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TITLE: Agent Orange Exposure and Bladder Cancer

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

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14. ABSTRACT Dr. Williams has applied advanced degree coursework acquired during months 1-24 (MS graduation) to the project's objectives and training-specific tasks. Dr. Williams attended meetings (Freedland, group, professional development advisory committee), albeit in a more remote capacity due to present circumstances, through October 2021. Research specific tasks, specific Aim 1, Subtask 1 complete (months 1-4), Subtask 2 complete (months 1-18), with database completion, and Subtask 3 (months 18-24) including matching and analyses complete. Natural language processing auditing to verify and ensure integrity of data has been completed. Subtask 4 (months 12-24) manuscript preparation, submission and publication were delayed accordingly with NLP development as well as re-identification of the cohort to run additional analyses and will be completed in the following year. Specific Aim 2, Subtask 1 (months 24-30) has begun and we have both VINCI mortality data and NDI date and cause of death data. Subtask 2 (months 30-36) and Subtask 3 (months 24-36) expected to be completed. Day to day management activities of the PI were upheld during this time period. Upon re-identification of the cohort, analyses will be re-run and the manuscript will be prepared and submitted for publication in the following year.					
15. SUBJECT TERMS Bladder Cancer, Agent Orange, Veterans Affairs, VAHCS, Retrospective					
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1. INTRODUCTION:

There will be an estimated 74,000 new cases and 16,000 deaths from bladder cancer in the United States in 2015 ¹. Bladder cancer is more commonly diagnosed in the elderly which correspond to the age group of most Vietnam veterans ². A majority of bladder cancer patients are diagnosed with non-muscle invasive disease where transurethral resection with subsequent intravesical chemotherapy and/or immunotherapy are the standard of care ³. Approximately 20-40% of patients either present with or develop muscle-invasive disease ⁴. Mortality from bladder cancer increases exponentially once it invades the muscle ⁵.

From 1962 to 1971, the US military sprayed herbicides over Vietnam to destroy the thick jungle canopy which could conceal opposition forces ². Agent Orange is a 50:50 mixture of 2,4-dichlorophenoxyacetic acid (2,4-D) and 2,4,5-trichlorophenoxyacetic acid (2,4,5-T) as well as 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) which was a toxic unintended contaminant generated during production of Agent Orange ². Agent Orange has been previously linked to increased risk of prostate cancer, non-melanoma skin cancer and other malignancies ^{6,7}. The Institute of Medicine recently released a report stating there is “inadequate or insufficient” evidence to “limited or suggestive” evidence of association between bladder cancer and Agent Orange exposure ². Moreover, the interplay between exposure on treatment and oncologic outcomes is an area of needed research ². Based upon this, the VA is considering including bladder cancer as an Agent Orange related disease ². This PRCRP Career Development Award research proposal addresses bladder cancer (Topic Area) and Agent Orange exposure (Focus Area) as well as treatments and outcomes (Focus Area).

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 nationwide 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:

Bladder Cancer, Agent Orange, Veterans Affairs, VAHCS, Retrospective

3. ACCOMPLISHMENTS:

What were the major goals of the project?

Training-specific tasks

Tasks	Target Months	Actual Completion Dates	% 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	12/31/17	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 DVAHCS 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 and 5/3-6/19; SUO: 11/29-12/1/17 and 12/4-6/19 Conferences and meetings with Dr. Freedland attended virtually in 2020 and 2021	100
Subtask 4: Professional development committee meetings 4x per year	1-36	Quarterly with last 10/21	100

Subtask 5: Drs. Freedland/Williams every other week, one-hour telephone conference meetings.	1-36	Complete 8/2021	100
Subtask 6: Dr. Freedland team weekly telephone research in progress meetings	1-36	Complete 8/2021	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 audits	1-36	Complete 8/2021	100
Subtask 8: Database team weekly telephone conference meetings	1-36	Complete 8/2021	100
Subtask 9: Statistician team weekly telephone conference meetings to discuss and review current and future analyses	1-36	Complete 8/2021	100
Subtask 10: DVAHCS/Freedland Lab Director bi-monthly telephone conference meetings to discuss database programmer, statisticians and proposal timeline	1-36	Complete 8/2021	100
Subtask 11: UTMB Department of Surgery grants manager monthly meeting to go over proposal timeline, budget and future applications	1-36	Complete 8/2021	100

Research-specific tasks

Tasks	Target Months	Actual Completion Dates	% of Completion
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	1-18	Complete 9/20/20	100

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			
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, 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.	18-24	Complete 6/30/2021	
Subtask 4: Manuscript preparation, submission and publication	12-24	In progress, pending re-run analyses	
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 DVAHCS 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	1-24	Complete	100

1. UTMB Department of Surgery grants manager monthly one-hour meeting to go over proposal timeline, budget and future applications 2. DVAHCS/Freedland Lab Director bi-monthly one-hour telephone conference meetings to discuss database programmer, statisticians and proposal timeline 3. DVAHCS 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 4. DVAHCS database team weekly telephone conference meetings 5. DVAHCS statistician team weekly telephone conference meetings to discuss and review current and future analyses 6. DVAHCS 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 DVAHCS bladder cancer database was developed. The analyses determining the association and results pertaining to the risk of BC according to AO exposure are under review and discussed at 6/30/2021 meeting to finalize. These will be published pending completion of manuscript at end of NCE period	1-24	Complete 6/30/2021	

Specific Aim 2: Explore whether AO exposure is linked with BC-specific mortality.	24-36		
Major Task 2: Explore whether AO exposure is linked with BC-specific mortality.			
Subtask 1: Identify and test the link between AO and BC death. Out of 3.15 million patients, an estimated 0.9% or 28,350 will have bladder cancer. Of these, an estimated 10% will die we expect 2,835 deaths will be needed to detect clinically insignificant results. 1. Extract mortality data from aim 1 cohort using VINCI 2. Determine cause of death linked to the NDI 3. Extract treatment data from aim 1 cohort using diagnoses (all ICD-9 and -10 codes), procedures (all CPT codes) and natural language processing (NLP) 4. Extract and develop an SQL server database with key data points 5. Source to home data programming 6. Self-auditing and clean data	24-30	Complete, 9/20/2020	100
Subtask 2: Perform analysis. 1. Perform multivariable modeling as outlined above in Aim 1 but using a competing-risk model. 2. Interaction testing and evaluating descriptive statistics will be performed as in Aim 1. As mentioned in Aim 1, if no significant interaction between AO and age, gender, obesity, and smoking status is found, data will be analyzed together and not stratified by these factors. If a significant interaction is found, only stratified results will be reported. 3. We will include the propensity score variable described above predicting which treatment was received.	30-36	Complete 6/30/2021	

Subtask 3: Manuscript preparation, submission and publication	24-36	In progress, pending re-run analyses	
Subtask 4: Day-to-day management activities of the PI. Monday (am/pm) and Tuesday (am/pm) clinic and operative days, respectively. Wednesday (am/pm) and Friday (am/pm) research days. Travel to Cedars-Sinai 2x per year, Travel to DVAHCS 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. DVAHCS/Freedland Lab Director bi-monthly one-hour telephone conference meetings to discuss database programmer, statisticians and proposal timeline 3. DVAHCS programmer weekly 1-2-hour telephone conference meetings to discuss and review Aim 2: database development/data extraction, database management, data queries and audits, natural language processing, extraction and audits, review timeline and goals 4. DVAHCS database team weekly one-hour telephone conference meetings 5. DVAHCS statistician team weekly one-hour telephone conference meetings to discuss and review current and future analyses 6. DVAHCS statistician weekly telephone conference 1-2 hours telephone meeting (months 30-36)	24-36	Complete 8/2021	100

7. Drs. Freedland/Williams every other week, one-hour telephone conference meetings review Aim 2 and future grant submissions. 8. Dr. Freedland team weekly one-hour telephone research in progress meetings 9. Weekly ad-hoc one-hour telephone conference calls to answer and go over any database or analysis questions			
Milestone(s) Achieved: The analyses and results determining BC-specific mortality according to AO exposure will be published, as per milestone noted above for Specific Aim 1 Major Task 1, by end of NCE period. Results discussed 6/30/2021.	24-36	Complete 6/30/2021	

What was accomplished under these goals?

Training-Specific Tasks:

Major Task 1; Subtask 1: *Complete – nothing to report*

Major Task 2, Subtask 1: *Complete – nothing to report*

Dr. Williams completed his thesis and received MS in Clinical Sciences, Health Services Research in 8/19.

Major Task 3: Meetings (Freedland, group, professional development advisory committee): *All meetings, including mentorship provided by Dr. Freedland and supplemented by the professional development committee and DVAMC research personnel and Director, have allowed necessary IRB, HRPO, and DVAMC IRB submissions/approvals to be secured to move forward with project and provided invaluable mentorship and research experience. Meetings and conference attendance activities are as described below:*

Subtask 1: Travel to Cedars-Sinai 2x per year - *Dr. Williams last visited in person in December 2019, and curtailed July 2020 and subsequent trips due to COVID-19 circumstances.*

Subtask 2: Travel to DVAMC 5x per year - *Dr. Williams last traveled to DVAMC 3/20, and curtailed 5/20 and 7/20 planned travel due to COVID-19 circumstances. No travel to DVAMC occurred during the current quarter. Continued to meet with DVAMC and Freedland teams via increased teleconference frequency through 8/2021.*

Subtask 3: Travel to American Urological Association (AUA) and Society of Urological Oncology (SUO) conferences and meet Dr. Freedland 2x per year - *Drs. Williams and Freedland attended and met at Society of Urologic Oncology Meeting, 11/19, but curtailed meeting prior to AUA in 5/20 due to COVID-19 circumstances. AUA was attended virtually. Dr. Williams continued to meet frequently with Dr. Freedland in virtual format to maintain mentorship and to discuss research activities through 10/2021.*

Subtask 4: Professional development committee meetings 4x per year - *Dr. Williams last met with committee on 10/21*

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 often move these meetings to weekly occurrence. Present circumstances have not hindered these progress and mentorship meetings.*

Subtask 6: Dr. Freedland Team weekly telephone research in-progress meetings. *Dr. Williams attended research in-progress meetings, which occurred monthly, to discuss research project IRB approvals, projects being begun, and in-progress project status updates. These meetings ended 8/2021.*

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

And **Subtask 8:** Database team weekly telephone conference meetings

These meetings have concluded as each of the associated tasks have been completed. Discussions related to these items, such as they are needed, are discussed with Programmer, Data Operations Manager and statisticians at analysis meetings, per Subtask 9.

Subtask 9: Statistician team weekly telephone conference meetings to discuss and review current and future analyses – *Dr. Williams and statisticians continue these concluded these meetings as of 8/2021 after initial analyses.*

Subtask 10: DVAHCS/Freedland Lab Director bi-monthly telephone conference meetings to discuss database programmer, statisticians and proposal timeline – *Dr. Williams continued these meetings through 8/2021.*

Subtask 11: UTMB Department of Surgery grants manager monthly meeting to go over proposal timeline, budget and future applications – *Dr. Williams has met monthly.*

Research-Specific Tasks:

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

Subtask 1: *Complete – nothing to report*

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 significant 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

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, 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.

Subtasks 1-3 complete, including refinement of NLP model necessary to achieve tasks. Active user healthy control and AO cohorts identified, and associated analyses for Aims 1 and 2 (below) are currently being reviewed. Delay from Subtask 2 (months 1-18), database completion, was due to natural language processing (NLP) development, as we needed to refine, audit, and validate stage information; NLP model development previously completed and applied to cohort. Major Task 1 Subtask 3 (months 18-24) and Major Task 2 Subtask 2 (months 30-36) analyses, which were consequently delayed, are under review currently and will be complete by end of the NCE period. All queried data and NDI mortality data received. Remaining subtasks (i.e. manuscript preparation) to be completed by end of NCE one-year period, ending 08/2021.

Subtask 4: Manuscript preparation, submission and publication – *Dr. Williams confirms, upon review of redone analyses, manuscript preparation will begin.*

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

Monday (am/pm), Tuesday (am) and Wednesday (1/2am) coursework at GSBS.- *Complete – nothing to report.*

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

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

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 – *Note the training-specific activities and comments above; same reflected here.*

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

Major Task 2: Explore whether AO exposure is linked with BC-specific mortality.

Subtask 1: Identify and test the link between AO and BC death. Out of 3.15 million patients, an estimated 0.9% or 28,350 will have bladder cancer. Of these, an estimated 10% will die; we expect 2,835 deaths will be needed to detect clinically insignificant results.

1. Extract mortality data from aim 1 cohort using VINCI
2. Determine cause of death linked to the NDI
3. Extract treatment data from aim 1 cohort using diagnoses (all ICD-9 and -10 codes), procedures (all CPT codes) and natural language processing (NLP)
4. Extract and develop an SQL server database with key data points
5. Source to home data programming
6. Self-auditing and clean data

Subtask 2: Perform analysis.

4. Perform multivariable modeling as outlined above in Aim 1 but using a competing-risk model.
5. Interaction testing and evaluating descriptive statistics will be performed as in Aim 1. As mentioned in Aim 1, if no significant interaction between AO and age, gender, obesity, and smoking status is found, data will be analyzed together and not stratified by these factors. If a significant interaction is found, only stratified results will be reported. We will include the propensity score variable described above predicting which treatment was received.

Similar to Major Task 1, above, Subtasks 1 and 2 complete, including final validation of NLP model necessary to achieve completion of subtasks noted here. Analyses for Aims 1 and 2 completed and being reviewed. We noted over 5500 BC deaths. All remaining subtasks (manuscript preparation, months 12-24, 24-36) to be completed by end of NCE period, ending 08/2021.

Subtask 3: Manuscript preparation, submission and publication

As above, Dr. Williams confirms, upon review of redone analyses, manuscript preparation will begin.

Subtask 4: Day-to-day management activities of the PI.

Monday (am/pm) and Tuesday (am/pm) clinic and operative days, respectively. *Dr. Williams confirms this schedule continues*

Wednesday (am/pm) and Friday (am/pm) research days. *Dr. Williams confirms this schedule continues*

Travel to Cedars-Sinai 2x per year, Travel to DVAHCS 5x per year, Travel to American Urological Association and Society of Urological Oncology conferences and meet Dr. Freedland 2x per year. *Note the training-specific activities and comments above; same reflected here.*

Meet with professional development committee 4x per year

10. UTMB Department of Surgery grants manager monthly one-hour meeting to go over proposal timeline, budget and future applications – *Dr. Williams confirms*
11. DVAHCS/Freedland Lab Director bi-monthly one-hour telephone conference meetings to discuss database programmer, statisticians and proposal timeline - *Dr. Williams confirms*
12. DVAHCS programmer weekly 1-2-hour telephone conference meetings to discuss and review Aim 2: database development/data extraction, database management, data queries and audits, natural language processing, extraction and audits, review timeline and goals - *Dr. Williams confirms*
13. DVAHCS database team weekly one-hour telephone conference meetings - *Dr. Williams confirms*
14. DVAHCS statistician team weekly one-hour telephone conference meetings to discuss and review current and future analyses - *Dr. Williams confirms*
15. DVAHCS statistician weekly telephone conference 1-2 hours telephone meeting (months 30-36) - *Dr. Williams confirms*

16. Drs. Freedland/Williams every other week, one-hour telephone conference meetings review Aim 2 and future grant submissions. - *Dr. Williams confirms; often weekly*
17. Dr. Freedland team weekly one-hour telephone research in progress meetings - *Dr. Williams confirms*
18. Weekly ad-hoc one-hour telephone conference calls to answer and go over any database or analysis questions. - *Dr. Williams confirms*

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

- 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 – *Note the training-specific activities and comments above; same reflected here.*
 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.*
 4. DVAMC database team weekly telephone conference meetings-*These meetings have occurred every 2 weeks.*
- Drs. Freedland/Williams every other week, one-hour telephone conference meetings. *Dr. Freedland/Williams have one-hour telephone meetings every other week, and often move these meetings to weekly occurrence. Present circumstances have not hindered these progress and mentorship meetings.*

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?

Nothing to report.

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

a. Actual Problems or delays and actions to resolve them

A current problem that will cause delay for this project is confirmation of cohort identification. Upon review after initial analyses for all tasks had been completed, it was discovered that the cohort could not be recreated based on recorded criteria. Due to this, bias could have been initially introduced into the cohort and we desire to re-identify the cohort and then re-run the analyses to confirm results for manuscript preparation and dissemination of results.

b. Anticipated Problems/Issues

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.

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:

- **Publications, conference papers, and presentations**

- 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 DVAHCS 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 DVAHCS protocol submission/approval, research personnel organization, hiring, and implementation as well as direct supervision.
Name:	Amanda De Hoedt
Project role:	Director, DVAHCS
Researcher Identifier:	NA
Nearest person month worked:	5
Contribution to Project:	Ms. De Hoedt has performed work in the area of IRB, HRPO and DVAHCS protocol preparation, submission and approval. She has recruited a programmer to work on the project and coordinated integration of the Freedland research team.
Name:	Michael Burns
Project role:	Data Operations Manager, DVAHCS
Researcher Identifier:	NA
Nearest person month worked:	
Contribution to Project:	Mr. Burns oversees all data operations and coordinates the activities of and oversees the work produced by the programmers.
Name:	Ruixin Yang
Project role:	Data Scientist, DVAHCS
Researcher Identifier:	NA
Nearest person month worked:	
Contribution to Project:	Mr. Yang trained and developed the natural language processing (NLP) model.
Name:	Dan Long
Project role:	Database Programmer, DVAHCS
Researcher Identifier:	NA
Nearest person month worked:	
Contribution to Project:	Mr. Long has developed SQL queries utilized to perform the data queries associated with the project.
Name:	Jessica Janes
Project role:	Statistician, DVAHCS
Researcher Identifier:	NA
Nearest person month worked:	
Contribution to Project:	Ms. Janes has performed work as a research statistician with the Durham VA and performs data analysis across all Aims on this 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?

Nothing to report.

What other organizations were involved as partners?

Nothing to report.

8. SPECIAL REPORTING REQUIREMENTS

COLLABORATIVE AWARDS: *Not Applicable*

QUAD CHARTS:

Nothing to report.

9. APPENDICES:

Nothing to report.

10. REFERENCES

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2015. *CA: a cancer journal for clinicians*. 2015;65(1):5-29.
2. Committee to Review the Health Effects in Vietnam Veterans of Exposure to H, Board on the Health of Select P, Institute of M, National Academies of Sciences E, Medicine. *Veterans and Agent Orange: Update 2014*. Washington (DC): National Academies Press (US) Copyright 2016 by the National Academy of Sciences. All rights reserved.; 2016.
3. Hall MC, Chang SS, Dalbagni G, et al. Guideline for the management of nonmuscle invasive bladder cancer (stages Ta, T1, and Tis): 2007 update. *The Journal of urology*. 2007;178(6):2314-2330.
4. Stein JP, Lieskovsky G, Cote R, et al. Radical cystectomy in the treatment of invasive bladder cancer: long-term results in 1,054 patients. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 2001;19(3):666-675.
5. Scher H, Bahnson R, Cohen S, et al. NCCN urothelial cancer practice guidelines. National Comprehensive Cancer Network. *Oncology (Williston Park)*. 1998;12(7A):225-271.
6. Ovadia AE, Terris MK, Aronson WJ, et al. Agent Orange and long-term outcomes after radical prostatectomy. *Urologic oncology*. 2015;33(7):329.e321-326.
7. Nosrati N, Han J, Flores R, Sood R, Tholpady SS. The effect of Agent Orange on nonmelanoma skin cancer regression rates. *JAMA surgery*. 2014;149(11):1205-1206.