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TITLE: Agent Orange Exposure and Bladder Cancer

PRINCIPAL INVESTIGATOR: Stephen B. Williams, MD

CONTRACTING ORGANIZATION: The University of Texas Medical Branch
                                                    Galveston, TX 77555

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14. ABSTRACT

Training specific tasks including advanced degree coursework during 1-24mo have been completed. Dr. Williams has applied this coursework towards attaining an MS degree and has entered candidacy, submitted thesis, with anticipated graduation during months 12-18. Dr. Williams has and continues to attend meetings (Freedland, group, professional development advisory committee). Research specific tasks, specific aim 1, subtask 1 has been complete (months 1-4) and subtask 2 (months 1-18) is on target for database completion. We are set to complete Specific Aim 1 and enter analysis within the 18-24mo target time frame as stated in the SOW. We identified 11,692,562 patients and populated all fields queried in our database except stage and grade of bladder cancer. Natural language programming is being used to collect stage and grade of bladder cancer followed by internal audit to clean and verify integrity of data. Manuscript preparation, submission and publication will commence during months 12-24 on target. Day to day management activities of the PI have been upheld during this time period.

15. SUBJECT TERMS
Agent Orange, bladder cancer, statement of work (SOW), database, analysis

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON USAMRMC
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1. **INTRODUCTION:** To date, only limited data exist regarding the link between Agent Orange (AO) and bladder cancer (BC) risk and mortality. The Institute of Medicine (IOM) concluded the interplay between AO exposure and BC outcomes is an area of needed research. Based upon this, the Veterans Affairs (VA) is considering BC as an AO related disease. Indeed, the Department of Defense Peer Reviewed Cancer Research Program (PRCRP), for the first time, included a focus area on BC and AO. Therefore, our proposal is not only timely but will help answer two key questions: Is AO linked with BC risk and/or mortality? Using one of the largest databases ever assembled for BC research containing data on over 5.7 million people, we will test whether AO is linked with increased BC and death from BC. Hypothesis/Objective: We hypothesize AO exposure will be linked with increased BC and worse BC-specific survival. Aim 1. Determine whether AO exposure is linked with BC risk. We will develop a nation-wide cohort of people in the VA Health system since 2000. We will query this cohort for AO exposure to test if AO exposure is linked with increased BC risk. Results will be adjusted for potential confounders such as smoking, age, and race. Aim 2. Explore whether AO exposure is linked with BC-specific mortality. Using the cohort from Aim 1, we will ascertain cause of death from the national death index (NDI). Results will be adjusted for potential confounders as in Aim 1 but also clinical stage and treatment(s) received. The mentorship team has been directed under Stephen J. Freedland, M.D. Dr. Freedland (mentor) and Dr. Williams (PI) are located at different organizations with the proposed research to be conducted at the Durham VA. Dr. Freedland has supervised and mentored Dr. Williams through teleconferences, screen sharing via Microsoft Lync, as well as face-to-face meetings. The research findings will provide much needed information discerning if AO exposure is linked to increase risk of BC (Topic Area) in the VA population. The guidance/mentorship by Dr. Freedland and the entire professional development advisory committee will further reinforce Dr. Williams' research development and bring his current and future research to the next level. At the conclusion of 3 years, Dr. Williams will have a BC research team with the largest database ever created to study AO and BC (with patient tissues) to successfully apply for further grant funding opportunities.

2. **KEYWORDS:** Agent Orange, bladder cancer, incidence, risk

3. **ACCOMPLISHMENTS:**

- **What were the major goals of the project?**

Training-Specific Tasks: *(only applicable to training award mechanisms)*

	Target Months	Actual Completion Dates	Percentage of Completion
Major Task 1: Complete coursework in data management and biostatistics methodology			
Subtask 1: Coursework: Data management PHS 6210, Biostatistics PHS 6343	1-12	12/31/17	100
Milestone(s) Achieved: Complete coursework	1-12	6/1/18	100
Major Task 2: Complete coursework in Population oriented research and research design			
Subtask 1: Coursework: Research design PHS 6322, Population oriented research PHS 6213	12-24	6/1/18	100
Milestone(s) Achieved: Complete coursework	12-24	6/1/18	100
Major Task 3: Meetings (Freedland, group, professional development advisory committee)	1-36		
Subtask 1: Travel to Cedars-Sinai 2x per year	1-36		100
Subtask 2: Travel to DVAMC 5x per year	1-36		100
Subtask 3: Travel to American Urological Association (AUA) and Society of Urological Oncology (SUO) conferences and meet Dr. Freedland 2x per year	1-36	AUA: 5/17-5/19/18; SUO: 11/29-12/1/17	100
Subtask 4: Professional development committee meetings 4x per year	1-36	Quarterly with last 7/11/18	100
Subtask 5: Drs. Freedland/Williams every other week, one-hour telephone conference meetings.	1-36	Ongoing	100
Subtask 6: Dr. Freedland team weekly telephone research in progress meetings	1-36	Ongoing	100
Subtask 7: Programmer weekly telephone conference meetings to discuss and review: 1. Database development/data extraction 2. Database management 3. Data queries and audits 4. Natural language processing, extraction and	1-36	Ongoing	100

audits			
Subtask 8: Database team weekly telephone conference meetings	1-36	Ongoing	100
Subtask 9: Statistician team weekly telephone conference meetings to discuss and review current and future analyses	1-36	Monthly at present ongoing as database building ongoing at present	na
Subtask 10: DVAMC research manager bi-monthly telephone conference meetings to discuss database programmer, statisticians and proposal timeline	1-36	Monthly last 8/1/18	100
Subtask 11: UTMB Department of Surgery grants manager monthly meeting to go over proposal timeline, budget and future applications	1-36	Monthly last 8/1/18	100

Research-Specific Tasks:

Specific Aim 1: Determine whether AO exposure is linked with risk of BC.	1-24		
Major Task 1: Determine whether AO exposure is linked with risk of BC.			
Subtask 1: Regulatory review and approval by the USAMRMC Human Research Protection Office (HRPO)	1-4	11/15/17	100
Subtask 2: Identify VA patients according to AO exposure and determine BC risk. A total of 3.15 million patients will need to be identified to detect clinically insignificant results. 1. Identify patients in VINCI with and without AO exposure and query these patients using diagnoses (all ICD-9 and -10 codes), procedures (all CPT codes) and natural language processing 2. Extract and develop an SQL server database with key data points 3. Source to home data programming 4. Self-auditing and clean data	1-18	Ongoing with target on schedule for completion 1/31/19	80
Subtask 3: Perform analyses. 1. Interaction testing between AO exposure and smoking, age (< vs. > median), gender, and obesity. 2. Perform multivariable Cox hazards analysis adjusting for age, gender, race, comorbidities,	18-24		

SES (median household income of home zip code), VA center and smoking status. 3. ANOVA-tests for normally distributed continuous variables, Kruskal-Wallis tests for non-normally distributed continuous variables, and chi-square tests for categorical variables. 4. Logistic regression to test if AO is related to muscle invasiveness.			
Subtask 4: Manuscript preparation, submission and publication	12-24	Ongoing (database stage and grade pending followed by analysis)	0
Subtask 5: Day-to-day management activities of the PI. Monday (am/pm), Tuesday (am) and Wednesday (1/2am) coursework at GSBS. Tuesday (pm) and Wed/Thursday (pm) operative and clinic days, respectively. Wednesday (1/2am), Thursday (am) and Friday (am/pm) research days. Travel to Cedars-Sinai 2x per year, Travel to DVAMC 5x per year, Travel to American Urological Association and Society of Urological Oncology conferences and meet Dr. Freedland 2x per year Meet with professional development committee 4x per year 1. UTMB Department of Surgery grants manager monthly one-hour meeting to go over proposal timeline, budget and future applications 2. DVAMC research manager bi-monthly one-hour telephone conference meetings to discuss database programmer, statisticians and proposal timeline 3. DVAMC programmer weekly 1-2 hour telephone conference meetings to discuss and review Aim 1: database development/data extraction, database management, data queries and audits, natural language processing,	1-24	ongoing	100

extraction and audits, review timeline and goals			
4. DVAMC database team weekly telephone conference meetings			
5. DVAMC statistician team weekly telephone conference meetings to discuss and review current and future analyses			
6. DVAMC statistician weekly telephone conference 1-2 hours telephone meeting (months 18-24)			
7. Drs. Freedland/Williams every other week, one-hour telephone conference meetings.			
8. Dr. Freedland team weekly telephone research in progress meetings			
9. Weekly ad-hoc 1 hour telephone conference calls to answer and go over any database or analysis questions			
Milestone(s) Achieved: The DVAMC bladder cancer database is developed. The analyses determining the association and results pertaining to the risk of BC according to AO exposure will be published.	1-24	Ongoing with NLP stage and grade with analyses to be complete followed by publication	50

- **What was accomplished under these goals?**

  (See Training specific task accomplishments in following section)

  Research-Specific Tasks:

  Major Task 1: Determine whether AO exposure is linked with risk of BC.

  Subtask 1: Regulatory review and approval by the USAMRMC Human Research Protection Office (HRPO). *This was approved by HRPO on 11/15/17.*

Subtask 2: Identify VA patients according to AO exposure and determine BC risk. A total of 3.15 million patients will need to be identified to detect clinically insignificant results.

1. Identify patients in VINCI with and without AO exposure and query these patients using diagnoses (all ICD-9 and -10 codes), procedures (all CPT codes) and natural language processing

2. Extract and develop an SQL server database with key data points

3. Source to home data programming

4. Self-auditing and clean data

As mentioned above, we have secured a programmer and have another senior programmer.

Subtask 5: Day-to-day management activities of the PI.

Monday (am/pm), Tuesday (am) and Wednesday (1/2am) coursework at GSBS.- *Dr. Williams confirms.*

Tuesday (pm) and Wed/Thursday (pm) operative and clinic days, respectively.- *Dr. Williams confirms.*

Wednesday (1/2am), Thursday (am) and Friday (am/pm) research days.- *Dr. Williams confirms.*

Travel to Cedars-Sinai 2x per year, Travel to DVAMC 5x per year, Travel to American Urological Association and Society of Urological Oncology conferences and meet Dr. Freedland 2x per year

Meet with professional development committee 4x per year -*Dr. Williams confirms.*

1. UTMB Department of Surgery grants manager monthly one-hour meeting to go over proposal timeline, budget and future applications- *Dr. Williams confirms.*

2. DVAMC research manager bi-monthly one-hour telephone conference meetings to discuss database programmer, statisticians and proposal timeline- *Dr. Williams confirms.*

3. DVAMC programmer weekly 1-2 hour telephone conference meetings to discuss and review Aim 1: database development/data extraction, database management, data queries and audits, natural language processing, extraction and audits, review timeline and goals- *As mentioned above, we have secured a programmer.*

4. DVAMC database team weekly telephone conference meetings-*These meetings have occurred every 2 weeks.*

Research-Specific Tasks:

Major Task 1: 11/15/17 approval by the USAMRMC Human Research Protection Office

(HRPO). Adherence to weekly schedule, research planning, hiring programmer, integrating

existing Freedland research team into project initiated data mining in January 2018 with all data

fields populated except tumor stage/grade which natural language programming needs to extract.

Database for Aim 1 will be complete as scheduled.

Below are the patient counts from our active user cohort:

Total active user patient count: 11,692,562

Bladder Cancer dx: 181,200

Agent Orange: 962,287

BCa + A0: 16,447

- **What opportunities for training and professional development has the project provided?**

  Training-Specific Tasks:

  Major Task 1: Complete coursework in data management and biostatistics methodology. Major Task 2: Complete coursework in Population oriented research and research design Completed above and additional coursework including Translational Epidemiology I: Patient Oriented Research PHS 6212, Translational Epidemiology II: Population Oriented Research PHS 6213, Research Design PHS 6322, Introduction to Linear Models PHS 6344, Seminar PHS 6195 and Research PHS 6097. I have taken this coursework and turned into a formal MS degree which I have entered candidacy, completed thesis (under review) and goal graduation 12/31/18.

  Major Task 3: Meetings (Freedland, group, professional development advisory committee).

  Subtask 1: Travel to Cedars-Sinai 2x per year-Dr. Williams visited Cedars-Sinai in February 23, 2018 and June 9, 2018. Dr. Williams scheduled to visit again for 2nd yr of award in November, 2018.

  Subtask 2: Travel to DVAMC 5x per year-Dr. Williams traveled to DVAMC 6/21-22/17, 1/24-25/17, 3/29/18, 6/26/18 and next in November 2018.

  Subtask 3: Travel to American Urological Association and Society of Urological Oncology conferences and meet Dr. Freedland 2x per year-Dr. Williams/Freedland attended/met at Society of Urologic Oncology Meeting 12/1/17; Dr. Williams/Freedland met at the American Urological Association Meeting May 18-24, 2018. They have and continue to meet as scheduled.

  Subtask 4: Professional development committee meetings 4x per year-Dr. Williams met with committee on 11/21/17, 1/8/18, 4/1/18, 8/1/18 and continue to meet quarterly as scheduled.

  Subtask 5: Drs. Freedland/Williams every other week, one-hour telephone conference meetings. Dr. Freedland/Williams have one-hour telephone meetings every other week and sometimes weekly.

Subtask 6: Dr. Freedland team weekly telephone research in progress meetings. Dr. Williams attends research in progress meetings which have occurred monthly as research project IRB approvals, project getting started.

Subtask 7: Programmer weekly telephone conference meetings to discuss and review:

1. Database development/data extraction

2. Database management

3. Data queries and audits

4. Natural language processing, extraction and audits

We have secured a programmer and have another senior programmer work on project. We have developed the aim 1 cohort except for tumor stage/grade information which natural language programming will have completed as scheduled in SOW.

- **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?**
- Database completion with all fields queried including auditing to verify integrity. Proceed with analysis for specific aim 1, manuscript preparation, submission and publication defining incidence of bladder cancer according to Agent Orange exposure. Start aim 2 and national death index query to define mortality associated with bladder cancer according to Agent Orange.

4. **IMPACT:**
- **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:**

- **Changes in approach and reasons for change**

  Nothing to Report.

- **Actual or anticipated problems or delays 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**

  Nothing to Report.

6. **PRODUCTS:** Nothing to Report.

- **Publications, conference papers, and presentations**
  Nothing to Report.
- **Journal publications.** Nothing to Report.
- **Books or other non-periodical, one-time publications.** Nothing to Report.
- **Other publications, conference papers, and presentations.** Nothing to Report.

- **Website(s) or other Internet site(s)**

  Nothing to Report.

- **Technologies or techniques**

  Nothing to Report.

- **Inventions, patent applications, and/or licenses**

  Nothing to Report.

- **Other Products**

  Nothing to Report.

7. **PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS**

- **What individuals have worked on the project?**

Name:	Stephen B. Williams
Project role:	PI
Researcher Identifier:	226832185
Nearest person month worked:	4
Contribution to Project:	Dr. Williams has performed work in the area of IRB, HRPO and DVMAC protocol submission/approval, research personnel organization, hiring, and implementation.

Name:	Stephen J. Freedland
Project role:	Mentor
Researcher Identifier:	NA
Nearest person month worked:	1, effort as needed
Contribution to Project:	Dr. Freedland has performed work in the area of mentoring Dr. Williams on IRB, HRPO and DVMAC protocol submission/approval, research personnel organization, hiring, and implementation as well as direct supervision.

Name:	Amanda DeHoedt
Project role:	Research Manager DVAMC
Researcher Identifier:	NA
Nearest person month worked:	5
Contribution to Project:	Ms. DeHoedt has performed work in the area of IRB, HRPO and DVMAC protocol preparation, submission and approval. She has recruited a programmer to work on the project and coordinated integration of the Freedland research team.

- **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.

  What other organizations were involved as partners?

  Organization Name: Durham VAMC / IMR
  Location of Organization: Durham, North Carolina
  Partner's contribution to the project: Dr. Freedland is the PI's mentor. The team at DVAMC provides protocol/regulatory support and data analyses.

8. **SPECIAL REPORTING REQUIREMENTS**

   COLLABORATIVE AWARDS: Nothing to Report.

   QUAD CHARTS: Nothing to Report.

9. **APPENDICES:** Not applicable.