AWARD NUMBER: W81XWH-19-1-0138

TITLE: PTSD Prevention using Oral Hydrocortisone in the Immediate Aftermath of Trauma

PRINCIPAL INVESTIGATOR: Rachel Yehuda, PhD

CONTRACTING ORGANIZATION: Icahn School of Medicine at Mount Sinai, Department of Psychiatry

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6. AUTHOR(S): Dr. Rachel Yehuda, Heather Bader, Migle Staniskyte

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Icahn School of Medicine at Mount Sinai
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13. SUPPLEMENTARY NOTES

14. ABSTRACT

This project, PTSD Prevention Using Oral Hydrocortisone in the Immediate Aftermath of Trauma (PI: Rachel Yehuda), proposes to test a one-time prophylactic pharmacologic intervention – administration of oral hydrocortisone (HCORT) – for the prevention of post-traumatic stress disorder (PTSD) and related mental health disturbances. HCORT is a synthetic glucocorticoid similar to the body's own cortisol, and has numerous clinical uses as an anti-inflammatory agent. In response to acute stress, ample cortisol levels are critical to activating, and then containing, systems mobilized as part of the fight-or-flight response. There is evidence that people with lower cortisol levels at the time of trauma exposure are at elevated risk for PTSD.

15. SUBJECT TERMS
PTSD, prevention, hydrocortisone, trauma

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

There is currently no evidence-based intervention for individuals exposed to trauma that is designed to aid recovery and prevent the development of chronic disorders such as post-traumatic stress disorder (PTSD). This project proposes to test a one-time prophylactic treatment for the prevention of symptoms of PTSD and related mental health disturbances and the promotion of resilience using a single dose of hydrocortisone (HCORT), administered within six hours of trauma exposure.

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

Trauma; hydrocortisone; PTSD; prevention, prophylaxis

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.

Major Task 1 – establishment of regulatory and data acquisition infrastructure (**90% complete**)
Task 2 – develop and coordinate study staffing for clinical trial (**90% complete**)
Task 3 – participant recruitment, randomization, participant evaluation
Task 4 – execution of biomarker assays (each assay performed on samples from 150 subjects such that each assay performed across 5 collection time-points)
Task 5 – Data Analysis
Task 6 – Manuscript completion and transition planning

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.

Major Task 1 – establishment of regulatory and data acquisition infrastructure.

The subaward has been executed between ISMMS and SMC.

IND exemption by the FDA for the study has been received.

Key decisions to finalize study procedures and synchronize procedures across study sites have been made in the last reporting period. Efforts to synchronize medication administration between NYC and Israel have been made. Initial application submission to the Institutional Review Boards at both institutions have been completed. Meetings with IRB representatives and subsequent conversations with the IRB chairs regarding study procedures have occurred. IRB submissions at both ISMMS and SMC have passed administrative review and have been fully reviewed at the respective IRB meetings. Both sites are currently waiting for the final approval letters and documents in order to submit the study for HRPO submission. The process of gaining full IRB approval had been delayed in order to make the necessary efforts to synchronize study procedures and experienced further delay due to institutional shutdowns involved in the COVID-19 pandemic.

Submission for the use of the ISMMS Clinical Research Unit (CRU) and the Investigational Drug Service (IDS) have been completed and submitted. The DoD HRPO application has been drafted so the submission can be completed upon receipt of the final IRB approval letters.

Full R&D approval for the protocol from the James J. Peters VA Medical Center, where all participant biological samples will be analyzed, has been secured.

Submission to Clinicaltrials.gov is pending IRB approval.

Major Task 2: Develop and coordinate study staffing for clinical trial

We have hired personnel required for the study. Training of a clinical research coordinator and a study evaluator has been accomplished. Additional hiring has been intentionally delayed in order to conserve funds given the delays in subject recruitment procedures as the result of securing regulatory approval and delays resulting from the COVID-19 pandemic. A new private office at ISMMS has been secured to be used for clinical evaluations.

The study data collection framework and database using REDcap has been created and troubleshooting is underway. All Hebrew self-report measures to be completed at SMC have been created and provided for entry into REDcap. Self-report measures in Hebrew are currently being reviewed for consistency with the original English measures.

A sample management template is currently being created in the Freezerworks program.

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.

Post-doctoral evaluators are being trained on SCID and CAPS administration.

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.

Nothing to report.

What do you plan to do during the next reporting period to accomplish the goals?
If this is the final report, state "Nothing to Report."

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

Over the next reporting period, the research team plans to receive full board approvals from both institutions (Icahn School of Medicine and Chaim Sheba Medical Center), which are just waiting for Chair signoff. The HRPO application will be submitted and reviewed.

The study data collection framework within REDCap will be fully completed and utilized.

Recruitment guidelines and processes will be finalized.

Recruitment and randomization of participants will be initiated.

Evaluation of participants will be underway.

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:*

Nothing to report. No significant changes in the project of its direction.

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.

As previously reported, delays in securing regulatory approval were necessary in order to ensure that procedures at ISMMS and SMC were synchronized. Currently, we are awaiting final approval from the Icahn School of Medicine at Mount Sinai Institutional Review Board. Due to the Covid-19 crisis and its impact on New York City and Israel, we have experienced delays receiving regulatory approval as the IRB has been establishing rules related to the research shutdown throughout all of its' institutions. We are closely monitoring the situation in New York and will adhere to any policies set forth by the IRB at the Icahn School of Medicine. Due to the fact that study recruitment is planned to be initiated out of the Mount Sinai Emergency Department, we expect additional delays the study recruitment initiation.

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.

Given that study recruitment has not yet begun, study expenditures have been minimal. Expenditures were intentionally and strategically reduced from the original proposal in line with study delays so that the proposed work could still be accomplished within the original budget.

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

Nothing to report.

Significant changes in use or care of vertebrate animals

Nothing to report.

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).*

Nothing to report.

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: Rachel Yehuda, PhD
Project Role: Principal Investigator
Researcher Identifier: YEHUDAR01
Nearest person month worked: 2
Contribution to Project: As the Study PI of this multi-center project, she will be responsible for overseeing the overall project, working with the Site PI at Chaim Sheba Medical Center (CSMC), and the completion of all tasks on the SOW. She is responsible for the overall decisions on synchronization and finalization of study procedures.

Name: Janine Flory, PhD
Project Role: Co-Investigator
Nearest person month worked: 1
Contribution to Project: Dr. Flory ensures adherence to the protocol by supervising study evaluators and collaboration efforts between the ISMMS and Chaim Sheba Medical Center sites, which includes training and monitoring of rater fidelity.

Name: Linda Bierer, MD
Project Role: Co-Investigator and Medical Advisor
Nearest person month worked: .5
Contribution to Project: Dr. Bierer has assisted with medically relevant decisions, such as medication dosages and exclusion criteria.

Name: Tom Hildebrandt, PhD
Project Role: Co-Investigator and Statistician
Nearest person month worked: 1
Contribution to Project: Dr. Hildebrandt has updated the study aims, power analysis, and analytic plans as well as advised on the development of the database.

Name: Joseph Zohar, PhD
Project Role: Subaward Principal Investigator
Nearest person month worked: 2
Contribution to Project: Dr. Zohar has participated in biweekly conference calls with all study staff to finalize and synchronize study procedures.

Name: Lior Carmi, PhD
Project Role: Co-Investigator
Nearest person month worked: 3
Contribution to Project: Dr. Carmi participates in the bi-weekly conference calls and serves as the administrative contact at SMC until a clinical research coordinator is hired.

Name: Heather Bader
Project Role: Project Manager
Nearest person month worked: 2
Contribution to Project: Heather leads the bi-weekly conference calls and initiates discussions about the logistics involved in implementing the study protocol. She has supervised the drafting of all regulatory documents.

Name: Migle Staniskyte
Project Role: Clinical Research Coordinator
Nearest person month worked: 1
Contribution to Project: Migle has drafted the regulatory documents for the ISMMS site and takes notes at the biweekly conference calls.

Name: Emmanuel Ruhamyankaka
Project Role: Data Manager
Nearest person month worked: 1
Contribution to Project: Emmanuel has created the REDcap data capture infrastructure for the study.

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.*

Organization Name: Sheba Medical Center
Location of Organization: Tel Hashomer, Ramat Gan, Israel
Funding: Grant Funded
Partner's contribution to the project
Facilities: The Emergency Department at SMC will be used for subject recruitment. Outpatient psychiatry will be used for follow-up visits.
Collaboration: Additional recruitment site. Samples will be collected, processed, and sent to JJP VAMC for assay.

Organization Name: James J. Peters VAMC
Location of Organization: Bronx, NY
Partner's contribution to the project
Facilities: All participant biological samples will be transported to the James J. Peters VAMC for analysis. This facility is an affiliate of ISMMS.
Collaboration: occasionally, VA staff work on this research project.

8. SPECIAL REPORTING REQUIREMENTS

COLLABORATIVE AWARDS: *For collaborative awards, independent reports are required from BOTH the Initiating Principal Investigator (PI) and the Collaborating/Partnering PI. A duplicative report is acceptable; however, tasks shall be clearly marked with the responsible PI and research site. A report shall be submitted to* ***https://ers.amedd.army.mil*** *for each unique award.*

QUAD CHARTS: *If applicable, the Quad Chart (available on https://www.usamraa.army.mil) should be updated and submitted with attachments.*

9. APPENDICES:

Attach all appendices that contain information that supplements, clarifies or supports the text. Examples include original copies of journal articles, reprints of manuscripts and abstracts, a curriculum vitae, patent applications, study questionnaires, and surveys, etc.