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TITLE: Examining the Reproductive Health of Gulf War Veterans and the Subsequent Health and Development of Their Children

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14. ABSTRACT For many years veterans of the 1990-1991 Gulf War (GW) have continued to express concern about the health of their family members, specifically their children. Despite multiple early indications of excess birth defects and reproductive anomalies in families GW veterans after the 1990-91 GW, long-needed follow up and further assessment of these issues have not been conducted. Most surprisingly, no studies have specifically evaluated whether reproductive, birth and children's health outcomes differentially affect veterans with GW illness (GWI), and only a limited few have considered these outcomes in relation to hazardous exposures during GW service. The proposed study is therefore designed to directly address these longstanding questions, focusing specifically on the association of GWI and characteristics of GW service with birth and reproductive issues in veterans' families and health outcomes in veterans' children. We will specifically evaluate whether GWI and exposures during GW deployment were associated with increased risk for adverse reproductive health outcomes for GW veterans and differences in developmental and overall health of their children. We hypothesize that exposures experienced during the GW contribute to adverse reproductive health outcomes and neurodevelopmental outcomes for GW veterans, particularly those with GWI.						
15. SUBJECT TERMS Gulf War exposure, Gulf War Illness, Children's Health, Reproductive Health, General Health and Well-Being, Intergenerational, Survey						
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1. INTRODUCTION:

While the Gulf War (GW) was relatively short, veterans have suffered long-lasting debilitating health effects because of their deployment. Few research studies have explicitly looked at service in the GW and the reproductive health of our veterans. While a limited amount of research was conducted on reproductive outcomes among veterans, previous research found that GW veterans (GWVs) have greater rates of adverse pregnancy outcomes, such as birth defects and one study found that GWVs have an increased risk of serious birth defects, like congenital heart defects. The objectives of this proposal are to examine 1) GWV reproductive health and birth outcomes 2) if GWI or GW exposures play a role in reproductive health and/or birth outcomes 3) the development and overall health of children of GWVs 4) if GWI and/or GW exposures impacted development or overall health of GWVs' children. While previous research studies have found evidence that veterans experience a higher number of adverse reproductive outcomes, questions remain about how GW deployment may affect the development and overall health of the children of GWVs. In addition, no previous studies have examined reproductive outcomes as it relates to GWI.

2. **KEYWORDS:** Gulf War Exposures, Gulf War Illness, Children's Health, Reproductive Health, General Health and Well-Being, Intergenerational, Survey

3. ACCOMPLISHMENTS

Major tasks of the project 1-3.

The approved statement of work lists the major goals of the project and the timeline for achieving each goal:

Statement of work: LEGACY Protocols

Research Specific Tasks:	Timeline	Location
Major Task 1: Obtain IRB approval	months	Site(s)
Subtask 1: Obtain local IRB approvals or exempt status	1-3	1-6
Subtask 2: Obtain HRPO approval or exempt status	3-6	1-6
<i>Milestone(s) Achieved: Obtained local IRB and HRPO approvals</i>	1-6	
Major Task 2: Survey creation and testing (parent)		
Subtask 1: Create survey questions to be included in parent survey	6-12	1 & 2
Subtask 2: Test survey questions	12	1 & 2
<i>Milestone(s) Achieved: Complete GW parent survey and ready for administration</i>	6-12	

Major Task 3: Survey creation and testing (adult child)		
Subtask 1: Create survey questions to be included in adult child survey	6-12	1 & 2
Subtask 2: Test survey questions	12	1 & 2
<i>Milestone(s) Achieved: Complete adult child survey and ready for administration</i>	6-12	
Major Task 4: Administer parent and adult child surveys		
Subtask 1: Recruit subject for GW parent survey and administer surveys (N=725)	12-30	1-4
Subtask 2: Recruit subjects for adult child survey and administer surveys (N=325)	12-30	1-4
<i>Milestone(s) Achieved: Recruit and administer all parent and adult child surveys</i>	12-30	
Major Task 5: Recruit subjects (parent/child pairs N=100, total of 200 people) for blood draws		
Subtask 1: Recruit subjects for blood draw and collect and store blood	12-30	1
<i>Milestone(s) Achieved: Collect all blood samples from 100 parent/child pairs (200 total individuals)</i>	12-30	1
Major Task 6: Data Analysis for gene-exposure analysis		
Subtask 1: Perform exposure outcome data analyses (preliminary and final)	18-36	1-5
<i>Milestone(s) Achieved: final data analysis completed</i>	12-36	
Major Task 7: Disseminate study results		
Subtask 1: Present finding at scientific meetings	24-36	1-5
Subtask 2: Prepare manuscripts and submit for publication	28-36	1-5
<i>Milestone(s) Achieved: preliminary data presented at annual scientific conferences and manuscript submission of final data analysis</i>	28-36	
Major Task 8: Write annual and final reports for DoD		
Subtask 1: Write annual reports for DoD	12, 24	1-5
Subtask 2: Write final report for DoD	36	1-5
<i>Milestone(s) Achieved: Annual and final reports will be submitted to DoD</i>	12, 24, 36	

Statement of Work:

The statement of work for year 1 is inclusive of tasks 1-3 above. Major task 1 has achieved partial completion, as we have obtained exempt status for our study from the IRB at Boston University, and our application has been submitted to OHRO. Major task 2 has made significant progress, with the parent survey being completed and testing of survey questions scheduled as soon as the REDcap platform is established. The same goes for Major task 3 (i.e. The survey is drafted and awaiting to be tested in REDcap when synthesized).

Major Task 1: Obtain IRB approval

Subtask 1: Obtain local IRB approvals or exempt status

Subtask 1 has been completed with Boston University obtaining Institutional Review Board (IRB) exempt status.

Subtask 2: Obtain OHRO approval or exempt status

We received local IRB approval but have decided to change the name of the study to the LEGACY study and are awaiting the amendment approval. Once we receive that approval we will submit the OHRO paperwork.

Major Task 2: Survey creation and testing (parent)

Subtask 1: Create survey questions to be included in parent survey

Survey for GWV parents has been completed. The next step is for the data coordinating center at BU to develop this survey on the REDcap electronic database and this work is underway.

Subtask 2: Test survey questions

Our survey questions have been reviewed with our collaborators through the development process. Once the REDcap survey is synthesized we will then invite our collaborators and Gulf War veteran advocates to test the survey. We decided to wait until the REDcap survey is developed to test out the survey questions in this capacity since there is complex branching logic built in and should be reviewed to enhance the respondent's experience.

Major Task 3: Survey creation and testing (adult child)

Subtask 1: Create survey questions to be included in adult child survey

Survey for adult children has been completed. The next step is for the data coordinating center at BU to develop this survey on the REDcap electronic database.

Subtask 2: Test survey questions

Similar to the parent survey (major task 2), our survey questions have been reviewed with our collaborators through the development process. This survey is an adapted version of the parent

survey and informed by Gulf War Veteran testimonies. Once the REDcap survey is synthesized we will then invite our collaborators and Gulf War Veteran advocates to test the survey. We decided to wait until the REDcap survey is developed to test out the survey questions in this capacity since there is complex branching logic built in and should be reviewed to enhance the respondent's experience.

Major Task 4: Administer parent and adult child surveys

Subtask 1: Recruit subjects for GW parent survey and administer surveys (N=725)

A recruitment protocol has been developed and approved by the IRB. Additionally, recruitment materials such as the study website, flyers, and scripts have also been finalized and are ready for launch. Once our REDcap platform is ready, we will begin recruiting participants.

Subtask 2: Recruit subjects for adult child survey and administer surveys (N=325)

Similar to subtask 1, recruitment protocols and materials are ready to launch. We will need to wait until Gulf War Veterans have completed the parent survey and indicated that they have children 18 years old or older. We will then reach out to those parents and share recruitment materials with them to share with their adult children.

Opportunities for training and professional development:

Research Staff Training:

Personnel who will be using the web systems for either direct data capture, participant tracking, or viewing reports have been trained to ensure uniformity of procedures, to achieve the ultimate aim of ensuring high quality protocol implementation and data collection. As a large academic community, Boston University also provides opportunities for students to get real world experience. This study can serve as a practicum experience for students or an opportunity to intern in the field of health communication and/or environmental health research. Doctoral students in related fields can also be brought on to aid in this project. This is also a training and professional development opportunity for the research assistant involved in the study as they are responsible for synthesizing study materials, connecting with veterans and their families, as well as abiding by the IRB protocol/standards.

How results will be disseminated to communities of interest:

The research team will employ the study website as a platform for open dissemination of research findings. Moreover, we will establish a collaborative partnership with the BBRAIN research group, leveraging their well-established outreach network that has been operational for numerous years. This network includes their Facebook page, boasting over 3,000 dedicated followers, many of whom actively engage with and share its content.

Furthermore, Boston University benefits from a highly proactive media team that consistently produces news stories, which are widely circulated. Notably, BU's professional publication highlighting the grant funding for this study garnered significant attention from veterans and advocacy groups. We anticipate that our targeted community will continue to frequent these sources for updates on the study's findings and their implications for the Gulf War veteran community and their families.

Plan for upcoming reporting period to accomplish goals:

In the next reporting period, we plan to:

- Recruit Gulf War veterans and their adult children
- Administer the survey to Gulf War veterans and their adult children
- Begin analyzing survey responses
- Obtain IRB and OHRO approval for the blood draw part of the study
- Begin recruiting parent/child pairs for the blood draw part of the study

4. IMPACT:

While there has been some focused study on reproductive health outcomes among Gulf War veterans the data are still limited and many questions remain for these veterans and their spouses. In addition, these same veterans have, for many years, had questions about whether their services could have negatively impacted the health of their children. Unfortunately, this topic has received very limited scientific exploration. In addition to general service concerns, GW veterans have concerns related to GWI and reproductive and family health. Determining whether maternal or paternal GWI or in-theater environmental exposures play a role in these outcomes and establishing a parent/child repository for epigenetic studies will be critical to further document and understand these toxicant exposure-related outcomes, which have now become a focus for Congressional and senior government officials.

Impact on other disciplines

Nothing to report.

Impact on technology transfer

Nothing to report.

Impact on society beyond science and technology

Nothing to report.

5. CHANGES/PROBLEMS:

We experienced delays in developing the survey because we received rich information from Gulf War Veteran testimonies and valuable insights from veterans who learned about the study through Boston University's grant funding post and reached out. In light of this valuable input, our research team decided to review and enhance both surveys by incorporating feedback from veterans and advocates, while also taking into account the viewpoints of our collaborators.

Additionally, the study title underwent multiple iterations. Initially this study was referred to as the "Repro Study" which was then critiqued for only emphasizing the reproductive health aspect of the study. In response, the research team renamed the study to the "Children's Health and Intergenerational Development Study (CHILD) Study" but collaborators were concerned that this might discourage veterans without children from participating. Ultimately, we settled on the name "Longitudinal Effects of The Gulf War: Veteran Reproductive Health and Children's Health Survey (LEGACY) Study" as it accurately captures the full scope of this project.

Furthermore, we decided to submit an IRB amendment to modify the eligibility criteria. Originally, our intention was to recruit exclusively from previous studies (such as BBRAIN, NEW BBRAIN, GWIC, etc.). However, we have reconsidered this approach, recognizing that it would exclude a significant number of Gulf War Veterans who are interested in participating but did not meet the original qualifications. This decision stems from the substantial interest generated by BU's post about the grant funding.

Unfortunately, these delays prevented us from submitting the Institutional Review Board (IRB) protocol early enough for the Office of Human Research Oversight (OHRO) to approve it within the first year.

Finally, we did not obtain IRB approval or exempt status for the blood sample component of this study. The IRB recommended that we file a distinct IRB application for the blood draw, as attempting to integrate it with the survey component could potentially complicate and delay that aspect of the study. The research team reached a consensus on this recommendation and prioritized the completion of the survey protocol. Our plan is to develop and submit the IRB application for the blood draw once recruitment has commenced and survey completion is well underway.

6. PRODUCTS:

- Publications, conference papers, and presentation
Nothing to Report
- Website(s) or other Internet sites
 - Study website ready to launch (bu.edu/legacystudy/): This website was designed to familiarize site visitors with information on the Gulf War (i.e., events, exposures, and gulf war illness), the specific goals of the study, current findings and literature gaps, contact information, as well as answers to anticipated questions about study involvement.
- Technologies or techniques
Nothing to Report
- Inventions, patent applications, and/or licenses
Nothing to Report
- Other Products
 - Gulf War parent and adult child Surveys: These surveys are novel in that they evaluate general health, reproductive health, and children health outcomes associated with Gulf War exposures and illness (if applicable).

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

Individuals that have worked on the project:

Name: Patricia Janulewicz Lloyd	Project Role:	<i>PI of LEGACY Study</i>
	Researcher Identifier (e.g. ORCID ID):	
	Nearest person month worked:	<i>12</i>
	Contribution to Project:	
	Funding Support:	
Name: Kimberly Sullivan	Project Role:	<i>Co-Investigator, Boston University</i>
	Researcher Identifier (e.g. ORCID ID):	<u>https://orcid.org/0000-0001-7940-6123</u>

	Nearest person month worked:	12
	Contribution to Project:	<i>Oversee the biorepository at BUSPH; oversee the recruitment and participation of NEW BBRAIN (200 participants); oversee data and sample coordination of all prospective and retrospective BBRAIN sites.</i>
	Funding Support:	
Name: Nancy Klimas	Project Role	<i>Co-Investigator, Nova Southeastern University</i>
	Researcher Identifier (e.g. ORCID ID):	<u>https://orcid.org/0000-0003-1459-3268</u>
	Nearest person month worked:	
	Contribution to Project:	<i>Oversee sharing recruitment material with participants from Miami VA medical center who have agreed to future contact.</i>
	Funding Support:	
Name: Lea Steele	Project Role	<i>Co-Investigator, Baylor College of Medicine</i>
	Researcher Identifier (e.g. ORCID ID):	
	Nearest person month worked:	
	Contribution to Project:	<i>Oversee sharing recruitment material with participants from Houston who have agreed to future contact.</i>
	Funding Support:	
Name: Linda Chao	Project Role	<i>Co-Investigator, NCIRE/San Francisco (VA)</i>
	Researcher Identifier (e.g. ORCID ID):	<u>https://orcid.org/0000-0002-8593-2434</u>
	Nearest person month worked:	

	Contribution to Project:	<i>Oversee sharing recruitment material with participants from San Francisco who have agreed to future contact.</i>
	Funding Support:	
Name: Emily Sisson	Project Role	<i>Data Manager/Analyst, Boston University</i>
	Researcher Identifier (e.g. ORCID ID):	N/A
	Nearest person month worked:	
	Contribution to Project:	<i>Data Management Specialist</i>
Name: Timothy Heeren	Project Role	<i>Co-Investigator, Boston University</i>
	Researcher Identifier (e.g. ORCID ID):	https://orcid.org/0000-0001-5643-3559
	Nearest person month worked:	
	Contribution to Project:	<i>Senior Biostatistician</i>
Name: Maxine Kregel	Project Role	<i>Co-Investigator, VA Boston Health Care System</i>
	Researcher Identifier (e.g. ORCID ID):	https://orcid.org/0000-0001-7632-590X
	Nearest person month worked:	
	Contribution to Project:	<i>Oversee sharing recruitment material with participants from BU who have agreed to future contact.</i>

- **Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?**

Nothing to report.

- **Other organizations serving as partners:**

Nothing to report.

8. SPECIAL REPORTING REQUIREMENTS

o COLLABORATIVE AWARDS:

Nothing to report.

9. APPENDICES:

Nothing to report