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TITLE: Women's Ischemia Trial to Reduce Events in Non-Obstructive CAD (WARRIOR)

PRINCIPAL INVESTIGATOR: Carl J. Pepine, MD

CONTRACTING ORGANIZATION: University of Florida

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Carl J Pepine, Eileen M.Handberg

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University of Florida
207 Grinter Hall
Gainesville, FL 32611-0001

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14. ABSTRACT
The WARRIOR trial is a multicenter, prospective, randomized, blinded outcome evaluation (PROBE design) evaluating intensive medical therapy vs usual care in 4,422 symptomatic women with ischemia but no obstructive CAD. The study aims to determine whether an intensive medication treatment strategy to modify risk factors in women with chest pain and/or abnormal stress tests, but non-obstructed coronary arteries will reduce their likelihood of dying, having a heart attack, stroke or being hospitalized. This project will activate 50-125 recruitment sites from across the US to enroll and follow these women for up to three years to assess adverse outcomes.

15. SUBJECT TERMS
Heart disease, women, non-obstructive coronary artery disease, chest pain, angina, quality of life, outcomes

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1. INTRODUCTION:

The WARRIOR is a multicenter, prospective, randomized, blinded outcome evaluation (PROBE design) of intensive medical therapy vs usual care in 4,422 symptomatic women with symptoms and/or signs of ischemia but no obstructive CAD. The study aims to determine whether an intensive medication treatment strategy to modify risk factors will reduce the likelihood of dying, having a heart attack, stroke or being hospitalized for angina and/or heart failure. This project was designed to activate 50-125 recruitment sites from across the US to enroll and follow these women for up to three years to assess adverse outcomes.

Year 5 Progress Summary

The Trial was funded Sept 15, 2017, and operationalized in the first quarter of 2018, as planned, and the first patient was enrolled on February 9, 2018 the second quarter of the award. Details of the first 5 years of activity have been summarized in previous quarterly and annual reports. Recruitment of sites, and more importantly subjects, have been severely impacted by the COVID-19 pandemic (see below) which has continued to be a major public health concern. The spread of new variants, particularly in the Southern part of the US where most of the active sites are located, has continued to negatively impact site performance due to local shifting of staff to care for pandemic-related hospitalizations. To compensate, a revised plan to add additional recruitment sites resulted in 81 WARRIOR sites being contracted (31 more the original plan of 50 sites) but although enrollments increased (**from 1712 to 2140 as of September 14, 2022**) the trial continues to lag recruitment goals. With recommendations from the DSMB to continue the study as planned and Project Officer support, a second No Cost Extension was applied for and approved in order to continue the trial to completion. The following report provides a summary of activities utilizing the original Scope of Work and Major Tasks to outline performance in each area.

COVID-19

The COVID-19 pandemic, which emerged in the USA in January 2020, continues to have a major impact on WARRIOR study conduct. Recruitment was halted for over 4-7 months, based on local regulations in 2020. Gradual "return to work" took place during the late fall of 2020 at most sites, but resurgence of the "delta" variant in the late summer of 2021 with new surges in hospitalizations impacted site performance based on research staff and/or patient issues. Additional variants including Omicron presented across the country in 2022 and while the impact in terms of hospitalizations and limited access to facilities has not been as much of an issue, the occurrence of COVID cases in staff at WARRIOR Sites has limited recruitment efforts. Some coordinators have had COVID 3 and 4 times. In addition, while there is considerable variability from state to state, many patients (potential WARRIOR subjects) continue to restrict their use of medical facilities and do not want to come to the clinics for enrollment visits or Emergency Departments even when they have accelerating symptoms of chest pain or heart failure. As reported previously, the protocol was revised during the first wave of the pandemic to allow for virtual (remote) enrollment and randomization, as well as follow-up visits. This has been partially effective in maintaining follow up at sites but has been much less successful to encourage potential new enrollments. The "face to face" interaction at a screening visit is critically important to establish a relationship between the study team and the patient. Continued slow recruitment has not only impacted new enrollments, but also the planned 3 year follow up. This has necessitated, as reported previously, protocol modification to continue follow up until the last patient enrolled completes their 36-month visit**. The pandemic has impacted most non-COVID clinical trials that have made modifications similar to those that we have made, and those trials are continuing. All site contracts are being updated to extend the duration of trial. Plans are underway to allow for continued follow up beyond the second no cost extension to increase length of follow up.**

Hurricane Related Constraints

During the last quarter of this No-Cost Extension Year (Year 5), and into the first quarter of the second no cost extension Puerto Rico, Florida and the Southeast have experienced two major hurricanes impacting patient recruitment. Follow up can be maintained virtually as the protocol allows for that, but 5-7 sites may be adversely affected by the storms since they had a major impact on infrastructure. The DCC is currently evaluating the need to assist with virtual follow up at affected centers.

DSMB Review of Trial Feasibility

Considering the continued impact of COVID-19 on the trial, the DSMB met in June 2022 and reviewed the conduct of the trial. Although recruitment continues to lag projected goals, event rates are occurring at expected rates and the DSMB recommended that the trial continue into the second no cost extension period in order to try and achieve recruitment goals and outcomes. Adverse events continue to be adjudicated and there were no safety concerns identified. The DSMB strongly recommended that the Investigators obtain additional funding to carry out the trial in order to answer the question proposed in the original design evaluating MACE events in this population of women with signs and symptoms of ischemia with no obstructive coronary artery disease.

2. KEYWORDS:

Heart disease, women, non-obstructive coronary artery disease, chest pain, angina, quality of life, outcomes

3. ACCOMPLISHMENTS:

What were the major goals of the project?

The approved statement of work had a start date of September 15, 2017, and included 18 major tasks (e.g., goals). Each of these major tasks were further divided into sub-tasks that were assigned a general timeline and a research site responsible for the sub-tasks (please see attached statement of work for a full list of tasks). The status of each task and progress of the sub-tasks for the **fifth year (period 5) are summarized below**. The original projected timeline is ***[bolded]*** after the task listing, and current status is updated and if completed the completion date/period is **[bolded]** at the end of the section detailing the work.

Major Task #1 – Protocol Finalization ***[Months 1-3]:***

This task was completed in the first quarter**.** The protocol was updated to allow for provision of aspirin (dispensed or reimbursed) in order to improve compliance. The duration of follow-up has been extended to 60 months to allow for 36 months of follow-up for the last participant enrolled. Due to impact of COVID-19, the protocol has been amended to allow for both virtual enrollment and follow-up. All versions of the protocol have been approved by the IRB and approved/acknowledged by HRPO. **The current operational version of the protocol is version 16.0. The history of IRB/HRPO activity is summarized below and activity during this year is bolded for ease of review.**

SUBMITTED TO AND APPROVED BY:

- V1.0 Submitted to the University of Florida IRB – 05/24/17

- V1.0 Approved by the University of Florida IRB – 06/07/17
- V2.0 Submitted to the University of Florida IRB – 07/08/17
- V2.0 Approved by the University of Florida IRB – 06/13/17
- V3.0 Submitted to the University of Florida IRB – 11/08/17
- V3.0 Approved by the University of Florida IRB – 11/30/17
- V2.0 Submitted to HRPO – 06/17/17
- V2.0 Approved by HRPO – 11/30/17
- V3.0 Submitted to HRPO – 12/11/17
- V3.0 Approved by HRPO – 12/12/17
- V4.0 Submitted to the University of Florida IRB – 06/01/18
- V4.0 Approved by the University of Florida IRB – 06/11/18
- V4.0 Submitted to HRPO – 06/13/18
- V5.0 Submitted to the University of Florida IRB – 06/14/18
- V5.0 Approved by the University of Florida IRB – 06/15/18
- V5.0 Submitted to HRPO – 06/13/18
- V6.0 Submitted to the University of Florida IRB – 07/17/18
- V6.0 Approved by the University of Florida IRB – 07/27/18
- V7.0 Submitted to the University of Florida IRB – 09/07/18
- V7.0 Approved by the University of Florida IRB – 09/19/18
- V7.0 Submitted to HRPO – 09/24/18

YEAR 2 IRB/HRPO ACTIVITY

- V8.0 Submitted to IRB – 10/16/18
- V8.0 Approved by University of Florida IRB – 10/31/18

PROTOCOL READY FOR ENROLLMENT

- UF Biorepository BEAWARRIOR submitted to University of Florida IRB – 07/10/18
- UF Biorepository BEAWARRIOR approved by University of Florida IRB – 08/03/18
- UF Biorepository BEAWARRIOR submitted to HRPO – 10/30/18
- UF Biorepository BEAWARRIOR approved by HRPO – 11/20/18
- V9.0 Submitted to HRPO – 11/21/18
- V10.0 Submitted to University of Florida IRB – 01/19/19
- V10.0 Approved by University of Florida IRB – 01/25/19
- V10.0 Submitted to HRPO – 01/31/19
- V11.0 Submitted to University of Florida IRB – 03/21/19
- V11.0 Approved by University of Florida IRB – 03/28/19
- V11.0 Submitted to HRPO – 03/22/19
- Annual IRB Review and Approval for UF Site – 05/15/19
- Annual IRB Approval Submitted to HRPO – 06/03/19
- Annual IRB Review and Approval for Data Coordinating Center – 05/09/19
- Annual IRB Approval Submitted to HRPO – 06/06/19
- Annual IRB Review and Approval for BEAWARRIOR Biorepository – 05/16/19
- Annual IRB Approval Submitted to HRPO – 07/22/19
- V12.0 Submitted to University of Florida IRB – 06/14/19
- V12.0 Approved by University of Florida IRB – 08/16/19
- V12.0 Submitted to HRPO – 08/20/19

YEAR 3 IRB/HRPO ACTIVITY

- V13.0 Submitted to University of Florida IRB – 3/16/20
- V13.0 Approved by the University of Florida IRB – 3/26/20
- V13.0 Submitted to HRPO – 3/26/20
- V13.0 Acknowledged by HRPO – 3/30/20
- Annual IRB Review for Data Coordinating Center to UF IRB – 4/29/20
- Annual IRB Approval for Data Coordinating Center from UF IRB – 5/01/20
- Annual IRB Approval for DCC Submitted to HRPO – 5/08/20
- Annual IRB Approval for DCC HRPO Approved – 6/10/20
- Annual IRB Review for UF Site to UF IRB – 4/27/20
- Annual IRB Approval for UF Sites from UF IRB – 5/22/20
- Annual IRB Approval for UF Sites by UF IRB Submitted to HRPO – 5/22/20

YEAR 4 IRB/HRPO ACTIVITY

- V14.0 Submitted to University of Florida IRB --09/25/20
- V14.0 Approved by the University of Florida IRB --10/21/20
- V14.0 Submitted to HRPO --11/04/20
- V14.0 Acknowledged by HRPO --12/02/20
- V14.1 Submitted to University of Florida IRB --11/02/20
- V14.1 Approved by the University of Florida IRB --11/03/20
- V14.1 Submitted to HRPO --11/04/20
- V14.1 Acknowledged by HRPO --12/02/20
- V14.2 Submitted to University of Florida IRB --12/15/20
- V14.2 Approved by the University of Florida IRB --12/23/20
- V14.2 Submitted to HRPO --12/23/20
- V14.2 Acknowledged by HRPO --12/28/20
- Protocol revision submitted to FDA for inclusion of Vascepa --04/26/21
- Annual IRB Review of Data Coordinating Center to UF IRB --04/27/21
- Annual IRB Approval of Data Coordinating Center from UF IRB --04/29/21
- FDA approved IND exemption with revision --04/30/21
- Annual IRB Approval of Data Coordinating Center to HRPO --05/05/21
- Annual IRB Approval of DCC HRPO Approved --05/05/21
- Annual IRB Review of UF Site to UF IRB --04/26/21
- Annual IRB Approval of UF Sites from UF IRB --05/26/21
- Annual IRB Approval of UF Sites by UF IRB to HRPO --06/02/21
- Annual IRB Approval of UF Sites HRPO Approved --06/09/21
- V15.0 Submitted to University of Florida IRB --06/11/21
- V15.0 Approved by the University of Florida IRB --07/20/21
- V15.0 Submitted to HRPO --07/23/21
- V15.0 Acknowledged by HRPO --08/13/21
- V16.0 Submitted to University of Florida IRB --08/12/21

- V16.0 Approved by the University of Florida IRB --08/17/21
- V16.0 Submitted to HRPO --09/01/21
- V16.0 Acknowledged by HRPO --09/02/21

YEAR 5 IRB/HRPO ACTIVITY

- **Annual IRB Approval of UF Sites from UF IRB --05/24/22**
- **Annual IRB Approval of UF Sites by UF IRB to HRPO --06/08/22**

A separate IRB submission was required for the WARRIOR Biorepository ("BE A WARRIOR") that was detailed in the original grant submission. This has been IRB and HRPO approved as noted above. The BE A WARRIOR Biorepository is currently collecting samples and operating on Protocol Version 1.0. This project was reviewed on 2/23/2022 and now expires on 2/23/2023.

Major Task #2 – Electronic Case Report Form (eCRF) and additional study materials: **[PRE-Months 1-3]**

The majority of these subtasks were completed in the first quarter ***[January 2017]***. Refinement of the data capture forms continues reflecting protocol revisions, the REDCap data system is live, new sites are continually being activated, and new patients are being enrolled**.** The REDCap team has been meeting with the Executive team weekly since the beginning of the project to review data system performance, revise as appropriate, and generate weekly project performance reports for Executive Committee review. The team interacts with the Statistical Core to generate data sets for analysis for DSMB and other reports. **The eCRF and data is reviewed weekly by the operations team and at the Executive Committee meeting held every Monday.**

Major Task #3 – Institutional Review Board**: [Pre-award]**

The initial IRB approval task was completed ***[PRE-AWARD].*** The study is currently enrolling patients under the most recent IRB and HRPO approved **protocol version 16.0. See above for submissions and approvals during this reporting year.**

Major Task #4 – Investigator Recruitment and Site Contracts**: [Months 1-3]**

The initial official contact of investigators began at the time of the award **09/15/17**. IRB/HRPO approval of operational protocol was required to initiate contracts and IRB submissions. A total of 50 sites were identified during the originally projected time period. All sub-tasks are ongoing. **As reported previously the original goal was 50 sites, which was attained. The revised goal for sites was 50-125. Initially there were 81 active sites. Six sites have been closed due to inability to activate, loss of investigators or staff resulting in 75 active sites.**

Table 1 summarizes site activation activities over the first four years and the most recent year by quarter and a cumulative total.

Table 1. Summary of Cumulative Site Activation Activities

Site Activity	Year 1 9/15/17 9/14/18	Year 2 9/15/18 9/14/19	Year 3 9/15/19 9/14/20	Year 4 9/15/20 9/14/21	Q1 Year 5 9/15/2021 12/14/2021	Q2 Year 5 12/15/2021 3/14/2022	Q3 Year 5 3/15/2022 6/14/2022	Q4 Year 5 6/15/2022 9/14/2022	Year 5 9/15/21 9/14/22
Contacted	286	443	873	879	879	879	879	879	879
CDA Sent	155	309	668	673	673	673	673	673	673
Completed CDAs Returned	52	120	223	227	227	227	227	227	227
Contract Fully Executed	17	41	82	96	96	96	96	96	96
Contracts Negotiating	50	26	28	0	0	0	0	0	0
UF IRB Approved	19	37	66	87	87	87	87	87	87
HRPO Approved	13	29	63	87	87	87	87	87	87
Activated for Enrollment	13	27	59	81	81	81	81	81	81
Deactivated Sites	0	2	2	2	2	2	4	6	6
Currently Enrolling Sites	13	25	57	79	79	79	77	75	75
Anticipated Total Sites	50	50	75	81	81	81	81	81	81
Patients Enrolled Cumulative	76	584	970	1712	1841	1947	2049	2140	2140
Yearly Enrollment	76	508	386	742	129	106	102	91	428

*Six sites have been deactivated as follows: 2 for pharmacy issues, 2 due to budget limitations, 1 not allowed to use vendor contract and 1 site closed due to PI leaving and no replacement.

Activation of sites able to recruit active duty, retired and military dependents was successful. During year 2, the DCC has successfully subcontracted with Geneva Foundation, and received approval for **5** active duty military sites.

As previously reported, this trial has been successful in onboarding 4 active duty military facilities and three VA Medical Centers in order to recruit active duty military and military dependents. The history of that is summarized here. Details of this activity are summarized in Table 2. As was anticipated there has been turnover of principal investigators due to tour of duty changes. Not anticipated was the significant reduction in clinical services being provided at several of the smaller facilities (NAS Jacksonville and Pensacola) due to the lack of clinician availability the majority of care is being provided by the local medical community and recruitment has been limited.

Table 2. Military Sites

LOCATION	P.I.	STATUS
Pensacola NAS	Dr. Gray/Mr. Thronson	Enrolling as of 6/13/19
Jacksonville NAS	Dr. Volk/Dr. Sadler	Enrolling as of 6/13/19
Walter Reed	Dr. Weber/Dr. Harrell	Enrolling as of 3/16/2020
BAMC	Dr. Pickett	Enrolling as of 3/16/2020
TAMC	Dr. Marn	Withdrawn due to PI staffing shortage
Ft. Belvoir	Dr. Crimm	Withdrawn due to PI staffing shortage
Puerto Rico VA	Dr. Vincenti	Enrolling as of 8/15/2019
Gainesville VA	Dr. Schmalfuss	Enrolling as of 7/19/2019
Tampa VA	Dr. Leonelli	Enrolling as of 6/1/21

The geographic distribution of sites is illustrated in Figure 1.

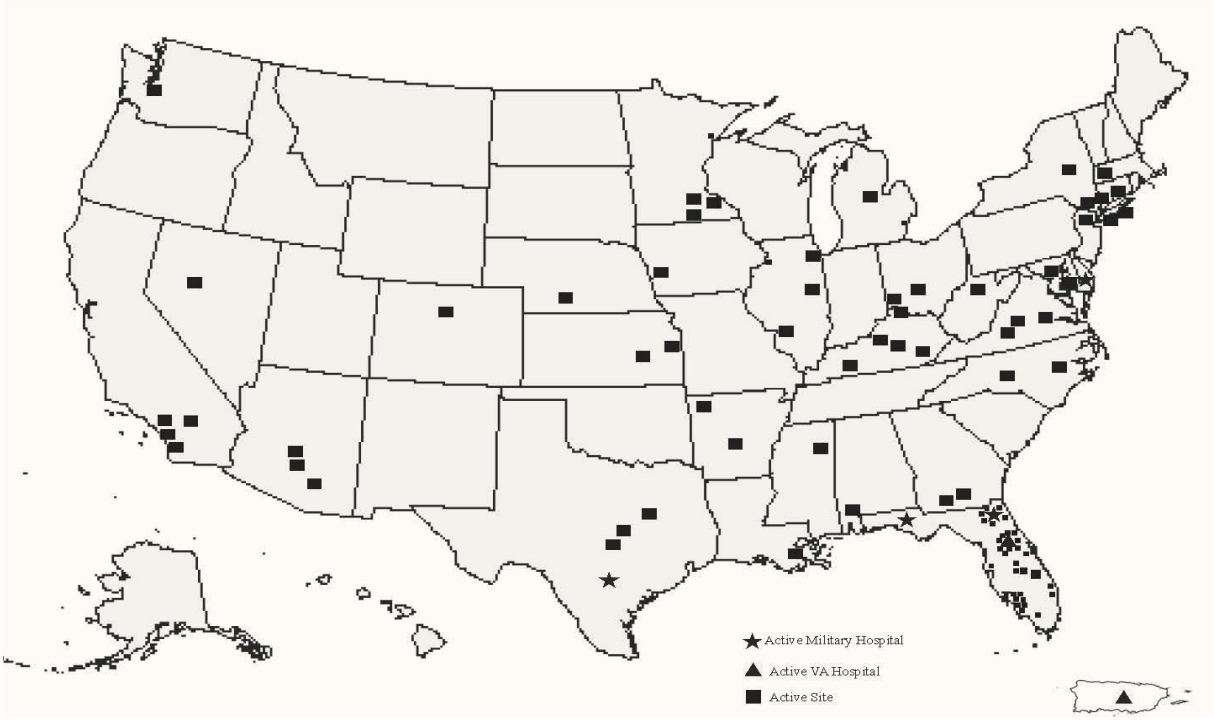


Figure 1. Geographic Distribution of Active/Pending Sites and Imaging Referral Centers

Overview of Pending Site progress:

As summarized in Table 1, **as of this report there are 75 active sites. All of the previous reported grant modifications to extend recruitment until the last patient has been followed for 36 months have been completed. We have had 7 PI changes during the reporting year (mostly pandemic-related), which have**

required additional regulatory review of a new PI for the sites.

1) Identification of additional sites

Previous efforts to identify sites in Canada were successful. But after continued due diligence it became apparent that it would not be possible to enroll sufficient numbers to justify the additional regulatory expenses and resources required to obtain Canadian Health Authority approval for study medications, the required regulatory oversight as it would not be IND exempt (Canadian equivalent) and additional contracting would be required for the site cardiologists.

During Year 4 the potential to add International Sites was explored with Dr. Beltrame in Australia. With support of the Executive Committee, WARRIOR supported an application by Dr. Beltrame and colleagues in South Australia to the Australian Federal Funding Agency. If successful with this award, they would activate 8 sites in Australia to participate in WARRIOR. Funding for site operations would be provided as part of that grant. Submission was completed in September 2021 with review anticipated late November 2021 and funding in the first quarter of 2022. This would add ~500 patients to the WARRIOR Trial funded by an external source and their patient data would be entered in to the database using the same REDCap forms.

Due to the COVID-19 lockdown in Australia the granting agency finally reported out findings and the grant was not funded. The previously reported second submission was put forth in February 2022 and has not yet been reviewed. A second international query has been received from Dr. Colin Berry from Scotland to utilized British Heart Foundation funding to provide administrative support to bring on centers in Scotland. A request to DoD for inclusion of an additional foreign site is being submitted and an anticipated start of late fall is planned. 2-3 sites are anticipated to enroll 2-300 participants.

2.) Reducing delays in contracting and regulatory approvals

2.1) Delays in site activation

Delays in site activations have been relatively limited during this reporting year.

2.1.1) Contracting

The protocol was amended to allow for the provision of icosapent ethyl for the treatment of high-risk women in the IMT arm with a donation of drug from Amarin has been in process for 9 months. Delays in contracting for distribution have held up implementation of this. **Supply chain issues did not allow this to be implemented so this was removed from the protocol. All sites are now being issued contract amendments in order to carry out the second year no cost extension.**

2.1.2) Regulatory approvals

Each investigator requires Central UF IRB approval (or local IRB approval), and DoD HRPO approval. During Year 5, there were minor episodic issues with delays in regulatory processing. HRPO and UF IRB staff have continued to work with WARRIOR regulatory staff to improve the process. **Annual IRB/HRPO reviews were submitted and approved as follows: UF sites were approved by UF IRB 5/24/2022 and Approval of UF Sites UF IRB to HRPO 6/8/2022.**

Major Task #5 – Pre-Study Preparation**: [Months 1-6]**

All sub-tasks are ongoing. IRB submissions are currently underway as detailed above. The University of Florida is serving as the Single IRB for WARRIOR. Regulatory processing, documentation of training and submissions for IRB and HRPO approval are underway**.** ***[Completed]***

Major Task #6 – Investigator Meeting (Bi-Annual)**: [Months 1-48]**

All sub-tasks are ongoing. Investigator meetings have been held as outlined in the SOW. **The last Steering Committee Meeting was held on March 3, 2022. The first face to face Steering Committee/Investigator meeting post COVID was held April 3, 2022 during the American College of Cardiology Annual Symposium in Washington DC. There was limited PI attendance as many investigators are still not traveling due to local restrictions and availability of virtual sessions. The DCC continued monthly PI calls to review study progress, discuss site issues related to recruitment, strategy compliance and update them on study activities. An in-person investigator/coordinator meeting took place on September 16, 2022. Historically there are usually increases in enrollment post meetings as the enthusiasm for the trial is increased. The meeting agenda is attached in the appendix. The meeting was attended by 35 study coordinators and investigators. The meeting was offered in a live streaming format and all sessions were made available to those investigators that could not attend in real time. Impact of the meeting will be reported in the next quarterly report.** ***[Ongoing, within SOW projections]***

Major Task #7 – Training Meeting: **[Months 1-9]**

All sub-tasks are ongoing. As reported previously all site training has occurred by teleconference/WebEx training. Sites are provided BOX access for all study related materials (protocol, approved consents, training and recruitment materials). Sites are scheduled after IRB approval is received, while waiting HRPO approval. Once HRPO approval is received, site database access is authorized, and they are activated to enroll. Additional site calls have been held with low enrolling sites to offer additional training and trouble shoot issues with enrollment. Monthly PI investigator calls have been initiated to review current trial status for recruitment, strategy compliance and discuss operational issues. Site initiations and training have been held prior to site activation with the PI/study coordinators. Monthly coordinator calls continue to update staff and update training based on review of site performance reports. Site monitoring visits were initiated in the fourth quarter of Year 4 and additional training is taking place during these monitoring calls. **Site training for new staff and PI's has been conducted for several new site PI's during Year 5. New coordinators have been trained as they have been hired and assigned to WARRIOR.** ***[Ongoing]***

Major Task #8 – Project Management: **[Months 1-48]**

All sub-tasks are ongoing. The DCC is, and will continue to be, the primary contact for the DoD and will disseminate information from the DoD to all appropriate groups. Teleconferences with the DoD are scheduled and attended as needed. The project is registered on Clinicaltrials.gov NCT 03417388. The WARRIOR website is online and housed in the University of Florida Web Domain. https://ufhealth.org/research-study/women-s-ischemia-trial-reduce-events-non-obstructive-cad-warrior-0. It is fully functional as the communication portal. ***[Ongoing, within SOW projections]***

Major Task #9 – Site Management**: [Months 1-48]**

All sub-tasks are ongoing. Study subject recruitment began with randomization at the UF vanguard site on February 9, 2020. As **of 9/14/22 a total 2140** subjects have been randomized to the project **from 81 activated sites. Six prior activated sites have been closed due to lack of enrollment.**

Since the inception of the trial the DCC, including the Study PI, the Cedars Biostatistical Center PI, and operational staff from both groups have been meeting weekly to review all operational activities of the trial. Additional operational groups also meet weekly i.e. Data management group, IMT Monitoring Work Group, Geneva/DCC work group etc. The focus of the Operations Work Group meetings has been on site identification, recruitment and onboarding. Participant tracking and reporting is conducted weekly and is reviewed at the Executive Committee Meetings. The Optimal Medical Therapy Committee has developed metrics for assessing treatment compliance and crossovers. Dr. Margaret Lo (University of Florida) has taken the DCC lead to develop site metrics and has initiated calls with high performing sites to ascertain best practices to share with other sites. She has participated in both PI and coordinator calls and Site Initiation Virtual Visits.

Additionally, the DCC has initiated PI and Co-I calls with site investigators for sites that are low enrollers to identify barriers and solutions to improve enrollment. This has resulted in over 40 PI calls (approximately 1/week excluding holidays) to review performance, identify barriers, and discuss solutions to improve patient recruitment. Response to calls has been highly variable in terms of improving site recruitment. Regulatory document collection is ongoing on time, and the DCC is continuing to serve as the primary contact for scientific and management questions as planned. . **Receipt of the second no cost extensions requires contract amendments for all sites and subcontracts and these are in process.** ***[Ongoing, within SOW projections]***

Major Task #10 – Site Monitoring**: [Months1-48]**

All sub-tasks are ongoing. The site monitoring guide and training plan are ongoing. The DCC oversees site monitoring. Site activity is monitored daily. Performance is reviewed on the weekly Executive/Operations call and site contacts are operationalized (PI vs coordinator contact). Monthly coordinator training calls are ongoing. Monthly PI calls have been implemented as sites have come back on line. **Virtual site visits have been conducted during Year 5 to monitor site data quality and resolve data queries and missing data. To date, 34 of the 81 sites are complete. On site visits were conducted at four sites: UCLA, LA BioMed, Cedars-Sinai, and Ocala Research Institute. Additional in person visits are planned for Year 6, Quarter 1.** ***[Ongoing, within SOW projections]***

Major Task #11 – Audits: **[Months1-48]**

All sub-tasks are ongoing. Vendor audits are occurring as needed. During YEAR 4 the DCC had weekly conference calls with Cedars Sinai (statistical core), LA BioMed (CT recruitment center and Core Lab), BE A WARRIOR (UF Biorepository), monthly calls with Geneva Foundation (military site CRO), Community Health IT (consortium of practice sites) and as needed calls with Clinical Endpoint Committee to review work performance. **These calls have continued in Year 5.** All subcontractors are functioning as outlined in the contracted SOW. Evaluation of performance is assessed in an ongoing fashion. The Community Health IT effort has been discontinued as it did not yield additional sites. **There have been no performance issues identified.** ***[Ongoing, within SOW projections]***

Major Task #12 – Safety Surveillance and Medical Monitoring: **[Months 1-48]**

This task is completed and has moved into monitoring, including preparing a safety plan and SAE form, developing a method of receiving SAE information and creating a database for all SAEs, creating a method for forwarding SAE reports to the CSC, CEC and DSMB and creating an SAE tracking system. Most of the SAE process will be automated with email reminders being sent to DCC coordinators when a new SAE occurs. The study team will continue to monitor for all SAEs, provide clinical review, create narratives and provide reconciliation within the database. Adverse events and serious adverse events have been reported, as scheduled, to the Independent DSMB on September 24, 2019.

During YEAR 3 there was a planned DSMB for March 2020, but due to COVID-19 and halting of recruitment and based on discussions with the DSMB Chair, the planned DSMB meeting was postponed. As requested, an interim update was submitted.

During Year 4, the DCC remained in close contact with the DSMB chair to review project performance and to determine timing of the next DSMB meeting. The Year 3 annual report was shared with the DSMB chair as requested. The DSMB met on 3/12/21 and the recommendation was made to continue the study. At this meeting, the DSMB also requested that an Independent Advisory Committee (IAC) be convened and charged with reviewing the study conduct and aggregate results (without access to any randomized group data) and make recommendations regarding the trial. On April 1, 2021 Dr. Pepine sent a letter to Dr. John Beltrame inviting him to chair this committee. Dr. Beltrame (cardiologist, vascular biologist and medical school Dean), accepted and is joined by committee members Dr. Angela Maas (cardiologist focused on woman's CVD), Dr. Colin Berry (cardiologist focused on clinical trials), and Dr. Samar El Khoudary (statistician and epidemiologist). All IAC members have experience in the field of angina or ischemia without obstructive CAD. An initial teleconference meeting was held on June 4, 2021, with the Executive Committee and Dr. Beltrame to establish the charge and to provide the protocol, including the a priori determined contingency plans for recruitment and outcomes, and the published design manuscript. A first teleconference meeting of the entire IAC was held on June 17, 2021. The current status of the study was reviewed and Dr. Pepine (PI) answered questions. The IAC requested additional data regarding current and projected enrollment utilizing no cost extensions, current event rates and the impact on previously calculated power, and financial and other potential feasibility concerns related to extending recruitment and follow up.

During Year 5 additional data as requested by the IAC were provided and a second teleconference meeting was held on October 4, 2021. The DSMB deferred their September 2021 meeting in order to have the IAC report for review. The DSMB met on October 29, 2021. Their recommendation was to continue to the study and to do all that was possible to increase recruitment and secure funding to be able to carry out the trial. The DSMB requested a meeting with study statistical staff on February 11, 2022 only to look at rate of event accrual and recruitment feasibility. The DSMB did not make any additional recommendations after this review.

The DSMB met on June 21, 2022 and did a full review of the project including recruitment, adverse events and safety data as well as outcome data. The DSMB final report is still pending but the preliminary recommendation was to continue the trial and to get the original sample size enrolled as quickly as possible. The second No Cost Extension has been applied for and received. Advance Payment to carry out the trial is in process. ***[Ongoing, within SOW projections]***

Major Task #13 – Data Management: **[Months 1-48]**

The majority of the subtasks to set up the system have been completed, including identifying clinical data coordination, developing eCRF screens, programming the REDCap-UFDMS with eCRFs and query rules, creating query rule specifications, testing query rules, hosting the University of Florida Data Management System (UFDMS) database, conducting coding process, and providing dictionaries. Training for using the UFDMS will occur either in-person or via a webinar, depending on site/investigator location. A detailed Manual of Procedures has been developed and it outlines how a site interacts with the UFDMS. A data cleaning plan and query rule specifications are currently in development. All of the remaining tasks are in-progress.

The UFDMS staff provide weekly reports of all data elements including recruitment status, adverse event reporting, IMT compliance by site, and payment updates. ***[Ongoing, within SOW projections]***

Major Task #14 – Clinical Events Classification: **[Months 1-48]**

This task was completed in the first quarter. The CEC process, and charter was created and approved the CSC and DCC. The CEC Committee members and been identified, reviewed and approved. Adjudication meetings and independent reviews have been established. The CEC will provide ongoing adjudication throughout the trial. The Clinical Endpoint Committee (CEC) was trained in September 2018 and they have adjudicated the initial set of outcomes data. Review of the endpoint adjudication system/process is continuous, and the system is being adjusted to accommodate necessary changes based on reviewer feedback.

During YEAR 5 the CEC has continued to adjudicate events as they are reported. These were reported and reviewed by IRB during the continuing renewal and the DSMB at the June 21, 2022 meeting. There were no recommendations regarding safety concerns from the DSMB. ***[Ongoing, within SOW projections]***

Major Task #15 – Executive, Steering and Other Study Committees: **[Months 1-48]**

During Year 5, the DCC and Statistical Core continued to conduct weekly scheduled EC calls that were attended by investigators and other involved parties, as needed. The DCC also continues scheduled weekly operations calls with study staff to resolve issues and update the investigators on progress of various tasks. The DSMB met on June 21, 2022. They will meet again in October/November. This task has occurred within the SOW timeline. ***[Ongoing, within SOW projections]***

Major Task #16 – Blood Repository: **[Months 1-9]**

The BE A WARRIOR Biorepository continues to be operational. **All sites have been trained and are operational and have sent samples on 1018 patients which have been processed and stored. This has provided 16,525 aliquots for analysis. Sample collections that were deferred due to site restrictions are being collected at next protocol visits.** In the original proposal the Biorepository was funded from DoD for sample collection but not for any sample processing or freezer storage. The McJunkin Family Foundation Trust has continued to recognize the importance of the WARRIOR project by providing financial resources during two funding cycles for a total of . This has permitted initial sample analysis, partition of samples and freezer storage.

During Year 5 sample collection has continued and the number of samples is provided above. Some data from these samples has been analyzed and reported. See Task #18 for details. ***[Ongoing, delayed sample collection due to delayed enrollment]***

Major Task #17 – Statistical Analysis: **[Months 1-48]**

All sub-tasks in the pre-study phase and months 1-3 are completed. The Independent Data Safety and Monitoring Committee (DSMB) was created and a charter and analysis plan were finalized. The DSMB met on October 17, 2018, and reviewed an interim update on June 6, 2019. They held another meeting on September 24, 2019. After reviewing reported events and other project activities they recommended that the study continue, as planned with a continue focus on rapid recruitment of new sites and participants. During Year 3 an interim report was provided to the DSMB in lieu of a full meeting, which was postponed due to COVID-19 disruption of site activities. The DSMB Chair requested and received site and patient recruitment updates and reviewed the year 3 annual report. No recommendations have been received regarding trial conduct other than "to continue as planned". The statistical Core and PI and DCC staff have met to review the statistical plan and contingency plans in the event of lower-than-expected enrollment. The DSMB met March 12, 2021, and recommended the trial continue, focus on recruitment and also convene an Independent Advisory Committee to make recommendations regarding projected enrollment, contingency plans and potential alternative strategies

for data analysis.

In Year 5 the DSMB met June 21, 2022 and recommended all efforts be applied to completing recruitment as originally planned and to continue with the primary outcomes as specified in the original design. The next DSMB meeting is tentatively scheduled for late October/early November 2022. The remaining sub-tasks are on-going within the SOW timeline. ***[Ongoing, within SOW projections]***

Major Task #18 – Manuscripts: **[Months 1-48]**

The sub-task for months 1-3 were completed in the first quarter. Publication plans have been formulated, and as planned the Executive Committee (EC) will also function as the Publication Committee.

Year 5

The cumulative publication activities for this trial are summarized below. Because this pivotal trial has the ability to inform guidelines, its conduct and completion have been commented on and reported in multiple other publications and these supporting publications are listed below.

Publications

Manuscripts

1. Handberg EM, Bairey Merz CN, Cooper-Dehoff RM, Wei J, Conlon M, LoMC, Boden W, Frayne SM, Villines T, Spertus JA, Weintraub W, O'MalleyP, Chaitman B, Shaw LJ, Budoff M, Rogatko A, Pepine CJ. Rationale anddesign of the Women's IschemiA TRial to Reduce Events In Non- ObstRuctive CAD (WARRIOR) Trial. *Am Heart J.* 2021; 237:90–103.
2. Bairey Merz CN, Beltrame JF, Berry C, Boden WE, Camici PG, Crea F, Hochman JS, Kaski JC, O'Gara PT, Ong P, Pepine CJ, Shimokawa H, Sechtem U, Stone GW. Insights to advance our management of myocardial ischemia: from obstructive epicardial disease to functional coronary alterations. *Am Heart J Plus*. 2021;11:100060. doi: 10.1016/j.ahjo.2021.100060.
3. Bairey Merz CN, Pepine CJ. Acute and chronic Ischemic Heart Disease in the Absence of Obstructive Epicardial Disease. In: Bittner V, ed. Adult Clinical Cardiology Self-Assessment Program (ACCSAP). Washington, DC: American College of Cardiology; 2022. Available at www.acc.org/accsap.
4. Keeley EC, Li HJ, Cogle CR, Handberg EM, Bairey Merz CN, Pepine CJ. Specialized proresolving mediators in symptomatic women with coronary microvascular dysfunction (from the Women's Ischemia Trial to Reduce Events in Nonobstructive CAD [WARRIOR] trial. *Am J Cardiol*. 2022;162:1–5.
5. Keeley EC, Handberg EM, Wei J, Bairey Merz CN, Pepine CJ. Coronary microvascular dysfunction as a chronic inflammatory state: Is there a role for omega-3 fatty acid treatment? *Am Heart J Plus*. 2022;13:100098. doi: 10.1016/j.ahjo.2022.100098.
6. Pepine CJ. ANOCA/INOCA/MINOCA: Open artery ischemia. *Am Heart J Plus*. In press.
7. Ya'Qoub L, Elgendy IY, Pepine CJ. Non-obstructive plaque and treatment of INOCA: More to be learned. Curr Atheroscler Rep. 2022;24:681–7. PMID: 35781776
8. Feuer DS, Handberg EM, Mehrad B, Wei J, Bairey Merz CN, Pepine CJ, Keeley EC. Microvascular dysfunction as a systemic disease: A review of the evidence. Am J Med. 2022;135(9):1059–68. PMCID: PMC9427712

Abstracts (Invited presentations at ACC21)

1. Resolvins in Women with Coronary Microvascular Dysfunction - Results from the Women's Ischemia Trial to Reduce Events in Non-Obstructive Coronary Artery Disease (WARRIOR) Trial (NCT03417388). Ellen C. Keeley, Han J. Li, Christopher R. Cogle, Eileen M. Handberg, C. Noel Bairey Merz, Carl J. Pepine. ACC 21 Featured Oral Presentation. *J Am Coll Cardiol.* 2021;77(18 suppl 1):1.
2. Comparison of Risk Profiles of Women with INOCA Diagnosed by Coronary Computed Tomography Angiography vs Invasive CoronaryAngiography - A Substudy of the Women's Ischemia Trial to Reduce Events In Non-Obstructive Coronary Artery Disease (WARRIOR) Suvasini Lakshmanan, Janet Wei, Galen Cook-Wiens, Andre Rogatko, Carl J. Pepine, Eileen M. Handberg, Leslee J. Shaw, Matthew Budoff, C. Noel Bairey Merz. ACC 21 Poster Presentation. *J Am Coll Cardiol.* 2021;77(18 suppl 1):1357.
3. The Impact of the COVID-19 Pandemic on a Multi-Center Clinical - Adapting in Real-time to Maintain Trial Integrity. Osama Dasa, Eileen M Handberg, George Sopko, Chrisandra L Shufelt, Janet Wei, André Rogatko, C Noel Bairey Merz, Carl J Pepine. ACC 21 Poster Presentation.*J Am Coll Cardiol.* 2021;77(18 suppl 1):3268.

Based on the potential impact in terms of clinical guidance, the WARRIOR trial has been discussed in multiple other publications as listed below.

1. Wei J, Shufelt C, Bairey Merz CN. Women's health: making cardiovascular disease real. *Curr Opin Cardiol*. 2018 Sep;33(5):506-513. doi: 10.1097/HCO.0000000000000544. PMID: 29985202; PMCID: PMC6629037
2. Bairey Merz CN, Pepine CJ, Shimokawa H, Berry C. Treatment of coronary microvascular dysfunction. *Cardiovasc Res*. 2020;116(4):856–70. PMCID: PMC7061279
3. Ya'qoub L, Elgendy IY, Pepine CJ. Syndrome of nonobstructive coronary artery diseases: A comprehensive overview of open artery ischemia. *Am J Med*. 2021;134:1321–9. PMID: 34343507; PMCID: PMC8754003
4. Pacheco C, Mullen KA, Coutinho T, Jaffer S, Parry M, Van Spall HGC, Clavel MA, Edwards JD, Sedlak T, Norris CM, Dhukai A, Grewal J, Mulvagh SL. The Canadian Women's Heart Health Alliance Atlas on the Epidemiology, Diagnosis, and Management of Cardiovascular Disease in Women - Chapter 5: Sex- and Gender-Unique Manifestations of Cardiovascular Disease. *CJC Open*. 2021;4(3):243–62. PMCID: PMC8978072
5. Elgendy IY, Ya'Qoub L, Chen KH, Pepine CJ. Coronary Microvascular Dysfunction in Patients with Non-Obstructive Coronary Arteries: Current Gaps and Future Directions. *Drugs*. 2022;82(3):241-250. PMID: 35092594
6. Canan A, Navar AM. Limitations of observational studies for aspirin in primary prevention and the need for randomized trials. *Radiol Cardiothorac Imaging*. 2022;4:e220079. PMCID: PMC9059079
7. Garg K, Patel TR, Kanwal A, Villines TC, Aggarwal NR, Nasir K, Blumenthal RS, Blaha MJ, Douglas PS, Shaw LJ, Sharma G. The evolving role of coronary computed tomography in understanding sex differences in coronary atherosclerosis. *J Cardiovasc Comput Tomogr*. 2022;16(2):138–49. PMCID: PMC9358989
8. Thakker RA, Rodriguez Lozano J, Rodriguez Lozano P, Motiwala A, Rangasetty U, Khalife W, Chatila K. Coronary microvascular disease. *Cardiol Ther*. 2022;11(1):23–31. PMCID: PMC8933600
9. Bairey Merz CN, Marbáan E. Stem cell therapy targets: Repêchage! *Circ Res*. 2022;130(3):339–42. PMID: 35113658

10. Rodriguez Lozano PF, Rrapo Kaso E, Bourque JM, Morsy M, Taylor AM, Villines TC, Kramer CM, Salerno M. Cardiovascular imaging for ischemic heart disease in women: Time for a paradigm shift. *JACC Cardiovasc Imaging*. 2022;1488–1501. PMID: 35331658
11. Dyall SC, Balas L, Bazan NG, Brenna JT, Chiang N, da Costa Souza F, Dalli J, Durand T, Galano JM, Lein PJ, Serhan CN, Taha AY. Polyunsaturated fatty acids and fatty acid-derived lipid mediators: Recent advances in the understanding of their biosynthesis, structures, and functions. *Prog Lipid Res*. 2022;86:101165. PMCID: PMC9346631
12. Serhan CN, Libreros S, Nshimiyimana R. E-series resolvin metabolome, biosynthesis and critical role of stereochemistry of specialized pro-resolving mediators (SPMs) in inflammation-resolution: Preparing SPMs for long COVID-19, human clinical trials, and targeted precision nutrition. *Semin Immunol*. 2022;101597. PMCID: PMC8847098
13. Iribarren A, Diniz MA, Merz CNB, Shufelt C, Wei J. Are we any WISER yet? Progress and contemporary need for smart trials to include women in coronary artery disease trials. *Contemp Clin Trials*. 2022;117:106762. PMCID: PMC9156573
14. Bradley C, Berry C. Definition and epidemiology of coronary microvascular disease. *J Nucl Cardiol*. 2022;29(4):1763–75. PMCID: PMC9345825
15. Ang DTY, Berry C, Kaski JC. Phenotype-based management of coronary microvascular dysfunction. *J Nucl Cardiol*. 2022; doi: 10.1007/s12350-022-03000-w. PMID: 35672569
16. Huang J, Kumar S, Toleva O, Mehta PK. Mechanisms of coronary ischemia in women. *Curr Cardiol Rep*. 2022; doi: 10.1007/s11886-022-01745-x. PMID: 35904668

The remaining sub-tasks are on- going and within the SOW timeline. ***[Ongoing, within SOW projections]***

WHAT WAS ACCOMPLISHED UNDER THESE GOALS?

During this **Year 5** annual reporting period the WARRIOR trial grant proposal **has successfully processed 81 sites after contacting over 1,000 potential sites. Of those 81, there are now 75 active enrolling sites.** There are no major outcomes, findings or conclusions available related to the specific aims. However, one conclusion is clearly apparent—recruitment of women into ischemic heart disease trials during a pandemic is a challenge.

WARRIOR sites have recruited 2140 women as of 9/14/22; during YEAR 5 there have been 428 women enrolled. In spite of this success, recruitment continues to be impacted by the COVID-19 pandemic which has continued to be a major public health issue due to the development of mutations such as the delta and omicron variants which have emerged in YEAR 5 and resulted in a surge in cases, hospitalizations and deaths due to COVID-19. This has resulted in continued diversion of WARRIOR Trial research nursing staff to support COVID Trials and the clinical enterprise. In addition, the pandemic has resulted in many nurses leaving the workforce, changes in jobs due to high paying travel nursing opportunities which has resulted in turnover and staffing shortages. Recruitment of participants continues to lag from original projections, and the issues, barriers, and operational solutions have been presented in real time as part of each quarterly report and will be summarized here.

Operationalization of this pragmatic clinical trial was on target in terms of protocol finalization, IRB/HRPO approvals, and designing, testing, and completing the eCRFs and modifying REDCap. Vendor contracting and use of the Single IRB has reduce the time required to activate sites. Web based data entry streamlines data.

This pragmatic trial has limited per patient reimbursement as is characterized by trials that incorporate clinical follow up into the budgeting framework. Financial incentives for enrolments were offered in Year 2 and proved to be only minimally successful. During year 4 and year 5 we have reached out to over half of the site PI's in PI to PI calls to discuss barriers to recruitment, offer solutions and support to assist in recruitment. Monthly PI and Coordinator calls have been in place for the last 3 years to attempt to identify barriers and recommend solutions.

We have held two in person Coordinator/Investigator meeting to bring best practices and additional training directly to study staff to identify barriers to recruitment and encourage renewed enrollment efforts.

Projected recruitment has now extended through YEAR 5 and will continue, pending DSMB review in October into the second of two planned No Cost Extensions. The NCE has sufficient funds to carry out the work of the project since the per patient recuited reimbursement funding has not been spent and is available to continue enrollment as planned.

An early protocol revision allows for the payment of a coronary CT angiogram to confirm eligibility has proven to be very successful in allowing women who have not had imaging done as part of their clinical evaluation for chest pain enroll in the trial. Approximately half of the cohort enrolled have been evaluated by coroanry CTA imaging. A second DoD grant "QUantifIEd Coronary Artery Plaque and OuTcomes (QUIET): WARRIOR Ancillary Study" leverages the investment made to carry out a landmark trial by utilizing already collected CCTA data and biorepository samples to better understand the pathophysiology behind the findings that will be collected in WARRIOR and was submitted in 2022. The project is currently under review with expected funding if awarded in the first quarter of 2023.

We have continued to incorporate the patient voice in our efforts to reach women who are affected and are the target of this trial. The Executive Committee Member who is our patient advocate Dr. Barbara Harris helps direct our new plan, and spoke to the Investigators and Coordinators at our meeting in September. We continue to work with "INOCA International" another advocacy group to utilize their global presence to provide information for potential participants. Utilization of "MyChart" (by EPIC) as a recruitment mechanism has also been very successful. This method reaches out to potentially eligible women and those that are interested can contact the site for more information. This method has been transmitted to all sites who use EPIC for their EHR.

The Ancillary Trial "Effect of Intensive Medical Treatment on Quantified Coronary Artery Plaque Components with Serial Coronary CTA in Women with Non-Obstructive CAD", which was submitted by Dr. Balaji Tamarappoo at Cedars Sinai Medical Center with the full support of the WARRIOR Executive Committee was funded (9/20) by the NHLBI. Patients who are approaching 3 years of follow up are approached for participation and collection of repeat coronary CT angiograms.

We continue to work on potential collaboration with several imaging analysis companies including HeartFlow, INC (reported previously) and now Euclid to apply their computational fluid dynamic applications to further analyze the CCTAs from WARRIOR. This effort has the potential to provide supplemental funding in year 2 of the NCE.

Additionally, we have had a favorable response for supplemental funding with the UF Foundation and the McJunkin Family Foundation Trust to shift their funding commitment for the biorepository to the main WARRIOR trial DCC in year 2 of the NCE.

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

At this point in the project, local and national lectures, slide presentations, and mentoring by Drs. Pepine and Bairey Merz have provided an opportunity to inform trainees and professionals in Cardiovascular Medicine, Internal Medicine, Family Medicine, Emergency Medicine and Nursing, as well as the public, about the problem of ischemic heart disease in women who have no obstructive CAD.

How were the results disseminated to communities of interest?

The Rationale and Design manuscript was published in the American Heart Journal in March 2021. See Major Task #18 for a complete list of manuscripts to date.

The following abstracts were also selected for presentation at the American College of Cardiology 70th Annual Meeting:

Keeley E, Li H, Cogle C, Handberg E, Bairey Merz CN, Pepine C. Resolvins in women with coronary microvascular dysfunction—Results from the Women's Ischemia Trial to Reduce Events in Non-Obstructive Coronary Artery Disease (WARRIOR) Trial (NCT03417388). *J Am Coll Cardiol*. 2021 May;77(18_Suppl_1):1.

Lakshmanan S, Wei J, Cook-Wiens G, Rogatko A, Handberg E, Pepine C, Shaw L, Budoff M, Bairey Merz CN. Comparison of risk profiles of women with INOCA diagnosed by coronary computed tomography angiography vs invasive coronary angiography—A substudy of the Women's Ischemia Trial to Reduce Events in Non-Obstructive Coronary Artery Disease (WARRIOR). *J Am Coll Cardiol*. 2021 May;77(18_Suppl_1):1357.

Dasa O, Handberg E, Sopko G, Shufelt CL, Wei J, Rogatko A, Cooper-DeHoff R, Bairey Merz CN, Pepine C. The impact of the COVID-19 pandemic on a multi-center clinical trial–Adapting in real-time to maintain trial integrity. *J Am Coll Cardiol*. 2021 May;77(18_Suppl_1):3268.

What do you plan to do during the next reporting period to accomplish the goals?

The DCC will continue the enhanced efforts to complete recruitment during the next 6-9 months of an approved second no cost extension, with a focus on inclusion of more African American women. As reported in the last quarterly report, the following activities will continue. Throughout the project the DCC and Executive Committee increased all efforts to assist site PI's and coordinators to train new staff and encourage more effective recruitment strategies. Site visits will be increased at all sites that have potential to increase enrollment. The Investigator/Coordinator meeting interactions resulted in some targeted sites who have requested support. Monthly Coordinator and PI calls will continue to review recruitment, discuss strategy compliance, and AE/SAE reporting. Direct site support has been provided, which is beginning to yield additional recruitment.

The in-person conference was held September 16 in Orlando, FL. Historically, in other clinical trials, we have observed an increase in recruitment after convening an investigator/ coordinator meeting. This was implemented in late February 2020 but its impact was mitigated by the closure of sites in early March 2020 due to COVID-19. The impact of the recent meeting will be evaluated in the next quarter and is expected to result in a significant increase in enrollment.

As reported previously, the DSMB meeting was held on June 21, 2022. They reviewed study progress and, they recommended that the trial continue as planned and also encouraged our international plans, and all efforts to complete the trial as originally planned. The DSMB expressed concern about delayed enrollment and encouraged the Executive Committee to work to secure additionally funding and resources to continue this pivotal trial beyond the no cost extensions if enrollment cannot be completed in the next 6-12 months.

WARRIOR additional funding has also been solicited from the SALAL Foundation and it potentially could fund in early 2023. These funds would be utilized to extend follow up.

4. IMPACT:

Although we no outcomes data to report, the publications and presentations associated with the WARRIOR trial have raised awareness of the problem of ischemic heart disease without obstructive disease in the epicardial coronary arteries.

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

The difficulties with site recruitment and activation have been detailed in the scope of work report above. As was stated, the pandemic has impacted most non-COVID clinical trials that have made modifications similar to those that we have made, and those trials are continuing. The protocol has been updated to allow for virtual recruitment and follow up in the event that sites are closed again due to resurgence of COVID-19 or a bad flu season. Virtual enrollment also enables us to work with sites adversely impacted by the recent hurricanes.

Actual or anticipated problems or delays and actions or plans to resolve them

Delays in contracting, IRB/HRPO approvals in order to initiate patient recruitment have been detailed above. Biweekly operations staff meetings are held to assess study progress in order to identify issues, develop solutions and implement necessary changes. Changes and modifications of operations have been outlined in detail above and include increasing staff resources, modifying the site budget, meetings with the IRB and HRPO to streamline processes to improve efficiency have been implemented. Ongoing evaluation of these changes is taking place.

Changes that had a significant impact on expenditures

There has been a delay in spending as projected due to the delay in site activation and patient enrollment. Patient care costs will be deferred to later in the budget cycle.

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

No changes.

Significant changes in use or care of vertebrate animals

Not applicable.

Significant changes in use of biohazards and/or select agents

Not applicable.

6. PRODUCTS:

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

Papers published or accepted:

Handberg EM, Bairey Merz CN, Cooper-Dehoff RM, Wei J, Conlon M, Lo MC, Boden W, Frayne SM, Villines T, Spertus JA, Weintraub W, O'Malley P, Chaitman B, Shaw LJ, Budoff M, Rogatko A, Pepine CJ. Rationale and design of the Women's IschemiA TRial to Reduce Events In Non- ObstRuctive CAD (WARRIOR) Trial. *Am Heart J.* 2021; 237:90–103.

Bairey Merz CN, Beltrame JF, Berry C, Boden WE, Camici PG, Crea F, Hochman JS, Kaski JC, O'Gara PT, Ong P, Pepine CJ, Shimokawa H, Sechtem U, Stone GW. Insights to advance our management of myocardial ischemia: from obstructive epicardial disease to functional coronary alterations. *Am Heart J Plus*. 2021;11:100060. doi: 10.1016/j.ahjo.2021.100060.

Bairey Merz CN, Pepine CJ. Acute and Chronic Ischemic Heart Disease in the Absence of Obstructive Epicardial Disease. In: Bittner V, ed. Adult Clinical Cardiology Self-Assessment Program (ACCSAP). Washington, DC: American College of Cardiology; 2022. Available at www.acc.org/accsap.

Keeley EC, Li HJ, Cogle CR, Handberg EM, Bairey Merz CN, Pepine CJ. Specialized proresolving mediators in symptomatic women with coronary microvascular dysfunction (from the Women's Ischemia Trial to Reduce Events in Nonobstructive CAD [WARRIOR] trial. *Am J Cardiol*. 2022;162:1–5.

Keeley EC, Handberg EM, Wei J, Bairey Merz CN, Pepine CJ. Coronary microvascular dysfunction as a chronic inflammatory state: Is there a role for omega-3 fatty acid treatment? *Am Heart J Plus*. 2022;13:100098. doi: 10.1016/j.ahjo.2022.100098.

Pepine CJ. Open artery ischemia: ANOCA/INOCA/MINOCA. *Am Heart J Plus*. 2022, In press.

Ya'Qoub L, Elgendy IY, Pepine CJ. Non-obstructive plaque and treatment of INOCA: More to be learned. *Curr Atheroscler Rep*. 2022;24:681–7. PMID: 35781776

Feuer DS, Handberg EM, Mehrad B, Wei J, Bairey Merz CN, Pepine CJ, Keeley EC. Microvascular dysfunction as a systemic disease: A review of the evidence. *Am J Med*. 2022;135(9):1059–68. PMCID: PMC9427712

Abstracts presented at American College of Cardiology 70th Annual Meeting, May 15-17, 2021, Virtual:

Keeley E, Li H, Cogle C, Handberg E, Bairey Merz CN, Pepine C. Resolvins in women with coronary microvascular dysfunction—Results from the Women's Ischemia Trial to Reduce Events in Non-Obstructive Coronary Artery Disease (WARRIOR) Trial (NCT03417388). *J Am Coll Cardiol*. 2021 May;77(18_Suppl_1):1.

Lakshmanan S, Wei J, Cook-Wiens G, Rogatko A, Handberg E, Pepine C, Shaw L, Budoff M, Bairey Merz CN. Comparison of risk profiles of women with INOCA diagnosed by coronary computed tomography angiography vs invasive coronary angiography—A substudy of the Women's Ischemia Trial to Reduce Events in Non-Obstructive Coronary Artery Disease (WARRIOR). *J Am Coll Cardiol*. 2021 May;77(18_Suppl_1):1357.

Dasa O, Handberg E, Sopko G, Shufelt CL, Wei J, Rogatko A, Cooper-DeHoff R, Bairey Merz CN, Pepine C. The impact of the COVID-19 pandemic on a multi-center clinical trial–Adapting in real-time to maintain trial integrity. *J Am Coll Cardiol*. 2021 May;77(18_Suppl_1):3268.

Presentations:

Talks/Lectures that included WARRIOR Sept 15, 2021 to Sept 14, 2022

Eileen Handberg, PhD

Regional Presentations:

- Research and Why It Matters. PrimeTime Institute. Virtual Event. February 17, 2022.
- Research and Why It Matters. White Coat Wednesday. Del Webb Stonecreek-Ocala. March 2, 2022.
- Research and Why It Matters. Oak Hammock Mini Medical School. Gainesville, FL. March 8, 2022.

Noel Bairey Merz MD

International Presentations:

- The challenges of research and treatment of atherosclerotic disease in women, 18th Brazilian Congress of Atherosclerosis, Brazilian Cardiology and Department of Atherosclerosis, Brazil, Virtual Event, October 16, 2021.
- Sex, Menopause and Coronary Atherosclerosis: Why Do More Women have INOCA (ischemia with no obstructive CAD), 19th International Symposium on Atherosclerosis ISA 2021, Kyoto, Japan, Virtual Event, October 26, 2021.
- Sex Differences in ACS Presentation, MUHC Third Annual Women's Heart Health Symposium, Division of Cardiology, McGill University, Montréal, Canada, Virtual Event, November 18, 2021.
- More than a single menses disorder: Polycystic ovarian syndrome and cardiovascular disease in women, South American Congress of Cardiology, II Latino American Symposium of Cardiovascular Disease in Women, Santiago, Chile, Virtual Event, November 30, 2021.
- Round Table, Sex-specific Risk Factors in Women, South American Congress of Cardiology, II Latino American Symposium of Cardiovascular Disease in Women, Santiago, Chile, Virtual Event, November 30, 2021.
- Key Note Speaker, Crossing Borders in Women's Cardiovascular Health, Sex and Gender Issues in Cardiovascular Disease: Sex as A Biological Variable, Nijmegen, Netherlands, April 22, 2022
- Lecture, HRT and Cardiovascular Risk, Virtual Conference, Sex Differences in Cardiovascular Health, June 4, 2022

National Presentations:

- Women & Heart Disease: Detection, Evaluation, and Management, 32nd Annual National Conference on Women's Healthcare, CME, Symposia Medicus, Las Vegas, Nevada, September 20, 2021.
- What We Do and Do Not Know About the Leading Killer of Women and What We Should Do About It. Advancing NIH Research on the Health of Women: A 2021 Conference. The National Institutes of Health (NIH) Office of Research on Women's Health (ORWH), Virtual Event, October 20, 2021.
- Panelist, Plenary Session 1: Brain–Heart–Gut Interactions, Specialized Centers of Research Excellence (SCORE) 2021 Annual Meeting, Virtual Event, December 14, 2021.
- Presidential Keynote Lecture, "What We Know about the Leading Killer of Women", AMWA Annual Meeting, March 25, 2022.
- Speaker and Panelist, Sex-Specific Considerations in the Pathophysiology of Myocardial Infarction, Lancet Women and Cardiovascular Disease Commission Educational Program, ACC 22, April 1, 2022.
- "Cardiac CT Advances - Sex Differences in Prognostic Significance of Plaque Burden and Distribution Measured by Coronary Computed Tomographic Angiography (CCTA) in Younger Patients" American College of Cardiology, April 2, 2022.
- "Ischemic Heart Disease: Special Populations 8 - Prevalence and Characteristics of Women with Takotsubo Syndrome and Persistent Angina: A Report from the Women's Ischemia Syndrome Evaluation - Coronary Vascular Dysfunction (WISE-CVD) Project" American College of Cardiology, April 3, 2022.
- "Ischemic Heart Disease: Special Populations 8 - Left Ventricular Ejection Fraction Temporal Trend Association with Myocardial Perfusion and Left Ventricular Remodeling Assessed with Cardiac Magnetic Resonance Imaging: Results from the Women's Ischemia Syndrome Evaluation – Coronary Vascular Dysfunction Project" American College of Cardiology, April 3, 2022
- "Cardiac MRI State of the Art - Left Ventricular Morphology, Remodeling, and Diastolic Function Trends Across Left Ventricular Ejection Fraction Subgroups in Women with Ischemia and No Obstructive Coronary Artery Disease; Results from the Women's Ischemia Syndrome Evaluation - Coronary Vascular Dysfunction Study" American College of Cardiology, April 3, 2022.
- "What's in a Name? The Diagnosis, Treatment and Future of INOCA and MINOCA" American College of Cardiology, April 3, 2022.
- "The Challenge of MINOCA and INOCA: Novel Insights - Prior Myocardial Infarction in Women with Signs and Symptoms of Ischemia and No Obstructive Coronary Arteries: A Report from the Women's Ischemia Syndrome Evaluations- Coronary Vascular Dysfunction (WISE-CVD) Project" American College of Cardiology, April 4, 2022.
- Co-Chair, Myocardial Infarction With No Obstructive CAD (MINOCA) and Ischemia With No Obstructive CAD (INOCA): Myth or Reality in Imaging, American College of Cardiology 22, April 4, 2022.
- Panelist, "Ongoing Controversies After the New Chest Pain Guidelines", American College of Cardiology, April 4, 2022.
- Lecture, Rationale and Design of the Women's Ischemia Trial to Reduce Events In Non-Obstructive CAD (WARRIOR), WARRIOR Meeting, Virtual, May 13, 2022.
- Lecture, Sex/Gender-Specific COVID-19 Outcomes and Management Relevant for Heart, Lung, Blood, and Sleep Disorders: From Bench to Bedside, NIH Meeting, Virtual, June 17, 2022.
- Lecture, Cardiovascular Disease in Women, Society of Magnetic Resonance Angiography Annual Meeting, August 24, 2022.

- Women in CCTA Trials, Society of Cardiac Computed Tomography (SCCT) Annual Scientific Meeting, Las Vegas, NV, July 15, 2022.
- Lecture, Cardiometabolic Health Congress Women's Health Masterclass Event, Rancho Palos Verdes, CA, September 9, 2022

Regional and Extramural Local Presentations:

- An Update on Coronary Microvascular Dysfunction. GW Cardiology Grand Rounds, Division of Cardiology, The George Washington University, Virtual Event, September 22, 2021.
- Women and Coronary Microvascular Dysfunction: Update 2022, Department of Medicine Grand Rounds, Annual Leon Resnekov Lecture, University of Chicago, Virtual Event, January 5, 2022.
- Diets, Exercise, Herbs and Supplements: What Really Works? Providence Health CM, Providence Saint Joseph Medical Center, Virtual Event, February 1, 2022.
- Community Lecture, The New Age of Women's Heart Health, Brentwood Country Club of Los Angeles, May 13, 2022

Cedars-Sinai Presentations:

- Lecture, The Dilemma of Takotsubo Syndrome: Why is it More Prevalent in Women. Smidt Heart Institute Research Seminar (SHIRS) Series. Los Angeles, CA, June 7, 2022

Carl J Pepine, MD Talks/Lectures that included WARRIOR Sept 15, 2021 to Sept 14, 2022.

International Presentations:

- Small Vessel Disease in the Heart and Brain**,** COVADIS, August 29, 2022, Barcelona, Spain.
- Open Artery Ischemia. Sept 10, 2022, ACC Latin American Initiative, Mexico City. Mexico.

National Presentations:

- Open Artery Ischemia: ANOCA/INOCA/MINOCA. Lee Health System, Fort Meyers and SW Florida, May 10, 2022.

University of Florida Presentations:

- CMD Clinical Trials, May 5, 2022, University of Florida, College of Pharmacy, Gainesville, Florida

- **Books or other non-periodical, one-time publications.**

Nothing to report.

- **Please see above other publications, conference papers and presentations**.

Nothing to report.

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

The WARRIOR website is online https://ufhealth.org/research-study/women-s-ischemia-trial-reduce-events-non-obstructive-cad-warrior-0.

- **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?

UNIVERSITY OF FLORIDA

Name:	**Carl J. Pepine, MD**
Project Role:	PI
Researcher Identifier (e.g. ORCID ID):	0000-0002-6011-681X
Nearest person month worked:	5
Contribution to Project:	Dr. Pepine provides oversight of the WARRIOR project as the Principal Investigator
Funding Support:	NA

Name:	**Eileen Handberg, PhD**
Project Role	Co-Investigator
Researcher Identifier (e.g. ORCID ID):	0000-0002-7805-9577
Nearest person month worked:	6
Contribution to Project:	Dr. Handberg assists Dr. Pepine with overall management of the trial.
Funding Support:	NA

Name:	**Rhonda Cooper-DeHoff, PharmD**
Project Role:	Co-Investigator
Researcher Identifier (e.g. ORCID ID):	0000-0002-5198-130X
Nearest person month worked:	1
Contribution to Project:	Dr. Cooper-DeHoff oversees pharmacy operations for WARRIOR.
Funding Support:	NA

Name:	**Margaret Chin-Tzu Lo, MD**
Project Role:	Co-Investigator
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	1
Contribution to Project:	Dr. Lo serves as an executive committee member with responsibility for strategy compliance for all sites.
Funding Support:	NA

Name:	**Philip Chase**
Project Role:	Data Systems Manager
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	4
Contribution to Project:	Mr. Chase manages the data systems team for WARRIOR.
Funding Support:	NA

Name:	**Kyle James Chesney**
Project Role:	Data Systems Analyst
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	1
Contribution to Project:	Mr. Chesney manages the REDCap software and its extensions.
Funding Support:	NA

Name:	**Kristi Cromwell-Cain**
Project Role:	Contract Coordinator
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	5
Contribution to Project:	Ms. Cromwell-Cain facilitates site recruitment and contracting. She started with WARRIOR in December 2019.
Funding Support:	NA

Name:	**Laurence James-Woodley**
Project Role:	Data Systems Analyst
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	3
Contribution to Project:	Mr. James-Woodley writes and maintains the software that generates weekly reporting for day-to-day operations, AE Reporting, Deviation reporting, DSMB reporting, and IRB Renewal reporting.
Funding Support:	NA

Name:	**Debra Landers**
Project Role:	Regulatory Coordinator
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	12
Contribution to Project:	Ms. Landers assists new sites with IRB submission and other regulatory requirements for WARRIOR. She also processes payments to enrolling sites.
Funding Support:	NA

Name:	**Dana Leach**
Project Role:	Project Manager
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	10
Contribution to Project:	Ms. Leach is responsible for daily management of the WARRIOR trial.
Funding Support:	NA

Name:	**Melissa Reisman**
Project Role:	Contracting Coordinator
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	6
Contribution to Project:	Ms. Reisman facilitates site recruitment and contracting. She started with WARRIOR in November 2019.
Funding Support:	NA

Name:	**Gina Watson-Haley**
Project Role:	Process Coordinator
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	3
Contribution to Project:	Ms. Watson-Haley facilitates organization and communications for WARRIOR. She started with WARRIOR in April 2022.
Funding Support:	NA

Name:	**Taryn Stoffs**
Project Role:	Data Systems Analyst
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	4
Contribution to Project:	Ms. Stoffs is one of three staff that handle the REDCap data system for WARRIOR.
Funding Support:	NA

CEDARS-SINAI SUBAWARD

Name:	**C. Noel Bairey Merz, MD**
Project Role:	Co-Investigator
Researcher Identifier (e.g. ORCID ID):	0000-0002-9933-5155
Nearest person month worked:	1
Contribution to Project:	Dr. Bairey Merz is responsible for protocol development and writing, identifies/screens potential study investigators, investigator communications, chairs / hosts / organizes all Executive / steering / operation / publication meetings, monitors compliance with medical therapy, reviews AE/SAEs, negotiates agreements with executive committee and steering committee members, selects DSMB members, develops DSMB analysis plan, attends DSBM meetings.
Funding Support:	NA

Name:	**Andre Rogatko PhD**
Project Role:	Co-Investigator, Principal Investigator of Biostatistical Core
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	< 1
Contribution to Project:	Dr. Rogatko provides statistical consultation and support, provides statistical expertise in the study design, sample size determination, and plans for interim reviews and final analysis, assists with the writing of statistical components of manuscripts, reviews the integrity and statistical soundness of all studies, provides statistical analysis for all projects using appropriate statistical and computing methodologies, and assists in the interpretation and presentation of results.
Funding Support:	N/A

Name:	**Marcio A. Diniz, PhD**
Project Role:	Co-Investigator, Principal Investigator of Biostatistical Core
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	< 1
Contribution to Project:	Dr. Diniz provides statistical consultation and support, provides statistical expertise in the study design, sample size determination, and plans for interim reviews and final analysis, assists with the writing of statistical components of manuscripts, reviews the integrity and statistical soundness of all studies, provides statistical analysis for all projects using appropriate statistical and computing methodologies, and assists in the interpretation and presentation of results.
Funding Support:	N/A

Name:	**Janet Wei, MD**
Project Role:	Co-Investigator
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	< 1
Contribution to Project:	Dr. Wei assists Dr. Bairey Merz in overseeing all the activities of this project, including project implementation, organizing/attending meetings, identifying/screening potential study investigators, investigator communications, monitoring compliance with medical therapy, reviewing AE/SAEs, negotiating agreements with executive committee and steering committee members, data analysis, abstract and manuscript preparation.
Funding Support:	N/A

Name:	**Jenna Maughan**
Project Role:	Data Coordinator
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	3
Contribution to Project:	Ms. Maughan coordinates data aspects of non-invasive CMRI and invasive CRT/LV pressure, maintaining study records, and ensuring data integrity and quality. She coordinates data entry, data clean, data transfer and data management, assisting with development of data collection instruments, and ensuring data quality. She maintains project logs and coordinates data communication with data coordinating center. She is responsible for all research data to be ready for biostatistician to analyze.
Funding Support:	N/A

Name:	**Okezi Obrutu**
Project Role:	Data Coordinator
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	4
Contribution to Project:	Ms. Obrutu also coordinates data aspects of non-invasive CMRI and invasive CRT/LV pressure, maintaining study records, and ensuring data integrity and quality. She coordinates data entry, data clean, data transfer and data management, assisting with development of data collection instruments, and ensuring data quality. She maintains project logs and coordinates data communication with data coordinating center. She is responsible for all research data to be ready for biostatistician to analyze.
Funding Support:	N/A

Name: **Nicole Tovar**

Project Role: Coordinator
Researcher Identifier (e.g. ORCID ID):
Nearest person month worked: 6
Contribution to Project: Ms. Tovar assists the investigators by performing research related duties including coordinating activities related to CEC and serving as a point of contact for the communications between CEC and the primary institution (UFL). She also assists with scheduling and setting up committee meetings and DSMB meetings, and distributes meeting agendas, and completes meeting minutes.
Funding Support: N/A

Name: Leslie Aguilar-Hernandez

Project Role: Coordinator
Researcher Identifier (e.g. ORCID ID):
Nearest person month worked: < 1
Contribution to Project: Ms. Aguilar-Hernandez assists the investigators by performing research related duties, assisting with data collection and maintaining study related records.
Funding Support: N/A

Name: **Yolanda Rojas**

Project Role: Coordinator
Researcher Identifier (e.g. ORCID ID):
Nearest person month worked: < 1
Contribution to Project: Ms. Rojas assists the investigators by performing research related duties, assisting with data collection and maintaining study related records.
Funding Support: N/A

Name: **Lilit Gevorkian**

Project Role: Coordinator
Researcher Identifier (e.g. ORCID ID):
Nearest person month worked: < 1
Contribution to Project: Ms. Gevorkian assists the investigators by performing research related duties, assisting with data collection and maintaining study related records.
Funding Support: N/A

Name:	**Rohan Paul**
Project Role:	Coordinator
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	< 1
Contribution to Project:	Mr. Paul assists the investigators by performing research related duties, assisting with data collection and maintaining study related records.
Funding Support:	N/A

Name:	**Tracie Huynh**
Project Role:	Coordinator
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	< 1
Contribution to Project:	Ms. Huynh assists the investigators by performing research related duties, assisting with data collection and maintaining study related records.
Funding Support:	N/A

Name:	**Claire Yi**
Project Role:	Coordinator
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	< 1
Contribution to Project:	Ms. Yi assists the investigators by performing research related duties, assisting with data collection and maintaining study related records.
Funding Support:	N/A

Name:	**Dominique White**
Project Role:	Coordinator
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	< 1
Contribution to Project:	Ms. Dominique assists the investigators by performing research related duties, assisting with data collection and maintaining study related records.
Funding Support:	N/A

ST. LOUIS UNIVERSITY SUBAWARD

Name:	**Bernard Chaitman, MD**
Project Role:	Principal Investigator
Researcher Identifier (e.g. ORCID ID):	0000-0002-9216-5317
Nearest person month worked:	1
Contribution to Project:	Principal investigator for subaward site
Funding Support:	NA

Name:	**Jane Eckstein, RN**
Project Role:	Research Nurse
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	1
Contribution to Project:	Nurse project manager to site PI.
Funding Support:	NA

Name:	**Gloria Skelton**
Project Role:	Admin Coordinator
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	1
Contribution to Project:	Provides support to Dr. Chaitman.
Funding Support:	NA

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

The Site PI and Investigators have had changes in non-WARRIOR funding but these changes have not affected effort for WARRIOR.

What other organizations were involved as partners?

Cedars Sinai Medical Center Consortium (CSC)
Sponsored Research & Fund Administration
PO Box 115500 6500 Wilshire Blvd, Suite 1150
Los Angeles, CA 90048
PI: Noel Bairey Merz, M.D. (NBM)

VA Medical Center Consortiums
Malcolm Randall VA Medical Center -contracted
Gainesville FL

Tampa VA Medical Center – contracted
Tampa, FL

Puerto Rico VA Medical Center-contracted

Active Duty Military Medical Facilities
Pensacola Naval Air Station-contracted
Jacksonville Naval Air Station-contracted
Fort Belvoir-removed
Tripler Army Medical Center-removed
Brookes Army Medical Center-contracted
Walter Reed Army Medical Center-contracted

Other
Geneva Foundation-contracted
LABioMED- contracted as a site/recruitment/imaging Core
Community Health IT- completed

8. SPECIAL REPORTING REQUIREMENTS COLLABORATIVE AWARDS:

Not applicable

QUAD CHARTS:

Women's Ischemia Trial to Reduce Events in Non-Obstructive CAD (WARRIOR)

PR161603
W81XWH-17-2-0030

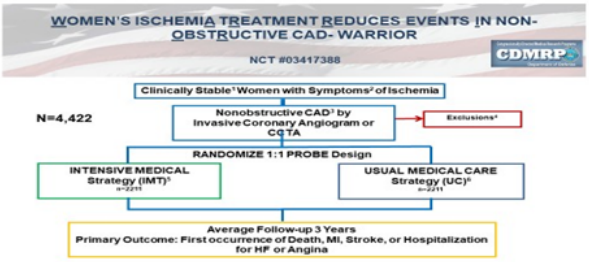
PI: Carl J. Pepine, MD **Org:** University of Florida **Award Amount:** $14,915,728.

Study Aim

- To determine whether an **intensive medication treatment strategy** to modify risk factors in women with chest pain and abnormal stress tests but non obstructed coronary arteries will reduce their likelihood of dying, having a heart attack, stroke, or being hospitalized.
- Results will provide data necessary to inform future guidelines regarding how best to treat this growing population of women, and ultimately improve their cardiac health and quality of life and reduce health-care costs.

Approach

The proposed **WARRIOR** trial is a multicenter, prospective, randomized, blinded outcome evaluation (PROBE design) evaluating IMT vs. usual care (UC) in 4,422 symptomatic women with ischemia but no obstructive CAD.



Accomplishment: Project is initiated and there are no scientific accomplishments to report. Operational accomplishments include first patients enrolled in second quarter of funding.

Timeline and Cost

	2017	2018	2019	2020	2021	2022	2023
Site Start Up		WARRIOR Enrollment					
		WARRIOR Follow-Up					
Protocol, IRB, Contracts		WARRIOR Data Acquisition					
		WARRIOR Data Publications					

Estimated Budget ($K)

$3,258	$4,935	$3,531	$3,192	NCE1	NCE2

Updated: 9/14/22

Goals/Milestones
CY17 Goal – Prepare to begin enrollment
✓ Protocol approval; site identification
Databases built
CY18 Goal – Subject Enrollment-Ongoing
✓ 103/3,329 subjects enrolled
CY19, CY20 and CY 21 Goal – Subject Enrollment and Follow Up
✓ 1,827/4,422 subjects enrolled
CY22 Goal – Subject Enrollment and Follow Up
✓ 2,987/4,422 subjects enrolled
Comments/Challenges/Issues/Concerns-COVID-19, Delays related to recruitment; changes in site PI and Coord staffing
Budget Expenditure to Date (9/14/2022)
Projected Expenditure: **$ 14,714,263**
Actual Expenditure: **$ 9,624,210**

9. APPENDICES:

A. Subject Recruitment
B. WARRIOR PI and Coordinator Meeting Agenda
C. Original Scope of Work

APPENDIX A. SUBJECT RECRUITMENT

WARRIOR Recruitment by Site as of 9/14/2022

Site Number	Site Name	Activation Date	Past Week	Cumulative	Avg Enr / Mn	Past 30 Days
WAR01	University of Florida - Anderson	06-Feb-18	0	169	3.02	0
WAR02	University of Florida -Lo	06-Feb-18	0	12	0.21	0
WAR03	University of Florida -Holland	06-Feb-18	0	1	0.02	0
WAR04	University of Florida - Wright	06-Feb-18	0	4	0.07	0
WAR05	University of Florida - Park	06-Feb-18	0	182	3.25	2
WAR06	University of Florida - Goede	06-Feb-18	0	3	0.05	0
WAR07	University of Florida - Maska	06-Feb-18	0	13	0.23	0
WAR08	Interventional Cardiac Consultants	19-Oct-18	0	37	0.77	0
WAR09	Daytona Heart Group	10-Oct-18	0	10	0.21	0
WAR11	Pepin Heart Institute (AdventHealth Orlando)	10-Oct-18	0	27	0.56	0
WAR12	Ocala Research Institute	19-Oct-18	0	32	0.67	0
WAR13	Baptist Health: Jacksonville	29-Nov-18	0	34	0.74	0
WAR14	Cedars-Sinai	12-Dec-18	0	268	5.83	0
WAR15	Orlando Health	12-Dec-18	0	43	0.93	1
WAR16	Los Angeles Biomedical Center	20-Dec-18	0	113	2.51	0
WAR17	South Palm Cardiovascular	12-Jan-19	0	9	0.2	0
WAR18	University of Kentucky	04-Feb-19	0	23	0.52	0
WAR19	Naval Hospital Jacksonville	15-May-19	0	2	0.05	0
WAR20	Naval Hospital Pensacola	15-May-19	0	6	0.15	0
WAR21	Clearwater Cardiovascular Consultants	29-Mar-19	0	70	1.67	1
WAR22	Silver State Cardiology	16-Apr-19	0	55	1.31	0
WAR23	Baylor Scott & White	20-May-19	0	55	1.38	0
WAR25	Heart House Research Foundation - Dr. Rizvi	13-Dec-19	0	38	1.12	0
WAR26	VA Gainesville	01-Aug-19	0	20	0.53	0
WAR27	VA Puerto Rico	15-Aug-19	0	17	0.45	0
WAR28	Southwest Cardiovascular (FL res Inst)	12-Sep-19	0	6	0.16	0
WAR29	Cardiovascular Center of Sarasota	30-Aug-19	0	26	0.7	0
WAR30	Peak Clinical Trials	02-Mar-20	0	2	0.06	0
WAR31	Card Assoc Mobile	07-Apr-20	0	11	0.37	0
WAR32	CHI Health Research Center and CHI Health Clinics- Cardiology	09-Dec-19	0	4	0.12	0
WAR33	Chippenham Hospital	09-Mar-20	0	6	0.19	0

Site Number	Site Name	Activation Date	Past Week	Cumulative	Avg Enr / Mn	Past 30 Days
WAR34	Seton Heart Institute	04-Dec-19	0	30	0.88	0
WAR35	West Virginia University	02-Mar-20	0	12	0.39	0
WAR36	Essentia Health	10-Feb-20	0	30	0.94	1
WAR37	Midwest Heart and Vascular Specialists	03-Feb-20	0	23	0.72	1
WAR38	UF JAX	07-Jan-20	0	25	0.76	0
WAR39	Cardiovascular Institute of Central Florida	16-Jan-20	0	14	0.44	0
WAR40	Jamaica Hospital	16-Jan-20	0	2	0.06	0
WAR41	Minneapolis Heart Institute Foundation	02-Mar-20	0	28	0.9	0
WAR42	The Research Group of Lexington	02-Mar-20	0	30	0.97	0
WAR43	Brooke Army Med Ctr	16-Mar-20	0	0	0	0
WAR44	Walter Reed National Military Medical Center	16-Mar-20	0	13	0.43	0
WAR45	Midwest Cardiovascular Research and Education Foundation	04-Jun-20	0	43	1.54	0
WAR46	Bassett Healthcare Network	24-Jul-20	0	7	0.27	0
WAR47	U Virginia	09-Sep-20	0	16	0.64	0
WAR48	Baycare CV Res	24-Jul-20	0	22	0.85	0
WAR49	Loyola University Chicago	16-Sep-20	0	6	0.25	0
WAR50	Cards Assoc Res	22-Jul-20	0	5	0.19	1
WAR51	San Antonio Endovascular and Heart Institute	17-Aug-20	0	22	0.88	0
WAR52	University of Arkansas	12-Oct-20	0	9	0.39	0
WAR53	Mayo Clinic- Jacksonville	01-Oct-20	0	7	0.29	1
WAR54	Advent Hlth Sebring	02-Sep-20	0	17	0.68	0
WAR55	CV Cons of S. Georgia	17-Aug-20	0	7	0.28	0
WAR56	Guardian Res	02-Sep-20	0	16	0.64	0
WAR57	Charles Croft	07-Sep-20	0	69	2.76	1
WAR58	Pinehurst med Ctr	02-Sep-20	0	2	0.08	0
WAR60	Valley Hospital (The)	26-Oct-20	0	14	0.61	0
WAR61	Austin Heart	12-Oct-20	0	64	2.78	1
WAR62	Western Kentucky Heart and Lung	14-Oct-20	0	28	1.22	0
WAR63	Berkshire	04-Nov-20	0	3	0.13	0
WAR64	Carilion	15-Mar-21	0	45	2.5	1
WAR65	U Arizona Sarver Hrt	07-Dec-20	0	10	0.45	1
WAR66	Trihealth	25-Jan-21	0	7	0.35	0
WAR67	Dignity Health Gilbert-Chandler	25-Jan-21	1	23	1.15	2
WAR68	MidMichigan Health	30-Mar-21	0	16	0.89	0

Site Number	Site Name	Activation Date	Past Week	Cumulative	Avg Enr / Mn	Past 30 Days
WAR69	Medicorcium	26-Feb-21	0	19	1	0
WAR70	Carle Foundation	26-Feb-21	0	5	0.26	0
WAR71	UCLA	22-Oct-21	1	4	0.36	1
WAR72	Loma Linda U Health	26-Feb-21	0	13	0.68	0
WAR73	Christ Hospital (The)	12-Apr-21	0	90	5.29	3
WAR75	NYU Langone	12-Apr-21	0	1	0.06	0
WAR76	AdventHealth Orlando	26-Apr-21	0	0	0	0
WAR77	Dignity Health St. Joes Hosp	26-Apr-21	0	13	0.76	0
WAR78	Lutheran Medical Group	20-Apr-21	1	1	0.06	1
WAR79	Weill School of Med - Cornell	07-Jun-21	0	0	0	0
WAR80	Tulane	07-Jun-21	0	0	0	0
WAR81	Tampa VA	25-Jan-21	0	0	0	0
WAR82	Emory	14-Sep-21	0	3	0.25	0
WAR83	Georgetown U	14-Sep-21	0	1	0.08	0
WAR84	University of Maryland	27-Sep-21	0	27	2.25	0
Totals			3	2140		19

APPENDIX B. WARRIOR PI and Coordinator Meeting Agenda

Agenda: WARRIOR PI and Coordinator Event Friday,
September 16, 2022
8:00 AM – 2:00 PM
UF Research and Academic Center Lake Nona

Time	Activity	Speaker
7:00 – 8:00	Breakfast	
8:00 – 8:30	Welcome - Update on the State of Science	Dr. Carl Pepine
8:30 – 8:50	Women and Ischemic Heart Disease: Why we must complete the Women's IschemiA TRial to Reduce Events In Non-ObstRuctive CAD (WARRIOR) trial!	Dr. Noel Bairey Merz
8:50 – 9:05	Study Demographics	Dr. Eileen Handberg
9:05 – 9:25	Strategy Compliance	Dr. Margaret Lo
9:25 – 9:45	Break	
9:45 – 10:30	Warrior from the Patient's Perspective Panel Discussion	Dr. Eileen Handberg Dr. Barbara Harris Katie Bottoms
10:30 – 11:10	A Clinician's Guide to Smartwatch "Interrogation"	Dr. Michael Massoomi
11:10 – 11:30	Update on Recruitment and Successful Recruitment Panel	Vanessa De Pue Pam Jones Mark Hoyle Donya Shahnavaz
11:30 – 12:00	Breakout Sessions: PIs: Writing Groups/Biorepository/Publications Coordinators: Promotional Strategies	 Dr. Carl Pepine Dr. Eileen Handberg Debbye Landers Melissa Reisman
12:00 – 1:00	Lunch	
1:00 – 1:30	WISE: The Psychosocial Journey	Dr. Thomas Rutledge
1:30 – 1:40	AE and SAE Reporting – Study Outcomes	Dr. Eileen Handberg Melissa Reisman
1:40 – 2:00	Closing Thoughts, Adjournment	Dr. Eileen Handberg

APPENDIX C. Scope of Work

W81XWH-17-2-0030
PI: Carl J. Pepine, M.D.
WARRIOR Trial

STATEMENT OF WORK – June 5, 2017
PROPOSED START DATE –October 1, 2017

Site 1: University of Florida (DCC)
(CSC) 219 Grinter Hall
PO Box 115500
Gainesville, FL 32611
PI: Carl J. Pepine, M.D. (CJP)
Co-I: Eileen Handberg, PhD (CJP)

Site 2: Cedars Sinai Medical Center Consortium
Sponsored Research & Fund Administration
6500 Wilshire Blvd, Suite 1150
Los Angeles, CA 90048
PI: Noel Bairey Merz, M.D. (NBM)
Statistical PI: Andre Rogatko,PhD (AR)

Site 3: OneFlorida Clinical Data Research Consortium
Up to 47 clinical recruitment sites

Site 4: VA Medical Center Consortiums
Malcolm Randall VA Medical Center
Gainesville FL
Tampa VA Medical Center
Tampa, FL
Others Pending

Site 5: Active Duty Military Medical Facilities Sites Pending

Abbreviations: DACC=Data and Administrative Coordinating Center; CSC= Cedars Sinai Medical Center Consortium; GMT=Guidelines Medical Therapy; IMT=Intensive Medical Therapy; OFL= OneFlorida Clinical Data Research Consortium; MACE=major adverse cardiovascular events; VAC= VA Medical Center Consortiums; ADMMF=Active Duty Military Medical Facilities

Selection of SOW responsibility was not detailed to the individual investigator/staff for each individual task as there will be multiple personnel assigned to each task both from the DACC and the CSC.

Specific Aim: To conduct a randomized clinical trial (n=4,422) among symptomatic women with ischemia and no obstructive CAD, to determine if an IMT strategy of potent statin plus ACE-I (or ARB), compared with primary risk factor GMT:

Primary Aim- IMT *will reduce* MACE (first occurrence of all-cause death, non-fatal-MI, non-fatal-stroke, or hospitalization for angina or HF) compared to GMT.

Secondary Aims- IMT *will improve* quality of life, time to "return to duty"/work, health resource utilization, Seattle Angina Questionnaire, PCL-5, and Beck Depression metrics, and incidences of CV death and primary outcome components compared to GMT.

Specific Aim 1: To conduct a randomized clinical trial (n=4,422) among symptomatic women with ischemia and no obstructive CAD, to determine if an IMT strategy of potent statin plus ACE-I (or ARB), compared with primary risk factor GMT		**Research Sites**				
Task	**Timeline Months**	**DACC**	**CSC**	**ONF**	**VA**	**ADMMF**
Major Task #1 – Protocol Finalization						
Provide clinical input for study design and protocol development	PRE	X	X			
Provide statistical input for study design and protocol development	PRE		X			
Write protocol and protocol amendments	PRE	X	X			
Distribute protocol and protocol amendments	1-3	X	X	X	X	X
Major Task #2 - Electronic Case Report Form (eCRF) and additional study materials						
Create eCRF contents (i.e., data variables and eCRF instructions)	PRE	X	X			
Design layout of eCRF and eCRF instructions	PRE	X	X			
Provide eCRF and instructions		X	X	X	X	X
Design, print, and distribute other study materials (i.e., patient brochure, posters, advertisements)	1-3	X		X	X	X
Draft informed consent form (ICF) template	PRE	X				
Finalize ICF	PRE	X	X	X	X	X
Provide translation of study documents as needed	1-3	X		X	X	X
Major Task #3 - Institutional Review Board						
Submit protocol and DACC to IRB	PRE-JUNE 7	X				
Submit protocol to HRPO, DONHRP	JUNE 12	X				
Major Task #4 - Investigator Recruitment and Site Contracts						
Identify and screen potential study investigators	PRE	X		X	X	X
Identify final study investigators	1-3	X		X	X	X
Establish CRADA with VA sites	PRE				X	
Establish CRADA with Military Medical Facilities	PRE					X
Negotiate study budgets with investigators	1-3	X		X	X	X
Negotiate contractual agreements with investigators	1-3	X		X	X	X
Administer payment to investigators	1-36	X		X	X	X

Task	Timeline Months	DACC	CSC	ONF	VA	ADMMF
Major Task #5 - Pre-Study Preparation						
Assist sites in obtaining IRB approval of ICF, protocol, amendments	1-6	X		X	X	X
Distribute regulatory submission packets to sites	1-3	X		X	X	X
Collect investigative site regulatory documents	1-3	X		X	X	X
Major Task #6 - Investigator Meeting (Bi-annual)						
Arrange investigator meeting (i.e., plan for meeting, host meeting, coordinate logistics)	1-48	X	X			
Attend Investigator Meetings	1-48	X	X	X	X	X
Develop Investigator Meeting agendas	1-48	X	X			
Prepare presentations for meetings	1-48	X	X			
Present study information during meetings	1-48	X	X	X	X	X
Maintain records of attendance (sign-in log) and provide certificates of attendance for site investigators	1-48	X				
Major Task #7 - Training Meeting						
Arrange training meeting (i.e. plan for meeting, host meeting, coordinate logistics)	1-9	X		X	X	X
Develop Training Meeting Agenda	1-9	X	X			
Prepare Training Materials	1-9	X	X			
Prepare presentations for meetings	1-9	X	X			
Present study information during meetings	1-9	X	X			
Maintain records of attendance (sign-in log) and provide certificates of attendance for site personnel	1-9	X				
Develop and distribute post-meeting report that lists specific issues and agreed-upon solutions	1-9	X				
Major Task #8 - Project Management						
Act as primary communicator between DoD	1-48	X				
Organize scheduled teleconferences with DoD	1-48	X				
Participate in scheduled teleconferences with DoD	1-48	X	X			
Disseminate key information to study participants as needed	1-48	X		X	X	X
Prepare and update both external and internal FAQ log	1-48	X				
Prepare newsletters to sites	1-48	X		X	X	X
Post newsletters to Ischemia-IMT Website	1-48	X				
Draft and distribute teleconference minutes	1-48	X				
Approve meeting minutes	1-48	X	X			
Prepare project status reports	1-48	X	X			

Task	Timeline Months	DACC	CSC	ONF	VA	ADMMF
Major Task #9 - Site Management						
Track patient enrollment and screen failure and generate report	1-48	X		X	X	X
Create and maintain subject enrollment tracking tool	1-48	X				
Perform routine phone contact with study sites	1-48	X		X	X	X
Engage in regular contact with site investigators concerning enrollment	1-48	X		X	X	X
Generate standard reports	1-48	X	X			
Complete ongoing regulatory document collection	1-48	X		X	X	X
Identify poor performing clinical sites	1-48	X		X	X	X
Serve as primary contact for site study coordinators and principal investigators for scientific questions	1-48	X				
Serve as primary contact for site study coordinators and principal investigators for site management questions	1-48	X				
Coordinate/manage Clinical Helpline activities (provide 24/7 phone coverage)	1-48	X		X	X	X
Provide Data Query report to CSC	1-48	X	X			
Resolve outstanding data queries with sites	1-48	X	X	X	X	X
Monitor compliance with medical therapy (site- by-site review of periodic report to assess % of patients on appropriate therapy and reaching risk factor goal)	1-48	X		X	X	X
Assist site with drug delivery problems	1-48	X		X	X	X
Major Task #10 - Site Monitoring						
Develop, maintain, and follow site monitoring plan	1-48	X				
Provide monitor training	1-48	X				
Prepare for and conduct interim on-site monitoring visits	1-48	X		X	X	X
Prepare monitoring visit reports and follow-up letters for on-site monitoring visits	1-48	X				
Receive, review and approve monitoring visit reports/follow-up letters for on-site monitoring visits	1-48	X				
Adjust monitoring visit intervals according to site performance, protocol adherence, and data quality	1-48	X		X	X	X
Conduct site closeout phone calls	40-48	X		X	X	X

Task	Timeline Months	DACC	CSC	ONF	VA	ADMMF
Prepare site closeout reports and follow-up letters	40-48	X				
Monitoring for Ischemia-IMT interpretation and protocol adherence	1-48	X	X	X	X	X
Major Task #11 - Audits						
Complete vendor audits as applicable for the respective subcontractors	1-48	X				
Major Task #12 - Safety Surveillance and Medical Monitoring						
Prepare safety plan including SAE form	1-3	X	X			
Receive SAE information from investigative sites	1-46	X		X	X	X
Database SAEs	1-46	X	X			
Code SAEs using MedDRA dictionary	1-46	X	X			
Contact sites for missing / additional information	1-46	X		X	X	X
Provide clinical review of SAEs	1-46	X	X			
Write SAE narratives	1-46	X				
Forward SAE reports to CSC who manages Clinical Endpoint Committee and DSMB	1-46	X	X			
Notify investigative sites of reportable SAEs	1-46	X	X	X	X	X
Maintain an SAE tracking system	1-46	X	X	X	X	X
Provide SAE reconciliation with clinical database	1-46	X	X			
Major Task #13 - Data Management (Electronic Data Capture through UFDMS)						
Provide data management plan	1-3	X	X			
Approve data management plan	1-3	X	X			
Provide clinical data coordination	1-48	X				
Develop data cleaning plan and coordinate data cleaning	1-3	X	X			
Approve data cleaning plan	1-3	X	X			
Develop eCRF screens	PRE	X	X			
Program UFDMS database including eCRFs and query rules	1-3	X				
Create query rule specifications	PRE	X	X			
Perform user acceptance testing for query rules	PRE	X				
Perform technical user acceptance testing	PRE	X				
Perform clinical user acceptance testing of database including eCRF screens and query rules	PRE	X				
Host UFDMS database	PRE	X				

Task	Timeline Months	DACC	CSC	ONF	VA	ADMMF
Create and manage site and user accounts in UFDMS	1-48	X				
Provide non-trial-specific UFDMS training materials	1-3	X				
Provide online self-directed, non-trial-specific UFDMS training modules	1-3	X				
Track UFDMS user training	1-48	X				
Develop coding process	1-3 or pre	X	X			
Provide coding dictionaries	1-3 or pre	X	X			
Perform coding	1-3 or pre	X				
Create and maintain coding guidelines	1-3 or pre	X				
Perform UFDMS site assessments	1-3	X		X	X	X
Prepare and deliver UFDMS presentation/demo for investigator meetings	1-6	X				
Provide UFDMS helpdesk support	1-48	X				
Design specifications for loaded external data	1-3	X				
Program database to receive loaded external data	Pre	X				
Program customized data status reports	1-48	X	X			
Provide customized site payment reports	1-3	X				
Prepare and deliver hands-on UFDMS training at all investigator meetings	1-9	X				
Prepare and deliver UFDMS Training sessions via web-cast	1-9	X		X	X	X
Major Task #14 - Clinical Events Classification						
Set up CEC process and charter	1-3 PRE	X	X			
Approve CEC process	1-3 pre	X	X			
Provide input to CRF development and CEC data variable and screens	PRE	X	X			
Design event triggers, CEC reports, CEC patient data listings, and CEC tracking requirements	PRE	X	X			
Identify CEC committee members	PRE		X			
Review and approve CEC committee members	PRE		X			
Provide training for CEC committee members	1-3	X	X			
Coordinate independent reviews and adjudication meetings	1-3		X			
Provide final adjudicated results and enter directly into database	1-48	X				
Administer payments to CEC committee members	1-48		X			

Task	Timeline Months	DACC	CSC	ONF	VA	ADMMF
Collect and translate CEC source documents as needed	1-48	X				
Major Task #15 - Executive, Steering, and Other Study Committees						
Organize EC and SC meetings/calls	PRE	X				
Attend EC and SC meetings/calls	1-48	X	X	X	X	X
Organize Leadership committee meetings/calls	1-48	X				
Attend Leadership Committee meetings/calls	1-48	X	X	X	X	X
Organize Operations Committee meetings/calls	1-48	X	X			
Attend Operations Committee meetings/calls	1-48	X	X			
Chair Ancillary Studies Committee/ organize meetings	1-48	X	X			
Major Task #16 - Blood Repository						
Manage and organize blood repository	1-3	X				
Print and distribute blood repository manual and/or training materials to sites	1-3	X				
Create kits for collection of study blood specimens	1-3	X				
Supply and resupply (as needed) of lab kits for sites	1-9	X				
Receive and process blood samples from sites	1-9	X				
Log in and store blood samples from sites	1-9	X				
Monitor sites for proper sample collection and shipping	1-9	X				
Database study assay results	1-9	X	X			
Major Task #17 - Statistical Analysis						
Develop randomization scheme	PRE	X	X			
Contract with DSMB members	PRE		X			
Negotiate honoraria with and administer payments to DSMB members	1-3		X			
Develop DSMB charter	1-3	X	X			
Develop DSMB analysis plan	1-3	X	X			
Develop analysis file specifications for DSMB analysis	1-3		X			
Program and validate SAS analysis files for DSMB analyses	1-42		X			
Prepare, validate, and review tables, listings, and figures for DSMB analysis	1-42	X	X			

Task	Timeline Months	DACC	CSC	ONF	VA	ADMMF
Transfer SAS files for preparation of DSMB	1-42	X	X			
Perform interim DSMB analyses	1-42		X			
Attend DSMB Meetings	1-42	X	X			
Prepare final analysis plan	1-42	X	X			
Develop analysis file specifications for final analysis	1-3		X			
Program and validate SAS analysis files for final analysis	42-48		X			
Prepare, validate, and review all tables, listings, and figures for final analysis	42-48		X			
Perform final analysis	42-48		X			
Provide final SAS datasets to DoD at end of study	48		X			
Archive project-specific SAS analysis files and SAS programs	48		X			
Transfer SAS database to DoD	48		X			
Major Task #18 - Manuscripts						
Organize publication committee meetings	1-3	X	X	X	X	X
Prepare study manuscripts	3-48	X	X	X	X	X
Provide editorial support for manuscript preparation	3-48	X				
Provide manuscript submission assistance	3-48	X				