

AWARD NUMBER: W81XWH-17-2-0030

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

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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 are 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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TABLE OF CONTENTS

	<u>Page</u>
1. Introduction	4
2. Keywords	5
3. Accomplishments	5
4. Impact	16
5. Changes/Problems	17
6. Products	18
7. Participants & Other Collaborating Organizations	21
8. Special Reporting Requirements	27
9. Appendices	28

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. Study aims are 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 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.

COVID-19

The COVID-19 pandemic emerged in late January and early February to impact WARRIOR, as well as all other clinical research being conducted in the US. As reported in the last quarterly report the WARRIOR Executive Committee was in continuous contact with institutional leadership, monitoring CDC, FDA and IRB guidance as the data were emerging to determine impact on WARRIOR. Based on mandates from the FDA, DoD, and University of Florida Division of Research, a hold on recruitment for most “non-essential” clinical trials were implemented to minimize risk of SARS-CoV-2 exposure to research staff and study subjects by restricting visits to health care facilities to only “urgent or emergent” visits. After 2-3 months remote “tele-visits” were permitted. These recommendations were issued across all of our WARRIOR sites. Interactions regarding WARRIOR Trial impact included communications between the PI and DCC PI with the DOD project officer by email on March 13, 2020 and teleconference on March 26, 2020 and thereafter frequently with all sites over ensuing months.

The original design of the WARRIOR protocol, allowing for phone visits at 3, 6 months and subsequent half year visits and the use, in most centers, of a mail order pharmacy allowed the follow-up of the trial participants to proceed, slowly, but at least without complete interruption. The data system was already capable of recording this type of visit. A temporary modification, to have all annual visit labs and biorepository specimen collections placed on hold was implemented until participants could return to the office. This necessitated protocol deviations, which were recorded and reported to the IRB at the annual review. On March 13, 2020 the WARRIOR DCC issued a memo to implement temporary changes modifying the protocol to have ALL follow-up visits conducted by telephone to eliminate the risk of participant exposure to healthcare systems. On March 26, 2020, all WARRIOR sites were advised to temporarily halt subject recruitment, but strongly encouraged to continue all other research activities including AE/SAE data clean-up, conduct scheduled follow-up visits by phone, and where feasible (based on institutional guidance) screen and identify potential participants and if possible schedule visits for June, 2020.

The full impact of COVID-19 is difficult to assess at this time. But it clearly has resulted in at least a **6-month halt or major decline of recruitment activity** and for some sites, closures were required by local regulations to be extended into August and September related to gradual local reopening, delays in reopening research, staff working remotely limiting screening and enrollment for those sites that have reopened etc.

As of September 15, 2020, the majority of sites are now back on-line for screening and recruitment. In anticipation of potential secondary and possible tertiary surges of COVID-19 cases, combined with the upcoming influenza season and the potential for sites to close to in person research visits, consultations continued with the IRB and DSMB Chairs. Based on these discussions the WARRIOR protocol has been modified to allow for continued virtual enrollment, as well as follow up. A revision to this effect is currently under UF IRB review and will then be submitted to HRPO.

During the period that sites were closed to recruitment visits, the DCC has focused on completing new site identification, contracting and IRB/HRPO approval to reach the goal of 100+ enrolling sites. As reported in detail in the supplement, these activities have been successful but for the most part, but some potential sites have continued to have limited contracting personnel and/or IRB efforts due to local COVID-19 protocols or IRB staff with limited hours, and other sites have been required to continue to slow down all research activities and/or focus only on specific COVID-19 protocols. Despite these challenges and related limitations, the DCC has successfully contracted with additional sites since the last quarterly report.

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 includes 18 major tasks (e.g. goals). Each of these major tasks are further divided into sub-tasks that are assigned a general timeline and a research site responsible for the sub-tasks. Please see the attached statement of work for a full list of tasks. The status of each task and progress of the sub-tasks for the **third year (period 3) 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 has been periodically amended to allow for updates and changes based on COVID-19, Steering and Executive Committee feedback, and feasibility of implementation. All sub-tasks in this category have been completed for the most recent version of the protocol. A summary of all submissions and approvals appears below. All versions of the protocol have been sent to HRPO. The current operational version of the protocol is version 13.0. Version 14, allowing for virtual enrollment and follow up is currently undergoing regulatory 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 on January 31st 2019 – 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
- V14.0 Submitted to University of Florida IRB – 9/25/2020

A separate IRB submission was required for the WARRIOR Biorepository (“BEAWARRIOR”) that was detailed in the original grant submission. This has been IRB and HRPO approved as noted above. The BEAWARRIOR 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. **Recruitment materials have been developed, IRB approved and distributed to sites to assist the recruitment process.**

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 13.0. **During the past year the UF site (which houses all of the sites using the IRB as the central IRB), the Data Coordinating Center (which also houses sites using their local IRB), the Statistical Coordinating Center and Cedars clinical site, and the BEAWARRIOR Biorepository have been submitted for annual review and all have been approved and these submissions have been submitted and reviewed by HRPO. All subsequent revisions have been submitted to HRPO but have not changed the specific aims or risks to require HRPO re-review for approval to implement.**

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. **Study site investigator finalization is continuing, with study budget and contract negotiations occurring simultaneously. This task is lagging the original timeline as outlined in previous quarterly and annual reporting. Based on Executive Committee review of individual site performance early in year 2 recruitment feasibility assessments indicated more sites would need to be recruited to meet recruitment goals and total site estimates were to target 100-125 sites. Additional contracting was brought in during the first quarter of year 3. A detailed accounting of coordinating center activity to achieve site recruitment and patient enrollment follows.**

Table 1 summarizes site activation activities over the first two 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	Q1 9/15/19- 2/14/19	Q2 12/15/19- 3/14/20	Q3 3/15/20- 6/14/20	Q4 6/15/20- 9/14/20	Year 3 9/15/19- 9/14/20
Contacted	286	443	523	677	797	873	873
Interested in Participating-CDA Sent	155	309	318	472	592	668	668
Completed CDAs Returned	52	120	135	165	199	223	223
Contracting Fully Executed	17	41	45	57	72	82	82
Contracts Negotiating	50	26	66	34	49	28	28
UF IRB Approved	19	37	42	48	55	66	66
HRPO Approved	13	29	40	47	52	63	63
Activated for Enrollment	13	27	34	42	48	59	59
Patients Enrolled	76	584	685	791	827	970	970

Activation of sites able to recruit active duty, retired and military dependents has been successful. During year 2, the DCC has successfully subcontracted with Geneva Foundation, and received approval for 5 active duty military sites. **During YEAR 3 two additional military sites (Walter Reed and BAMC) have been onboarded** with Pensacola and Jacksonville Naval Air Stations and are all actively recruiting. **Tripler Army Medical Center is in final stages IRB processing (delayed due to COVID-19). In addition, the final VAMC (Tampa) is completing HRPO submission** with two of three in Gainesville Florida/Puerto Rico are approved and enrolling participants. **Details of this activity are summarized in Table 2.**

Table 2. Military sites.

<u>LOCATION</u>	<u>P.I.</u>	<u>STATUS</u>
Pensacola NAS	Dr. Gray	Enrolling as of 6/13/19
Jacksonville NAS	Dr. Volk	Enrolling as of 6/13/19
Walter Reed	Dr. Weber	Enrolling as of 3/16/2020
BAMC	Dr. Thomas	Enrolling as of 3/16/2020
TAMC	Dr. Fuentes	Submitting to eIRB for approval: Contracted
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	IRB approved, being submitted to HRPO

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 continues to actively solicit potential sites. **During Year 3,430** additional sites have been contacted and CDA's sent. Of the **total 873 potential sites contacted** over the course of the trial, **223 CDA's have been executed** which starts the feasibility assessment for both the site and the DCC. The DCC has executed **82 contracts**, of those **74 sites have fully executed contracts**. **Fifty-nine (59)** are activated sites, **15** are contracted and pending regulatory approval and **5** contracts are IRB approved but contracts are pending. This surpasses the original goal of 50 sites with a current total of 79 sites with 28 contracts still in negotiations which brings site totals to 108 sites as per the revised goal. These efforts exceeded Year 2 with a doubling of sites contacted and ultimately contracted. COVID-19 did delay processing at some centers as regulatory efforts and contracted were diverted to COVID-19 protocols; and /or staff were on leave or working remotely which increased processing times.

1) Identification of additional sites

Previous efforts to identify sites in Canada were successful. But after 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 the study medications and the required regulatory oversight as it would not be IND exempt (Canadian equivalent).

1.1) Previous site initiatives:

1.1.1) The previously reported pilot utilizing the Emergency Department as a recruitment arm at the UF site initiated and direct referral has not been successful, but **screening ED discharges** has been **VERY SUCCESSFUL** resulting in **130 women enrolled to the UF cluster of sites in the last year**. This method of recruitment has been added to the site MOP. Based on these findings, SIREN network outreach has been deemed **not helpful** to add at already enrolling sites.

1.1.2) The DCC contacted the 800+ US investigators who participated in the INVEST project to assess interest/ability to participate in WARRIOR. These sites were able to enroll over 17,000 US patients with ischemic heart disease and hypertension, of which 50% were women. Initial contacts are localized to the Southeast US, where there was the largest concentration of sites. We learned that the **majority of sites contacted were not interested (sites were primary care focused, lacked female patients or lacked access to cardiac catheterization/CCTA logs for screening)**.

1.1.3) As reported in the last quarterly report, new sites are being identified from the Community Health IT Group which is a consortium of health care practices including federally qualified health centers, which has 20 potential sites. To date 5 centers have completed CDA's and are entering contracting/regulatory processing. **This effort has resulted in 1 new site and was not deemed to be successful.**

2.) Reducing delays in contracting and regulatory approvals

2.1) Delays in site activation

Delays continue to occur in both contract negotiation (budget or language issues), and regulatory (IRB and HRPO review). Identified issues and solutions that have been addressed during YEAR 3 are summarized below.

2.1.1) Contracting

Contracting delays are inherent in clinical trials and sites with long delays have been dropped in order to focus on more efficient sites. This has increased the ability to reach out to additional sites. Larger practices/institution processing times vary from 2 weeks to 6 months.

2.1.2) Regulatory approvals

Each investigator requires Central UF IRB approval (or local IRB approval), and DoD HRPO approval. During Year 3, there were no significant issues with delays in regulatory processing. HRPO and UF IRB staff have continued to work with WARRIOR regulatory staff to improve the process. The UF IRB has instituted an investigator submission pathway that does not hold up revision reviews which has greatly improved site processing.

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. *[Ongoing]*

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 3 there was a face to face Steering Committee meeting for all of those attending the AHA on November 16, 2019 in Philadelphia, PA. Due to COVID-19 a second Steering Committee Meeting was planned to be held in March 2020 but due to the pandemic and site closures, the meeting was postponed.** *[Ongoing, within SOW projections]*

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

All sub-tasks are ongoing. During YEAR 3, 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. *[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](https://clinicaltrials.gov/NCT03417388). The WARRIOR website is online <https://warriorwomenstrial.com> and is fully functional as the communication portal. Social media efforts are underway with “Microvascular Angina Facebook group” and several additional patient stakeholder groups such as “WomenHeart” and the “WomenVeterans PPRN. A FAQ log”, and project newsletters are in development. *[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 09/27/20 a total 969 subjects have been randomized to the project from 59 activated sites. Two 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.

Additionally, the DCC is in regular contact with site investigators and sites both by site visits or phone/conference calls/emails. 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.** *[Ongoing, within SOW projections]*

Major Task #11 – Audits: [Months1-48]

All sub-tasks are ongoing. Vendor audits are occurring as needed. **During YEAR 3 the DCC has weekly conference calls with Cedars Sinai (statistical core), LA BioMed (CT recruitment center and Core Lab), BEAWARRIOR (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. 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. (see attached appendix C)** *[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 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 3 the CEC has continued to adjudicate events as they are reported.** *[Ongoing, within SOW projections]*

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

During YEAR 3 the DCC and CSC continue to conduct weekly scheduled EC calls that are well 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. Steering Committee meetings continue and are on schedule as planned. The planned DSMB meeting for March 2020 was postponed. The DSMB has requested to review the annual Progress Report and then will set the date for the next meeting. This task has occurred within the SOW timeline. *[Ongoing, within SOW projections]*

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

The BEAWARRIOR Biorepository is operational. During YEAR 3 all sites have been trained and are operational and have sent samples on 479 patients, and all have been processed and stored. This has provided 6,351 aliquots for analysis. 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 \$390,000.00. This has permitted initial sample analysis, partition of samples and freezer storage. **In YEAR 3 additional sample analyses have been generated and are undergoing evaluation for potential ancillary trial submission to the NIH or DoD.**

The Biorepository underwent annual IRB review and no issues were identified. Dr. Keith March is the Biorepository PI and during YEAR 3 Dr. Ellen Keeley has been added as Co-PI of the biorepository. During the COVID-19–related closure of sites to onsite research visits, all biorepository sample collection was deferred until visits were deemed safe and were deferred until the next in person visit. *[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

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. After favorable discussion with the Editor, it was agreed that it will be submitted to the American Heart Journal. **The Rationale and Design Manuscript is in final review by the EC and planned for submission early October 2020.** Additional ideas for proposed publications are being collected and the publication schedule is a standing agenda item during EC meetings. **Writing Group participation requests have been solicited from Steering Committee members and the site PIs.** 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 3** annual reporting period the WARRIOR trial grant proposal **has successfully contracted with 79 of the expanded plan to extend the number of sites to 100-125 to facilitate enrollment. An additional 28 sites remain in contracting, which should result in 107 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 **970 women as of 9/27/20**; during YEAR 3 there have been **386 women enrolled.** As noted in the introduction, COVID-19 resulted in temporary halt of patient recruitment at all centers **which lasted for 4-6 months.** Reopening of sites has been variable and some centers are just coming back on line in August and September 2020. In addition, there have been three hurricanes in the SW US that have affected two of the centers during the Fall of 2019 and the Summer/Fall of 2020. Recruitment of sites and 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.

Pragmatic trials characteristically have lower per patient reimbursement and the limited budget has been a deterrent to attracting many new sites. This is particularly true when sites capable of quality clinical investigation have many alternative trial opportunities with much better reimbursement. Accordingly, in YEAR 2, financial incentives were offered that resulted in increase in enrollments at some sites. Since a large number of new sites have been added since March 2020 and all prior sites are now reopened, the DCC has implement October WARRIOR Month with recruitment incentives to encourage subject recruitment. Low-enrolling sites, pre COVID-19, have been contacted to address low performance, and we have offered support for advertising and patient oriented recruitment materials.

Projected recruitment with additional sites was projected to be completed by the end of YEAR 3. Due to the limited recruitment for 4-6 months, expected recruitment of the planned 4,422 participants shifts into year 4. To achieve sufficient follow-up, the no cost extensions previously discussed with our DoD

Project Officer will be very important. However, sufficient funding is available to support the full scope of work since the majority of unspent funds are those that we have designated for per patient recruitment.

During YEAR 3, we continued efforts that we have found to be successful. One example is reimbursement for coronary CT angiograms which has resulted in additional recruitment. Referrals from radiology imaging centers, however, had only limited success. Also, radio and/or social media advertising in the limited coverage that was financially feasible was not successful. Utilization of “MyChart” (by EPIC) as a recruitment mechanism has been very successful, and this method has been transmitted to all sites who use EPIC.

Historically in large-scale clinical trials, recruitment increases after investigator/coordinator meetings and success of clinical trials is dependent on study coordinator performance. Unfortunately, our meeting was held the weekend of February 6-7, just before the COVID-19–related closures. Another Coordinator Meeting is planned for the beginning of January to further train, share best practices and motivate sites to focus on recruitment in order to reduce the recruitment period and will be focused on coordinators. The meeting was held in February and 4 weeks later the sites closed due COVID-19 so the impact of this meeting was unrealized.

During YEAR 3 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.**

The **OVERALL AIM** is to provide rigorous comparison of changes in atherosclerotic plaque features, plaque composition and plaque inflammation-related characteristics of PCAT and to evaluate their relationship with clinical symptoms among women with nonobstructive CAD who undergo IMT vs UC in the WARRIOR trial.

AIM 1. To compare changes-from baseline to exit at 3 years-in coronary plaque characteristics and their hemodynamic significance using CTA in WARRIOR women treated with IMT vs UC.

Hypothesis: IMT will result in beneficial changes in visually and quantitatively assessed high-risk plaque features including, necrotic core, fibrofatty and fibrous plaque volumes, and CDD an index of FFR, compared to UC.

AIM 2. To compare changes in plaque inflammation-related characteristics in PCAT in WARRIOR women treated with IMT in combination with ACEI and/or ARB vs UC.

Hypothesis: IMT will be associated with a decrease in plaque inflammation as reflected by decreased PCAT density quantified by CTA attenuation vs UC.

AIM 3. To relate plaque burden, plaque composition, CT flow reserve assessment, and PCAT density changes to angina score changes measured by the Seattle Angina Questionnaire (SAQ) in IMT and UC WARRIOR women.

Hypothesis: Changes in plaque burden, plaque composition, CDD and PCAT density by quantitative CTA will indirectly relate to change in SAQ and anginal symptoms in WARRIOR women.

The DCC is working with the PI to operationalize the project.

In addition, a second Ancillary Trial application has been submitted 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.

Both projects have been reported to the DSMB and received support.

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 has provide an opportunity to inform trainees and professionals in Cardiovascular Medicine, Internal Medicine, Family Medicine, Emergency Medicine and Nursing about the problem of ischemic heart disease in women.

How were the results disseminated to communities of interest?

No results are available to disseminate. The Rationale and Design manuscript has been written and is being submitted to the American Heart Journal the first week in October 2020.

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

Activation of WARRIOR sites will continue until the end of year, while focusing on weekly recruitment from all sites in order to reach goal of 4,422 participants.
Collect data as outlined.

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**

Carl J. Pepine, MD Talks/Lectures that included WARRIOR Sept 15, 2019 to Sept 14, 2020

Sept 19, 2019. UF Dept of Medicine Grand Rounds- “What Constitutes Optimal Medical Therapy in Stable Angina?” Included WARRIOR Trial, Rationale and Design

Annual Scientific Sessions of the American Heart Association, Philadelphia, PA
Nov 16, 2019 7:00am “Diagnosis of Coronary Microvascular Disease: Invasive Imaging”

Nov 16, 2019 11:00am-1:00pm – “WARRIOR Trial Staff Update”
Hampton Inn Center City - Independence Conference Room 1301 Race Street Phil PA 19107

Jan 28, 2020- UF College of Public Health and Health Professions Epidemiology Course “A New Era in CVD Clinical Trials” Included WARRIOR

Jan 28, 2020- Oak Hammock at the UF- CVD Update (included Hypertension in Women and WARRIOR)

February 7-9th, 2020- 20th Annual National Sarasota Congress for Cardiovascular Disease Prevention, Update 2020: Time to Focus on Early Cardiovascular Disease Prevention and Optimal Diagnosis and Management of Primary and Secondary Cardiovascular Diseases, Hyatt Regency, Sarasota, FL

Feb 9, 2020. “Ischemic Heart Disease in Women” Followed by a “Roundtable Discussion”

March 30, 2020 ACC20 “WARRIOR UPDATE”-Steering Committee

Sept 27, 2019 NYU Cardiology Grand Rounds- Hypertension and Resistant Hypertension in Women

Sept 26, 2019 NYU Fellows Dinner Conference Spoke on WARRIOR.

Dec 13, 2019 UF Regenerative Medicine Course-
“HFpEF: Hypothetical Construct from Clinical Observations of Women with INOCA”

Dec 20, 2019 Morristown Memorial Hospital
Cardiology Grand Rounds- A Novel Approach to Heart Failure post-MI

Dec 19, 2019 Dinner meeting Spoke to Cardiology Program Directors on WARRIOR

February 7, 2020 8am –3pm WARRIOR Coordinators Event
Dockside Lake Nona: 13623 Sachs Avenue, Orlando, FL
10:30-11:15am “Microvascular Dysfunction in Women and the WARRIOR Trial”

Eileen Handberg, PhD Talks/Lectures that included WARRIOR Sept 15, 2019 to Sept 14, 2020

Sept 14, 2019 **Handberg E.** Microvascular Angina/Women and Heart Disease. PCNA First Coast Fall Learning Program. Jacksonville, F

February 7, 2020 8am –3pm WARRIOR Coordinators Event
Dockside Lake Nona: 13623 Sachs Avenue, Orlando, FL

Feb 21, 2020 **Handberg E**, panelist. Expert Panel Discussion. 2020 South Florida Go Red for Women Luncheon. Aventura, FL,

Feb 28-29, 2020 **Handberg E**. Heart Disease in Women. Broward Health's 2nd Annual Cardiovascular Symposium. Ft. Lauderdale

May 20, 2020 **Handberg E**. What does ID in Women Look Like in 2020? PCNA Virtual Cardiovascular Nursing Symposium

Noel Bairey Merz MD Talks/Lectures that included WARRIOR Sept 15, 2019 to Sept 14, 2020

September 16, 2019 Cardiovascular Disease in Women – Myths and Reality. 2019 Meeting of Minds, INOCA International – A Patient Partnership. Video Presentation. The Dorchester, Park Lane, London, UK.

October 6, 2019 Preventative Medicine for Women/Men. Sharp HealthCare's 2019 Heart and Vascular Conference, Hotel Del Coronado, Coronado, CA,

October 24, 2019 Ischemic Heart Disease in Women: Monet vs Manet (Why Women Have More Adverse Outcomes). 19th Annual Maui Cardiovascular Symposium, The Fairmont Kea Lani, Maui, Hawaii,

November 16, 2019 Microvascular Disease: Prevalence and Unmet Needs. Advancing Cell Therapies for Coronary Microvascular Dysfunction: Experts Roundtable. AHA Scientific Sessions 2019, Philadelphia, PA,

November 19, 2019 Female-Pattern Ischemic Heart Disease: Monet vs Manet or Why Women Have More Adverse IHD Outcomes. Cardiac Grand Rounds at Sentara Heart Hospital, Norfolk, VA.

December 6, 2019 Ischemic Heart Disease in Women. Cedars-Sinai 17th Annual Emergency Medicine Symposium – A Practical Update. Los Angeles, CA

January 28, 2020 Covering the Heart Beat. National Press Foundation. West Palm Beach, FL

January 23, 2020 Cardiovascular Medicine Grand Rounds. Penn Medicine- Division of Cardiovascular Medicine. Philadelphia, PA

January 31, 2020 Women and Ischemic Heart Disease: Update 2020. The University of Arizona-Sarver Heart Center Grand Rounds. Tucson, AZ

February 19, 2020 Women and Heart Disease: What You need to Know. Los Angeles Oasis WISE & Healthy Aging Center. Baldwin Hills, CA

June 22, 2020 Advancing Women's Cardiovascular Health, Libin Cardiovascular Institute, Keynote Speaker, Calgary, Canada

August 29, 2020 State-of-the-art lecture- How to investigate suspected coronary artery disease in 2020, Diagnostic Approach in Patients with Suspected Coronary Artery Disease in 2020, ESC CONGRESS 2020

- **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://warriorwomenstrial.com>

- **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):
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):
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):
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: 12
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:	Taylor Galloway
Project Role:	New Site/Marketing Coordinator
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	12
Contribution to Project:	Ms. Galloway is responsible for marketing and new site initiations for WARRIOR.
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 which came to her in January 2020.
Funding Support:	NA

Name:	Dana Leach
Project Role:	Project Manager
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	8
Contribution to Project:	Ms. Leach is responsible for daily management of the WARRIOR trial.
Funding Support:	NA
Name:	Martin Noguera
Project Role:	Fiscal Coordinator
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	2
Contribution to Project:	Mr. Noguera processed payments to enrolling sites. He terminated in January 2020.
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):	
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.
NA

Funding Support:

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:

Kyler Conn (9/15/20-6/20/20) Replaced With Nicole Tovar

Project Role:

Coordinator

Researcher Identifier (e.g. ORCID ID):

Nearest person month worked:

9

Contribution to Project:

Mr. Conn assisted 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). He also assisted with scheduling and setting up committee meetings and DSMB meetings, and distributed meeting agendas, and completed meeting minutes.

Funding Support:

N/A

Name:

Norma Priscilla Moy

Project Role:

Coordinator

Researcher Identifier (e.g. ORCID ID):

Nearest person month worked:

8

Contribution to Project:

Ms. Moy assisted the investigators by performing research related duties assisted with data collection and maintaining study related records.

Funding Support:

N/A

Name:

Nicole Tovar (6/20/20 – present)

Project Role:	Coordinator
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	4
Contribution to Project:	As was the case with Mr. Conn, 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:	Timothy Wynter
Project Role:	Coordinator
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	1
Contribution to Project:	Mr. Wynter assisted the investigators by performing research related duties assisted 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):	
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 --contract pending
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--contracting

Brookes Army Medical Center--contracting

Walter Reed Army Medical Center--contracting

Geneva Foundation--contracted

LABioMED- contracted as a site/recruitment/imaging Core

Community Health IT- consortium of sites for recruitment

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

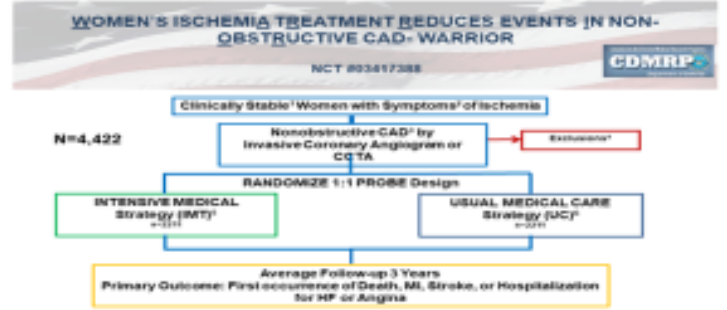
Award Amount: \$14,915,728.

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.



The LMP ACS, MI, or Stroke outcome group or angina equivalent (ACE) outcome group. Excludes for 4% of non-compliance, HF, MI, or Stroke. Excludes for 10% of non-compliance. Excludes for 10% of non-compliance. Excludes for 10% of non-compliance. Excludes for 10% of non-compliance.

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
Site Start-Up			WARRIOR Enrollment		
			WARRIOR Follow-Up		
Protocol, IRB, Contracts			WARRIOR Data Acquisition		
		Q3	WARRIOR Data Publications		

Estimated Budget (\$K)				
	\$3,258	\$4,935	\$3,531	\$3,192

Updated: 9/14/20

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
 - ✓ 970/4,422 subjects enrolled
 - ✓ Subject Follow-up
 - CY21 Goal** – Subject Recruitment and Follow Up
- Comments/Challenges/Issues/Concerns-COVID-19** Temp closures
Delays related to initiating contracts/IRB approvals/recruitment
Budget Expenditure to Date (06/15/2020)
Projected Expenditure: \$ 11,723,631
Actual Expenditure: \$ 5,785,237

9. APPENDICES:

- A. Subject Recruitment
- B. Current Status of IRB/HRPO submissions for Pending Sites
- C. DSMB Interim Update 1/17/2020
- D. Original Scope of Work

APPENDIX A. SUBJECT RECRUITMENT

Table 1. WARRIOR Recruitment by Site as of 9/15/20

Sites:			Randomization:			
WAR	Name	Activation	Last week	Cumulative	Avg/Mo	Prev 30 Days
WAR01-07: Active	UF Heart & Vascular	18-Oct	0	290	12.61	7
WAR08: Active	Intv Cardiac Cons	18-Oct	0	35	1.52	0
WAR09: Active	Daytona Heart Grp	18-Oct	1	8	0.35	1
WAR11: Active	Pepin Heart Inst	18-Oct	0	22	0.96	0
WAR12: Active	Ocala Res Inst	18-Oct	0	26	1.13	0
WAR13: Active	Baptist Hlth JAX	18-Nov	0	27	1.23	1
WAR14: Active	Cedars-Sinai	18-Dec	2	178	8.48	4
WAR15: Active	Orlando Hlth	18-Dec	0	24	1.14	2
WAR16: Active	LA BioMed Res	18-Dec	0	102	4.86	0
WAR17	South Palm	19-Jan	0	3	0.15	0
WAR18	U Kentucky	19-Feb	0	8	0.42	0
WAR19	Naval Hosp JAX	19-May	0	2	0.13	0
WAR20: Active	Naval Hosp PNS	19-May	0	5	0.31	0
WAR21: Active	Clearwater Cardio	20-Mar	1	27	1.50	2
WAR22: Active	Silver State Card	19-Apr	0	53	3.12	1
WAR23: Active	Baylor Scott & White	19-May	0	25	1.56	1
WAR25: Active	Heart House Res Fnd	19-Dec	0	18	1.80	3
WAR26: Active	VA Gainesville	19-Aug	0	13	1.00	1
WAR27	VA Puerto Rico	19-Aug	0	5	0.38	0
WAR28: Active	Southwest FL Res Inst	19-Sep	0	4	0.33	0
WAR29: Active	CV Ctr Sarasota	19-Aug	1	8	0.62	4
WAR30: Active	Peak Clin Trials	20-Mar	0	2	0.29	0
WAR31: Active	Card Assoc Mobile	20-Apr	0	0	0.00	0
WAR32: Active	Chi Health	19-Dec	0	2	0.20	0
WAR33: Active	Chippenham	20-Mar	0	3	0.43	1
WAR34	Seton Heart Inst	19-Dec	1	10	0.90	0
WAR35: Active	WVU Hrt & Vasc	20-Mar	0	2	0.29	2
WAR36: Active	Essentia	20-Feb	0	10	1.25	4
WAR37: Active	Midwest Hrt & Vasc	20-Feb	0	7	0.88	1
WAR38: Active	UF JAX	20-Jan	0	0	0.00	0
WAR39: Active	CV Inst of Central FL	20-Jan	0	6	0.67	1
WAR40: Active	Jamaica Hosp	20-Jan	0	3	0.33	0
WAR41: Active	Minneapolis Hrt Inst	20-Mar	1	4	0.57	2
WAR42: Active	Res Grp of Lexington	20-Mar	0	15	2.14	2
WAR43: Active	Brooke Army Med Ctr	20-Mar	0	0	0.00	0
WAR44: Active	Walter Reed	20-Mar	0	5	0.71	1
WAR45: Active	Midwest Cardio Res	20-Jun	0	10	2.50	1

WAR46: Active	Bassett Med Ctr	20-Jul	1	2	0.67	1
WAR47: Active	U Virginia	20-May	0	0	0.00	0
WAR48: Active	Baycare CV Res	20-Jul	0	0	0.00	0
WAR50: Active	Cards Assoc Res	20-Jul	0	0	0.00	0
WAR51: Active	San Antonio Endovasc	20-Aug	0	2	1.00	1
WAR54: Active	Advent Hlth Sebring	20-Sep	0	0	0.00	0
WAR55: Active	CV Cons of S. Georgia	20-Aug	0	0	0.00	0
WAR56: Active	Guardian Res	20-Sep	0	0	0.00	0
WAR57: Active	Charles Croft	20-Sep	3	3	3.00	3
WAR58: Active	Pinehurst med Ctr	20-Sep	0	0	0.00	0
			11	970	59.41	47

*** RED indicates on HOLD**

APPENDIX B. IRB and HRPO Update of Current Pending Sites as of 9/28/20

Site Name	Status
Austin Heart	HRPO Approved – NEW
Western Kentucky	HRPO Submitted
Mayo Rochester	HRPO Submitted
Berkshire Medical Center	HRPO Submitted
Carillion Clinic	Submitted to IRB – NEW
Emory University	Submitted to IRB – NEW
UCLA	Submitted to IRB – NEW
Carle Foundation Hospital	Ready to Submit – NEW
Dignity Health Mercy Gilbert MC	Ready to Submit – NEW
Tampa VA	Site IRB Approved – NEW
Tripler Army Medical Center	Submitting to eIRB
Oregon Health and Science University	Submitting to Site IRB
MidMichigan Health Clinical Research	Submitting to Site IRB – NEW
St John Hospital	Working on IRB Packet Completion
Georgetown University	Working on IRB Packet Completion
University of Louisville	Working on IRB Packet Completion
Advent Orlando	Working on IRB Packet Completion
Johns Hopkins	Working on IRB Packet Completion
NYU Langone	Working on IRB Packet Completion – NEW
	Total IRB Pending: 19

DSMB Chair WARRIOR UPDATE 1/17/2020

The DSMB met by conference call on 10/18/19 to review the conduct of the WARRIOR trial. The DSMB recommended to continue the trial as planned. They also requested an informational report due January 2020, which would include updates on site recruitment and activation, and subject recruitment. This is the informational report requested and the information provided is based on data available as of close of business January 16, 2020.

Since the DSMB met the DCC has continued the previously documented site recruitment/activation activities as well as additional initiatives to secure sites and increase enrollment of subjects. This report is divided into two sections: 1) site recruitment and activation, 2) patient recruitment activities with an update of previously reported strategies and presentation of new strategies/activities.

1) SITE RECRUITMENT AND/ACTIVATION

Table 1. Site Contracting and IRB/HRPO Approvals and Activation

	3/25/19	9/18/19	1/7/20
Site CDAs Completed and Returned to DCC	94	110	131
Site Contracting Completed/Fully Executed	37	40	45
Site Contracts and IRB Still in Negotiation	35	25	68
UF IRB Sites Approved	25	29	42
Sites HRPO Approved	24	29	42
Sites Activated for Enrollment	23	27	34

As reported to the DSMB the original goal was 50 recruited sites located in Florida. That plan was modified to recruit sites from all of the US. While the expansion of sites across the US has been successful, we have also encountered some operational difficulties, particularly with smaller practice sites that do not have an affiliated pharmacy necessary for provision of study medication in the intensive strategy. Independent pharmacies are being contracted for those sites. We are now up to 34 sites active for enrollment. After analysis of site recruitment activity and discussion with the DSMB, **it was decided to increase the number of sites to 100-125 in order to allow for lower enrollment per site (20-30)**. While recruitment of 4 patients per month/site is feasible, the majority of sites are not functioning at this level of performance, making it unlikely that each site will be able to enroll the ~89 patients that was originally anticipated. Financial incentives have been offered to enrolling sites on 4 separate occasions in order to boost enrollment but this has also had only limited success.

As noted in Table 1, the DCC continues to contact potential sites for CDAs, focusing on PI/Co-I referrals to identify sites with good recruitment performance in previous trials. Since inception of this modified plan to increase to the number of sites to 100-125, over 523 sites have been contacted (as of 12/30/19) for potential participation and 131 have returned CDA's indicating interest in the trial. **As noted in the table, currently there are 42 IRB/HRPO approved sites and 34 of these sites are actively recruiting. The 8 other sites are undergoing finalization of contracting and will be able to begin enrollment very soon. There are an additional 68 sites that are in various stages of the contracting and approval process. Once all of those sites are finalized, there will be 110 sites onboard and available for patient enrollment.** Since 12/15/19 two additional staff have been added to help recruit additional sites and reduce the time to contract execution.

Since the DSMB meeting, the three major holidays (which are associated with prolonged down time in Universities and clinic practices) took place in late November through the end of the year. Therefore, finalization of paperwork was minimal over much of December. Since the first of the year, significant progress has been made in terms of contacting sites and processing documents.

Tables 2 summarizes approved sites and recruitment per site as of January 16, 2020. Table 3 updates status of military and VA site recruitment.

Table 2. Active Sites

Site Name	Status	Randomizations
WAR01: University of Florida, Anderson	Active	124
UF Emergency Department, Allen	Active	2
WAR02: University of Florida, Lo	Active	2
WAR03: University of Florida, Holland	Active	0
WAR04: University of Florida, Wright	Active	2
WAR05: University of Florida, Park	Active	93
WAR06: University of Florida, Goede	Active	3
WAR07: University of Florida, Maska	Active	9
WAR08: Interventional Cardiac Consultants	Active	33
WAR09: Daytona Heart Group	Active	5
WAR10: Advent Health, Tampa	Active	23
WAR11: Ocala Research Institute	Active	25
WAR12: Baptist Health: Jacksonville	Active	17
WAR13: Cedars-Sinai	Active	143
WAR14: Orlando Health	Active	14
WAR15: Lundquist Institute for Biomedical Innovation	Active	98
WAR16: South Palm Cardiovascular Research Institute	Active	3
WAR17: University of Kentucky	Active	8
WAR18: Naval Hospital Jacksonville	Active	2
WAR19: Naval Hospital Pensacola	Active	5
WAR20: Clearwater Cardiovascular Consultants	Active	18
WAR21: Silver State Cardiology	Active	46
WAR22: Baylor Scott & White	Active	11
WAR23: Alabama Heart and Vascular	Active	0
WAR24: Gainesville VA	Active	9
WAR25: Heart House Research Foundation	Active	1
WAR26: Puerto Rico VA	Active	3
WAR27: Southwest Florida Research Institute	Active	1
WAR28: Cardiovascular Center of Sarasota	Active	2
WAR29: CHI Health Research Center	Active	0
WAR30: West Virginia University	Active	0
WAR31: Seton Heart Institute	Active	3
WAR32: Cardiovascular Institute of Central Florida	Active	0
WAR33: Jamaica Hospital	Active	0
WAR34: Essentia Health	Active	0
Novel Research Institute	Deactivated	
	Total Active: 34	Total: 705

Table 4. Military and VA Site Status

LOCATION	P.I.	STATUS
Gainesville VA	Dr. Schmalfuss	Active
Jacksonville NAS	Dr. Volk	Active
Pensacola NAS	Dr. Gray	Active
Puerto Rico VA	Dr. Vincenti	Active
Walter Reed	Dr. Weber	Contracted, IRB approved, pending DHA/HRPO approval
BAMC	Dr. Thomas	Contracted, under IRB review, pending DHA/HRPO
Tampa VA	Dr. Leonelli	Submitted to their own IRB, awaiting approval
Ft. Belvoir	Dr. Crimm	Withdrawn due to staffing shortage
TAMC	Dr. Fuentes	Contracted, IRB submission underway

Update on Previously Reported Site Recruitment Initiatives:

- Collaborative agreement with WellFlorida:

The DCC entered into a collaborative agreement with WellFlorida, which is a consortium of Federally Qualified Health Centers and other practices located in Florida. WellFlorida has identified 32 practice sites which are interested in participating in the trial. Initial data query of one large practice in multiple cities indicates a potential population of 5,000 women and it has been estimated that 10% of this population may qualify (this practice serves an older to elderly population with many comorbidities). Contracting is underway.

2) Referral of Subjects

The DCC is continuing to work with existing sites to increase potential subject enrollment. This following update our efforts to date and highlight new initiatives.

Updates on Existing Initiatives:

- Social media.

Facebook ads in geographic areas of enrolling sites: reaching ~23,000 women. Enrollment generated from Facebook ads has been very limited to date.

- Radio Advertisements

This method of outreach was initiated for a large metropolitan area with multiple WARRIOR sites, and run for one month. Only 8 potential subjects who heard the radio ad reached out to the study site. Given the expense of the media source, this was determined to be unsuccessful.

- CTA Imaging Center Referrals

The DCC, utilizing the network of Dr. Matt Budoff at LA Biomed solicited CTA imaging centers to mail WARRIOR flyers to their population of patients who underwent CTA's referring interested women to local WARRIOR sites. Imaging centers were paired up geographically with enrolling sites. The effectiveness of

this has been limited to supporting recruitment in the LA geographic area. The DCC is continuing to attempt to pair up interested imaging centers with newly recruited sites in order to drive potential patients to the sites.

- Protocol Amendment

The protocol was revised to allow for reimbursement of coronary CTA's in women who otherwise meet eligibility criteria and agree to participate in WARRIOR. This has been successful in getting additional women enrolled. This utilization is shown in Table 3. This program will continue. **Over the previous 6-8 months the DCC has identified a shift from coronary CTA evaluations in the ER to high sensitivity troponin and echocardiogram and if negative, ER discharge. This will mean that there may be more utilization of study funded coronary CTA to establish coronary anatomy eligibility.** The impact on the budget is being evaluated.

TABLE 3. Coronary CTA Ordering and Randomizations

Site Name: PI	CTA Provided, Pending Randomization	CTA Provided, Randomized	Total CTA's Ordered
UF: WAR01-07	7	11	18
Shufelt: WAR14	2	2	4
Einhorn: WAR15	4	1	5
Budoff: WAR16	0	2	2
Parilak: WAR22	0	6	6
Widmer: WAR23	1	0	1
Shahawy: WAR29	0	1	1
	Total: 14	Total: 23	Total: 37

- DCC Coordinator Staff support for activated but low enrolling sites:

Several sites have been provided support from the DCC to help screen CTA/Cath Lab logs or review screening processes. Impact of this effort is still unclear. At one center 100+ potential subjects have been identified. The DCC provides additional staff support in the form of coordinator effort to one large health system with 3 hospitals that are agreeable to participation. It is hopeful that this effort will result in another large super center 100-200 patients.

- Utilization of Emergency Room collaborations is being tested at UF and to date has resulted in only limited enrollment. But the UF main site has been able to identify women who were discharged without being admitted and in December were able to recruit 20 subjects. Recruitment materials are being developed to provide to women with chest pain at discharge to link them with WARRIOR staff. This will be evaluated in the next 3 months.

New Site Recruitment Initiatives:

- Potential addition of Canadian Investigators from ISCHEMIA Trial

Dr. Pepine has worked with many Canadian sites in several NIH and industry funded trials over the past 25+ years and in most cases these centers were very high

enrollers. Dr. Bairey Merz has been working with the Canadian Investigators in the ISCHEMIA Trial. There were 9 centers that were able to enroll close to 500 subjects in ISCHEMIA. Contact has been made with Dr. Shaun Goodman who has worked with a consortium of cardiology investigators across Canada and discussions are underway to add Canadian sites. Initial discussion with the DoD Project Officer indicates that this may be allowable, and paperwork is in process to get approval. There are several very engaged cardiologists whose expertise is in Heart Disease in Women who have expressed interest, with one who has an active registry of this exact population. Determination of feasibility is in process and should be determined by the end of January.

- NIH SIREN Investigators

Given the proportion of women who are being identified from ER discharges, discussions are in process to determine the interest in potential collaboration with the ER Research Network funded by the NIH as potential referral sources to local WARRIOR sites.

- Coordinator Inertia

In spite of biweekly coordinator calls, there seems to be inertia of study staff to aggressively screen and recruit potential subjects. Feasibility of recruitment has been demonstrated at multiple centers. On-site visits of DCC staff has generally resulted in identification of subjects from the cath lab, clinics on the days of visits indicating inadequate screening and recruitment. Historically with most clinical trials, recruitment takes a significant upturn after coordinator/investigator meetings. Based on interactions with our patient stakeholder who is part of the Executive Committee and a study subject, a coordinator meeting is being held in Orlando on February 7th, 2020. The plan is to have a panel discussion with 5 women who are participating in the trial to help coordinators understand the importance of the trial to women with this disorder and to showcase best practices of recruitment and problem solve with centers that are struggling with recruitment. The DCC feels that this will create an upward inflection point for recruitment.

Subject Recruitment

Cumulative patient recruitment is shown in Figure 1. PI to PI calls have been taking place at both successful sites to determine additional best practices and trailing sites to problem solve jointly to encourage more robust enrollment. Successfully getting to targeted recruitment goals is focused this quarter on activating the additional 75 centers and boosting enrollment from existing centers.

Figure 1. Cumulative Site Recruitment Table as of January 16, 2020

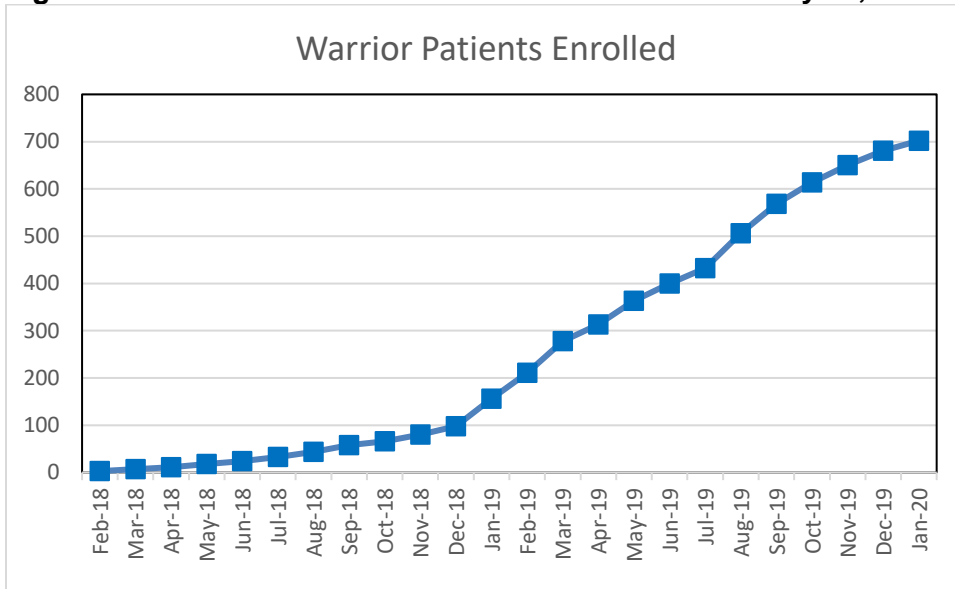
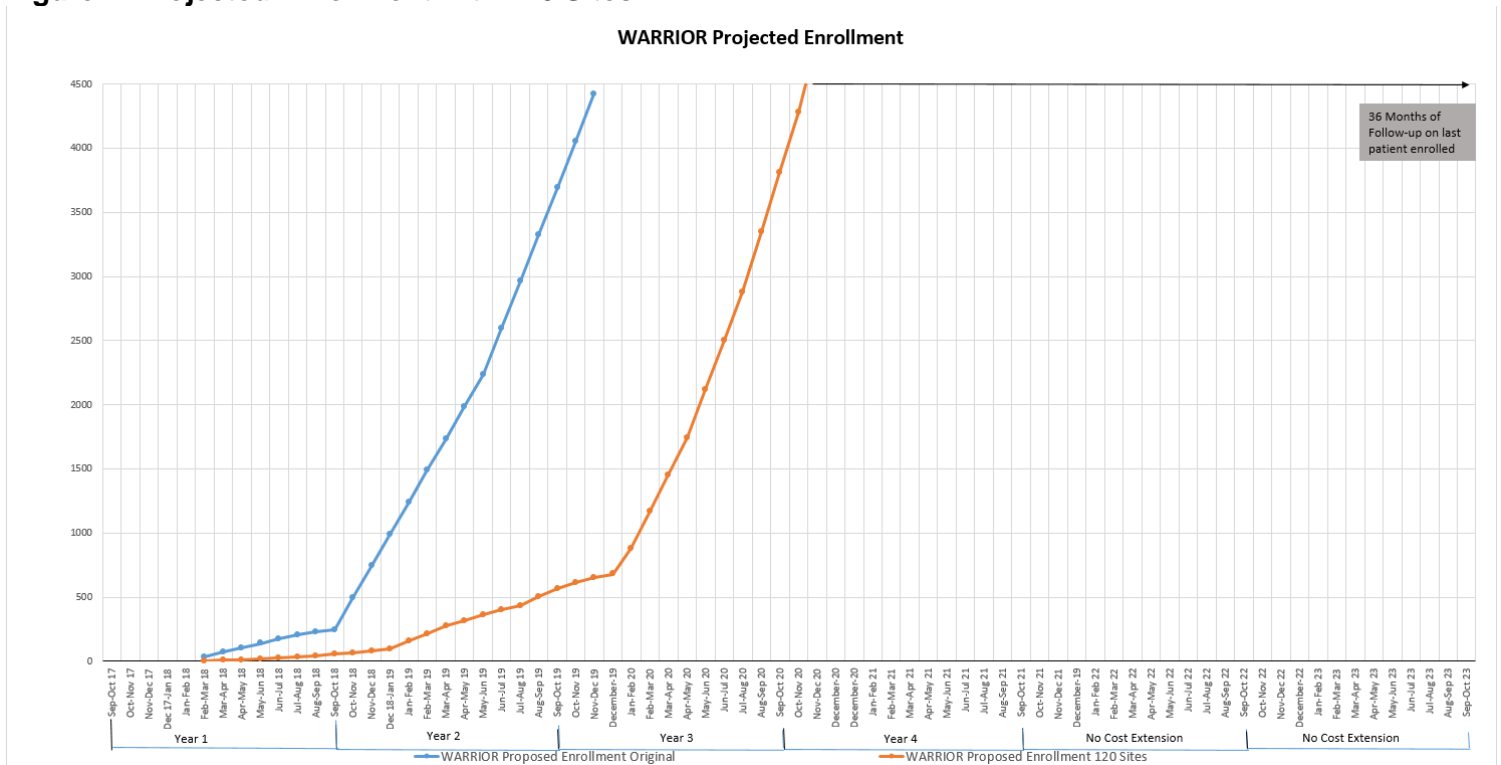


Figure 2 summarizes projected WARRIOR enrollment with 120 enrolling sites with the following assumptions: Logic for orange: all numbers through December 2019 are accurate. Cedars, LABioMed and UF will continue to recruit at the same rate and the rest of the sites will randomize 20 women in 4 months. We would need to have 60 sites by March 2020, 80 by June 2020, 100 by September 2020 and 120 by November 2020. This puts us at 4837 randomizations by December 2020. While the slope is steep, the inflection point is anticipated to occur after the coordinator meeting in 3 weeks. The DCC feels that reassessing enrollment in 4-6 months after a significant addition of sites is accomplished, will allow for a more accurate assessment of patient accrual.

Figure 2. Projected Enrollment with 120 Sites



APPENDIX D. 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				

Projected Quarterly Enrollment

Quarterly recruitment is currently divided based on the following assumptions of 50 sites from the three sources outlined below. Final numbers per group will be determined during site feasibility assessment:

There are 3 VA's who have agreed to participate; Gainesville, Tampa and Orlando. It is anticipated that a CRADA will be established with the Gainesville VA NFRE as lead site. Contacts are pending with Puerto Rico, Bay Pines, West Palm Beach and Miami.

There are 3 potential ADMMF's in Florida being contacted: Jacksonville NAS, Pensacola NAS, MacDill AFB. Contacts are pending with Walter Reed, San Diego NAS, Portsmouth, San Antonio.

OneFlorida Clinical Sites are being screened currently and it is estimated that 40+ sites will be from that Consortium.

Recruitment numbers are clustered by consortium based on enrollment of 88 per site over 15 months.

Original Projected Quarterly Enrollment

	Year 1				Year 2				Total
Target Enrollment Per Quarter	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	
ONF (n=43)		640	640	640	941	941			3802
VAC (n=4)		60	60	60	87	87			354
ADMMF (n=3)		45	45	45	66	65			266
Target Enrollment Cumulative		745	745	745	1094	1093			4422