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TITLE: Efficacy of Coenzyme Q10 Supplementation on Multi-Organ Dysfunction in Severely Burned Patients

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CONTRACTING ORGANIZATION: American Burn Association

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Efficacy of Coenzyme Q10 Supplementation on Multi-Organ Dysfunction in Severely Burned Patients

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6. AUTHOR(S)

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American Burn Association
Chicago, IL 60606

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13. SUPPLEMENTARY NOTES

14. ABSTRACT

Goal of the research: Assess therapeutic targets for the amelioration of adverse clinical outcomes seen in adults suffering severe thermal injury.
Aim 1: To evaluate the efficacy of reduced form Coenzyme Q10 (ubiquinol) supplementation in severely burned adult patients in the mitigation of multiple organ dysfunction syndrome between 72 hours after burn injury and 12 weeks, death, or discharge (whichever comes first).
Aim 2: To evaluate the effect of reduced form Coenzyme Q10 (ubiquinol) supplementation in severely burned adult patients on secondary clinical outcome events and biochemical measurements in plasma and urine between 72 hours after burn injury and 12 weeks, death, or discharge (whichever occurs first):
Study design: We will conduct a two-arm, prospective, double-blind, randomized, placebo-controlled clinical trial to evaluate the efficacy and safety of reduced form CoQ10 (ubiquinol) supplementation in severely burned adult patients (total n=290) at 15 mature burn centers across North America. Stratified block randomization will take place by site and Revised Baux score. The formula for the Revised Baux score is: Age + Percent Burn (%TBSA) + 17 x (Inhalation Injury, 1 = yes, 0 = no). This formula has been widely adopted for mortality prediction in burn patients. In previous studies, a trend has been shown for a sharp increase in mortality when the Revised Baux score exceeds approximately 110. Therefore, patients enrolled in this study will be stratified for randomization into two groups based on the Revised Baux score: (1) less than 110; and (2) equal to or greater than 110. The intervention will consist of a loading dose of reduced form CoQ10 of 1,800 mg/day tid for 4 weeks to be followed by a maintenance dose of 600 mg/day once daily from weeks 5 to 12. The intervention or allocation-controlled placebo will be administered by 72 hours after injury and will continue until 12 weeks after injury or until death or discharge, whichever comes first. Oral tablets (600 mg/tablet) will be administered to CoQ10 subjects who can swallow while a liquid form (100 mg/mL) will be administered to CoQ10 subjects requiring an enteral tube for nutrition. There will be no post-discharge study procedures.
Work completed during year 1: The fifteen centers were successfully recruited. IRB approval was achieved at the PI's home institution and inroads were made on using Smart IRB and reliance agreements as a mechanism for overall study approval, but unfortunately this pathway had to be aborted due to a change in employment (and therefore a new institutional home) for the PI. Given the delays that this administrative change entailed for the study, bids were solicited from external IRBs to be the IRB of record. Unfortunately, these were found to be cost prohibitive and this plan was aborted as well. Fortunately, around this time Dr. Masao Kineki (the original awardee) has become involved with the study once again as the circumstances which required his turning the study over to the current PI have resolved. Dr. Kineki's home institution of Massachusetts General Hospital has an IRB with the bandwidth to be able to support a SmartIRB application and we are pursuing this strategy at this time. An additional delay was encountered by HRPO who required that the PI interface with the FDA to obtain a ruling regarding the status of Dr. Kineki's previous IND exemption and it's applicability to the current study. The FDA required a formal request for this ruling, and the supporting application for same was submitted approximately 45 days ago. The FDA's determination on this question is still pending.

15. SUBJECT TERMS
Co-enzyme Q10, burn resuscitation, multicenter clinical study

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

TABLE OF CONTENTS

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

Objectives: (1) To determine the effects of coenzyme Q10 (CoQ10) supplementation, as an adjunctive therapy during the acute burn resuscitation period, on mitochondrial dysfunction and metabolic alterations in burn patients who are admitted to military and civilian hospitals; and (2) evaluate the safety of coenzyme Q10 supplementation in burn patients. This is a multi-center two-arm, prospective, double-blind, randomized, placebo-control study. Two hundred ninety (290) eligible adult burn patients will be enrolled in this study.

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

Co-enzyme Q10, burn resuscitation, multicenter clinical study

3. **ACCOMPLISHMENTS:** The PI is reminded that the recipient organization is required to obtain prior written approval from the awarding agency Grants Officer 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.

Objectives: (1) To determine the effects of coenzyme Q10 (CoQ10) supplementation, as an adjunctive therapy during the acute burn resuscitation period, on mitochondrial dysfunction and metabolic alterations in burn patients who are admitted to military and civilian hospitals; and (2) evaluate the safety of coenzyme Q10 supplementation in burn patients. This is a multi-center two-arm, prospective, double-blind, randomized, placebo-control study. Two hundred ninety (290) eligible adult burn patients will be enrolled in this study. STATUS: ONGOING **Task 1 Prepare Regulatory Documents** Task 1.1 Coordinate with Sites for IRB submission. Months 1-6. STATUS: The fifteen centers were successfully recruited. IRB approval was achieved at the PI's home institution of UT Southwestern and inroads were made on using Smart IRB and reliance agreements as a mechanism for overall study approval. Unfortunately this pathway had to be aborted due to the PI's changing employment (and therefore a new institutional home for the study). At the time of this writing, the PI is awaiting the imminent arrival of an employment contract from his new institution. Given the delays that this administrative change entailed for the study, bids were solicited by the PI from external IRBs to be the IRB of record. Unfortunately, these were found to be cost prohibitive and this plan was aborted as well. Fortunately, Dr. Masao Kineki (the original awardee) has become involved with the study once	

again as the circumstances which required his turning the study over to the current PI have resolved. Dr. Kineki's home institution of Massachusetts General Hospital has an IRB with the bandwidth to be able to support a SmartIRB application and we are pursuing this strategy at this time.

Task 1.2 Coordinate with Sites for DoD 2nd-level review (ORP/HRPO). Months 6-9.
STATUS: A submission was made to HRPO, but now an additional delay has been created by HRPO when that office required that the PI interface with the FDA to obtain a ruling regarding the status of Dr. Kineki's previous IND exemption and it's applicability to the current study. The FDA required a formal request for this ruling, and the supporting application for same was submitted approximately 45 days ago. The FDA's determination on this question is still pending.

Task 1.3 Submit amendments, adverse events and protocol deviations. AS NEEDED.
STATUS: None have been needed.

Task 1.4 Submit annual reports. ANNUALLY.
STATUS: The first annual report was submitted, deemed unacceptable, and has been resubmitted.

Milestone 1: Local IRB approval for all sites. Month 6
STATUS: See response to task 1.1 above

Milestone 2: HRPO approval for all sites. Month 9
STATUS: See response to task 1.2 above

Task 2 Subject Enrollment and Start of Study

Task 2.1 Finalize assessment measurements and case report form. Months 1-3.
STATUS: The PI and Dr. Kineki have interfaced with the Data Coordinating Center for the American Burn Association. A biostatistician and IT personnel have been assigned to the study and the CRF is currently under construction.

Task 2.2 Coordinate with Sites for flow chart for all study steps, web data collection and database requirements. Months 4-6.
STATUS: See above

Task 2.3 Begin subject enrollment. Months 7-8.
STATUS: Yet to start

Milestone 1: Study begins. Months 7-8.
STATUS: Yet to start

Milestone 2: 1st participant consented, screened and enrolled. Months 7-8.
STATUS: Yet to start

Task 3 Conduct Study and Interim Analysis

Task 3.1 Enroll subjects. Months 7-42.
STATUS: Yet to start

Task 3.2 Coordinate with Sites & Data Core for monitoring, enrollment, data collection and data quality. Months 7-42
STATUS: Yet to start

Task 3.3 Interim analysis. Months 7-29.
STATUS: Yet to start

Task 3.4 Data safety monitoring board activity. Months 7-43
STATUS: The PI has interfaced with the Data Coordinating Center's biostatistician for creation of DSMB charter verbiage related to stopping rules at the interim analyses.

Task 3.5 Perform interim analysis of effects of CoQ10 on outcome measures. Months 20-24
STATUS: Yet to start

Task 3.6 Reassess sample size, if necessary. Months 24-25
STATUS: Yet to start

Task 3.7 Interim assessment of safety of CoQ10/placebo supplementation. Months 20-25.
STATUS: Yet to start

Milestone 3: Report findings from interim analysis. Months 25-29.
STATUS: Yet to start

Task 4 Data Analysis

Task 4.1 Perform all analyses according to specifications, share output and finding with all investigators. Months 43-47.
STATUS: Yet to start

Task 4.2 Work with data core and dissemination of findings (abstracts, presentations, publications, DOD). Months 46-48.
STATUS: Yet to start

Milestone 4: Report results from data analyses. Months 46-48
STATUS: Yet to start

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.

Objective 1: Determine the effects of coenzyme Q10 (CoQ10) supplementation, as an adjunctive therapy during the acute burn resuscitation period, on mitochondrial dysfunction and metabolic alterations in burn patients who are admitted to military and civilian hospitals

The fifteen centers were successfully recruited. IRB approval was achieved at the PI's home institution and inroads were made on using Smart IRB and reliance agreements as a mechanism for overall study approval, but unfortunately this pathway had to be aborted due to a change in employment (and therefore a new institutional home) for the PI. Given the delays that this administrative change entailed for the study, bids were solicited from external IRBs to be the IRB of record. Unfortunately, these were found to be cost prohibitive and this plan was aborted as well. Fortunately, around this time Dr. Masao Kineki (the original awardee) has become involved with the study once again as the circumstances which required his turning the study over to the current PI have resolved. Dr. Kineki's home institution of Massachusetts General Hospital has an IRB with the bandwidth to be able to support a SmartIRB application and we are pursuing this strategy at this time. An additional delay was encountered by HRPO who required that the PI interface with the FDA to obtain a ruling regarding the status of Dr. Kineki's previous IND exemption and it's applicability to the current study. The FDA required a formal request for this ruling, and the supporting application for same was submitted approximately 45 days ago. The FDA's determination on this question is still pending.

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.

Nothing to Report

How were the results disseminated to communities of interest?

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."

The PI will finalize his employment contract with his new institution. The FDA ruling on the status of the IND exemption will be received and acted upon as needed. An IRB application will be made to Massachusetts General Hospital to be the IRB of record, and once achieved Smart IRB and reliance agreements will be initiated. CRF completion and electronic secure platforms for data input will be completed.

4. **IMPACT:** Describe 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?

Nothing to report.

What was the impact on other disciplines?

Nothing to report.

What was the impact on technology transfer?

Nothing to report.

What was the impact on society beyond science and technology?

Nothing to report.

5. **CHANGES/PROBLEMS:** The Project Director/Principal Investigator (PD/PI) is reminded that the recipient organization is required to obtain prior written approval from the awarding agency Grants Officer 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:

Changes in approach and reasons for change

In addition to the above, the following are accomplishments or changes in the last quarter:
1. A dialogue has begun with the ABA's Data Coordinating Center to create the CRFs. Dr. Sandy Taylor has been named the biostatistician who will assist in this endeavor.

2. The charter for the Data Safety Monitoring Board has been started. Dr. Taylor has promised to help with the verbiage for the stopping rules for safety, efficacy, and futility during the interim analyses.
3. Lori Palfalvi has begun the process of setting up the study in clinicaltrials.gov
4. Local co-investigator changes were required at Temple in Philadelphia and Univ of South Florida due to changes in personnel

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.

Nothing to report.

Changes that had a significant impact on expenditures

Nothing to report.

Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents

Significant changes in use or care of human subjects

Nothing to report.

Significant changes in use or care of vertebrate animals.

N/A

Significant changes in use of biohazards and/or select agents

N/A

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.

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.

None

- **Technologies or techniques**
  Identify technologies or techniques that resulted from the research activities. In addition to a description of the technologies or techniques, describe how they will be 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. State whether an application is provisional or non-provisional and indicate the

application number. 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;*
  - *biospecimen 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*

None

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."

Name:	Herb Phelan
Project Role:	Principal Investigator
Researcher Identifier:	
Nearest person month worked:	1
Contribution to Project:	

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?

Nothing to report.

8. SPECIAL REPORTING REQUIREMENTS

COLLABORATIVE AWARDS: For collaborative awards, independent reports are required from BOTH the Initiating 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: In addition to embedding an updated Quad Chart within this annual / final technical report, also submit a standalone copy as an attachment in PowerPoint file only (.ppt or .pptx) to CDMRP Reporting at usarmy.detrick.medcom-cdmrp.mbx.cdmrp-reporting@mail.mil and copy the assigned CDMRP Science Officer.

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.