used ($X^2 (1, N = 50) = 8.19, P = 0.0042$; **Figure 1**). One patient was referred to psychiatry for suicidal ideation.

Figure 1. MS CATCH Pilot RCT Cross-sectional Effectiveness. Visit notes documented a discussion of depressive symptoms in 75.0% of visits where MS CATCH was used vs. 34.6% of visits where it was not used ($X^2 (1, N = 50) = 8.19, P = 0.0042$).



MS CATCH Tool Refinement

Study participants

Overall, 45 individuals provided feedback on the tool during successive phases of development. These are summarized in *Table 3*.

Table 3. Demographic information for each round of interviews during the MS CATCH Intervention Refinement

Phase (cohort, round #)	Sample size (N)	Age range* (yrs)	Sex (Females: N, %)	Clinical Context
Discovery Interviews: Patients	5	30 – 57.6	3 (60%)	MS
Discovery Interviews: Clinicians	5	N/A	4 (80%)	MS (MD, NP, MSW)
Thinkalouds: Patients	7	30.4 – 66	6 (85.7%)	MS
Thinkalouds combined with Final Tool Testing: Clinicians	Thinkalouds: 5 Tool testing: 10	N/A	6 (60%)	MS
Final Tool Testing: Patients	20	29-63	15 (88.2%)	MS

MS = multiple sclerosis, * = (if applicable). N/A = not applicable

Discovery and Thinkaloud Sessions: Selected findings

Detailed findings and scores from each round of engagement, as well as iterative development steps, are presented in *Supplementary Materials* and summarized here. During the *Discovery Interviews* ($N=5$ patients, $N=5$ clinicians), each tool component was found to be useful and usable. A number of features and data types were identified that mapped to the COM-B principles of behavior change, and these resulted in design changes and interventions promoted to address potential boosters or blockers (*Supplementary Table 2*). For example, patients universally felt that the PHQ-9 should be delivered monthly if not more often, despite concerns by the study team that it would be too burdensome. The patient-facing survey was edited to support free text entry and addition of language at end of survey informing patients who score >15 to seek care urgently, since their care team may not see the score for 36 hours, and instructing patients to seek immediate care if experiencing a mental health crisis. During the *Thinkaloud sessions* ($N=7$ patients, $N=5$ clinicians), some patients articulated concern for how answers might be interpreted by their clinicians, for example, concern about sending up unnecessary “red flags” with their survey answers as symptoms addressed on the survey can overlap with MS symptoms. Relatedly, the free text box proved to be a popular design feature as it presents an opportunity to offer context for potentially concerning or MS symptom-related survey answers. Additional features were noted to be of value; for example, *neighborhood walkability* was specifically identified by patients as useful context for their clinicians to have within the clinical decision support view. Patients also universally expressed interest in having dashboard views available in a summary display for reference following appointments. All surveyed preferred an electronic summary format distributed through the patient portal (MyChart) as opposed to an alternative format that wasn’t integrated with their EHR portal. Clinician feedback led to a reduction in the visual “wordiness” of the original clinical decision support widget. One decision that could not be accommodated was the ability to include patient insurance information which substantially influences prescribing choices and referral decisions – since there is unfortunately no “ground truth” source for this information.

Final Changes Made to Tool before Scoring.

The patient survey was further developed to include an in-survey pop-up directing patients who screened positive for suicidal intent to seek immediate medical care (with contact information), a catalogue of mental health resources at the end, and a companion patient-facing mood tracker displaying the patient’s longitudinal mood survey results. On the dashboard side, the clinical decision support screen was further refined to be less “visually overwhelming”.

Qualitative feedback on the closed-loop system.

Clinician qualitative feedback on the potential impact of MS CATCH on the care delivery experience and quality of conversations with patients and caregivers ranged from appreciation for the intervention’s holistic approach, to concern that limited visit times will constrain the dashboards’ seemingly limitless potential.

- “Patients will feel empowered to make decisions using the information.”

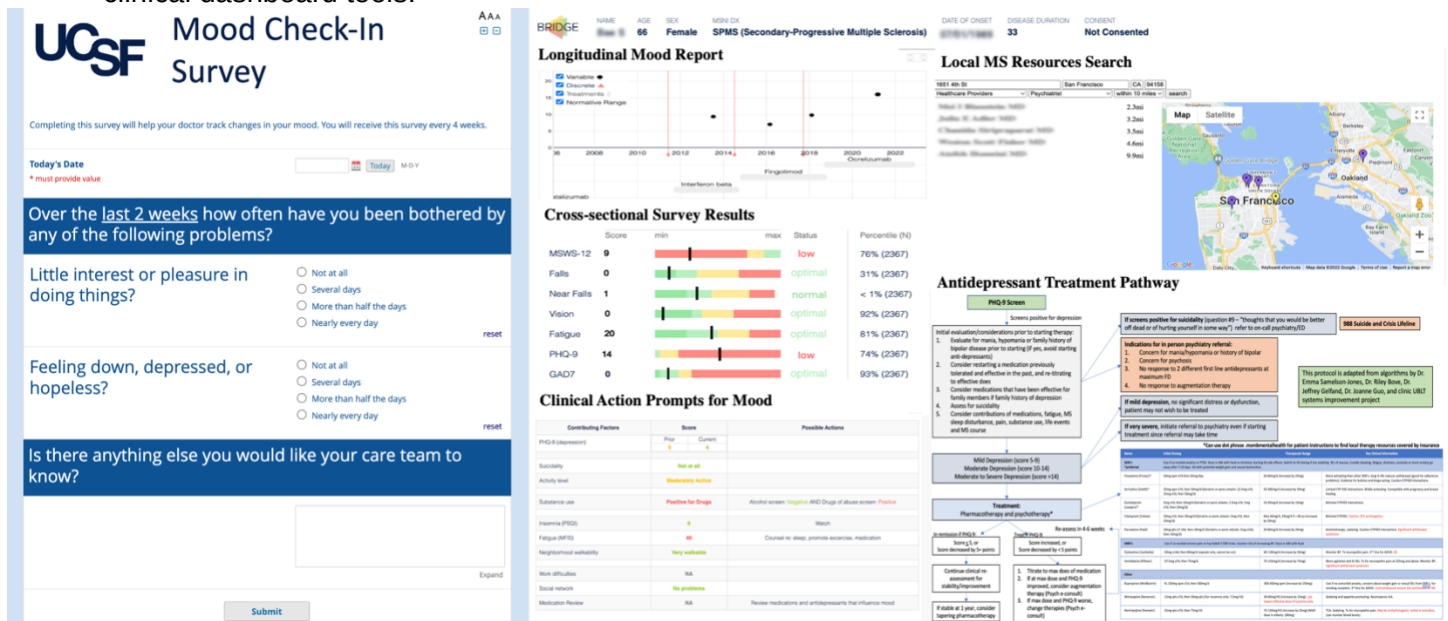
- “The value comes from physicians being able to see the patient’s trajectory, and from patients being able to have a longitudinal view.”
- “It will allow me to come into visits with more of a plan.”
- “While [BRIDGE] may not be useful for every problem, it can be valuable for high stakes symptoms (depression, falls).”
- “Feel like it gives me more to offer my patients.”
- “Reinforces what we should do.”
- “Helps to have an objective measure of symptom worsening. Is more reliable than past notes”.

Description of the Final MS CATCH prototype.

The final prototype is displayed in Figure 2.

Figure 2. Components of the MS CATCH Tool.

- Patient-facing survey and log.** Survey is easily accessible through email. PHQ-9 scores of 15 or more trigger an alert to the patient’s MS clinician’s EHR in-basket. *Patient resource:* The patient’s response history and resources relevant to depression self-management can be viewed at the end of the survey (see Supplementary Figure 2.)
- Clinician-facing dashboard.** The comprehensive mood evaluation and treatment dashboard launches from the EHR. *Patient resource:* This dashboard can be copied and pasted into the clinical notes as well as the patient’s After-visit summary to access at the end of the visit and between visits.
- Closed-loop system:** Diagram summarizing integration of the patient survey, in-basket messaging, and clinical dashboard tools.



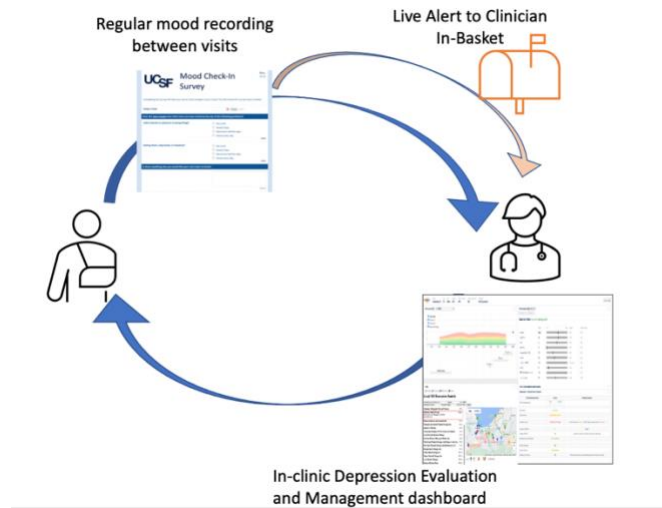


Figure legend.

The patient-facing survey. built and customized in REDCap, can launch from any device (smartphone, tablet or computer). It includes a short PHQ2-9 survey ascertaining mood in the prior four weeks, as well as an optional free-text box allowing patient to provide more context to their mood. **Patient summary.** At the end of the survey, mood scores are visually displayed along with a list of mental health resources, including a pop-up with resources for urgent mental health care triggered by severe scores. The survey's look and feel can be customized by patients (e.g., font size).

The In-visit Dashboard built and customized using the UCSF MS-BRIDGE architecture,[42] launches in one click from the Epic EHR and consists of several “widgets” that integrate and visualize data from multiple sources. The patient's survey-reported mood is displayed in a longitudinal widget for monitoring over time, as well as in a cross-sectional widget along with other PROs and functional assessments to support comprehensive evaluation. The treatment widget provides a useful reference for recommended monitoring of mood using PHQ-9, when to refer to psychiatry (revised from Goldman Consensus Protocol[43] by our UCSF psychiatrists and MS clinicians), as well as a chart of typical doses and cautions for commonly used antidepressants. The clinical action prompt widget displays comprehensive evidence-based action prompts to review contributors to depression as well. This integrates multiple complementary data streams relevant to depression in MS beyond patient mood reports and medications, such as fatigue levels or social network structure.[44] Combining these factors could enable an MS patient and their clinician to understand how these factors contribute to mood. The widget also integrates comprehensive evidence-based interventions to guide shared decision-making about depression treatment informed by the patient's condition; this can include: cognitive behavioral therapy (CBT),[3] lifestyle interventions, antidepressants, and considering social/community determinants of health. Extending beyond traditional one-treatment-modality-per-intervention models, multimodal treatment options are grounded in behavioral health as well as in up-to-date psychiatric care. We have preliminary evidence that this can be effective for changing behaviors likely to reduce symptom burden.[17] The local MS resources widget overlays the patient's home address with a list of the National MS Society-recommended MS-specific resources (psychotherapists, PT, OT, etc.) available across California. Since clinicians cannot be familiar with the varied interprofessional experts practicing across Northern California (wide catchment area for the Clinic),[45] displaying resources local to the patient's community could help reduce barriers to accessing local mental health and other rehabilitative care. **Patient-facing summary.** Visualizations (e.g., graph of mood over time, action item checklist) derived from the in-visit dashboard can be added to the clinical note as well as the patient's visit summary which allows for visual feedback to patients on their function and what self-management options are available.

In-basket messaging. A critical feature of the closed-loop approach is that surveys with concerning PHQ-9 scores above 15 trigger an alert to the MS clinician's in-basket, allowing for timely follow up within the usual care workflow, including an urgent referral to psychiatry.

Final Tool Scoring

A convenience sample of adults with MS (n=20) and clinicians (n=10) took part in final tool testing. Of participating clinicians, five practice at external (non-UCSF affiliated) institutions, and five are affiliated with UCSF. Target and achieved results are presented in *Table 4*.

Table 4. Final tool scoring by patients (N=20) and clinicians (N=10): Likeability and Usability. Prespecified targets and achieved results are presented; bolded results are at or above target.

	Tool	Patients (N=20)		Clinicians (N=10)	
		Target	Result	Target	Result
Likeability	Single question (“Do you like this tool?”) graded on a Likert scale* Metric: score ≥ 4 (agree/strongly agree)	80%	75%	80%	100%
	Net Promoter Score (NPS)**: “how likely are you to recommend this tool to another patient with MS/clinician?”[46]	Good: >0; favorable: >20; excellent: >50	50	Good: >0; favorable: >20; excellent: >50	40
Usability	System Usability Scale (SUS): a rapid, valid, scalable industry standard, reliable with small sample sizes	---	--	75 (68 is average)	78 (SD 11.8)
Perceived Usefulness	Health ITUES-based questions for perceived usefulness[40, 41] Metric: score ≥ 4 (agree/strongly agree)	80%	88%	100%	95%
Perceived Ease of use	Health ITUES-based questions for perceived ease of use[40, 41] Metric: score ≥ 4 (agree/strongly agree)	80%	97%	100%	100%

* Likert Scores ranged 1 (strongly disagree) – 5 (strongly agree)

** NPS responses (0 – 10 scale) were calculated by subtracting the percentage of detractors (those who scored 0 to 6) from the percentage of promoters (those who scored 9 or 10).

Patient assessment ratings exceeded goals in nearly all categories. Despite a patient NPS of 50 which is considered excellent, slightly fewer (75%) than the goal of 80% agreed/strongly agreed the tool is likeable (mean 4.25, SD 1.12). Of those (n = 5) who scored the tool ≤ 4 with regard to likeability, nearly all (n = 4) were neutral (score of 3). Reasons varied from lack of personal applicability, “Mood symptoms are due to MS, not depression,” and “I have a lot of anxiety, but not depression,” to survey design, “I don’t like the multiple-choice options,” to formatting “Font is small.” Concrete follow-on actions taken by the development team in response to this feedback were:

- Increasing the default survey font size, in addition to giving patients the option to adjust the font independently.
- Adding a note above the free text box indicating it can be used to add comments or clarify answers.
- Coaching physicians on how to communicate with patients about the survey, including how it can help detect anxiety and mood symptoms that may or may not be MS-related.

Similarly, clinician ratings exceeded goals in nearly all categories. A clinician NPS of 40 indicated strong favorability in terms of recommending to peers. Perceived usefulness was slightly under goal at 95%. While all but one clinician agreed/strongly agreed the tool is useful (mean 4.35, SD 0.75), one rated the tool ≤ 4 citing concerns around limited bandwidth and lack of financial incentives/reimbursable mechanisms for clinicians to address mood between clinical encounters. This feedback echoes concerns noted during discovery interviews about visit time limitations and the need for complementary workflows to ensure patient mood issues can be

monitored in a timely fashion, with the assistance of multidisciplinary staff (RN, MSW), and elevated to physicians as needed.

Discussion

Depression is a serious comorbidity in MS that is associated with increased risk of disability progression,[47] yet it remains severely undertreated: by one estimate, two thirds of individuals meeting the clinical criteria for major depressive disorder receive no antidepressant medications [48]. Worse, depression is often missed altogether by neurologists – even when it is severe and accompanied by suicidal ideation.[49, 50] We iteratively and extensively piloted and developed a closed-loop intervention designed to improve reporting, screening, and treatment of depression in a cohort of clinical patients with MS. The preliminary data presented here support our key premise underlying this closed-loop approach[9], that delivering reliable information about a patient's mood in an interpretable, visual format to the clinician would increase the likelihood that depression was detected (including, in one case, suicidality), and addressed in the clinical encounter. Further, our robust process of HCD and tool evaluation allowed us to maximize the likelihood that this tool would be adopted, by ensuring it met stringent goals of being likeable, easy to use, and perceived as being effective.

We are not aware of other closed-loop tools developed to support depression care in MS that are integrated with the EHR. Distinct from other mood apps on the market, the patient self-report directly connects to the clinician's in-basket so that the information can be efficiently streamlined. In full clinical use, the patient facing survey would be distributed once per month, and clinicians will not be reminded to launch BRIDGE. Studies have generally shown that integration between psychiatric and non-psychiatric care in the EHR is often low; better integration is associated with improved psychiatric care.[51] In the current study, we showed that viewing patients' self-reported mood at the point of care improved attention to depression in the clinical notes. This of course does not inform follow-through on this intention. To that end, our three-month pilot COACH-MS RCT (NCT03335618, (n=21 PwMS) showed that monitoring and responding to patients in real-time[17] was feasible, acceptable, and showed preliminary effect on behavioral change[12, 15] suggesting that sustained monitoring and feedback can promote behavioral change.[17]

After development, implementation into clinical workflows represents the final goal of health-related tools. From prior experience developing platforms for the clinical encounter, it was clear that socialization of a tool is a critical step. For patients, knowing that information about their mood will tie back to their care team and translate into improved attention to their care is an important component of tool use, as is the ability to self-monitor using the survey results. Further, direct actionable steps were implemented based on patient feedback, such as providing a list of resources at the end of the survey to reduce the activation energy required to access resources during a depressive episode. Similarly, clinicians are more likely to use and recommend a tool if they know that patients will have completed their surveys;[52] and more likely to want access to patient-generated data if it is clinically actionable. Integrating comprehensive management resources will support individualization of the treatment plan rather than “one size fits all” treatment interventions.

Many treatment trials for depression have to date focused on “one size fits all” approaches testing a specific intervention or combination of interventions. Novel approaches tested within MS include sequential blocks of medications[53] as well as combinations of behavioral and pharmacological interventions.[54] Extending beyond usual screening and care components (such as asking about moods retrospectively), MS CATCH will comprehensively visualize the other functions contributing to depression, including other conditions (e.g., sleep) and unmet social needs (e.g., substance use counseling, neighborhood unsafe for walking exercise). These will support *customized action prompts* to help patients self-manage, and clinicians tailor treatments, anticipate challenges, and make social and behavioral health referrals.

Some limitations were evident in the design, and compromises had to be made. For example, the PHQ2-9, while widely adopted as a screening tool, may not be particularly specific. For example, in response to the “constant bother” question, one participant responded: “MS is a constant bother”. This tool was selected however because of its brevity, extensive validation across multiple conditions including MS, and because it is comprised of the nine criteria that are identified in the DSM-IV depressive disorder diagnosis.[28] Another limitation is the lack of information about which insurance is accepted by mental health professionals. This unfortunately limits

actionability in terms of referrals to mental health professionals in the United States. For the resources map, we chose to focus on mental health professionals near the patient who were considered to have expertise for individuals with MS, but we also included a link to a website that includes insurance information to allow cross-checking. A third challenge is scalability. Key technological and clinical features were intentionally selected to ensure that the tool's modular infrastructure could be scaled to other symptoms, conditions and clinical settings. Technological factors designed to support scalability include (1) quality and content of static visualizations that can be disseminated broadly regardless of a clinic's technology, and (2) optimizing the industry technological standards used for the build so that the code can be shared for clinicians in other health settings (e.g., other MS centers using Epic EHR). However, the integration of the build into other health systems is ultimately dependent upon governance and motivation internal to that system.

MS CATCH is a comprehensive, low-burden closed-loop platform designed to reduce depression severity and prevalence in PwMS by supporting real-time communication and alerts, shared decision-making, and action prompts for comprehensive, personalized interventions. The research activities summarized here suggest that MS CATCH is likeable and useful, and that it improves attention to mood in individual clinic visits. In a complementary pilot study, we previously showed that remotely monitoring mood can lead to timely intervention.[17] Altogether, these findings support a planned randomized single-center clinical trial evaluating its effect on behaviors that support depression reporting, ascertainment and care. A similar model can be used to improve other clinical symptoms in MS, and for managing other chronic medical conditions with high prevalence of depression.

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Author contributions

Henderson: drafted manuscript

Koshal, Wijangco: collected preliminary data, revised manuscript

Reihm: trial design, conducted discovery interviews and interpreted results, revised manuscript

Feinstein, Mangurian, Doyle, Mallory, Guo, Oommen: contributed expertise from their respective fields through stakeholder feedback sessions and other avenues, revised manuscript

Sara, Miller: tool iterative development, revised manuscript

Bove: trial design, obtained study funding, drafted manuscript

Conflicts of interest

None declared

Abbreviations

BCW: behavioral change wheel

COM-B: capability, opportunity, and motivation for behavioral change

EHR: electronic health record

Health ITUEM: health IT usability evaluation model

HCD: human centered design

IRB: institutional review board
 Mtg: meeting
 MS: Multiple sclerosis
 MS CATCH: Multiple sclerosis care technology to ascertain, treat, and engage the community to heal depression in PwMS
 MS FIT: Multiple sclerosis falls insight track
 NPS: net promoter score
 OT: Occupational therapy/therapist
 PHQ-9: patient health questionnaire - 9
 PPMS: Primary progressive multiple sclerosis
 PRMS: Progressive relapsing multiple sclerosis
 PRO: patient reported outcome
 PT: Physical therapy/therapist
 PwMS: people with multiple sclerosis
 RCT: randomized clinical trial
 REDCap: research electronic data capture
 RRMS: Relapsing remitting multiple sclerosis
 SPMS: Secondary progressive multiple sclerosis
 SUS: system usability scale
 TAM: technology acceptance model
 UCSF: University of California, San Francisco

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Supplementary Table 1. Major inclusion and exclusion criteria for the pilot study participants

<i>Inclusion criteria:</i> • Diagnosis of MS (relapsing or progressive) by 2017 McDonald Criteria[55] • Ages 18 -80 • PHQ9 score of 5-19 • Any MS therapy, or no treatment	<i>Exclusion criteria:</i> • Cognitive dexterity or visual impairment that, in the opinion of the study neurologist (RB), would put the participant at risk or limit their ability to adhere to the study protocol • Inability to provide informed consent • Psychotic disorders: bipolar disorder, schizophrenia, schizoaffective disorder
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Supplementary Table 2. The relationship between tool features and COM-B principles of behavioral change.

A. Results of discovery interviews with patients mapping tool features to COM-B principles of behavioral change.

COM-B Domain	Tool feature – desired behavior	Patient feedback	Booster or blocker	Interventions to address identified or potential blockers
Capability - physical	Survey – mood reporting	Easy to adjust survey font size	Booster	N/A
	Survey – mood reporting	100% of patients reported owning a device (smartphone or computer) on which they receive email	Booster	Enablement – ensure patients have access to device before fielding survey
	Summary – depression treatment	100% of patients reported having access to the patient portal to receive after visit summaries	Booster	Enablement – ensure patients have access to patient portal before distributing summary
Capability - psychological	Survey – mood reporting	100% of patients reported the ability to use a device (smartphone or computer) to receive email; average confidence using the device 4.6 (5 = very confident).	Booster	Education – ensure patients have instructions for accessing survey link via email, if needed
	Dashboard and Summary – mood evaluation (discussion with clinician) and treatment	Agree (mean score >4) all views are easy to understand.	Booster	Education – add plain language definitions of all survey names
	Dashboard and Summary – mood evaluation (discussion with clinician) and treatment	Agree (mean score >4) information is useful for following views: • Longitudinal PROs • Cross sectional PROs • Resource map	Booster	Education – add plain language definitions of survey names
	Dashboard and Summary – mood evaluation (discussion with clinician) and treatment	Neutral (mean score <4) clinical decision support view is useful	Blocker	Education – advise clinicians to use discretion before including view in patient summary
Opportunity	Survey – mood reporting	100% of patients reported daily access to WiFi	Booster	Enablement – ensure patients have access to WiFi before fielding survey
	Survey – mood reporting	Frequency of assessments every 4 weeks is acceptable	Booster	N/A
Motivation - reflective	Survey – mood reporting	80% feel it is very important to pay attention to and do things to manage mood	Booster	Education – include survey introduction language that includes explanation of survey purpose

	Survey – mood reporting	60% feel it is very important to share how their mood is with their care team	Booster	Education – include survey introduction language that includes explanation of survey purpose; reinforce by showing dashboard during clinical encounters
	Survey – mood reporting	100% feel their care team can do things to help them manage mood	Booster	Education – include survey introduction language that includes explanation of survey purpose
Motivation - automatic	Survey – mood reporting	20% reported cultural barrier to mood reporting (topic is not discussed)	Blocker	Enablement – ensure summary is available in electronic and print formats so that it can be easily shared with family
	Survey – mood reporting	More than half reported concern that answering questions honestly would send up a false “red flag” about their mood, resulting in alarm for clinician	Blocker	Enablement – add free text box to PHQ2 and PHQ9 so patients can provide context for survey answers

B. Results of discovery interviews with clinicians mapping tool features to COM-B principles of behavioral change.

COM-B Domain	Tool feature – desired behavior	Clinician feedback	Booster or blocker	Interventions to address identified or potential blockers
Capability	Dashboard – mood evaluation	Clinicians all have access to dashboard during clinical encounters	Booster	N/A
	Survey – mood reporting	Clinicians feel PHQ-9 is agnostic way of raising mood topic	Booster	N/A
Opportunity	Dashboard – mood evaluation	Limited visit time is the universal factor limiting clinicians' opportunity to address mood-related issues; mood discussions can be sidelined if the patient has other pressing issues to cover	Blocker	Education – consider informing patients that a separate appointment can be scheduled to address mood Enablement – redesign the clinical decision support screen to be easier to digest at a glance; with fewer recommendations
	Survey – mood reporting (in-basket messaging)	Clinicians desire a formal clinic protocol in place to set expectations around responses to urgent mood reporting situations	Blocker	Enablement – include language informing patients who score >15 to seek care urgently; alert that care team may not see score for 36 hours Education – consider informing patients that a

				separate appointment can be scheduled to address mood
	Survey – mood reporting	Clinicians are concerned about getting too many “yes” alerts to #9 given prevalence of passive SI within MS population	Blocker	Enablement – add free text box to PHQ9 so patients can provide context for survey answers
Motivation	Dashboard – mood evaluation	Clinicians all reported feeling confident asking patients about mood, but confidence can vary based on how well they know the patient and availability of resources to act on the information.	Blocker	Enablement – include adequate resources in dashboard Training – ensure clinicians routinely open BRIDGE to normalized mood discussions during appointments
	Survey – mood reporting	Clinicians feel it is very important to be informed about patient mood because it can impact other symptoms, is treatable, and impacts QoL.	Booster	Education – encourage patients to report mood by stressing symptoms can be addressed
	Dashboard – mood evaluation and treatment	Clinicians are motivated address mood issues, treat mood, and refer patients to supports out of a desire to care for patients.	Booster	Enablement – include adequate resources in dashboard
	Dashboard and Summary – mood evaluation and treatment	Clinicians report concerns about treatment efficacy knowing resources are scarce from both the patient navigation assistance and mental health provider perspectives.	Blocker	Enablement – include smart phrase instructions to guide patients on referral follow-through and system navigation; ensure adequate resources included in dashboard
	Summary – mood treatment	Clinicians report giving patients the option of making dashboard views available is “not harmful,” but they are not sure how much patients will use them, with possible exception of resources; perception that more useful for higher literacy patients	Blocker	Education – add plain language definitions of all survey names; advise clinicians to use discretion before including view in patient summary

Supplementary Results: Findings from the Discovery interviews and Thinkaloud Sessions

Discovery Interviews (N=5 patients, 5 clinicians)

Participants' initial evaluation of ease of use (patients only) and usefulness (patients and clinicians) of the various prototype features are summarized in *Table 3*. All tool components were easy to understand. The clinical decision support dashboard view scored <4 by both patients and clinicians. Clinicians felt it was "too busy" as designed and that the overwhelming number of recommendations did not feel "actionable" given limited appointment times. Patients felt that while the view's color-coded status section was helpful, it was comparatively less meaningful than the cross-sectional display which shows current status within the context of a green/yellow/red continuum. The resource map had a high mean perceived usefulness among patients (4.8, SD 0.45), but a lower mean perceived usefulness (2.4, SD 0.89) and the lowest mean importance rating among clinicians (1.6, SD 0.89). Specifically, clinicians noted the importance of providing information about insurance for any resources in order to make the information actionable (prescribing choices and referral decisions) and patients (ability to follow through). Patients acknowledged these challenges but still appreciated the user-friendly design and having "a place to start" with regard to referrals that would reduce the burden of seeking resources when actively experiencing emotional distress. Both audiences noted the need for resources to be current and drawn from reliable sources. A number of features and data types were identified that mapped to the COM-B principles of behavior change, and these resulted in design changes and interventions promoted to address potential boosters or blockers (*Supplementary Table 2*).

Supplementary Table 3. Patient (n = 5) and clinician (n = 5) participants' assessment of the ease of use and usefulness of the various tool components.

	PATIENTS				CLINICIANS	
	How <u>useful</u> would this information be to you?		How <u>easy</u> is this information to understand?		How <u>useful</u> would this information be to you?	
	Mean	SD	Mean	SD	Mean	SD
BRIDGE DASHBOARD						
Longitudinal PROs	4.40	0.55	4.20	1.30	4.50	1.12
Cross-sectional PROs	4.00	1.73	4.60	0.55	4.70	0.67
Clinical decision support	3.60	1.67	4.50	0.71	3.90	0.89
Resource map	4.80	0.45	4.95	0.11	2.40	0.89
Antidepressant treatment pathway	-	-	-	-	4.38	0.48
Mood Survey						
Your patients' mood survey results	-	-	-	-	4.60	0.89
In-Basket Alerts						
In-basket alerts triggered by your patients' mood survey results	-	-	-	-	4.75	0.50

Score 1 (strongly disagree) – 5 (strongly agree)

Thinkaloud Sessions

Prior to the thinkaloud sessions, the prototype was refined in response to the discovery interviews (*vide infra* for tails). The survey was iterated to incorporate changes designed to address identified or potential blockers that emerged from discovery interviews. Changes to the patient-facing features included the addition of free text box at end of PHQ2 and PHQ9 surveys, refinement of introductory language at top of the survey, and section formatting to clearly delineate individual questions from summary question sections. The clinician-facing dashboard was also iterated to incorporate changes designed to address identified or potential blockers that

emerged from discovery interviews. Changes included the addition of smart phrase instructions to guide patients on referral follow-through and system navigation; addition of language at end of survey informing patients who score >15 to seek care urgently; alert that care team may not see score for 36 hours and instructing patients to seek immediate care if experiencing a mental health crisis.

Patient Sessions (n = 7).

Patient survey.

During thinkaloud sessions, patients assessed the survey for usability and understandability in different scenarios. They were subsequently shown designs and asked questions about the BRIDGE dashboard and any BRIDGE dashboard screens that they would like to have access to in a summary display following appointments.

Survey feedback.

Patients were universal in their desire to receive the survey at least every four weeks, if not more often. All patients strongly agreed the survey was easy to open using the link (Table 4). In Scenario A, patients were asked to pretend they had not been bothered by mood-related problems over the last few weeks in order to only receive the PHQ-2 survey. In Scenario B, patients were asked to pretend they had been bothered “several days,” “more than half,” or “nearly every day,” by mood-related problems over the last few weeks in order to receive the PHQ-9 survey. The slightly longer and more complex PHQ9 was still graded as easy to complete and understand relative to the PHQ-2. Some patients articulated concern for how answers might be interpreted by their clinicians, for example, concern about sending up unnecessary “red flags” with their survey answers as symptoms addressed on the survey can overlap with MS symptoms. Relatedly, the free text box proved to be an extremely popular design feature as it presents PwMS who are experienced in recognizing their own symptoms, an opportunity to offer context for potentially concerning or MS symptom-related survey answers.

Supplementary Table 4. The patient responses to ease of use during Thinkaloud sessions (N=7)

	Mean		SD	
How easy was it to open the survey using the link?	5.00		0.00	
	Scenario A: PHQ-2		Scenario B: PHQ-9	
	Mean	SD	Mean	SD
How easy was it to complete the survey?	5.00	0.00	4.93	0.19
How easy were the questions to understand?	5.00	0.00	4.50	0.76

Score 1 (strongly disagree) – 5 (strongly agree)

Dashboard and Summary Display.

When ranking each dashboard view according to how important it was to them, participants during the 23 thinkaloud sessions ranked views as more important (longitudinal PROs and resource map) that had differed from those during the discovery interviews (cross-sectional PROs and clinical decision support), indicating the importance of allowing patients to choose what dashboard images appear in their after visit summary displays. Neighborhood walkability was specifically identified by patients as useful context for their clinicians to have within the clinical decision support view. Patients universally expressed interest in having dashboard views available in a summary display for reference following appointments. All surveyed preferred an electronic summary format distributed through the patient portal (MyChart).

Clinician Sessions (n = 5)

During 23 thinkaloud sessions, clinicians were shown live, interactive demonstrations using sample data to illustrate how various MS CATCH intervention components (patient survey, in-basket messaging, BRIDGE dashboard) work together to form a closed-loop system. Clinicians were asked to rate each of five dashboard views for usefulness and importance, as well as share qualitative feedback about overall completeness, understandability, and potential impact on care delivery.

Dashboard.

Interestingly, the clinical decision support screen was deemed among the most important views (mean 4.2, SD 1.1), along with the longitudinal PROs (mean 5.0, SD 0) and the resource map (mean 4.5, SD 0.87) (Table 5). However, as currently designed, clinicians perceived the clinical decision support screen as less useful (mean: 3.20, SD 1.15) because it was perceived as potentially overwhelming (“wordy”) and the guidance too generic. Some felt it would be more useful for newer clinicians. Others worried about accomplishing all recommended tasks during a single visit. In contrast, the longitudinal and cross-sectional PROs, as well as the resource map were perceived as most useful. Critiques of the antidepressant treatment pathway were conflicting. Some reported it included too much information, others said not enough information. Several spoke of a bias to refer to psychiatry rather than prescribe. Echoing discovery interview feedback, nearly all clinicians expressed a desire to incorporate patient insurance information as it influences prescribing choices and referral decisions.

Supplementary Table 5. Clinician responses to usefulness and importance during Thinkaloud sessions (n = 5)

	How useful would each display be to you?		How important is each display to you?	
	Mean	SD	Mean	SD
Longitudinal PROs	4.30	0.45	5.00	0.00
Cross-sectional PROs	4.30	1.30	3.60	1.67
Clinical decision support	3.20	1.15	4.20	1.10
Resource map	4.70	0.45	4.50	0.87
Antidepressant treatment pathway	3.60	1.29	2.40	0.55

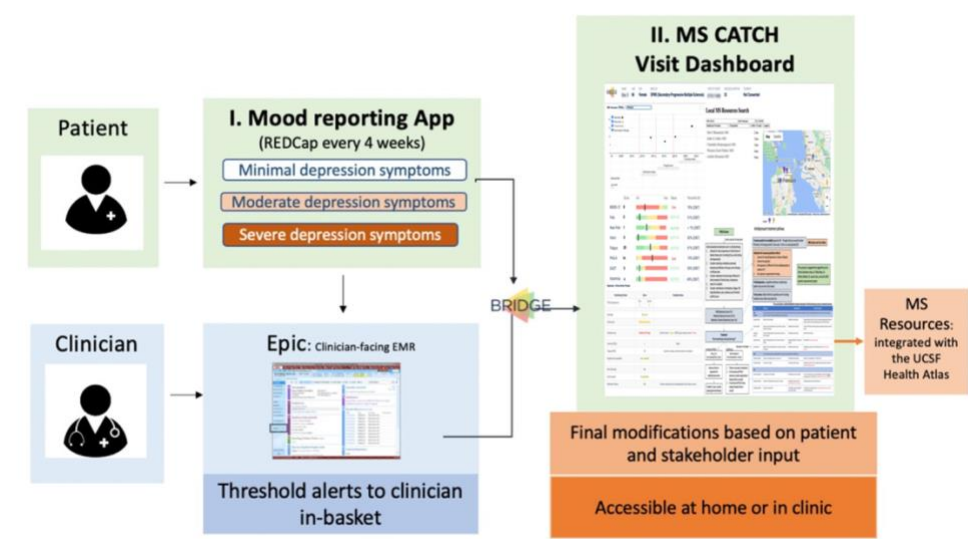
Score 1 (strongly disagree) – 5 (strongly agree)

Final Changes Made to Tool before Scoring.

Design changes.

In response to feedback received from patients and clinicians during thinkaloud sessions, the tool was further refined. Patient-facing aspects of the tool were iterated to include a catalogue of mental health resources at the end, an in-survey pop-up directing patients who screened positive for suicidal intent to seek immediate medical care (with contact information), and a companion patient-facing mood tracker displaying the patient’s longitudinal mood survey results. In response to feedback from clinicians that the clinical decisions support screen was too visually overwhelming, stylistic changes were made to make it less so. Instead of having bright red, yellow, and green filled boxes behind the text, the text colors were changed to a muted red, yellow, and green.

Supplementary Figure 1. The prototype for MS CATCH.



Supplementary Figure 2. The patient’s response history and resources relevant to depression self-management can be viewed at the end of the survey.

UCSF Weill Institute for Neurosciences

Mental Health Resources

You may find these resources helpful for dealing with stress, anxiety, and depression.

Mental Health Resources

If you have had thoughts that you would be better off dead or of hurting yourself in some way, **call 988 today.**

Therapy and Crisis Resources	
National MS Society Website	Resources for support groups, programs, events, diet, emotional well-being, and more
US National Warmlines	If in need of someone to talk to: San Francisco 24/7 Crisis Line: 415-781-0500 24/7 Confidential Support: Text MYLIFE to 741741 Peer Workforce Supportive Services (PWSS) Support Line: 415-288-7160 Suicide Prevention TTY/TDD — telephone access for the deaf/hearing impaired: 415-227-0245
Local San Francisco Hotlines	
CalHope	Providing crisis support for impacted communities and individuals.
Anxiety and Depression association of America	Offers prevention, treatment, and support for anxiety, depression, OCD, PTSD, and more
SupportLine Someone with Depression	Educates loved ones on how to support someone with depression.
Open Counseling	Provides a searchable directory for anyone who is in need of local affordable counseling.

Mood Screening Longitudinal Report

This is an overview of your mood that you have reported over the months. This information is for you, if you would like to personally keep track of your mood.

	Date	Total Score	How difficult have these problems made daily tasks?	Comments
Month 1	03-15-2023	5	Somewhat difficult	_____
Month 2	03-16-2023	4	Somewhat difficult	I am feeling okay!
Month 3	03-17-2023	0	_____	I feel great this month!
Month 4	03-18-2023	21	Very difficult	This has been a really hard month. There have been a lot of changes
Month 5	03-19-2023	0	_____	_____
Month 6	03-20-2023	17	Very difficult	Feeling better.
Month 7	04-20-2023	6	Somewhat difficult	_____
Month 8	04-20-2023	11	Extremely difficult	It has been really hard lately