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Protocol for Neuro-Oncology Anywhere: Deploying Mayo Clinic's remote cognitive assessment battery and wearable device monitoring platform while assessing the impact of metformin on cognition and quality of life in patients with history of cranial radiation

Ugur Sener [a,b,*], Bryan Neth [a,b], Taylor Galloway [c], Heather Hughes [d], Samantha Caron [b], Nicole R. Batty [e], Eva C. Alden [f], Nikki H. Stricker [f], John L. Stricker [g], Sani H. Kizilbash [b], William G. Breen [h], Eric Lehrer [h], Jian Campian [b], Joon Uhm [a,b], Michael W. Ruff [a,b], Stacy D. D'Andre [b], Terry C. Burns [i], Tufia C. Haddad [b], Lynn M. Flickinger [e], Katrina Chan [e], Carolyn Mead-Harvey [j], Susan M. Geyer [k]

[a] Department of Neurology, Mayo Clinic, Rochester, MN, United States of America
[b] Department of Oncology, Mayo Clinic, Rochester, MN, United States of America
[c] Clinical Trials Beyond Walls, Mayo Clinic, Rochester, MN, United States of America
[d] Oncology Clinical Research, Mayo Clinic, Rochester, MN, United States of America
[e] Cancer Center Clinical Research Office, Mayo Clinic, Rochester, MN, United States of America
[f] Department of Psychiatry and Psychology, Mayo Clinic, Rochester, MN, United States of America
[g] Department of Information Technology, Mayo Clinic, Rochester, MN, United States of America
[h] Department of Radiation Oncology, Mayo Clinic, Rochester, MN, United States of America
[i] Department of Neurosurgery, Mayo Clinic, Rochester, MN, United States of America
[j] Clinical Trials and Biostatistics, Mayo Clinic, Scottsdale, AZ, United States of America
[k] Clinical Trials and Biostatistics, Mayo Clinic, Rochester, MN, United States of America

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ABSTRACT

Cognitive symptoms are among the most frequently reported issues in cancer patients treated with cranial radiation, yet they remain inadequately assessed in clinical practice and are suboptimally treated. Cranial radiation is an integral part of treatment for primary and metastatic brain tumors that contributes to progressive and irreversible cognitive decline with currently limited therapeutic options. Development of effective interventions that can prevent or delay this neurocognitive toxicity requires accurate assessment of symptom burden. However, formal neuropsychological testing is resource intensive and time consuming. Repeated in-person assessments are often not feasible for cancer patients who must travel great distances to specialized cancer centers. The Neuro-Oncology Anywhere (NOA) study is a fully decentralized clinical trial with an overarching goal to evaluate remote cognitive assessments while simultaneously evaluating benefits of health promotion through use of a wearable watch device and metformin in preventing radiation-related cognitive decline. The primary objective of this study is to determine the feasibility of completing serial remote cognitive, activity/sleep, and self-reported assessments among patients who have previously received cranial radiation. Key secondary objectives are to assess satisfaction of patients with remote monitoring, evaluate adherence to study drug, and compare neurocognitive function scores and the impact of receiving metformin and health promotion with a wearable device compared to wearable device alone. Determination of the remote platform's feasibility among patients with brain tumors will provide a strong scientific foundation for routinely integrating scalable remote cognitive assessment strategies into future clinical trials, enabling accelerated evaluation of potentially effective interventions unconstrained by geographic limitations.
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* Corresponding author. Mayo Clinic, 200 First St SW, Rochester, MN, 55905, United States of America.
E-mail address: sener.ugur@mayo.edu (U. Sener).

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1. Introduction

Cranial radiation is a cornerstone of treatment for patients with primary and metastatic brain tumors, and has been associated with often progressive and disabling cognitive dysfunction [1]. Neuropsychological assessment is effective for evaluating cognitive dysfunction, but testing in routine oncology practice is limited, in part because it can be time consuming and cumbersome to cancer patients [2]. Despite the high prevalence of cognitive symptoms related to cranial radiation among patients with brain tumors, available pharmacotherapeutic interventions are of limited benefit [3]. As an example, in a phase III randomized placebo-controlled clinical trial, treatment with donepezil did not improve the overall composite cognitive score in patients treated with cranial radiation [4]. In another randomized placebo-controlled clinical trial, memantine delayed time to cognitive decline, but the study did not reach statistical significance for its primary endpoint in part due to significant attrition from disease progression and death [5]. There is a critical need to implement effective assessment strategies that can be conducted in the home setting, and to evaluate the effectiveness of potential interventions without undue financial burden or inconvenience to patients with brain cancer. Without such knowledge, cognitive outcomes will remain incompletely understood and potentially effective treatments unrealized.

The Neuro-Oncology Anywhere (NOA) clinical trial deploys a digital health platform that brings cognitive evaluations and interventions to patients' homes, using a combination of serial remote cognitive assessments with Mayo Test Drive (MTD), video-enabled telehealth visits for clinical evaluations, device-based monitoring and health promotion, and mail order medication delivery with remote phlebotomy services. By eliminating need for travel and making cellular-enabled tablet devices available to participants without Internet or cellular access, the clinical trial ensures that all patients have access to care, unconstrained by geographic boundaries or need for travel.

1.1. Digital cognitive test – Mayo Test Drive

MTD is a web-based application for remote self-administered cognitive assessment. MTD is compatible with multiple device types (e.g., smartphone, tablets, computers) and has demonstrated high usability, with 98% completion rates in a large community-based sample spanning ages 35-100 [6]. An MTD session, including administration of the Stricker Learning Span (a computer adaptive word list memory test) and Symbols Test (an open-source measure of processing speed and executive functioning), typically takes 15 min to complete and both subtests show good reliability [6,7]. Prior work has supported convergent validity with and similar distributional properties as in-person neuropsychological measures, significant associations with measures of neurodegeneration, amyloid and tau positron emission tomography (PET) Alzheimer's disease biomarkers, and white matter hyperintensity volume, and low follow-up attrition rates [6–8]. The cognitive science basis of the computer adaptive word list memory test and rationale for remote test design decisions has been described [9]. The remotely administered computer adaptive word list memory test showed similar ability to differentiate Alzheimer's disease imaging biomarker-defined groups as the in-person administered Rey Auditory Verbal Learning Test, establishing criterion validity (n = 353, older adults) [10]. Normative data for remote, unsupervised sessions are available and are sensitive to cognitive impairment [11].

1.2. Wearable device for health monitoring and promotion

Wearable devices have been utilized in the field of neurology for seizure detection [12] and assessment of patients with movement disorders [13]. Wearable device technology has also been implemented for remote monitoring of cancer patients [14] and for cancer clinical trials [15]. However, prior studies have not assessed feasibility of longitudinal testing with MTD or device-based monitoring for patients with brain tumors treated with radiation.

1.3. Metformin

Similarly, metformin's potential benefits on cognition have been assessed in prior studies. As an example, in a preclinical study, metformin stimulated neurogenesis following radiation [16]. Metformin use has also been associated with reduced Alzheimer's disease risk [17]. However, prior studies have not assessed metformin's ability to mitigate risk of cognitive decline following cranial radiation. These effects may be further augmented by the addition of device-based physical activity promotion, as evidenced by a study that demonstrated positive cognitive effects of exercise in patients with brain cancer [18].

Standard approaches to evaluating and managing cognitive symptoms in patients with brain tumors remain limited. Most patients experience symptoms, yet few undergo formal longitudinal evaluation with limited available interventions to meaningfully alleviate symptom burden. The NOA clinical trial addresses this issue by deploying remote cognitive assessment and real-time, device-based data collection, reducing the need for lengthy, in-person assessments that may be burdensome for patients with brain cancer. Simultaneously, NOA tests the effectiveness of device-based health promotion with or without metformin on cognitive function of patients who received cranial radiation.

2. Materials and methods

2.1. Study design

In this single-site phase 2 fully decentralized clinical trial, patients with a history of cranial radiation for primary or metastatic brain tumors undergo serial remote cognitive evaluations (Fig. 1). All participants receive wearable watch devices for health promotion and for the collection and monitoring of activity and sleep data. Participants are also randomized to receive metformin or not, to assess the preliminary effectiveness of this agent in improving cognitive outcomes among patients who have received cranial radiation. Each participant is enrolled for a total of 12 months, with study assessments occurring every three months either virtually or in person. The study was approved by the Institutional Review Board (IRB). The trial was activated on May 31, 2024. The final participant enrolled January 15, 2026.

2.2. Eligibility

Patients age $\geq$18 years with a diagnosis of brain tumor, during or up to 5 years after completion of radiation therapy administered for treatment of primary or metastatic cranial tumor are eligible for enrollment. Participants are required to have an ECOG Performance Status of 0, 1, or 2 and Karnofsky Performance Status (KPS) of $\geq$70, as well as expected survival $\geq$6 months in the opinion of the treatment team at the time of enrollment. Participants must be able to complete cognitive assessments on their own or with assistance from a caregiver. Participants who do not have devices that permit telehealth visits will be provided with cellular-enabled tablets to facilitate study-related activities for the duration of the study. Individuals with uncontrolled and/or intercurrent illness or other conditions limiting safety of or compliance with study proceedings are not eligible. Individuals unable to swallow tablets or with known hypersensitivity to metformin, or already taking metformin who cannot safely discontinue if randomized to the control group, are not eligible. Individuals concurrently taking resveratrol, coenzyme Q10, coconut oil/other medium chain triglyceride-containing supplements, or curcumin and unwilling to discontinue prior to registration and remain off these agents for study duration are also ineligible.

2.3. Recruitment

Study staff review the electronic health record (EHR) for patients with brain tumors who are either undergoing or have completed cranial radiation therapy for primary or metastatic brain tumors. Eligible patients are approached by the study team members, who describe the study, answer questions, and explain requirements for participation. Interested patients eligible for enrollment provide remote or in-person electronic or paper written informed consent and are registered to the trial.

2.4. Interventions

Participants undergo serial remote cognitive evaluations using MTD, which is a web-based application that can be accessed through computers, tablet devices, or cellular phones. The application includes an adaptive word list memory test (the Stricker Learning Span) and a symbol-matching test to measure processing speed and executive functioning (Symbols Test). Performances on these subtests are combined into an MTD composite [8].

Participants are also evaluated with the Kokmen Short Test of Mental Status (STMS) test as a second test of cognition [19] and a modified Neurological Assessment in Neuro-Oncology (NANO) evaluation [20]. The Kokmen STMS is a 38-point multi-domain cognitive screening test that measures orientation (8 points), attention (7 points), learning (4 points), calculation (4 points), abstraction (3 points), information (4 points), construction (4 points) and recall (4 points) that has been validated for evaluation of cognitive function among patients with neurodegenerative diseases [21–23].

Patients can undergo STMS and NANO evaluations either in-person or by video-enabled telehealth visits. The NANO scale involves assessment of behavior, level of consciousness, language function, visual fields, facial strength, upper and lower extremity strength, coordination, sensation in upper and lower extremities, and gait. The full NANO scale assessment is completed during in-person visits. Since visual fields and sensation cannot be assessed by telehealth without assistance from a trained individual who assists in testing the study participant, those components are omitted during video visits.

All participants receive wearable devices to monitor health data including steps, exercise and standing time, calories burned, resting heart rate, heart rate variability, total sleep time, REM sleep time, sleep oxygen levels, and respiratory rate. The device is also used for health promotion, providing participants and their caregivers a mechanism to track physical activity levels. The device may be picked up during the baseline screening visit for the study or shipped to the patient. Health data is securely transferred to the study team through the wearable device application. Participants may keep the wearable devices after completing the study. The device, which is valued at less than $100, is provided in place of monetary compensation and is considered essential for participation. This approach helps reduce barriers to participation while avoiding any undue influence on a patient's decision to enroll. Participants are not required to complete the entire study in order to keep the device.

Participants are also randomized (1:1) to receive metformin or not. Individuals randomized to the treatment medication (Group A) take metformin twice daily. The starting dose is 500 mg twice daily for 7

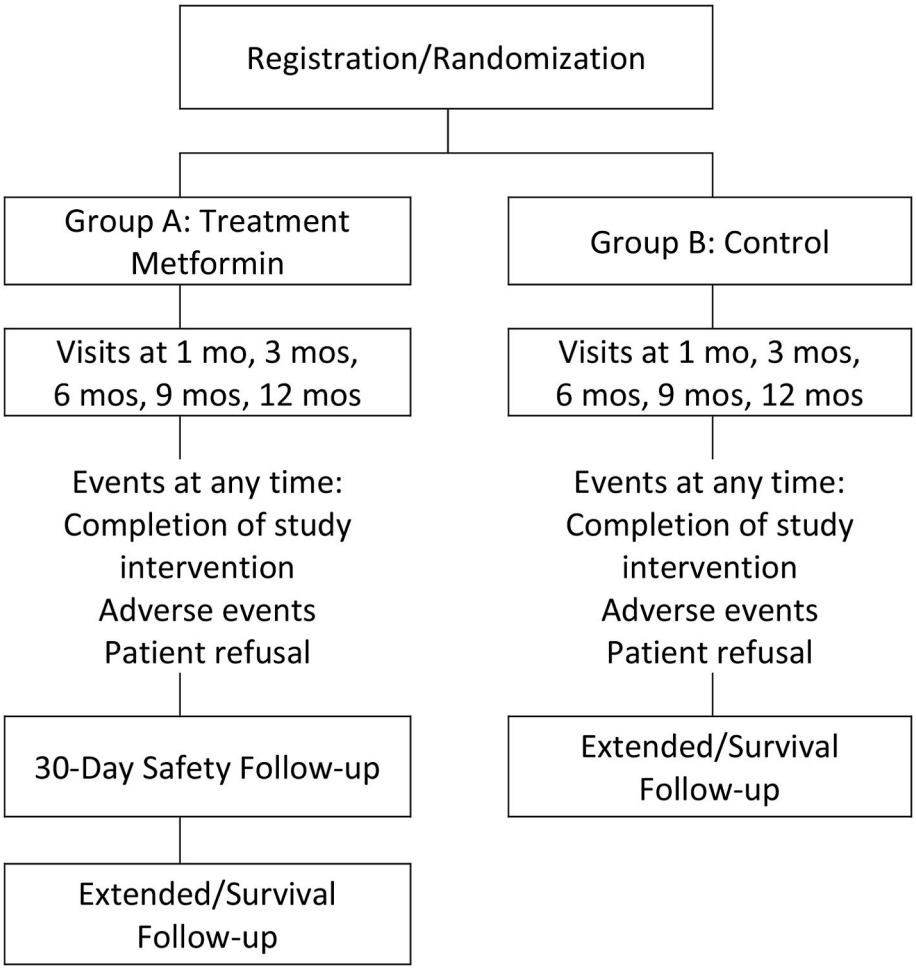

Fig. 1. Trial schema.

days, increased to 1000 mg twice daily thereafter if tolerated. Adherence is tracked with a digital medication diary. While metformin is usually well tolerated, the medication does have known gastrointestinal toxicities such as nausea and diarrhea [24] as well as risk of lactic acidosis [25]. Accordingly, adverse events are tracked throughout the study and participants undergo laboratory evaluations at baseline, at end of study, and as needed to ensure safe administration of the agent.

Participant functional status is measured using Karnofsky Performance Status (KPS) [26] and Eastern Cooperative Oncology Group (ECOG) Performance Status [27]. Participant quality of life is measured by the European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30 survey, which is a 30-item questionnaire that is specifically designed to evaluate cancer patients' health-related quality of life [28]. QLQ-C30 has been previously used for evaluation of quality of life among patients with glioma who underwent proton beam radiation therapy [29]. QLQ-C30 has also been validated among patients with intracranial meningiomas [30]. In the study, EORTC QLQ-C30 is delivered and completed digitally. Digital delivery of this survey has been previously evaluated among patients with glioma [31] and thus was determined to be an optimal choice for this trial.

2.5. Study measures

Study measures are completed according to the schedule in Table 1. Participants undergo performance status evaluation, cognitive assessment with MTD, and neurological examinations at baseline and every three months. Safety labs and glycosylated hemoglobin are assessed at baseline, at end of study, and as needed. Glycosylated hemoglobin is also repeated at 6 months. Health and sleep data are continuously transferred from wearable devices. Patient reported outcomes are assessed after registration and every three months.

2.5.1. Measurement of effect

Participants are patients with brain tumors who have been treated with cranial radiation therapy. There are four core study visits as part of the trial with a total of 12 months of treatment. The data used for assessment of study goals are obtained during these visits. These visits include collection of remote neuropsychologic evaluation, wearable health data, and remote neurologic assessment.

2.5.2. Primary endpoint

The primary endpoint is to determine feasibility of completing serial cognitive assessments in patients who have previously received cranial radiation using MTD. All participants meeting eligibility criteria who have signed a consent form and who have completed study procedures will be evaluable for the primary endpoint.

2.5.3. Secondary endpoints

A key secondary endpoint is to determine the feasibility and acceptance of completing serial self-reported symptom assessments and activity/sleep assessments. Patient reported outcomes are measured using the EORTC QLQ-C30 questionnaire, evaluating change in quality of life every three months for the duration of study participation. Sleep and activity data are continuously transmitted through wearable watch devices.

Other secondary endpoints are to determine the impact of metformin with health promotion via wearable device relative to patients receiving wearable watch alone on cognition and quality of life measures at 12 months as compared to the baseline assessment. The impact on cognition will be determined by results of the MTD and Kokmen STMS assessments. The impact on quality of life will be measured using the EORTC QLQ-C30 questionnaire responses.

To evaluate the safety and tolerability of metformin in patients who

Table 1
Schedule of trial activities.

Tests and procedures[a]	Screening		Active Monitoring Phase							
	≤30 days prior to reg[b]	After reg	Day 8	End of Month 1[c]	End of Month 3	End of Month 6	End of Month 9	End of Month 12	EOS[d]	30-Day Safety Follow-up[e]
Window		±7 days	±2 days	±7 days	±14 days	±14 days	±14 days	±14 days	±14 days	−3/+15 days
Medical history and exam[f]	X									
Height, weight if available	X[g]									
Performance status[h]	X			X	X	X	X	X	X	X
Adverse event assessment	X		X[i]	X	X	X	X	X	X	X
Cognitive assessment	X			X	X	X	X	X	X	
Neurologic exam[j]	X			X	X	X	X	X	X	
Safety labs[k]	X								X	
Glycosylated hemoglobin (HbA1c)[l]	X					X		X	X	
Pregnancy testing[m]	X									
Health/sleep data transfer		X		X	X	X	X	X	X	
Patient reported outcomes		X			X	X	X	X	X	

[a] All visits may be done remotely. Any tests and procedures may be ordered as needed for clinical care.
[b] Reg: Registration.
[c] 1 month = 28 ± 7 days.
[d] EOS: end of study, may be combined with month 12 or other visit as needed.
[e] At least 30 days after last dose of metformin; NOTE: May coincide with EOS visit. If there is a clinical concern, additional blood testing may be done.
[f] Extracted from medical record/visit ≤90 days prior to registration. Exam can be completed virtually if needed.
[g] Height and/or weight may be from most recent values in medical record ≤3 months prior to registration, if available.
[h] Include both ECOG and Karnofsky performance scores.
[i] For patients on metformin, this visit includes discussion with study staff prior to changing metformin dose.
[j] May be done in-person if participant is on campus for other appointments or by telehealth.
[k] Safety labs include: ALT (CPT 84460), AST (CPT 84450), Creatinine (CPT 82565); Lactate (CPT 83605).
[l] At any time, clinical spot glucose or HbA1c per standard of care may be ordered per treating provider's discretion.
[m] For persons of childbearing potential only. Must be completed ≤8 days prior to registration.

have previously received cranial radiation, we assess and evaluate data on the incidence of reported adverse events based on the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v5.0. We assess the type of adverse event, the grade of the event, and the perceived attribution to study treatment.

2.6. Adverse event evaluations

From the time of registration until ≤30 days after the administration of the last dose of study drug or therapy, the Principal Investigator (PI) is responsible for ensuring that all adverse events (AEs) observed by study team or provided by external sources are reported. After 30 days from last dose of administration of the last dose of study drug or therapy, only adverse events that are attributed to the study drug (possibly, probably, or definitely related) are required to be recorded on the adverse event forms.

The investigators are responsible for AE diagnosis or syndrome(s), if known (if not known, signs or symptoms), dates of onset and resolution (if resolved), severity, and assessment of the relationship to study treatment. Investigators are asked to determine the relationship of the AE with any study mandated activity, review laboratory test results and determine whether an abnormal value in an individual study subject represents a clinically significant change from the subject's baseline values and to follow reported AEs until resolution.

3. Statistical analyses

This is a prospective randomized, pilot study to determine the feasibility of completing serial remote neuropsychologic assessment, remote neurologic examination, wearable activity/sleep, and self-report assessments in clinical trial participants who have previously received cranial radiation. Through this decentralized clinical trial, we will assess feasibility in terms of compliance as well as drug adherence and will obtain preliminary data on the use of metformin and health promotion with wearable devices (vs. only wearable devices) and its ability to improve neurocognitive outcomes.

In this trial, patients are randomized to one of two treatment groups: metformin + health promotion with wearable device vs. wearable device alone. This randomization is done in a 1:1 allocation to these two groups and stratified based on age group (<70 vs. 70+ years) and disease group (primary vs secondary, glioblastoma vs all other glioma vs brain metastases vs meningioma). Given the focus on feasibility of this study in a decentralized approach, and the prohibitive expense of a placebo compared to generic metformin in this relatively small pilot study, a placebo control was not used in this trial.

The analyses for primary endpoint, secondary and correlative outcomes will begin once all participants have completed the trial protocol procedures.

3.1. Analysis of the primary endpoint

The primary objective of this trial is to determine the feasibility of completing serial cognitive, self-reported symptom, and activity/sleep assessments in patients who have previously received cranial radiation. Our primary focus, and the primary endpoint of this trial, will be on the feasibility of completing serial remote cognitive assessments using the MTD tool in this patient population in a decentralized setting. As such, specific hypothesis testing was not planned for our primary analysis. Instead, evaluation of feasibility and compliance in this pilot setting will use confidence bounds to ensure a level deemed clinically meaningful for this population.

All participants meeting eligibility criteria who have signed a consent form and who have completed study procedures will be evaluable for the primary endpoint. Here, compliance will be defined as completing the baseline, 3-month, and 6-month cognitive assessments using the Mayo Test Drive platform. Feasibility will be considered demonstrated if a one-sided 95% binomial confidence lower bound for compliance is >60%, e.g. if at least 69 of 100 evaluable participants complete these three time points.

To assess compliance, we will assume that whether or not a patient is compliant is a binomially distributed variable (completed these three visits vs. not) and will use a one-sided 95% binomial confidence lower bound to help determine if the true compliance rate associated with this remote monitoring and testing is at least 60%. Here, across all 100 patients, we will need to observe 69 or more of these patients complete at least 3 visit time points as defined above to conclude that this study indicates sufficient evidence of compliance and thus feasibility (69/100 = 69%; one-sided 95% binomial confidence interval: 60.5% to 100%).

Despite the lack of formal hypothesis tests, we will also evaluate whether or not patients are compliant using logistic regression models, where we will evaluate several factors and their influence on this compliance. These factors will include assessment of the influence of treatment group, age group, and disease group as well as other potential factors such as biological sex and health disparities information. With n = 100 patients, logistic regression models will have 80% power to detect an odds ratio of 1.75 between groups ($\alpha = 0.05$). Differences in this compliance between the treatment groups will also be evaluated, where with 100 patients (50/group), we will have 80% power to detect a true difference of 20% in the compliance rates between groups (e.g., 65% vs. 85%; 1-sided $\alpha = 0.06$). Finally, compliance in terms of the number of visits completed will also be evaluated, where this will be treated as a count measure, and we will use Poisson regression to model this and the influence of the factors already mentioned.

3.2. Analysis of secondary endpoints

Several secondary outcomes will be used to determine the feasibility of this remote-based monitoring and assessment of this patient population as well as the impact of metformin with health promotion via wearable watch device relative to patients receiving wearable watch alone.

Feasibility of completing serial self-reported symptom and activity/sleep assessments in patients who have previously received cranial radiation will be assessed by the rates of compliance at each of the time points and the percentage of patients in each of the treatment arms who complete the baseline, 3-month, and 6-month evaluations for these measures. Similarly, we will also evaluate completion and compliance across all scheduled assessment time points as well.

Acceptance or satisfaction of patients with the remote monitoring in this trial will be assessed as an overall measure and by treatment group. This will be done using a survey where the outcomes will be evaluated as continuous/ordinal data as well as dichotomized to satisfied vs. not. These will be summarized both graphically and quantitatively and compared between the treatment groups.

Adherence to taking metformin as determined through the remote monitoring app will be assessed in those patients who are randomized to receive metformin. Here, adherence is defined as taking at least 80% of the prescribed doses. This dichotomized outcome will be assumed to be binomially distributed, and where we will consider this group to have sufficient adherence to study drug if we observe 43 or more patients of these 50 randomized to metformin treatment taking 80% or more of the prescribed doses. This corresponds to an observed rate of 86%, and where the one-sided 95% binomial confidence interval is 75.3% to 100% and will be considered sufficient evidence that the true adherence rate is at least 75%. Logistic regression models will also be used here to assess potential factors that influence whether or not patients were adherent to taking their prescribed metformin.

Neurocognitive function scores will be evaluated for all patients and how these scores change in relation to baseline. These results will be based on the MTD subtests and the composite score. Neurocognitive scores will be assessed based on the remotely administered MTD battery

of tests and tools. We will evaluate the composite measure of neurocognition at 12 months in relation to baseline, and how these differ between the two treatment groups as well as adjusting for the other factors of interest (e.g., age, tumor location, time from radiation therapy, and disease groups). We will also evaluate changes in the neurocognitive measures using repeated measures models. Missing measures will also be interrogated and summarized in relation to other factors of interest. These can include how this corresponds to drug adherence or adverse events in those randomized to metformin, or if there are issues with item non-responses or domain or tool-specific missingness patterns. The key objective of the study is to evaluate the feasibility of completing digital and telehealth-based cognitive assessments among patients with brain tumors treated with radiation therapy. Thus, evaluating patterns of missingness is also an important feature of this trial. Given the heterogeneous patient population, cognitive testing trends obtained through the twelve months of participation in this study, including potential benefit of treatment with metformin as well as completion, will be critical for utilizing these remote approaches in future trials.

Direct comparisons of digitally obtained MTD scores to STMS and NANO assessments completed by telehealth are not planned as part of this study where the primary objective is to evaluate the feasibility of completing remote assessments. However, exploratory comparisons between the testing modalities are anticipated and will also be considered hypothesis-generating. We will additionally compare acceptance of the two testing strategies (digitally administered MTD vs. telehealth-based STMS and NANO evaluations) by participants as well as providers who perform the telehealth visits.

Safety and tolerability will be assessed in patients randomized to receive metformin, where adverse events will be summarized by type along with grade and perceived attribution to metformin based on the NCI CTCAE version 5. We will also summarize any gaps in treatment/adherence issues as well as any tolerability issues and modifications to dose. These will be descriptively summarized for all patients randomized to the metformin treatment group.

4. Discussion

Brain tumors are associated with a high symptom burden and neurologic disability [32,33]. Cognitive symptoms are common among this patient population, particularly in the setting of prior treatment with cranial radiation [1]. However, testing to characterize cognitive issues for brain tumor patients is limited in clinical practice, in part due to the length of time and personnel required for formal neuropsychiatric evaluations [2]. Available treatments provide modest benefit [3], leaving many brain tumor patients with disabling cognitive symptoms that are poorly understood and inadequately treated. There is a great need for longitudinal measurements of cognition in this patient population, which will lead to better characterization of the issues experienced and facilitate development of effective treatments. This fully decentralized clinical trial evaluates the ability of brief cognitive and neurologic assessments completed through app-based solutions and telehealth visits, to establish feasibility of a testing platform that can be rapidly implemented into routine clinical practice. The study simultaneously evaluates the efficacy of device-based health promotion with or without metformin in addressing the cognitive symptoms experienced by this patient population.

Remote assessments utilized in this study will reduce personnel needs for completion of screening assessments, representing a cost saving strategy. The modular and scalable design of the digital health platform allows implementation of additional assessment tools in the future with potential for customization by assessment goals and disease process studied. Remote device-based monitoring, health data tracking, and quality of life surveys utilized in this study are expected to permit earlier detection of clinical decline, providing clinical teams the opportunity for earlier intervention with potential benefits beyond monitoring cognitive status.

Importantly, the Response Assessment in Neuro-Oncology (RANO) group has previously proposed the combination of the Hopkins Verbal Learning Test-Revised (HVLT-R), the Trail-Making Test (TMT), and the Control Oral Word Association Test (COWAT) as a standardized neurocognitive battery that can be used among patients with brain metastasis who have undergone radiation therapy [34,35]. The NOA clinical trial represents the first prospective evaluation of MTD among patients with brain tumors and history of cranial radiation. As such, MTD has not been specifically validated against the combination of HVLT-R, TMT, and COWAT. However, the Stricker Learning Span component of MTD has been evaluated against the Auditory Verbal Learning Test (AVLT), which is a similar test to HVLT-R [7]. Likewise, the Symbols Test component of MTD has been evaluated against Trails A and Trails B, lending optimisim to the validity of MTD against the cognitive battery suggested by RANO [7]. If the NOA clinical trial demonstrates feasibility of administering MTD among patients with brain tumors who have received radiation therapy, the digital cognitive battery can be formally validated against the tests selected by RANO.

Further, this clinical trial utilizes a decentralized medication delivery strategy with remote tracking of patient adherence and adverse events, reducing the need for in-person assessments and personnel for a drug trial. This strategy reduces the need for participant travel for clinical trial related assessments, providing a mechanism where participation in a supportive care study can be completed entirely in the remote setting.

Our primary goal with this study is to demonstrate feasibility of the decentralized approach to evaluation and treatment of cognitive symptoms among patients with brain tumors who have received intracranial radiation. Feasibility refers to the practicality of completing study assessments and administering the study interventions, which we have defined as successful completion of cognitive and quality of life assessments at predetermined time points [36]. We will additionally assess the feasibility of mail order drug delivery and remote treatment monitoring as part of this trial. Separately, we will evaluate acceptability of the platform by the patients by assessing whether participants find use of the platform convenient and completion of study related tasks reasonable. Successful completion of the study will provide strong support for conduct of decentralized interventional clinical trials in neuro-oncology.

The decentralized drug delivery and assessment approach addresses health disparities by providing a solution to reach underserved patient populations with limited financial means or difficulty with travel who are otherwise unable to participate in drug trials. The applications of these assessment and drug delivery strategies are not limited to patients with cancer. Demonstration of feasibility in this study can guide development of other clinical trials for cancer patients as well as trials in other patient populations, such as individuals with neurodegenerative diseases.

Ethical publication statement

The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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CRediT authorship contribution statement

Ugur Sener: Conceptualization, Funding acquisition, Investigation, Methodology, Project administration, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. **Bryan Neth:** Methodology, Project administration, Writing – review & editing.

Taylor Galloway: Conceptualization, Investigation, Methodology, Project administration, Resources, Validation, Writing – review & editing. **Heather Hughes:** Methodology, Resources, Writing – review & editing. **Samantha Caron:** Investigation, Writing – review & editing. **Nicole R. Batty:** Investigation, Validation, Writing – review & editing. **Eva C. Alden:** Investigation, Methodology, Writing – review & editing. **Nikki H. Stricker:** Investigation, Methodology, Writing – review & editing. **John L. Stricker:** Investigation, Methodology, Writing – review & editing. **Sani H. Kizilbash:** Investigation, Writing – review & editing. **William G. Breen:** Investigation, Writing – review & editing. **Eric Lehrer:** Investigation, Writing – review & editing. **Jian Campian:** Investigation, Writing – review & editing. **Joon Uhm:** Investigation, Writing – review & editing. **Michael W. Ruff:** Investigation. **Stacy D. D'Andre:** Investigation. **Terry C. Burns:** Investigation, Writing – review & editing. **Tufia C. Haddad:** Investigation, Methodology, Supervision, Writing – review & editing. **Lynn M. Flickinger:** Methodology, Visualization, Writing – review & editing. **Katrina Chan:** Methodology, Visualization, Writing – review & editing. **Carolyn Mead-Harvey:** Methodology, Validation, Writing – review & editing. **Susan M. Geyer:** Conceptualization, Investigation, Methodology, Project administration, Supervision, Validation, Writing – review & editing.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Ugur Sener has participated in professional services and activities for Merck & Co, Inc and Alexion Pharmaceuticals.

A Mayo Clinic invention disclosure has been submitted for the Stricker Learning Span and the Mayo Test Drive platform by Nikki H Stricker and John L Stricker.

Data availability

No data was used for the research described in the article.

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