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TITLE: Low-Dose Ketamine Infusion for the Treatment of Multiple Sclerosis Fatigue

PRINCIPAL INVESTIGATOR: Bardia Nourbakhsh

CONTRACTING ORGANIZATION: Johns Hopkins University

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6. AUTHOR(S)

Bardia Nourbakhsh

E-Mail:

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5e. TASK NUMBER

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Johns Hopkins University

8. PERFORMING ORGANIZATION REPORT NUMBER

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12. DISTRIBUTION / AVAILABILITY STATEMENT

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13. SUPPLEMENTARY NOTES

14. ABSTRACT: Fatigue, defined as a subjective feeling of lack of energy, is the most common symptom of multiple sclerosis (MS) and a major cause of disability among patients. It also does not have satisfactory treatments. This study is a single-center, phase II, randomized, double-blind, parallel-group, active-placebo-controlled trial of IV low-dose ketamine in patients with MS fatigue.
So far, the study has completed all regulatory requirements and started recruiting participants in January 2023. Up to this day, we have screened 19 participants, and 15 of them were eligible to participate and have received at least one infusion of the study medications. So far, nine participants have completed the study, and one participant, after completing the first period of the study, dropped out of the trial for personal reasons. We have scheduled at least six participants per month for the next two months. Because of the study team outreach and advertisement, we have been contacted by 50 people who expressed their interest in participating in this study. So, we have a large pool of potential participants for the next year, which guarantees continued recruitment for the study.

15. SUBJECT TERMS

NONE LISTED

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT	b. ABSTRACT	c. THIS PAGE			USAMRDC
U	U	U	UU	19	19b. TELEPHONE NUMBER *(include area code)*

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1. **INTRODUCTION:** *Narrative that briefly (one paragraph) describes the subject, purpose and scope of the research.*

The research is a clinical trial aimed at exploring the effectiveness of low-dose intravenous ketamine in managing fatigue, a pervasive symptom in Multiple Sclerosis (MS) patients. The purpose is to determine whether ketamine is superior to an active placebo (midazolam) in improving fatigue, if two infusions offer greater benefits than one, and how long the effects last. It also seeks to assess the safety and tolerability of ketamine in MS patients. The scope includes examining the impact of ketamine on momentary and daily fatigue severity, daily physical activity, and keystroke dynamics using a smartphone app. The study, comprising 110 participants, could potentially reveal a new, evidence-based treatment approach for MS fatigue.

2. **KEYWORDS:** *Provide a brief list of keywords (limit to 20 words).*

multiple sclerosis, fatigue, ketamine, MFIS, keystroke dynamic

3. **ACCOMPLISHMENTS:** *The PI is reminded that the recipient organization is required to obtain prior written approval from the awarding agency grants official whenever there are significant changes in the project or its direction.*

What were the major goals of the project?

List the major goals of the project as stated in the approved SOW. If the application listed milestones/target dates for important activities or phases of the project, identify these dates and show actual completion dates or the percentage of completion.

Specific Aims 1&2: Aim1A- To determine if an infusion of ketamine, as compared to midazolam, will improve fatigue severity over four weeks in patients with MS-related fatigue, as measured by traditional, recall-based, validated fatigue questionnaires. Aim 1B- To determine if two infusions of ketamine provide better improvement of fatigue, as compared to one infusion, and explore how long the effects of ketamine last. Aim 2- To determine the safety and tolerability of ketamine in patients with MS fatigue.	**Timeline**	**Status**
Major Task 1: Adapt the clinical trial protocol	Months	
Subtask 1: Prepare Regulatory Documents and Research Protocol for the clinical trial		
Finalize consent form & human subjects protocol	0	Completed before July 2022
IRB protocol submission	0	Completed before July 2022
Submission to Hopkins Clinical Research Unit (CRU)	1	Completed before July 2022
Coordinate with HRPO	0	Completed before July 2022

Clinicaltrial.gov registration	1	Completed before July 2022
Contact potential DSMB members	0	Completed before July 2022
Submit amendments, adverse events and protocol deviations as needed	As Needed	N/A
Annual IRB report for continuing review	Annually	5/12/2023
Milestone Achieved: IRB approval at JHU	2	Completed before July 2022
Formal submission of the IRB-approved protocol to HRPO	2	Completed in July 2022
JHU Clinical Research Unit review and approval of the protocol	2	Completed before July 2022
Milestone Achieved: HRPO approval for all protocols	4	Completed on 10/12/2022
Subtask 2: Coordinate study staff for the clinical trial		
Advertise and interview for project related staff	0	Completed before July 2022
Coordinate for space allocation for new staff	0	Completed before July 2022
Training staff until 100% concordance	3	Completed before July 2022
Milestone Achieved: Research staff trained	3	
Subtask 3: preparing study medications, database, CRFs, and stats		
Protocol review by the lead Hopkins ICTR statistician	0	Completed on 9/15/2022
Coordinating with Hopkins Investigational Drug Services (IDS) pharmacist for building the study templates, ordering meds, and developing the randomization procedure	0-2	Completed on 9/15/2022
Working with ICTR to build the study database and eCRF	0-2	Completed on 10/15/2022
Preparing the paper CRFs	0-3	Completed on 10/15/2022
Subtask 4: Finalizing all regulatory requirements		
Development of Manual of Operations	3	Completed on 11/1/2022
Finalize of Data and Safety Monitoring Board (DSMB) Charter and members list	3	Completed on 10/15/2022
Notification of posting final protocol on ClinicalTrials.gov	3	Completed before July 2022

Prepare the regulatory binder	3	Completed on 11/1/2022
Finalize the statistical Analysis Plan (SAP) with the study statistician	4	Completed on 9/15/2022
Milestone Achieved: All the required steps before starting the recruitment are completed	4	Completed on 11/1/2022
Major Task 2: Participant recruitment, treatment, and evaluation		
Start of recruitment (first patient in)	4	1/18/2023
Completion of 25% recruitment	11	Delayed due to starting enrollment later than expected
DSMB meeting #1	11	Delayed due to starting enrollment later than expected
Completion of 50% of recruitment	19	
DSMB meeting #2	19	
Completion of 75% of recruitment	27	
DSMB meeting #3	27	
Completion of 100% of recruitment	32	
Milestone achieved: Completion of 100 % follow-up data collection (last patient out) and data entry (N=110)	34	
Final statistical analyses of the primary, secondary, and safety outcomes	36	
Milestone achieved: completing the final study report, and submission of an abstract to a major neurology/MS conference	36	
Aim 3- To explore the effects of ketamine, as compared to midazolam on momentary and daily fatigue severity, daily physical activity (as measured by step count), and keystroke dynamics, all measured using a smartphone app (Neurokeys app).		
Major Task 1: Setting up an account with the vendor (Neurocast)		
Discussing the data collected through the append data collection process with Neurocast scientists	0	Completed before 1/1/2023
Negotiation and contract setup with Neurocast	0-3	Completed before 1/1/2023
Training the study staff the setup of the app on participants' phones	2-3	Completed before 1/1/2023
Milestone achieved: Neurokeys is ready to be installed on participants' phones and collect data	1	
Major Task 2: Neurokeys data collection and analysis		
Installing Neurokeys app on participants' phones	3 - 32	Ongoing
Troubleshooting issues participants can have using the app	3 - 34	Ongoing
Analysis of data obtained through Neurokeys app (exploratory outcomes)	35	
Milestone Achieved: Report findings from the exploratory outcomes		

What was accomplished under these goals?
For this reporting period describe: 1) major activities; 2) specific objectives; 3) significant results or key outcomes, including major findings, developments, or conclusions (both positive and negative); and/or 4) other achievements. Include a discussion of stated goals not met. Description shall include pertinent data and graphs in sufficient detail to explain any significant results achieved. A succinct description of the methodology used shall be provided. As the project progresses to completion, the emphasis in reporting in this section should shift from reporting activities to reporting accomplishments.

All the contractual and regulatory requirements were completed (including contracting with the sub-awardee (Neurocast B.V.), IRB approval, and OHRO approval of the protocol.
Before starting the recruitment, we amended the protocol to add blood biobanking to the study.
We started recruiting participants in January 2023, and so far screened 19 participants; 15 of them were eligible and received at least their first study infusion. Nine participants completed all study activities, and one participant dropped out due to personal reasons after completing only the first period of the study. There has been no SAE or unexpected AEs during the study.

What opportunities for training and professional development has the project provided?
If the project was not intended to provide training and professional development opportunities or there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe opportunities for training and professional development provided to anyone who worked on the project or anyone who was involved in the activities supported by the project. "Training" activities are those in which individuals with advanced professional skills and experience assist others in attaining greater proficiency. Training activities may include, for example, courses or one-on-one work with a mentor. "Professional development" activities result in increased knowledge or skill in one's area of expertise and may include workshops, conferences, seminars, study groups, and individual study. Include participation in conferences, workshops, and seminars not listed under major activities.

Mahsa Ghajarzadeh, MD, PhD, a post-doctoral fellow, who has worked as the study coordinator has been mentored by the PI (Dr. Nourbakhsh). She has learned about designing and running a clinical trial, regulatory issues, recruitment, and retention. Along with the PI, she published the study protocol as a peer-reviewed manuscript.

How were the results disseminated to communities of interest?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe how the results were disseminated to communities of interest. Include any outreach activities that were undertaken to reach members of communities who are not usually aware of these project activities, for the purpose of enhancing public understanding and increasing interest in learning and careers in science, technology, and the humanities.

Although we will not have the results of the study until completing the clinical trial, we published the trial protocol in a peer-reviewed journal (Ghajarzadeh, M., Roman, S., Vega, L., & Nourbakhsh, B. (2023). Low-dose ketamine infusion for the treatment of multiple sclerosis fatigue (INKLING-MS): Study protocol for a randomized, double-blind, active placebo-controlled phase II trial. Contemporary Clinical Trials, 126, 107106. https://doi.org/10.1016/j.cct.2023.107106)

Describe briefly what you plan to do during the next reporting period to accomplish the goals and objectives.

We will continue recruiting participants for the trial. We will also have our first DSMB meeting after recruiting 25% of the participants (after enrolling the 27th participant).

4. **IMPACT:** D*escribe distinctive contributions, major accomplishments, innovations, successes, or any change in practice or behavior that has come about as a result of the project relative to:*

What was the impact on the development of the principal discipline(s) of the project?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe how findings, results, techniques that were developed or extended, or other products from the project made an impact or are likely to make an impact on the base of knowledge, theory, and research in the principal disciplinary field(s) of the project. Summarize using language that an intelligent lay audience can understand (Scientific American style).

Nothing to Report.

What was the impact on other disciplines?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe how the findings, results, or techniques that were developed or improved, or other products from the project made an impact or are likely to make an impact on other disciplines.

Nothing to Report.

What was the impact on technology transfer?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe ways in which the project made an impact, or is likely to make an impact, on commercial technology or public use, including:

- *transfer of results to entities in government or industry;*
- *instances where the research has led to the initiation of a start-up company; or*
- *adoption of new practices.*

Nothing to Report.

What was the impact on society beyond science and technology?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe how results from the project made an impact, or are likely to make an impact, beyond the bounds of science, engineering, and the academic world on areas such as:

- *improving public knowledge, attitudes, skills, and abilities;*
- *changing behavior, practices, decision making, policies (including regulatory policies), or social actions; or*
- *improving social, economic, civic, or environmental conditions.*

Nothing to Report.

5. **CHANGES/PROBLEMS:** *The PD/PI is reminded that the recipient organization is required to obtain prior written approval from the awarding agency grants official whenever there are significant changes in the project or its direction. If not previously reported in writing, provide the following additional information or state, "Nothing to Report," if applicable:*

In our initial application, we had designated Neurocast (the provider the smartphone app we planned to use in the trial) as a vendor. However, it was later determined that Neurocast would qualify as a subcontractor. The required changes delayed the start of the recruitment.

Actual or anticipated problems or delays and actions or plans to resolve them
Describe problems or delays encountered during the reporting period and actions or plans to resolve them.

The recruitment was slightly slower than what we anticipated. We partnered with the National MS Society and they sent the information about the trial to people with MS who have subscribed to the NMSS newsletter. After that, we received inquires from more than 50 people living with MS, expressing their interest in participating in the study.

Changes that had a significant impact on expenditures
Describe changes during the reporting period that may have had a significant impact on expenditures, for example, delays in hiring staff or favorable developments that enable meeting objectives at less cost than anticipated.

Nothing to Report.

Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents
Describe significant deviations, unexpected outcomes, or changes in approved protocols for the use or care of human subjects, vertebrate animals, biohazards, and/or select agents during the reporting period. If required, were these changes approved by the applicable institution committee (or

equivalent) and reported to the agency? Also specify the applicable Institutional Review Board/Institutional Animal Care and Use Committee approval dates.

Significant changes in use or care of human subjects

There has been no unexpected outcomes or safety concerns.
The minor changes in the protocol that were approved by the IRB are shown in the following table:

Date	Modification	Rationale
9/14/2022	• Added blood biobanking to the study	As suggested by the study team, to be able to explore the biomarkers of response to study medication in the future.
	• Added SDMT, and MFIS subscales as exploratory endpoints	As suggested by the study team, to be able to explore the effects of study medication on cognition and physical, cognitive, and psychosocial fatigue.
	• Added: "History of glaucoma" to the exclusion criteria	As suggested by the DSMB
11/17/2022	• Add validated parking for participants at all in-person visits (screening, visit 1, and visit 2)	As suggested by a patient advocacy group
	• Added a question for the study staff to ask participants at the end of each infusion visit, i.e. "what medication do you guess you received at this infusion visit?" The study nurse will also answer the question: "what medication do you guess thparticipantnt received at this infusion visit?"	As suggested by the study staff
	• Clarified that urine pregnancy test to be done before the infusions on Infusion Day 1 and Infusion day 2	As suggested by the study staff

	• Clarified that CADSS and BPRS+ will be done 3 times at each infusion visit: 1) pre-infusion, 2) immediate post-infusion, and 3) 1.5 hours post-infusion	As suggested by the study staff

Significant changes in use of biohazards and/or select agents

Nothing to Report.

6. PRODUCTS: *List any products resulting from the project during the reporting period. If there is nothing to report under a particular item, state "Nothing to Report."*

- **Publications, conference papers, and presentations**
  Report only the major publication(s) resulting from the work under this award.

  Journal publications. *List peer-reviewed articles or papers appearing in scientific, technical, or professional journals. Identify for each publication: Author(s); title; journal; volume: year; page numbers; status of publication (published; accepted, awaiting publication; submitted, under review; other); acknowledgement of federal support (yes/no).*

  Ghajarzadeh, M., Roman, S., Vega, L., & Nourbakhsh, B. (2023). Low-dose ketamine infusion for the treatment of multiple sclerosis fatigue (INKLING-MS): Study protocol for a randomized, double-blind, active placebo-controlled phase II trial. Contemporary Clinical Trials, 126, 107106. https://doi.org/10.1016/j.cct.2023.107106

Books or other non-periodical, one-time publications. *Report any book, monograph, dissertation, abstract, or the like published as or in a separate publication, rather than a periodical or series. Include any significant publication in the proceedings of a one-time conference or in the report of a one-time study, commission, or the like. Identify for each one-time publication: author(s); title; editor; title of collection, if applicable; bibliographic information; year; type of publication (e.g., book, thesis or dissertation); status of publication (published; accepted, awaiting publication; submitted, under review; other); acknowledgement of federal support (yes/no).*

Nothing to Report.

Other publications, conference papers and presentations. *Identify any other publications, conference papers and/or presentations not reported above. Specify the status of the publication as noted above. List presentations made during the last year (international, national, local societies, military meetings, etc.). Use an asterisk (*) if presentation produced a manuscript.*

Nothing to Report.

- **Website(s) or other Internet site(s)**
  List the URL for any Internet site(s) that disseminates the results of the research activities. A short description of each site should be provided. It is not necessary to include the publications already specified above in this section.

Nothing to Report.

- **Technologies or techniques**
  Identify technologies or techniques that resulted from the research activities. Describe the technologies or techniques were shared.

Nothing to Report.

- **Inventions, patent applications, and/or licenses**
  Identify inventions, patent applications with date, and/or licenses that have resulted from the research. Submission of this information as part of an interim research performance progress report is not a substitute for any other invention reporting required under the terms and conditions of an award.

Nothing to Report.

- **Other Products**
  Identify any other reportable outcomes that were developed under this project. Reportable outcomes are defined as a research result that is or relates to a product, scientific advance, or research tool that makes a meaningful contribution toward the understanding, prevention, diagnosis, prognosis, treatment and /or rehabilitation of a disease, injury or condition, or to improve the quality of life. Examples include:
  - *data or databases;*
  - *physical collections;*
  - *audio or video products;*
  - *software;*
  - *models;*
  - *educational aids or curricula;*
  - *instruments or equipment;*
  - *research material (e.g., Germplasm; cell lines, DNA probes, animal models);*
  - *clinical interventions;*
  - *new business creation; and*
  - *other.*

Nothing to Report.

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

Provide the following information for: (1) PDs/PIs; and (2) each person who has worked at least one person month per year on the project during the reporting period, regardless of the source of compensation (a person month equals approximately 160 hours of effort). If information is unchanged from a previous submission, provide the name only and indicate "no change".

Example:

Name:	*Mary Smith*
Project Role:	*Graduate Student*
Researcher Identifier (e.g. ORCID ID):	*1234567*
Nearest person month worked:	*5*
Contribution to Project:	*Ms. Smith has performed work in the area of combined error-control and constrained coding.*
Funding Support:	*The Ford Foundation (Complete only if the funding support is provided from other than this award.)*

Name:	*Bardia Nourbakhsh*
Project Role:	*PI*
Researcher Identifier (e.g. ORCID ID):	*N/A*
Nearest person month worked:	*3*
Contribution to Project:	*The project PI*
Funding Support:	*This award, NMSS, NIH, Genentech, Clinical work*

Name:	*Mahsa Ghajarzadeh*
Project Role:	*Research coordinator*
Researcher Identifier (e.g. ORCID ID):	*N/A*
Nearest person month worked:	*12*
Contribution to Project:	*Dr. Ghajarzadeh has been the coordinator of the study, in charge of finding potential participants, scheduling study visits, consenting, data collection.*
Funding Support:	*This award*

Name:	*Mahsa Ghajarzadeh*
Project Role:	*Research coordinator*

Name:	*Lauren Vega*
Project Role:	*Research nurse*
Researcher Identifier (e.g. ORCID ID):	*N/A*
Nearest person month worked:	*6*
Contribution to Project:	*Ms. Vega has been the research nurse of the study, in charge of infusion visits, data collection, and also helping with screening potential participants.*
Funding Support:	*This award, Genentech, NMSS*

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

If the active support has changed for the PD/PI(s) or senior/key personnel, then describe what the change has been. Changes may occur, for example, if a previously active grant has closed and/or if a previously pending grant is now active. Annotate this information so it is clear what has changed from the previous submission. Submission of other support information is not necessary for pending changes or for changes in the level of effort for active support reported previously. The awarding agency may require prior written approval if a change in active other support significantly impacts the effort on the project that is the subject of the project report.

Nothing to Report.

What other organizations were involved as partners?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe partner organizations – academic institutions, other nonprofits, industrial or commercial firms, state or local governments, schools or school systems, or other organizations (foreign or domestic) – that were involved with the project. Partner organizations may have provided financial or in-kind support, supplied facilities or equipment, collaborated in the research, exchanged personnel, or otherwise contributed.

Provide the following information for each partnership:
Organization Name:
Location of Organization: (if foreign location list country)
Partner's contribution to the project (identify one or more)

- *Financial support;*
- *In-kind support (e.g., partner makes software, computers, equipment, etc., available to project staff);*
- *Facilities (e.g., project staff use the partner's facilities for project activities);*
- *Collaboration (e.g., partner's staff work with project staff on the project);*
- *Personnel exchanges (e.g., project staff and/or partner's staff use each other's facilities, work at each other's site); and*
- *Other.*

Nothing to Report.

8. SPECIAL REPORTING REQUIREMENTS

COLLABORATIVE AWARDS: *N/A*

QUAD CHARTS: *N/A*

9. APPENDICES: *N/A*