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

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CONTRACTING ORGANIZATION: University of Florida, Gainesville, FL

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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 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.

Year 4 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. Details of the first 3 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 doubled (from **970 to 1712** as of September 14, 2021) it continues to lag behind recruitment goals. (Recruitment as of the report submission 10/15/21 is **1755**). With recommendations from the DSMB to continue the study as planned and Project Officer support, the first of two possible 1-Year No Cost Extensions 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 have continued to affect site performance based on research staff and/or patient issues. Research personnel are being shifted from research to work on “urgent COVID-19” protocols or to provide supplemental staffing for rapidly deployed additional COVID units, testing and/or vaccination locations. 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 only partially effective in maintaining follow up at sites but has been much less successful helping to encourage potential new enrollments for the study. The “face to face” interaction at a screening visit is critically important to establish a relationship between the study team and the patient for the WARRIOR Trial. Thus, 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. This would allow for project continuation through potentially two “No Cost Extension” periods or perhaps longer if funding is available. Site contracts have also been updated to reflect the longer period of the project. The request for the first NCE has been approved.

Considering the continued impact of COVID-19 on the trial, the DSMB in March 2021 requested that an Independent Advisory Committee be convened. This Committee would be charged with reviewing the study conduct and available aggregate results (without access to any randomized group data) and make recommendations regarding the future conduct of the trial. The latter was essential to minimize possible bias since the DSMB has continuously reviewed events and adverse experiences by randomized group assignment. The questions to be considered included the potential to modify the primary outcome, or to modify the project in some other manner for the project to acquire meaningful data. The Independent Advisory Committee has been established with experts in ischemic heart disease in women, coronary microvascular dysfunction/ ANOCA/INOCA, clinical trials and biostatistics.

The following individuals were invited, and all accepted.

Independent Advisory Committee (IAC)

John Beltrame, M.D.-Chair	Adelaide, AU
Angela Maas, M.D.	Amsterdam, NL
Colin Berry, M.D.	Glasgow, SCT
Samar El Khoudary, PhD	Pittsburgh, PA

An initial teleconference meeting was held on June 4, 2021, with the Executive Committee and Dr. Beltrame to establish the charge and to review the protocol, including the a priori determined contingency plans for recruitment and outcomes, and the study rationale and design manuscript (Handberg, et al. AHJ 2021, Mar 18). The initial meeting, (by video conference), of the entire IAC was held on June 17, 2021, with a review of the current status of the study and Dr. Pepine (PI) was present to answer questions from the committee. The IAC requested 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. These data were provided to the IAC and they reconvened on August 26, 2021, and requested additional data which was provided on September 14, 2021. Although beyond the reporting period for this report, the IAC reconvened on October 4th and their recommendations were submitted to the DSMB on October 11, 2021, for the DSMB meeting scheduled for October 29, 2021.

While impacts of the COVID-19 pandemic continue, both for patient recruitment and ascertainment of study outcomes, the trial is continuing at 81 enrolling sites. The DCC and Executive Committee have been focusing on working with sites to increase enrollment and to acquire data updates, with a focus on adverse event reporting.

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 **fourth year (period 4) 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**. During the past year 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 – 3/16/2020
- V13.0 Approved by the University of Florida IRB – 3/26/2020
- V13.0 Submitted to HRPO – 3/26/2020
- V13.0 Acknowledged by HRPO – 3/30/2020
- Annual IRB Review for Data Coordinating Center to UF IRB – 4/29/2020
- Annual IRB Approval for Data Coordinating Center from UF IRB – 5/01/2020
- Annual IRB Approval for DCC Submitted to HRPO – 5/08/2020
- Annual IRB Approval for DCC HRPO Approved – 6/10/2020
- Annual IRB Review for UF Site to UF IRB – 4/27/2020
- Annual IRB Approval for UF Sites from UF IRB – 5/22/2020
- Annual IRB Approval for UF Sites by UF IRB Submitted to HRPO – 5/22/2020

YEAR 4 IRB/HRPO ACTIVITY

- **V14.0 Submitted to University of Florida IRB --09/25/2020**
- **V14.0 Approved by the University of Florida IRB --10/21/2020**
- **V14.0 Submitted to HRPO --11/04/2020**
- **V14.0 Acknowledged by HRPO --12/02/2020**
- **V14.1 Submitted to University of Florida IRB --11/02/2020**
- **V14.1 Approved by the University of Florida IRB --11/03/2020**
- **V14.1 Submitted to HRPO --11/04/2020**
- **V14.1 Acknowledged by HRPO --12/02/2020**
- **V14.2 Submitted to University of Florida IRB --12/15/2020**
- **V14.2 Approved by the University of Florida IRB --12/23/2020**
- **V14.2 Submitted to HRPO --12/23/2020**
- **V14.2 Acknowledged by HRPO --12/28/2020**
- **Protocol revision submitted to FDA for inclusion of Vascepa --04/26/2021**
- **Annual IRB Review of Data Coordinating Center to UF IRB --04/27/2021**
- **Annual IRB Approval of Data Coordinating Center from UF IRB --04/29/2021**
- **FDA approved IND exemption with revision --04/30/2021**

- **Annual IRB Approval of Data Coordinating Center to HRPO --05/05/2021**
- **Annual IRB Approval of DCC HRPO Approved --05/05/2021**
- **Annual IRB Review of UF Site to UF IRB --04/26/2021**
- **Annual IRB Approval of UF Sites from UF IRB --05/26/2021**
- **Annual IRB Approval of UF Sites by UF IRB to HRPO --06/02/2021**
- **Annual IRB Approval of UF Sites HRPO Approved --06/09/2021**
- **V15.0 Submitted to University of Florida IRB --06/11/2021**
- **V15.0 Approved by the University of Florida IRB --07/20/2021**
- **V15.0 Submitted to HRPO --07/23/2021**
- **V15.0 Acknowledged by HRPO --08/13/2021**
- **V16.0 Submitted to University of Florida IRB --08/12/2021**
- **V16.0 Approved by the University of Florida IRB --08/17/2021**
- **V16.0 Submitted to HRPO --09/01/2021**
- **V16.0 Acknowledged by HRPO --09/02/2021**

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 is reviewed every three years and expires 5/16/22.

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.**

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 and there are 81 active sites.**

Table 1 summarizes site activation activities over the first three 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	Q1 Year 4 9/15/20 12/14/20	Q2 Year 4 12/15/20 3/14/21	Q3 Year 4 3/15/20 6/14/21	Q4 Year 4 6/15/21 9/14/21	Year 4 9/15/20 9/14/21
Contacted	286	443	873	874	877	879	879	879
CDA Sent	155	309	668	669	671	673	673	673
Completed CDAs Returned	52	120	223	224	226	227	227	227
Contract Fully Executed	17	41	82	89	96	96	96	96
Contracts Negotiating	50	26	28	12	3	0	0	0
UF IRB Approved	19	37	66	75	80	83	87	87
HRPO Approved	13	29	63	72	80	81	87	87
Activated for Enrollment	13	27	59	65	70	76	81*	81*
Anticipated Total Sites	50	50	75	100	81	81	81	81
Patients Enrolled	76	584	970	1246	1431	1582	1712	1712

*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.

Four of five planned military sites have been approved for participation. TAMC was withdrawn due to PI turnover and extensive delays in IRB review. All sites are actively recruiting but BAMC has been restricted due to COVID-19 issues. PI deployments/TOD changes have resulted in changes in PI at Jacksonville NAS, Pensacola NAS, and Walter Reed. Three VA sites have been onboarded. Details of this activity are summarized in Table 2.

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	**HRPO approved 12/21/20; enrolling as of 6/1/21**

The geographic distribution of sites is illustrated in Figure 1.

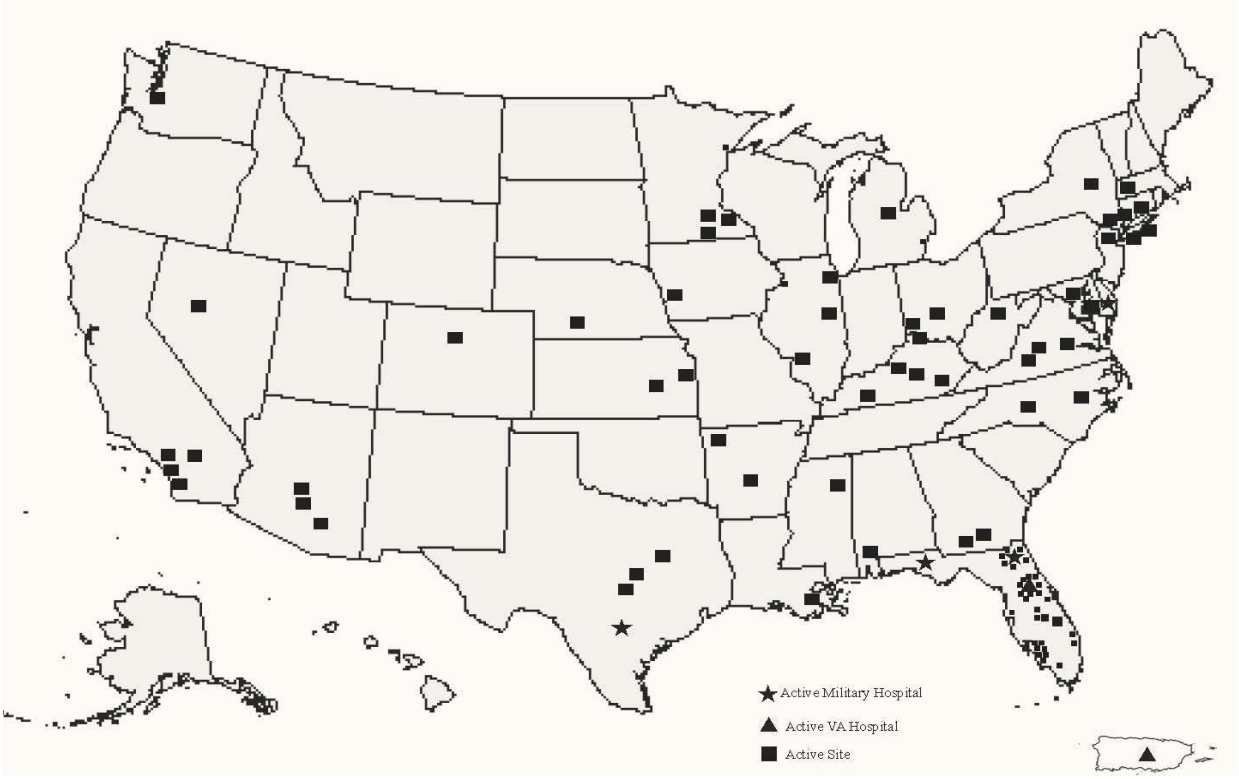


Figure 1. Geographic Distribution of Active/Pending Sites and Imaging Referral Centers

Overview of Pending Site progress:

As summarized in Table 1, the UF DCC **over the past year has focused on assisting the additional sites through contracting, IRB/HRPO review and approval. As of this report there are 81 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 the fourth quarter the potential to add International Sites is being explored with Dr. Beltrame in Australia. With support of the Executive Committee, WARRIOR has 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. A request to DoD for inclusion of a foreign site is being submitted.

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

As reported previously contracting delays are inherent in clinical trials and activities by sites with long delays were discontinued in order to permit the DCC to focus on more the efficient sites. Additional site referrals at this time have been limited only to sites who have the ability to complete contracting within 2-4 weeks. All of the protocol amendments to extend recruitment have been processed, which will include the period of a 12 month 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 4, 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: Data Coordinating Center was approved by UF IRB 4/29/2021, HRPO on 5/5/2021. UF sites were approved by UF IRB 5/26/2021 and HRPO 6/9/2021.**

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. **During YEAR 4 there have been no face-to-face investigator or Steering Committee meetings due to COVID-19 restrictions. The DCC continued monthly PI calls to review study progress, discuss site issues related to recruitment, strategy compliance and update them on study activities. A virtual Steering Committee Meeting was held on July 28, 2021, to update the Committee on trial activities.** ***[Ongoing, within SOW projections].***

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

All sub-tasks are ongoing. As reported in the Year 3 annual report, 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 and additional training is taking place during monitoring calls.** ***[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 9/14/21 a total 1712** subjects have been randomized to the project **from 81 activated sites. Six prior activated sites have been closed due to lack of enrollment.**

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. ***[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 will oversee 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 are currently being conducted to monitor site data quality and resolve data queries and missing data. To date, 12 of the 81 sites have been completed, 4 sites are scheduled, with plans to complete all virtual site visits by the end of 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 has 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. 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. (See Appendix C) 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. These data 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 next DSMB meeting is scheduled for October 29, 2021. ***[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 4 the CEC has continued to adjudicate events as they are reported. These were reported and reviewed by IRB during the continuing renewal.** ***[Ongoing, within SOW projections]***

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

During this reporting quarter, 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 next planned DSMB meeting is being scheduled for October 29, 2021. The DCC has provided data reports to the DSMB, IAC as requested. 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 is operational. **All sites have been trained and are operational and have sent samples on 870 patients which have been processed and stored. This has provided 14,048 aliquots for analysis. Sample collection 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 has continued to recognize WARRIOR 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 4 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 has been 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 to convene an Independent Advisory Committee to make recommendations regarding projected enrollment, contingency plans and potential alternative strategies for analysis.** 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. It was agreed that the initial manuscript to be submitted for publication will be the rationale and design for the project. **The Rational and Design paper was published in the American Heart Journal (Handberg EM, et al. Am Heart J. 2021 Mar 18:S00002-8703(21)00077-6. doi:10.1016/j.ahj.2021.03.011. Epub ahead of print. PMID:33745898). Currently in press is with the American Journal of Cardiology is a pilot study manuscript on pro-resolving mediators (Keeley EC, et. al. Specialized pro-resolving mediators in symptomatic women with coronary microvascular dysfunction: Results of a pilot study from the Women's Ischemia Trial to Reduce Events in Non-obstructive CAD (WARRIOR) trial. *Am J Cardiol*. In press.).**

Three abstracts were presented at the American College of Cardiology Annual Scientific Sessions for 2021 (ACC21):

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.

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 4** annual reporting period the WARRIOR trial grant proposal **has successfully processed 87 sites after contacting over 1,000 potential sites. Of those 87, there are now 81 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 is a challenge.

WARRIOR sites have recruited **1715 women as of 9/14/21 (1755 by the time of this report submission 10/15/21);** during YEAR 4 there have been **742 women enrolled**, **which is double the amount enrolled during the last year demonstrating the impact of adding the additional sites. 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 variant have resulted in a late summer early fall 2021 surge in cases, hospitalizations and deaths due to COVID-19. This has resulted in continued diversion of WARRIOR Trial research staff to support COVID Trials and the clinical enterprise. In addition, the pandemic has resulted in many leaving the workforce, changes in jobs due to high paying travel nursing opportunities which has resulted in turnover and staffing shortages. It is anticipated that the current surge is beginning to peak at areas that were hit early, but the variant has emerged over time across the US so the impact on sites is likely to continue into early 2022. 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 were offered in Year 2 and proved to be minimally successful. During year 4 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 try and identify barriers and solutions.

Projected recruitment has now extended through YEAR 4 and will continue pending DSMB review in October into the first of two planned No Cost Extensions, the first of which started 9/15/21 with a planned enrollment of the originally planned 4, 422 women who meet eligibility criteria. The NCE has sufficient funds to carry out the work of the project as the per patient 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 work up enroll in the trial. There are currently ~30 women who are pending CCTA results to be randomized into the trial.

Early in the trial social media was explored, specifically Facebook and it was not successful. During our review and assessment of recruitment efforts we have seen an increased utilization of social media for recruitment into clinical trials and we are finalizing a revised social media plan for recruitment. We are partnering with several advocacy groups and utilizing our Executive Committee Member who is our patient advocate Dr. Barbara Harris to help direct our new plan, set to launch in November 2021. We are working 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 continued to be very successful. This method reaches out to potentially eligible women and those that are interested contact the site for more information. This method has been transmitted to all sites who use EPIC.

During YEAR 4 the previously reported 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 and has been funded (9/20) by the NHLBI and patients who are approaching 3 years of follow up are being approached for participation and collection of repeat coronary CT angiograms.

The second Ancillary Trial application to look at more detailed characteristics of plaque morphology in a sample of 600 women who coronary CTA as their qualifying imaging study for WARRIOR. "*Coronary CT Angiographic Predictors of angina and Adverse Clinical outcomes In women with nonobsTructive coronarY plaque (CAPACITY)"* has been submitted by Dr. Balaji Tamarappoo from Cedars Sinai with the full support of the Executive Committee. It will reviewed in October. Both projects have been reported to the DSMB and received support.

We have developed a collaboration with HeartFlow, INC 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, 1 NHLBI R01 project (Dr. C. Noel Bairey Merz, PI) has been funded to repeat the CCTAs between 1-2 years in 200 WARRIOR patients and analyzed changes in nonobstructive plaque characteristics. An additional NHLBI R01 project application to further analyze WARRIOR CCTAs for 600 is currently under review. A third NHLBI application for comparison of CCTAs and cMRI is being submitted.

Additionally, we have had a favorable response for supplemental funding with the UF Foundation and the McJunkin Family Trust Foundation 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.

The following abstracts were also presented 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 plans to accomplish the goals of this project are outlined in the individual task items noted above. The primary efforts are focused on assisting sites in increasing recruitment efforts in order to meet recruitment goals over the next 6-9 months.

4. IMPACT:

Nothing to report.

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 noted, 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.

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 Nonobstructive CAD (WARRIOR) trial. *Am Heart J.* 2021;237:90–103.

Keeley EC, Li HJ, Cogle CR, Handberg EM, Bairey Merz CN, Pepine CJ. Specialized pro-resolving mediators in symptomatic women with coronary microvascular dysfunction: Results of a pilot study from the Women's Ischemia Trial to Reduce Events in Non-obstructive CAD (WARRIOR) trial. *Am J Cardiol*. In press.

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:

Carl J. Pepine, MD Talks/Lectures that included WARRIOR Sept 15, 2020 to Sept 14, 2021

March 10, 2021, University of Alabama, at Birmingham, Cardiology Grand Rounds, Resistant Hypertension, Depressive Hypertension, and Treating Women at High Risk.

May 11, 2021, The WARRIOR Study—a study to reduce the likelihood of stroke, heart attack, especially in women. Community Coalition for Older Adults Research Showcase 2021. Virtual.

May 15, 2021, Co-Chair "Men Are From Mars, Women Are From Venus: Sex-Specific Risk Factors That Enhance CVD Risk". American College of Cardiology (ACC21), Virtual Event.

May 17, 2021, Panelist, “Show and Tell with the Experts”. American College of Cardiology (ACC21), Virtual Event.

May 28-30, 2021, Sarasota FL-"International Society for Cardiovascular Disease Prevention: 21/21/21 Congress, 21st Annual National Sarasota Congress on Cardiovascular Disease Prevention: Update 2021", Advances in the Treatment of Cardiovascular Disease in Women.

August 5, 2021, HeartFlow Virtual Symposium, Conundrums in Cardiology, HeartFlow. Inc. "Open Artery Ischemia;ANOCA/INOCA/MINOCA".

Eileen Handberg, PhD Talks/Lectures that included WARRIOR Sept 15, 2020 to Sept 14, 2021

April 13, 2021, The WARRIOR Trial. ACC Federal Section Webinar: Roadmap of Cardiovascular Care for Women in the Military and Women Veterans.

May 11, 2021, The WARRIOR Study—a study to reduce the likelihood of stroke, heart attack, especially in women. Community Coalition for Older Adults Research Showcase 2021. Virtual.

Noel Bairey Merz MD Talks/Lectures that included WARRIOR Sept 15, 2020 to Sept 14, 2021

March 16, 2021, Women and Ischemic Heart Disease: Update 2021. Providence Health CME. Providence Saint Joseph Medical Center, Virtual Event.

May 6, 2021, Sex Differences in Aging – Why Women Live Longer or Does it Just Seem Longer?, 2021 Virtual Meeting of the Organization for the Study of Sex Differences, Founded by the Society for Women's Health Research, Virtual Event.

May 15, 2021, Phenotype-Based Management of Coronary Microvascular Disease: One Size Does Not Fit All, Cardiovascular Imaging For Diagnosis And Management of Coronary Microvascular Disease, ACC.2021, Virtual Event.

May 15, 2021, Panelist, Cardiovascular Imaging For Diagnosis And Management of Coronary Microvascular Disease, ACC.2021, Virtual Event.

May 15, 2021, Diagnostic Considerations: Does Gender Matter, Gender-Specific Care of Patients with Acute Coronary Syndrome, ACC.2021, Virtual Event.

May 16, 2021, Panelist: Recommendations from the Commission, Global Burden of Cardiovascular Disease in Women: Report of The Lancet Commission, ACC.2021, Virtual Event.

May 16, 2021, Panelist: Future Directions- The Research Roadmap, Global Burden of Cardiovascular Disease in Women: Report of The Lancet Commission, ACC.2021, Virtual Event.

May 25, 2021, Cardiovascular Disease Disparities and Prevention in Women or How Gender Bias in Cardiovascular Disease Impacts Women's Lives and What We Can Do About It, The Right Care Initiative, UC Berkeley Healthcare Education and Outcome Monitoring Program, Virtual Event.

June 1, 2021, Women and Heart Disease: What you Need to Know, San Fernando Valley Marketing and Admissions Professionals for Seniors, Virtual Event.

June 11, 2021, Sex and Gender- Relevance to Cardiovascular Disease Personalized Medicine, 55th Annual Scientific Meeting, European Society for Clinical Investigation ESCI- ASM 2021, Virtual Event.

June 11, 2021, Keynote Speaker, Women and Ischemic Heart Disease: Updated 2021, 27th Annual Cardiology Research Symposium, Emory University School of Medicine, Virtual Event.

July 17, 2021, Gender in cardiovascular imaging trials: past and present (Warrior), Clinical trial updates, Society of Cardiovascular Computed Tomography's 16th Annual Scientific Meeting (SCCT2021), Virtual Event.

July 27, 2021, Warrior Trial Presentation, H2O Cath Conference, Dignity Health Medical Group- Gilbert Cardiology, Gilbert, Arizona, Virtual Event.

August 10, 2021, Women's Heart Disease: Update 2021, Grand Rounds, Forrest General Hospital's Family Medicine Residency Program, Hattiesburg, MS, Virtual Event.

August 30, 2021, Nonobstructive coronary artery disease: diagnosis and treatment, ESC Congress 2021 - The Digital Experience, Virtual Event.

August 30, 2021, Global burden of cardiovascular disease in women; 20/20 vision for 2030: report of The Lancet commission, ESC Congress 2021 - The Digital Experience, Virtual Event.

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

Nothing to report.

- **Other publications, conference papers and presentations**.

Nothing to report.

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

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:	**Jill Boswell**
Project Role:	Regulatory Coordinator
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	7
Contribution to Project:	Ms. Boswell assists with adverse event collection and liaisons with the adjudication lead.
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:	**Robert Raske**
Project Role:	Contract Coordinator
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	12
Contribution to Project:	Mr. Raske contacts potential new sites and processes new site contracts for WARRIOR.
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:	**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:	**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

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

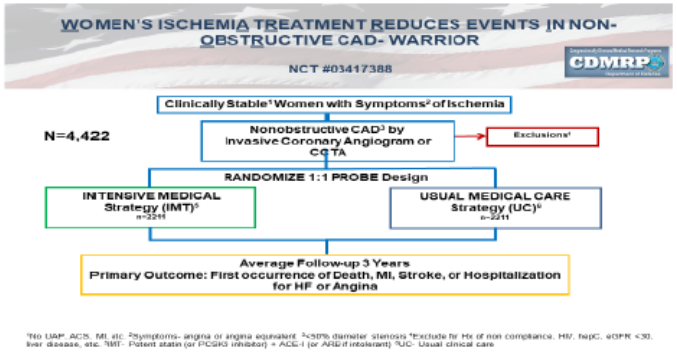
PI: Carl J. Pepine, MD **Org:** University of Florida **Award Amount:** $14,915,728.

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

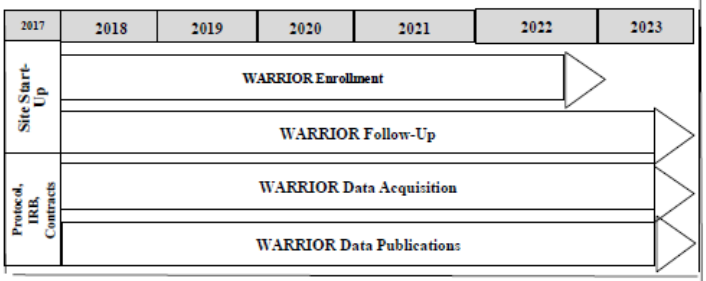
The proposed **WARRIOR** trial is a multicenter, prospective, randomized, blinded outcome evaluation (PROBE design) evaluating IMT vs. usual care (UC) in 4,422 symptomatic women with ischemia but no obstructive CAD.



[1]No UAP, ACS, MI, etc. [2]Symptoms- angina or angina equivalent. [3]>50% diameter stenosis [4]Exclude for Hx of non compliance, HIV, hepC, eGFR <30, liver disease, etc. [5]IMT- Potent statin (or PCSK9 inhibitor) + ACE-I (or ARB if intolerant) [6]UC- Usual clinical care

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



Estimated Budget ($K)

$3,258 $4,935 $3,531 $3,192 NCE 1

Updated: 9/14/21

Goals/Milestones

CY17 Goal – Prepare to begin enrollment
☑ Protocol approval; site identification
☑ Databases built
CY18 Goals – Subject Enrollment-Ongoing
✓ 103/3329 subjects enrolled
CY19 and CY20 Goal – Subject Follow-up
✓ 1431/4,422 subjects enrolled
✓ Subject Follow-up
CY21 Goal –Subject Enrollment/Follow up- Ongoing
✓ 1,712/4,422 subjects enrolled
✓ Subject Recruitment and Follow Up
Comments/Challenges/Issues/Concerns-COVID-19 Temp closures
Delays related to recruitment
Budget Expenditure to Date (9/14/2021)
Projected Expenditure: **$ 13,660,544**
Actual Expenditure: **$ 7,385,395**

9. APPENDICES:

A. Subject Recruitment
B. DSMB Recommendations
C. Original Scope of Work

APPENDIX A. SUBJECT RECRUITMENT

Table 1. WARRIOR Recruitment by Site as of 9/14/2021

Site Number	Site Name	Activation Date	Past Week	Cumulative	Avg Enr / Mn	Past 30 Days
WAR01	University of Florida - Anderson	06-Feb-18	0	163	3.7	1
WAR02	University of Florida -Lo	06-Feb-18	0	10	0.23	0
WAR03	University of Florida -Holland	06-Feb-18	0	1	0.02	0
WAR04	University of Florida - Wright	06-Feb-18	0	4	0.09	0
WAR05	University of Florida - Park	06-Feb-18	1	150	3.41	3
WAR06	University of Florida - Goede	06-Feb-18	0	3	0.07	0
WAR07	University of Florida - Maska	06-Feb-18	0	13	0.3	0
WAR08	Interventional Cardiac Consultants	19-Oct-18	0	37	1.06	0
WAR09	Daytona Heart Group	10-Oct-18	0	8	0.22	0
WAR11	Pepin Heart Institute (AdventHealth Orlando)	10-Oct-18	0	27	0.75	1
WAR12	Ocala Research Institute	19-Oct-18	0	25	0.71	0
WAR13	Baptist Health: Jacksonville	29-Nov-18	0	30	0.88	1
WAR14	Cedars-Sinai	12-Dec-18	1	242	7.12	5
WAR15	Orlando Health	12-Dec-18	0	37	1.09	0
WAR16	Los Angeles Biomedical Center	20-Dec-18	0	110	3.33	0
WAR17	South Palm Cardiovascular	12-Jan-19	0	6	0.19	0
WAR18	University of Kentucky	04-Feb-19	0	23	0.72	0
WAR19	Naval Hospital Jacksonville	15-May-19	0	2	0.07	0
WAR20	Naval Hospital Pensacola	15-May-19	0	6	0.21	0
WAR21	Clearwater Cardiovascular Consultants	29-Mar-19	0	54	1.8	0
WAR22	Silver State Cardiology	16-Apr-19	0	55	1.9	0
WAR23	Baylor Scott & White	20-May-19	0	41	1.46	1
WAR25	Heart House Research Foundation - Dr. Rizvi	13-Dec-19	0	36	1.71	0
WAR26	VA Gainesville	01-Aug-19	0	19	0.73	0
WAR27	VA Puerto Rico	15-Aug-19	0	5	0.2	0
WAR28	Southwest Cardiovascular (FL res Inst)	12-Sep-19	0	6	0.25	0
WAR29	Cardiovascular Center of Sarasota	30-Aug-19	0	23	0.92	0
WAR30	Peak Clinical Trials	02-Mar-20	0	2	0.11	0
WAR31	Card Assoc Mobile	07-Apr-20	0	9	0.5	1
WAR32	CHI Health Research Center and CHI Health Clinics- Cardiology	09-Dec-19	0	4	0.19	0
WAR33	Chippenham Hospital	09-Mar-20	0	6	0.33	0
WAR34	Seton Heart Institute	04-Dec-19	0	28	1.27	2
WAR35	West Virginia University	02-Mar-20	0	10	0.53	0
WAR36	Essentia Health	10-Feb-20	0	25	1.32	0
WAR37	Midwest Heart and Vascular Specialists	03-Feb-20	0	19	0.95	1
WAR38	UF JAX	07-Jan-20	0	22	1.05	0

WAR39	Cardiovascular Institute of Central Florida	16-Jan-20	0	13	0.65	0
WAR40	Jamaica Hospital	16-Jan-20	0	2	0.1	0
WAR41	Minneapolis Heart Institute Foundation	02-Mar-20	0	13	0.68	0
WAR42	The Research Group of Lexington	02-Mar-20	0	28	1.47	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	0.72	1
WAR45	Midwest Cardiovascular Research and Education Foundation	04-Jun-20	0	38	2.38	1
WAR46	Bassett Healthcare Network	24-Jul-20	0	5	0.36	0
WAR47	U Virginia	09-Sep-20	0	11	0.92	0
WAR48	Baycare CV Res	24-Jul-20	0	13	0.93	1
WAR49	Loyola University Chicago	16-Sep-20	1	4	0.33	1
WAR50	Cards Assoc Res	22-Jul-20	0	2	0.14	0
WAR51	San Antonio Endovascular and Heart Institute	17-Aug-20	0	22	1.69	0
WAR52	University of Arkansas	12-Oct-20	0	7	0.64	0
WAR53	Mayo Clinic- Jacksonville	01-Oct-20	0	0	0	0
WAR54	Advent Hlth Sebring	02-Sep-20	0	15	1.15	0
WAR55	CV Cons of S. Georgia	17-Aug-20	0	5	0.38	0
WAR56	Guardian Res	02-Sep-20	0	6	0.46	1
WAR57	Charles Croft	07-Sep-20	1	64	5.33	1
WAR58	Pinehurst med Ctr	02-Sep-20	0	2	0.15	0
WAR60	Valley Hospital (The)	26-Oct-20	0	8	0.73	0
WAR61	Austin Heart	12-Oct-20	0	46	4.18	0
WAR62	Western Kentucky Heart and Lung	14-Oct-20	0	27	2.45	0
WAR63	Berkshire	04-Nov-20	0	2	0.2	0
WAR64	Carilion	15-Mar-21	2	18	3	4
WAR65	U Arizona Sarver Hrt	07-Dec-20	0	2	0.22	0
WAR66	Trihealth	25-Jan-21	0	5	0.62	1
WAR67	Dignity Health Gilbert-Chandler	25-Jan-21	0	6	0.75	0
WAR68	MidMichigan Health	30-Mar-21	0	8	1.33	2
WAR69	Medicorcium	26-Feb-21	0	17	2.43	1
WAR70	Carle Foundation	26-Feb-21	0	3	0.43	0
WAR72	Loma Linda U Health	26-Feb-21	0	12	1.71	0
WAR73	Christ Hospital (The)	12-Apr-21	0	29	5.8	7
WAR75	NYU Langone	12-Apr-21	0	0	0	0
WAR76	AdventHealth Orlando	26-Apr-21	0	0	0	0
WAR77	Dignity Health St. Joes Hosp	26-Apr-21	0	5	1	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
Totals:			6	1712		38

APPENDIX B. DSMB Recommendations

EMORY UNIVERSITY SCHOOL OF MEDICINE

Department of Medicine
Division of Cardiology
Nanette Kass Wenger, MD

March 26, 2021

Carl J. Pepine, M.D.
Principal Investigator, WARRIOR Trial
1329 SW 16th Street, Suite 5130
Box 100288
Gainesville, FL 32608

RE: WARRIOR Trial DSMB Findings

Dear Carl:

The WARRIOR DSMB convened its planned meeting on March 12, 2021. The WARRIOR Trial Leadership presented the study's current status in detail to the DSMB in writing prior to the meeting and summarized it during the teleconference. The DSMB reviewed site and patient recruitment and follow-up activities, patient demographics and study outcomes, masked to treatment strategy. The Investigators were available for questions from the DSMB. After the open session, the DSMB met in closed session and based on their review of the data and discussion made the following recommendations:

1. *Continue the trial as planned*

2. *Continue to enroll as enthusiastically as possible, given COVID-19 related restrictions.*

3. *Any decision(s) for modifying primary and/or secondary outcomes should initially be made by the investigators after discussion among themselves. Perhaps trial leadership might want to consider an independent advisory committee, that has not had access to prior discussions or the outcomes data except for aggregate event rates, to provide recommendations for any modifications to the primary and/or secondary outcomes or trial follow-up.*

4. *Sometime in August, before the September data summary cut point date, provide up-dated information on enrollment, events, and renewed-statistical power considerations recognizing that many new enrollees will likely be in a lower risk group*

We recognize and thank you for the unplanned additional effort required during the pandemic. The DSMB will plan to reconvene in August as noted above, unless unforeseen circumstances create a need for unscheduled meetings.

Sincerely,

Nanette K Wenger MD, MACC, MACP, FAHA
Professor Emerita, Emory University, School of Medicine
Chair, WARRIOR DSMB

Emory University School of Medicine
Faculty Office Building
49 Jesse Hill Jr Drive SE
Atlanta, Georgia 30303

The Robert W. Woodruff Health Sciences Center
An equal opportunity, affirmative action university

Tel 404.616.4420
Fax 404.616.3093
nwenger@emory.edu

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				

	Timeline Months	DACC	CSC	ONF	VA	ADMMF
Approve meeting minutes	1-48	X	X			
Prepare project status reports	1-48	X	X			
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				

Task	Timeline Months	DACC	CSC	ONF	VA	ADMMF
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
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				

Task	Timeline Months	DACC	CSC	ONF	VA	ADMMF
Perform clinical user acceptance testing of database including eCRF screens and query rules	PRE	X				
Host UFDMS database	PRE	X				
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				

Task	Timeline Months	DACC	CSC	ONF	VA	ADMMF
Administer payments to CEC committee members	1-48		X			
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				