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

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**Gainesville, FL 32611**

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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 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 patients 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 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 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 patients and follow these women for up to three years to assess adverse outcomes.

## 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 **second year (period 2) 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 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 12.0.**

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 on December 12th, 2017
    - -[PROTOCOL READY FOR ENROLLMENT]
- 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**
- **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**

**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 12.0. **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. A detailed accounting of coordinating center activity to achieve site recruitment and patient enrollment follows.**

**Table 1 summarizes site activation activities over the past year. The UF DCC continues to solicit potential sites. Over the past year 103 additional sites have been contacted and CDA's sent. Of the total 389 potential sites contacted, 110 CDA's have been executed which starts the feasibility assessment for both the site and the DCC. Forty (40) sites have fully executed contracts and 26 are in active negotiations, which would exceed the original goal of 50 sites. That site goal was previously reported to be too low to meet recruitment goals in a timely manner and at new total of 75 sites were projected in the last quarterly progress report. As discussed below, anticipated site enrollment is now being increased to 100-125 sites.**

**Table 1 Summary of Cumulative Site Activation Activities**

| | 9/15/17-10/30/18 | 10/31/18-10/14/19 | Total for Year 2 |
|---|---|---|---|
| **Sites Contacted** | **286** | **443** | **157** |
| **Sites Interested in Participating/CDA Sent** | 155 | 309 | 154 |
| **Site CDAs Completed/Returned to DCC** | 52 | 120 | 68 |
| **Site Contracting Completed/Fully Executed** | 17 | 41 | 24 |
| **Site Contracts in Negotiation** | 50 | 26 | 24 |
| **Sites Approved by UF IRB** | 19 | 37 | 18 |
| **Sites Approved by HRPO** | 13 | 29 | 16 |
| **Sites Activated for Enrollment** | 13 | **27** | 14 |
| **Total Patients Enrolled** | 76 | **590** | **514** |

**Summary of patient enrollment and site activities in past year: A total of 514 women subjects have been enrolled during the past past year; ~ an 8 fold increase over the previous year. They are from 27 actively enrolling sites; a >2 fold increase over the previous year.**

**As detailed in original proposal, this project planned to also reach women who were active duty military, retired military, and military dependents in addition to those in the general population. During year 2, the DCC has successfully subcontracted with the Geneva Foundation, and received approval for 5 active duty military sites. Pensacola and Jacksonville Naval Air Stations are actively recruiting. Walter Reed, Tripler and Brookes Army Medical Centers are currently undergoing IRB processing. Additionally, two of three planned VA Medical Centers in FL/Puerto Rico are approved and enrolling. Table 2 summarizes details.**

**Table 2. Military and VA Site Status**

| LOCATION | P.I. | STATUS |
|---|---|---|
| Pensacola NAS | Dr. Gray | Enrolling as of 6/13/19 |
| Jacksonville NAS | Dr. Volk | Enrolling as of 6/13/19 |
| Walter Reed | Dr. Weber | Under eIRB review |
| BAMC | Dr. Thomas | Contracted, IAIR signed-working on eIRB submission for approval |
| TAMC | Dr. Fuentes | Contracted, IAIR signed-working on eIRB submission for approval |
| Ft. Belvoir | Dr. Crimm | Withdrawn due to PI staffing shortage |
| San Diego NAS | Contacted | Withdrawn due to time constraints |
| Puerto Rico VA | Dr. Vincenti | Enrolling as of 7/29/19 |
| Gainesville VA | Dr. Schmalfuss | Enrolling as of 7/19/2019 |
| Tampa VA | Dr. Leonelli | Actively working on IRB and R&D approval |

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:**

Details for individual site status for recruitment and activation are summarized in **APPENDIX A.**

**Due to contracting and IRB/HRPO approval delays and, slow enrollment at a majority of centers, the UF DCC has continued to focus efforts in four areas over the previous year to increase site/participant enrollment; 1) identification of additional interested sites, 2) continued efforts to reduce delays in contracting and regulatory approvals; 3) provide marketing and referral sources of potential participants to active sites; 4) incentivize centers with increased reimbursement for rapid enrollment of participants. These efforts are discussed below and items 3 and 4 are discussed under Major Task 9.**

**1) Identification of additional sites**

**Based on slow enrollment the Executive Committee (EC) conducted an internal analysis proposed expansion to 75 sites in the last quarterly report. Data were provided to demonstrate the continued feasibility of achieving study endpoints with the use of at least one no cost extension and this was discussed with the project officer. Based on additional recruitment results in the last quarter, and feedback from the September 24, 2019 DSMB meeting, the EC reached a decision to expand the number of sites to 100-125 in order to speed up study recruitment. After analyzing site activities, it is apparent that many sites have 20-30 women who meet enrollment criteria, are in their clinics and easy to enroll over a ~3-6 month period. Enrollment beyond that has proven to be more labor intensive and slower. By expanding to 125+ sites, we project that with ~100 sites enrolling 25-30 women per site will yield approximately 3,000 subjects, added to the current enrollment of 590 women and about 10% of sites enrolling 30-200 subjects will allow WARRIOR to enroll the originally planned sample size of 4,422. Additional sites are now being contacted for participation. Projections for participant accrual and follow up are provided in Major Task 9.**

**1.1) Previous site initiatives:**

**1.1.1) The previously reported pilot utilizing the Emergency Department as a recruitment arm at the UF site was delayed due to IRB annual renewal delays. IRB approval for that site was finally granted on 10/5/19, and has been submitted to HRPO. Evaluation of this effort will take place in the upcoming quarter.**

**1.1.2) Contact has been made with the NIH funded SIREN (Strategies to Innovate Emergency Care Clinical Trials Network) PI at UF to investigate the possibility of including emergency room department PI's at SIREN centers as WARRIOR sites or recruitment supplements for existing centers. This is opportunity remains under investigation and results expected in the first quarter of year 3.**

**1.1.3) The DCC is contacting the 800+ US investigators who participated in the INVEST Trial to assess interest/ability to participate in WARRIOR. These sites were able to enroll 22,535 patients with cardiovascular disease: women comprised 50% of that trial enrollees. Initial contacts are focused on southeast US, where there was a large concentration of sites.**

**1.1.4) 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, that has 20 potential sites. To date, 5 centers have completed CDA's and are entering contracting/regulatory processing.**

**2.) Reducing delays in contracting and regulatory approvals**

**2.1) Delays in site activation**

**As reported in the year report and quarterly reports for year 2, there continue to be delays in site activation. Delays 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 2 are summarized below.**

**2.1.1) Contracting**

**As reported previously, a vendor agreement mechanism was established which has streamlined the processing of applications. Currently delays in contracting are a result of sites requesting larger budgets than proposed, delays in sites providing necessary documents and getting agreements signed. Larger practices/institution processing times vary from 2 weeks to 6 months.**

**Startup funding and per patient fees have been modified providing incentives to rapidly complete documents, and initiate enrollment. This strategy has been effective for smaller centers. Sites with extended processing times are being removed from site selection if contracting has not been completed in the previous 6 months in order to focus DCC effort on approaching and activating more sites with higher potential to be activated in 30-60 days.**

**2.1.2) Regulatory approvals**

**Each investigator requires Central UF IRB approval (or local IRB approval), and DoD HRPO approval. During Year 1, there were issues with delays in HRPO approvals which were resolved, delays with SMART IRB which also have been resolved. Issues continue with site familiarity attempting to use a Single IRB process and this has delayed completion of regulatory documents for many submissions. The UF IRB has been very responsive to processing issues and continues to work with the WARRIOR DCC to streamline processes (internal and external with sites).**

**Extensive "one-on-one" SMART IRB education and training by the DCC staff has been required and the UF IRB and DCC have required multiple conference calls with local IRBs to local resolve SMART IRB process issues.**

**During the previous quarter, the protocol was revised to permit reimbursement of coronary CT angiograms for women who otherwise meet study criteria. Processing of this revision required 9 weeks to get approval and since sites are approved as a revision process, there are 8 sites who were IRB approved after a 9 week delay. They have been submitted for HRPO approval, which takes an additional ~2-3 weeks.**

**This has delayed adding new sites for IRB review and there are 5-9 sites with completed paperwork submitted this week.**

**Processing of 100 new sites will require additional FTE effort and staff (Jill Boswell) has been added to facilitate this additional effort. Funding for this was shifted from other areas.**

**HRPO staff have recently changed, and there is not a single contact for WARRIOR site approvals and delays have been noted in the last 3-4 weeks. Another call is scheduled with HRPO to review processing with newly assigned staff to avoid delays.**

**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 the second year, the third Investigator meeting was held November 2018 in New Orleans during the American Heart Association Annual Scientific Sessions. The last Steering Committee was held by teleconference on October 1, 2019 with all members who could attend the call. Progress of the trial was reviewed, findings from the latest DSMB meeting were discussed. These meetings were within the SOW timeline. The next "face to face" meeting will be held on November 16, 2019 in Philadelphia, PA during the American Heart Association Annual Scientific Sessions for all investigators and Steering Committee members attending the AHA meeting**. ***[Ongoing, within SOW projections]***

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

**All sub-tasks are ongoing. During year 2, 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.** ***[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.govNCT 03417388. 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 other 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.** Subject recruitment began with randomization at the UF vanguard site on February 9th. As of 10/15/19 a total 590 subjects have been randomized to the project from 27 of 29 activated sites. One activated site has been closed due to lack of enrollment; a second activated site is pending finalization of external pharmacy contracting.

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. The DCC has implemented the Clinical Helpline for sites. ***[Ongoing, within SOW projections]***

Subtask: Recruitment of Participants-

Recruitment of participants is behind the original anticipated enrollment due to much slower enrollment from activated sites and slower than expected contracting and site activation that was detailed in last year's annual report and subsequent quarterly progress reports. As discussed above, based on assessment of site performance over the previous year, and discussions with the DSMB the DCC has revised recruitment goals based on the following assumptions:

- IRB and HRPO processing issues have been addressed barring any unexpected issues
- Contracting has been streamlined and incentives have improved site performance
- A limited number of sites (~20%) will over perform i.e. > 90 participants
- A majority of sites are able to identify 20-30 women who are easily identified and available
- to be recruited with minimal coordinator effort and can be enrolled in 2-4 months of site activation
- Increasing the number of sites activated to 100-125+ by activating on average 20 sites every 2-3 months will provide the bolus of participants needed to enroll 4,422 women by October/November 2020
- As noted in Table 1, there are currently 120 signed CDA's with additional sites being contacted daily
- These enrollment projections account for 1-15% of sites to be low (1-10 participant) enrollers

This revision of projected enrollment will allow for follow up of 36 months of the last enrolled participant to be completed during the beginning to middle of a second no cost extension. The need for a second no cost extension has been discussed with the Project Officer and it is understood that an initial no-cost extension is part of the original contract and that given adequate progress, compliance with reporting requirements and feasibility of achieving project outcomes, there is high likelihood of DoD approval. This was also discussed with the DSMB who agreed with the current plan.

**Major Task #10** – Site Monitoring**: [Months1-48]**
**All sub-tasks are ongoing.** The site monitoring guide and training plan are ongoing. The DACC will oversee site monitoring. ***[Ongoing, within SOW projections]***

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

**All sub-tasks are ongoing.** Vendor audits are occurring as needed. **The DCC has weekly conference calls with Cedars Sinai (statistical core), LA BioMed (CT recruitment center and Core Lab), Geneva Foundation (military site CRO), Community Health IT (consortium of practice sites), BEAWARRIOR (UF Biorepository), 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. The complete report is provided in APPENDIX C and includes the status of recruitment for each activated site, processing status of all contact sites. After their review, no safety concerns were identified. The independent research monitor responded that she has not been contacted by any participant regarding safety or other concerns.** ***[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. The most recent DSMB meeting reviewed adverse events both adjudicated and nonadjudicated.** ***[Ongoing, within SOW projections]***

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

**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 next SC meeting be held in-person just prior to the American Heart Association Scientific Sessions November 15, 2019 in Philadelphia PA. Other committees will be organized and attended as needed. 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. Eight of the 27 active sites have sent samples on 284 patients, all have been processed, and stored (frozen). This has yielded 828 aliquots of plasma, 824 aliquots of samples for metabolomics and 1096 buffy coat aliquots. In the original proposal the Biorepository was funded from DoD for sample collection but not for sample processing and storage. The McJunkin Family Foundation has continued to provide financial resources during two funding cycles for a total of $390,000.00. This has permitted initial sample analysis. Pilot data have been generated and are supplied in APPENDIX C. for studies to be conducted on blood samples collected in the biorepository.**

**The Biorepository IRB underwent annual review and no issues were identified. Key Personnel will be changing as Dr. Cogle has been reassigned to other research and clinical activities. Dr. Keith March will become the Biorepository PI in November.**

**An NHLBI Ancillary Studies R01 application was submitted to provide additional funding for mechanistic studies related to the randomized treatment groups and study outcomes. That application was reviewed and scored but not funded. Accordingly, it was revised to address the reviewer's comments and recommendations and was resubmitted and did not achieve a fundable score, but it was then resubmitted to the AHA and is under review.**

**During the next quarter all currently active sites will be on boarded so that samples will be available for all participants.** ***[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) has been created and a charter and analysis plan has been finalized. The DSMB met on October 17th, 2018. They received an interim update on June 6, 2019. They held there second full meeting on September 24, 2019. They recommended that the study continue, as planned with a continue focus on rapid recruitment of sites and participants. A copy of the DSMB report open minutes was sent to the Project Officer and the DSMB recommendations have been provided in APPENDIX D. 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 the EC will also function as the Publication Committee. It was agreed that the initial manuscript will include the rationale and design for the project, and it will be submitted to the American Heart Journal. Additional ideas for proposed publications are being collected and the publication schedule is a standing agenda item during EC meetings. 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 2** annual reporting period the WARRIOR trial grant proposal **has continued to recruit study sites and participants** to address the specific aims of this clinical trial. Specifically, 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. There are no major outcomes, findings or conclusions available related to the specific aims.

WARRIOR has successfully recruited and activated 29 sites and to date has enrolled 584 women into the trial. Recruitment of sites and participants is behind 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 relatively easy in terms of protocol finalization, IRB/HRPO approval and completing the eCRF's. Identifying community-based practices to participate in clinical research efforts has yielded 443 potential sites, many are interested but do not have the research infrastructure to carry out the trial. For large sites capable of high enrollment, the DCC has implemented a plan of providing coordinator support from the DCC to staff the practice. This has resulted in successful enrollments from two military facilities and one large health system in Florida.

The regulatory paperwork necessary to activate clinical sites remains problematic with regards to its volume and complexity for busy practices but our efforts to provide data coordinating center support, trial design to utilize centralized IRB, pharmacy distribution, web-based data management

systems have assisted in site processing, setting up the WARRIOR trial sites as a consortium of investigators that can be deployed for projects beyond this trial. There continue to be unanticipated delays in IRB/HRPO processing that are addressed and resolved as they occur but have resulted in a total of 12 weeks of "down time" where additional investigators were not able to be processed through the IRB. A backlog of sites is now undergoing review which will reach our original goal of 50 enrolling sites by the end of this month. The additional 50-75 sites to reach our revised site goal of 100-125 are now being contacted as reported in the body of the report.

As reported in last year's annual report, pragmatic trials by their nature are lower per patient reimbursement, but site familiarity with larger industry-funded clinical trials enforces a negative regard for more streamlined, lean budget federally funded pragmatic trials. Accordingly, financial incentives have been implemented to accelerate contract and regulatory document processing, as well as to motivate recruitment, yet still maintain within the awarded budget. Current savings on pharmacy expenses and staffing are realizing cost savings that are being utilized for these incentives. This has been successful at some centers. This strategy will be redeployed when the additional 25+ sites are activated.

As provided the revised recruitment projections summarized in Major Task #9 estimate that patient recruitment will be achieved by October/November 2020 utilizing 100-125 sites. Original site recruitment projections were 89 participants per site over 15 months. This is feasible as evidenced by performance at three of the centers, but the majority of sites have not been able to meet the expected 4 patients per month. Revised projections are based on 75% of sites enrolling 25-30 women per site over a 3-6 -month period.

We initiated several plans over the past year to provide additional patient referrals to sites by working with independent imaging centers and chest pain centers located in nearby hospitals to advertise the WARRIOR trial and create a stream of referrals. Utilizing social medial advertising, achieved minimal results. Radio advertising is being piloted, as well as electronic health record notification of the trial. These are both novel approaches to recruitment that has the potential to reach thousands of women who have had coronary CT angiograms for chest pain, or have chest pain symptoms that have not been follow up on. Increasing potential referrals to sites utilizing LABiomed's network of CTA Imaging Centers has been only minimally successful with the 27 initial sites. This approach is going to be reassessed as the next 15-20 sites are activated in the next 3-6 weeks. The impact of radio advertising is being tested in a major metropolitan area with multiple sites.

In addition, after reviewing the barriers to enrollment at the screening practices, the protocol has been revised to enhance recruitment without compromising the aims of the project. Specifically, funded has been provided for coronary CTA's for women who are consented and only require documentation of non obstructive CAD. There have been ~10 patients who are being enrolled via this mechanism, after only 3 weeks of having this protocol amendment approved.

Historically in large scale clinical trials, recruitment increases after investigator/coordinator meetings and success of clinical trials is dependent on study coordinator performance. A 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.

**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. Social media, direct mail, radio advertising are being utilized to inform potential participants of the trial.

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

Activation of an additional 50+ WARRIOR sites for a total of 100-125.
Meet our revised quarterly recruitment goals.
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. No significant changes have been made to the project that would affect the goals/specific aims of the original proposal.

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

Delays in contracting, IRB/HRPO approvals in order to begin 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**

October 22, 2018
Carl J. Pepine, M.D.
Microvascular Disease in Women
Division of Cardiology Prevention Conference
Gainesville, FL

October 27, 2018
Carl J. Pepine, M.D.
"Coronary Microvascular Dysfunction in Women: Is it a pre HFpEF syndrome?"
Ohio – ACC 28th Annual Meeting & 7th Annual Richard Lewis Memorial Lecture
Columbus, OH

November 10, 2018
Carl J. Pepine, M.D.
AHA Scientific Sessions
"MI with Non-Obstructive CAD"
that included information about
WARRIOR
Chicago, IL

February 9, 2019
Carl J. Pepine, M.D.
2019 Lakeland Regional Hospital CV Symposium
"Strategies for Managing Resistant Hypertension: 2019 Update-
and WARRIOR update
Lakeland, FL

March 18, 2019
Carl J. Pepine, M.D.
ACC Scientific Sessions
Co-Chair – "Refractory Angina: Options for Patients With "No Options"
New Orleans, LA

May 1, 2019
Carl J. Pepine, M.D.
55th Annual Cardiovascular Symposium
"Evolving Concepts in HTN: Implications of Three Guideline Recommendations in Three Years"
Hartford, CT

June 24 - 25, 2019 (as part of the C3 Summit)
Carl J. Pepine, M.D.
"Lessons Learned in Coronary Artery Disease in Women"
"What Constitutes Optimal Medical Therapy in Stable Angina?"
Orlando, FL – Hilton Bonnet Creek

September 4, 2019
Carl J. Pepine, M.D.
Paris, France
"Is Cognitive Impairment the Brain's Version of Microvascular Angina? If So, What Can We Learn? (SPRINT MIND & INFINITY Trials)
7th Annual COVADIS Summit

September 27, 2019
Carl J. Pepine, M.D.
NYU Langone Health – Cardiology Grand Rounds and Visiting Professorship

November 10, 2018
Noel Bairey Merz, MD
Sex-Specific Outcomes for Commonly Used Risk Stratification Scores, AHA Scientific Sessions 2018
Chicago, IL

November 16, 2018
Noel Bairey Merz, MD
Introduction and Overview – Can Inclusion of Women Improve Men's Health, Controversies and Advances in the Treatment of Cardiovascular Disease – The Eighteenth in the Series
Los Angeles, CA

November 17, 2018
Noel Bairey Merz, MD
Gender Issues in the Management of Ischemic Heart Disease, Trends in Cardiovascular Medicine for Primary Care
Olympic Valley CA

November 29, 2018
Noel Bairey Merz, MD
Cardiovascular Disease in Women: Update 2018, 8th Annual Diagnostic & Therapeutic Modalities in Heart Failure Symposium
Big Island, Hawaii

January 8, 2019
Noel Bairey Merz, MD
Women's Health Talk, Mary Aggarwal Tea
Los Angeles, CA

January 18, 2019
Noel Bairey Merz, MD
Ischemia with No Obstructive CAD (INOCA): Fact or Fiction, Advances in Nuclear Cardiology, Cardiac CT and Cardiac MRI: 34$^{th}$ Annual Case Review with the Experts, Los Angeles, California

February 9, 2019
Noel Bairey Merz, MD Women's Heart Health: What You Need to Know, WDS Forum, Dallas, Texas

February 19, 2019
Noel Bairey Merz, MD
Update in Ischemic Heart Disease in Women: Monet vs Manet (Or why women have more adverse IHD outcomes), University of Illinois, Chicago, Hospital & Health Sciences System Medicine Grand Rounds
Chicago, Illinois

February 19, 2019
Noel Bairey Merz, MD Cardiovascular Disease in Women, Rambam Foundation Cardiology Innovation Symposium
New York, NY

February 28, 2019
Noel Bairey Merz, MD
Women's Heart Health, Little Company of Mary Medical Staff Meeting
Torrance, CA

March 1, 2109
Noel Bairey Merz, MD
Keynote Lecture – Women's Heart Disease, 15th Annual Biomarkers in Heart Failure and Acute Coronary Syndromes Diagnosis, Treatment and Devices
La Jolla, CA

March 8, 2019.
Noel Bairey Merz, MD
Women & Ischemic Heart Disease: Why Women Have More Adverse Outcomes, University of Utah, Division of Cardiovascular Medicine Grand Rounds
Salt Lake City, Utah

March 18, 2019
Noel Bairey Merz, MD
Treatment of INOCA; Empiric Clinical Therapy Versus Hard Data, ACC 68th Annual Scientific Session
New Orleans, LA

March 28, 2019
Noel Bairey Merz, MD
Coronary Microvascular Dysfunction and Heart Failure with Preserved Ejection Fraction: Why Women? University Hospitals Harrington Heart & Vascular Institute Grand Rounds, Harrington, PA

April 5, 2019
Noel Bairey Merz, MD
Female-pattern Ischemic Heart Disease: Monet vs Manet (or why women have more adverse IHD outcomes), RUSH University Cardiology Grand Rounds, Chicago, IL

April 12, 2019.
Noel Bairey Merz, MD
Cardiovascular Disease in Women, American College of Physicians
Philadelphia, PA

April 26, 2019.
Noel Bairey Merz, MD
Women and Ischemic Heart Disease: Monet vs Manet (or why women have more adverse outcomes), Grand Rounds at the Gagnon Cardiovascular Institute at Morristown Medical Center, Morristown, NJ

April 26, 2019.
Noel Bairey Merz, MD
Keynote Address, Heart To Heart Foundation – A Frank Discussion About Women's Heart Health for the Morristown Medical Center
Morristown, NJ

May 1, 2019.
Noel Bairey Merz, MD
Female-Pattern Ischemic Heart Disease: Monet vs Manet (or Why Women Have More Adverse Outcomes), Weill Cornell Medicine DOM Grand Rounds, NY, NY

May 2, 2019.
Noel Bairey Merz, MD
Women and Heart Disease – What You Need to Know, UCSF 2019 Heart Healthy Strategies
San Francisco, CA,

May 4, 2019.
Noel Bairey Merz, MD
Women and Heart Disease Microvascular Syndrome, EPICSEC Emory Practical Intervention Course
Atlanta, Georgia

May 7, 2019.
Noel Bairey Merz, MD
Sex differences in heart disease in T2D. OSSD 2019 2nd Joint OSSD/IGM Meeting, Washington, DC

May 29, 2019.
Noel Bairey Merz, MD Gender Bias in Biomedical Research/Female-Pattern Heart Disease, EMBL-EBI Science & Society Symposium at Cambridge
Cambridge, England,

June 3, 2019
Noel Bairey Merz, MD
How Gender Bias in Cardiovascular Disease Impacts Women's Lives and What We Can Do About It, University of Best Practices Summit – 5th Annual Heart Attack and Stroke Free Zone
La Jolla, California

July 23, 2019
Noel Bairey Merz, MD
Women's Healthcare Issues. Medical Education Speakers Network Lecture, Emanate Health Inter-Community Hospital
Covina, CA

September 3, 2019
Noel Bairey Merz, MD
Burden of Ischemic Heart Disease in Women: Focus on Sex-Specific Coronary Pathophysiology –Session Chair. ESC Congress
Paris, France

September 5, 2019
Noel Bairey Merz, MD
Women and Ischemic Heart Disease. Torsdagsakademin Guest Lecture, Karolinska Institute
Stockholm, Sweden

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

- **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: | 2 |
| Contribution to Project: | Dr. Cooper-DeHoff oversees pharmacy operations for WARRIOR. |
| Funding Support: | NA |

| | |
|---|---|
| **Name:** | **Tiago Bember Simeao** |
| Project Role: | Data Systems Analyst |
| Researcher Identifier (e.g. ORCID ID): | |
| Nearest person month worked: | 4 |
| Contribution to Project: | Mr. Bember Simeao is one of three staff that handle the REDCAP data system for WARRIOR. |
| Funding Support: | NA |

| | |
|---|---|
| **Name:** | **Philip Chase** |
| Project Role: | Data Systems Manager |
| Researcher Identifier (e.g. ORCID ID): | |
| Nearest person month worked: | 2 |
| Contribution to Project: | Mr. Chase manages the data systems team for WARRIOR. |
| Funding Support: | NA |

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

| | |
|---|---|
| **Name:** | **Monroe Crews** |
| Project Role: | Financial Coordinator |
| Researcher Identifier (e.g. ORCID ID): | |
| Nearest person month worked: | 1 |
| Contribution to Project: | Mr. Crews handles payment of expenses for WARRIOR. |
| Funding Support: | Mr. Crews' funding comes from internal unrestricted research funds. |

| | |
|---|---|
| **Name:** | **Dana Leach** |
| Project Role: | Project Manager |
| Researcher Identifier (e.g. ORCID ID): | |
| Nearest person month worked: | 7 |
| Contribution to Project: | Ms. Leach began as the project manager in July 2018 and is responsible for daily management of the WARRIOR trial. |
| Funding Support: | NA |

| | |
|---|---|
| **Name:** | **Marc Graslely** |
| Project Role: | Contracting Manager |
| Researcher Identifier (e.g. ORCID ID): | |
| Nearest person month worked: | 1 |
| Contribution to Project: | Mr. Graslely assisted in developing the contracting procedure for WARRIOR in the first six months and handles the processing of CRADAs. |
| Funding Support: | Mr. Graslely's funding comes from internal unrestricted research funds. |

| | |
|---|---|
| **Name:** | **Taylor Galloway** |
| Project Role: | New Site/Marketing Coordinator |
| Researcher Identifier (e.g. ORCID ID): | |
| Nearest person month worked: | 2 |
| Contribution to Project: | Ms. Galloway joined the team in July 2018 does marketing and new site initiations for WARRIOR. |
| Funding Support: | NA |

| | |
|---|---|
| **Name:** | **Debra Landers** |
| Project Role: | Regulatory Coordinator |
| Researcher Identifier (e.g. ORCID ID): | |
| Nearest person month worked: | 10 |
| Contribution to Project: | Ms. Landers assists new sites with IRB submission and other regulatory requirements for WARRIOR. |
| Funding Support: | NA |

| | |
|---|---|
| **Name:** | **Jill Boswell** |
| Project Role: | Regulatory Coordinator |
| Researcher Identifier (e.g. ORCID ID): | |
| Nearest person month worked: | 6 |
| Contribution to Project: | Ms. Boswell assists new sites with IRB submission and other regulatory requirements for WARRIOR. |
| Funding Support: | NA |

| | |
|---|---|
| **Name:** | **Robert Raske** |
| Project Role: | Contract Coordinator |
| Researcher Identifier (e.g. ORCID ID): | |
| Nearest person month worked: | 4 |
| Contribution to Project: | Mr. Raske joined the team in May 2018 and contacts potential new sites and processes new site contracts for WARRIOR. |
| Funding Support: | NA |

**Name:** **Taryn Stoffs**
Project Role: Data Systems Analyst
Researcher Identifier (e.g. ORCID ID):
Nearest person month worked: 2
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
Nearest person month worked: 1
Contribution to Project: Dr. Bairey Merz was responsible for protocol development and writing, identified/screened potential study investigators, investigator communications, chair / host / organize all Executive / steering / operation / publication meetings, monitored compliance with medical therapy, reviewed AE/SAEs, negotiated agreements with executive committee and steering committee members, selected DSMB members, developed DSMB analysis plan, attended DSBM meeting
Funding Support: NA

**Name:** **Galen Cook-Wiens**
Project Role: Data Manager
Researcher Identifier (e.g. ORCID ID):
Nearest person month worked: 2
Contribution to Project: Mr. Galen Cook-Wiens generated data reports and coordinated data management and communications with primary institution.
Funding Support: N/A

**Name: Reddysailaja Marpuri**
Project Role: Data Coordinator
Researcher Identifier (e.g. ORCID ID):
Nearest person month worked: 1
Contribution to Project: Ms. Reddysailaja Marpuri coordinated data entry, data clean, and data transfer and data management. She also assisted with development of data collection instruments.
Funding Support: N/A

| | |
|---|---|
| **Name:** | **Kyler Conn** |
| Project Role: | Executive Secretary |
| Researcher Identifier (e.g. ORCID ID): | |
| Nearest person month worked: | 10 |
| Contribution to Project: | Ms. 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 |

**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 |

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

Nothing to report.

**What other organizations were involved as partners?**

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

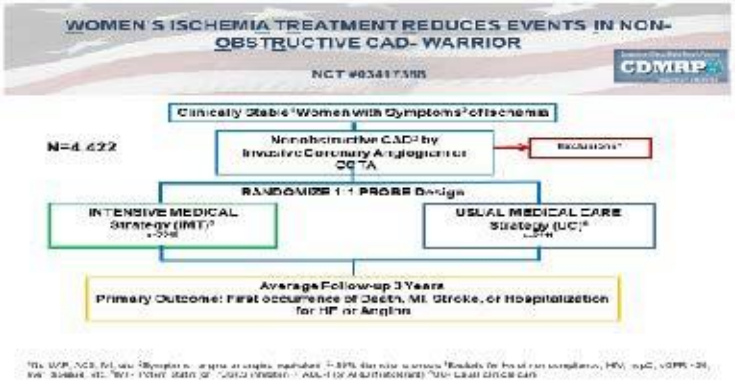
**PI:** Carl J. Pepine, MD **Org:** University of Florida **Award Amount:** $14,915,728.

### 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.

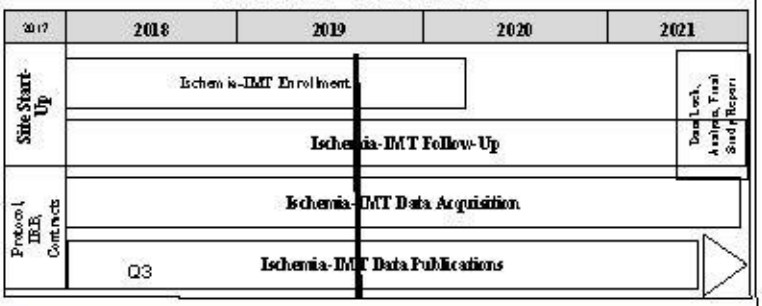
### Approach

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.




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 |

**Updated: 10/15/19**

### 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
☐ 590/4,422 subjects enrolled
☐ Subject Follow-up
**CY21 Goal** – Subject Follow
Subject Completion and Analysis/Reporting

**Comments/Challenges/Issues/Concerns**
delays related to initiating contracts/IRB approvals/recruitment

| **Budget Expenditure to Date (9/30/19)** | **For Year 2** |
|---|---|
| Projected Expenditure: $8,192,875 | **$4,934,755** |
| Actual Expenditure: $2,909,342 | **$1,938,494** |

## 9. APPENDICES:

A. Subject Recruitment
B. Current Status of all Warrior Sites
C. DSMB Report 9/24/2019\
D. DSMB Recommendations
E. Scope of Work

## APPENDIX A. SUBJECT RECRUITMENT

**Table 1. WARRIOR Recruitment by Site as of 10/15/19**

| PI: Acrostic | Site Name | Location | Total # of Randomizations to Date |
|---|---|---|---|
| UF: WAR01-07 | University of Florida | Gainesville, FL | 202 |
| Bayron: WAR08 | Interventional Cardiac Consultants | Trinity, FL | 31 |
| Rayos: WAR09 | Daytona Heart Group | Daytona Beach, FL | 4 |
| Lambert: WAR11 | Pepin Heart Institute | Tampa, FL | 22 |
| Prashad: WAR12 | Ocala Research Institute | Ocala, FL | 24 |
| Galani: WAR13 | Baptist Health: Jacksonville | Jacksonville, FL | 14 |
| Shufelt: WAR14 | Cedars-Sinai | Los Angeles, CA | 122 |
| Einhorn: WAR15 | Orlando Health | Orlando, FL | 10 |
| Budoff: WAR16 | Los Angeles Biomedical Center | Torrance, CA | 91 |
| Cardenas: WAR17 | South Palm Cardiology | Delray Beach, FL | 2 |
| Wells: WAR18 | University of Kentucky | Lexington, KY | 6 |
| Volk: WAR19 | Naval Hospital Jacksonville | Jacksonville, FL | 1 |
| Gray: WAR20 | Naval Hospital Pensacola | Pensacola, FL | 4 |
| Hakki: WAR21 | Clearwater Cardiovascular Consultants | Clearwater, FL | 12 |
| Parilak: WAR22 | Silver State Cardiology | Las Vegas, NV | 31 |
| Widmer: WAR23 | Baylor Scott and White | Temple, TX | 9 |
| Skelding: WAR24 | Alabama Heart and Vascular | Tuscaloosa, AL | 0 |
| Schmalfuss: WAR26 | Gainesville VA | Gainesville, FL | 3 |
| Vicenty: WAR27 | Puerto Rico VA | San Juan, PR | 2 |
| De La Rosa: WAR28 | Southwest Florida Research Institute | Sarasota, FL | 0 |
| Shahawy: WAR29 | Cardiovascular Center of Sarasota | Naples, FL | 1 |
| | | | **Total:** 590 |

## APPENDIX B. CURRENT STATUS OF ALL WARRIOR SITES

**Table 1. WARRIOR Site Status: Active, Closed, Contracted/IRB/HRPO Processing as of 10/15/19**

| Site Name | IRB Approval | HRPO Approval | Notes | Status |
|---|---|---|---|---|
| WAR01: Anderson | Approved | Approved | | Active |
| WAR02: Lo | Approved | Approved | | Active |
| WAR03: Holland | Approved | Approved | | Active |
| WAR04: Wright | Approved | Approved | | Active |
| WAR05: Park | Approved | Approved | | Active |
| WAR06: Goede | Approved | Approved | | Active |
| WAR07: Maska | Approved | Approved | | Active |
| WAR08: Bayron | Approved | Approved | | Active |
| WAR09: Rayos | Approved | Approved | | Active |
| WAR10: Varela | Approved | Approved | | Deactivated |
| WAR11: Lambert | Approved | Approved | | Active |
| WAR12: Prashad | Approved | Approved | | Active |
| WAR13: Galani | Approved | Approved | | Active |
| WAR14: Shufelt | Approved | Approved | | Active |
| WAR15: Einhorn | Approved | Approved | | Active |
| WAR16: Budoff | Approved | Approved | | Active |
| WAR17: Cardenas | Approved | Approved | | Active |
| WAR18: Wells | Approved | Approved | | Active |
| WAR19: Volk | Approved | Approved | | Active |
| WAR20: Gray | Approved | Approved | | Active |
| WAR21: Hakki | Approved | Approved | | Active |
| WAR22: Parilak | Approved | Approved | | Active |
| WAR23: Widmer | Approved | Approved | | Active |
| WAR24: Skelding | Approved | Approved | | Active |
| WAR25: Rizvi | Approved | Approved | Pending Pharmacy | Pending |
| WAR26: Schmalfuss | Approved | Approved | | Active |
| WAR27: Vicenty | Approved | Approved | | Active |
| WAR28: Shahawy | Approved | Approved | | Active |
| WAR29: De La Rosa | Approved | Approved | | Active |
| WAR30: Aambati | Approved | Submitted | | Pending |
| WAR31: Kanmantha | Approved | Submitted | | Pending |
| WAR32: Dietz | Approved | Submitted | | Pending |
| WAR33: Farris | Approved | Submitted | | Pending |
| WAR34: Cole | Approved | Submitted | | Pending |
| WAR35: Pollack | Approved | Awaiting Documents | | Pending |
| | **Total Approved:** 35 | **Total Approved:** 29 | | **Total Active:** 27 |

**APPENDIX C. DSMB Report 9/24/2019**

**Women's IschemiA TRial to Reduce Events In Non-ObstRuctive CAD (WARRIOR) Trial Data and Safety Monitoring Board (DSMB) Report**

**September 18, 2019**

**DSMB Members:**

| | |
|---|---|
| Nanette K. Wenger, MD, MACC, MACP, FAHA (DSMB Chair) | *Cardiologist* |
| Harmony Reynolds, MD | *Cardiologist* |
| Viviany Taqueti, MD | *Cardiologist* |
| Kerry Lee, PhD | *Biostatistician* |
| Daniel Mark, MD | *Cardiologist* |

**Clinical and Data Coordinating Center (University of Florida):**

| | |
|---|---|
| Carl Pepine, MD, MACC | *Executive Committee* |
| Eileen Handberg, PhD, ARNP | *Executive Committee* |
| Rhonda Cooper-DeHoff, PharmD, MS, FAHA, FACC | *Executive Committee* |

**Biostatistics Core (Cedars-Sinai Medical Center) Investigators:**

| | |
|---|---|
| C. Noel Bairey Merz, MD, FACC, FAHA, FESC | *Executive Committee* |
| Andre Rogatko, PhD | *Executive Committee* |
| Janet Wei, MD, FACC, FAHA | *Executive Committee* |

**Table of Contents:**

5. **Baseline Demographics of Participants**
6. **Adverse Events**
7. **Contingency Planning**
8. **WARRIOR Biorepository**
9. **Appendices**
    a. Appendix A. Current Status of all WARRIOR Sites
    b. Appendix B. Baseline Demographics of Participants and Adverse Events
    c. Appendix C. DoD Project Officer Email for No-Cost Extension
    d. Appendix D. McJunkin

**Women's IschemiA TRial to Reduce Events In Non-ObstRuctive CAD (WARRIOR) Trial**
**Data and Safety Monitoring Board (DSMB) Report**

**Executive Summary**
**September 20, 2019**

**DSMB Report Logistics**

**Data Locked 9/1/19 for MACE, Adverse Event Reporting**
**Report submitted to DSMB 9/11/19**
**Updated report includes updated table 4 as requested, and updated appendices as requested.**

**WARRIOR Status 9/20/19**

- **Active enrolling sites-27**
- **Sites in active IRB/HRPO submission/review- 25**
- **Patient enrollment-547**

**DSMB Queries from 4/1/19 DSMB Meeting:**

1. Definition of escalation of therapy
    a. Escalation of therapy is defined as an increase in prevention medication (statin/ACE/ARB) dose, or addition of a prevention medication (statin/ACE/ARB), and/or addition or increase of antianginal therapy or scheduled for a PCI or CABG.
2. Geographic distribution with recruitment volume by site
    a. Provided in Table 4 in the main report
3. Low/Modest vs. high-intensity statin data
    a. Provided in Appendix B, Table 7
4. CT vs. Cath entry demographics
    a. Provided in Appendix B, Table 5
5. Cardiac vs. Non-cardiac in AE/SAE reporting
    a. Incorporated in to tables
6. Post-baseline smoking data
    a. Provided in Appendix B, Table 6

**Supplemental Data:**

- **Appendix B has been updated with DSMB data queries**

**Adjudicated/Unadjudicated MACE event summaries provided in Appendix B.**

## Section 1- Introduction

The WARRIOR Clinical and Data Coordinating Center (CDCC) efforts continue to be focused on: a) improving recruitment performance of activated sites; b) identifying new sources of potential participants; c) facilitating the processing of previously identified sites through contracting and IRB/HRPO approval; d) identification of additional sites to target ~70 enrolling sites, and e) monitoring data quality.

This report will summarize site recruitment over the course of the trial and update numbers since the DSMB interim report that was provided 6/13/19 with details for contact, contracting, and regulatory (IRB and HRPO) approvals in **Section 2.0**. **Section 3** will detail participant enrollment, impact of imaging center referrals, protocol modification to reimburse coronary CTA to document eligibility, and other strategies to enhance weekly randomizations. Revised projected time lines will be presented with impact on power. **Section 4** will summarize baseline demographics of participants. **Section 5** will present adverse events and MACE outcomes. **Section 6** will summarize BE-A-WARRIOR Biorepository efforts. **Section 7** will summarize NHBLI ancillary trial/and other grant submissions.

### a. Lessons Learned from WARRIOR

The concept of a pragmatic trial and the implementation in both academic and private practice groups is not as fluid as it has been conceived to be. While reimbursement for coordinator effort is reasonable and time/rate appropriate in WARRIOR and leaving PI reimbursement to reimbursement for clinically indicated office follow up, the model is not as widely adopted at many centers. Based on this, the trial has focused efforts on trying to streamline contracting (using a vendor system rather than the typical subcontract model), IRB approval using a central IRB to reduce site burden and this has worked well in some practice settings but has been continued to be a source of delays in others. Having a lack of well trained, motivated staff to do the clinical trial in an office setting continues to be a hurdle for some centers and assistance with screening and recruitment has been offered from the DCC for Florida based sites to moderate success. Weekly calls with sites has been necessary to educate coordinators as to the optimal screening and recruitment techniques i.e. cath lab and CTA logs from hospitals utilized by the practice. Because the site coordinator is generally the link to success for site recruitment, and historically recruitment significantly improves after an Investigator Meeting, plans are underway to hold a Coordinator focused Study meeting in early November once the next bolus of sites are activated in order to highlight successful sites, acknowledge best practices, and provide support to incoming sites/coordinators.

## Section 2- Site Activation

Table 1 summarizes site and participant recruitment activity over the course of the trial. Since this is a very dynamic process, these numbers will be updated the day of the DSMB call as there are currently 9 sites that are currently in IRB review and expected out this week and could be HRPO approved and ready for activation by the time of the meeting. With two additional waves of sites also being processed.

**Table 1. Summary of Cumulative Site Activation Activities as of 9/18/19**

| Sites Contacted | 12/31/18<br>286 | 3/25/19<br>331 | 6/13/19<br>358 | 9/18/19<br>386 |
|---|---|---|---|---|
| **Sites Interested in Participating/CDA Sent** | 155 | 200 | 227 | 255 |
| **Site CDAs Completed and Returned to DCC** | 52 | 68 | 94 | 110 |
| **Site Contracting Completed/Fully Executed** | 20 | 33 | 37 | 40 |
| **Site Contracts and IRB Still in Negotiation** | 46 | 26 | 35 | 25 |
| **UF IRB Sites Approved** | 19 | 23 | 25 | 29 |
| **Sites HRPO Approved** | 17 | 21 | 24 | 29 |
| **Sites Activated for Enrollment** | 16 | 21 | 23 | 27 |

Because of the funding agency (Department of Defense), the original protocol plan included recruitment of both Military and VA Medical Centers, a primary source of active duty, retired and military dependent women. Table 2 summarizes the status of this focused site recruitment. Recruitment is active in half of the nine sites who expressed interest in the trial.

**Table 2. WARRIOR Military/VA Medical Center Status**

| **LOCATION** | **P.I.** | **STATUS** |
|---|---|---|
| Pensacola NAS | Dr. Gray | Enrolling |
| Jacksonville NAS | Dr. Volk | Enrolling |
| Walter Reed | Dr. Weber | Under DSP Review |
| BAMC | Dr. Thomas | Contracted: eIRB submission in process |
| TAMC | Dr. Fuentes | Contracted: eIRB submission in process |
| Ft. Belvoir | Dr. Crimm | Withdrawn due to staffing shortage |
| Puerto Rico VA | Dr. Vincenti | Enrolling |
| Gainesville VA | Dr. Schmalfuss | Enrolling |
| Tampa VA | Dr. Leonelli | Consent under review |

There are 8 sites undergoing IRB review that will clear IRB this week, with 4 sites ready for submission once these sites clear IRB. This will bring site enrollment numbers to 39 by the end of September. An additional 25 sites are completing contracting/regulatory document submission to the DCC, which would result in 64 active sites. The Community Health IT collaboration detailed below, has been projected to yield an additional 20 sites.

Revised projections for site activations reported at the DSMB interim update were delayed for 6 weeks due to delays in IRB annual approval due to the modification of the protocol to allow for reimbursement of coronary CTA for otherwise eligible women. This modification required revision of all sites consents and updated vendor contracting. This has been completed and all current sites have an updated protocol/consent/contract and all new sites will operate under this protocol version.

All of the sites are summarized in Appendix A. Enrollment of out-of-state sites continues and independent pharmacies are being contracted to provide intensive medical treatment (IMT) medications to patients. The geographic distribution of sites (active and pending) is shown in Figure 1 and as requested, geographic location has been added to **Table 4.**

**Table 3. WARRIOR Site Status: Active, Closed, Contracted/IRB/HRPO Processing as of 9/18/19**

| Site Name | IRB Approval | HRPO Approval | Notes | Status |
|---|---|---|---|---|
| WAR01: Anderson | Approved | Approved | | Active |
| WAR02: Lo | Approved | Approved | | Active |
| WAR03: Holland | Approved | Approved | | Active |
| WAR04: Wright | Approved | Approved | | Active |
| WAR05: Park | Approved | Approved | | Active |
| WAR06: Goede | Approved | Approved | | Active |
| WAR07: Maska | Approved | Approved | | Active |
| WAR08: Bayron | Approved | Approved | | Active |
| WAR09: Rayos | Approved | Approved | | Active |
| WAR10: Varela | Approved | Approved | | Deactivated |
| WAR11: Lambert | Approved | Approved | | Active |
| WAR12: Prashad | Approved | Approved | | Active |
| WAR13: Galani | Approved | Approved | | Active |
| WAR14: Shufelt | Approved | Approved | | Active |
| WAR15: Einhorn | Approved | Approved | | Active |
| WAR16: Budoff | Approved | Approved | | Active |
| WAR17: Cardenas | Approved | Approved | | Active |
| WAR18: Wells | Approved | Approved | | Active |
| WAR19: Volk | Approved | Approved | | Active |
| WAR20: Gray | Approved | Approved | | Active |
| WAR21: Hakki | Approved | Approved | | Active |
| WAR22: Parilak | Approved | Approved | | Active |
| WAR23: Widmer | Approved | Approved | | Active |
| WAR24: Skelding | Approved | Approved | | Active |
| WAR25: Rizvi | Approved | Approved | Pending Pharmacy | Pending |
| WAR26: Schmalfuss | Approved | Approved | | Active |
| WAR27: Vicenty | Approved | Approved | | Active |
| WAR28: Shahawy | Approved | Approved | | Active |
| WAR29: De La Rosa | Approved | Approved | | Active |
| WAR30: Giesler | Submitted | Awaiting IRB Approval | | Pending |
| WAR31: Zeb | Submitted | Awaiting IRB Approval | | Pending |
| WAR32: Aambati | Submitted | Awaiting IRB Approval | | Pending |
| WAR33: Kanmantha | Submitted | Awaiting IRB Approval | | Pending |
| WAR34: Dietz | Submitted | Awaiting IRB Approval | | Pending |
| WAR35: Jones | Submitted | Awaiting IRB Approval | | Pending |
| WAR36: Cole | Submitted | Awaiting IRB Approval | | Pending |
| WAR37: Pollack | Submitted | Awaiting IRB Approval | | Pending |
| | **Total Approved:** 29 | **Total Approved:** 29 | | **Total Active:** 27 |

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


### e. Additional Site Recruitment Initiatives

Based on the variability of site recruitment efforts from currently enrolling centers (0-11 randomizations per month), the original recruitment expectation of 4 subjects per month per site to reach a site enrollment of 89 participants over 15 months have not been achieved.

As reported previously, the DCC revised goal is to have 50-70 sites enrolling to reach the study goal of 4,422 women. As detailed in the appendix, 110 sites have returned CDA's which initiates the contracting process. There are currently 40 contracted sites with 24 still in process which would yield 64 active WARRIOR sites.

The DCC has recently entered a collaborative agreement with Community Health IT which is a consortium of community health practices located primarily in Florida and they have identified 20-30 practice sites which are interested in participating in the trial. These **ARE IN ADDITION** to the 64 currently identified sites. The feasibility of this strategy has recently become possible with the pending protocol revision as outlined above to pay for screening CTA's, as many of these potential participants are underinsured and would not have had eligibility testing. As of 9/6/19, 8 sites have completed CDA's. The DCC continues to get requests for information from the imaging center mail out and from contact with WARRIOR Investigators.

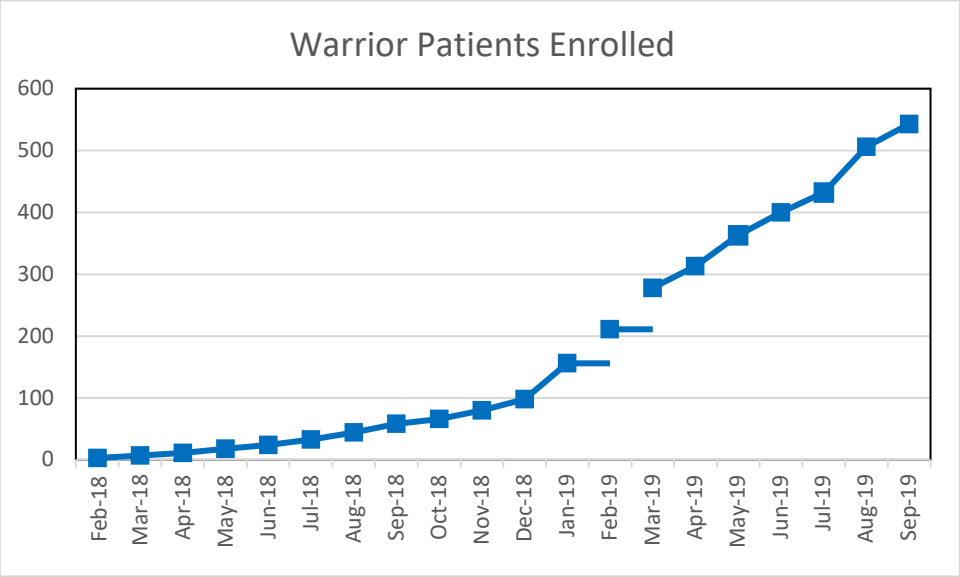
**Section 3- Subject Recruitment**

Current enrollment by site is summarized in **Table 4** and by Month in **Figure 2**. As requested by the DSMB, sites are identified by geographic location.

**Table 4. WARRIOR Recruitment by Site as of 9/18/19**

| PI: Acrostic | Site Name | Location | Total # of Randomizations to Date |
|---|---|---|---|
| UF: WAR01-07 | University of Florida | Gainesville, FL | 196 |
| Bayron: WAR08 | Interventional Cardiac Consultants | Trinity, FL | 29 |
| Rayos: WAR09 | Daytona Heart Group | Daytona Beach, FL | 2 |
| Lambert: WAR11 | Pepin Heart Institute | Tampa, FL | 20 |
| Prashad: WAR12 | Ocala Research Institute | Ocala, FL | 22 |
| Galani: WAR13 | Baptist Health: Jacksonville | Jacksonville, FL | 13 |
| Shufelt: WAR14 | Cedars-Sinai | Los Angeles, CA | 104 |
| Einhorn: WAR15 | Orlando Health | Orlando, FL | 9 |
| Budoff: WAR16 | Los Angeles Biomedical Center | Torrance, CA | 87 |
| Cardenas: WAR17 | South Palm Cardiology | Delray Beach, FL | 2 |
| Wells: WAR18 | University of Kentucky | Lexington, KY | 6 |
| Volk: WAR19 | Naval Hospital Jacksonville | Jacksonville, FL | 1 |
| Gray: WAR20 | Naval Hospital Pensacola | Pensacola, FL | 4 |
| Hakki: WAR21 | Clearwater Cardiovascular Consultants | Clearwater, FL | 10 |
| Parilak: WAR22 | Silver State Cardiology | Las Vegas, NV | 29 |
| Widmer: WAR23 | Baylor Scott and White | Temple, TX | 6 |
| Skelding: WAR24 | Alabama Heart and Vascular | Tuscaloosa, AL | 0 |
| Schmalfuss: WAR26 | Gainesville VA | Gainesville, FL | 2 |
| Vicenty: WAR27 | Puerto Rico VA | San Juan, PR | 0 |
| De La Rosa: WAR28 | Southwest Florida Research Institute | Sarasota, FL | 0 |
| Shahawy: WAR29 | Cardiovascular Center of Sarasota | Naples, FL | 1 |
| | | | **Total:** 543 |

**Figure 2. WARRIOR Trial Cumulative Recruitment by Month**




## Sources of Potential Study Participants

### i. Computed Tomographic Angiographic (CTA) Imaging Center Referral Network

As reported previously, we initiated a formal collaboration with Dr. Matt Budoff, UCLA, Harbor General Hospital, Torrance, CA. CTA imaging center Director at LA Biomed, which has relationships with imaging centers across the country. This contract was implemented to obtain referrals of women with angina who had recent CTAs documenting non-obstructive CAD and were imaged at centers located near activated WARRIOR sites. This activity went live January 10, 2019. Dr. Budoff identified 1659 imaging centers across the US that were contacted regarding the trial to participate as an imaging referral center, or to solicit collaborating practices that might be interested in participating in WARRIOR.

**Table 5. CTA Imaging Referral Centers Contracted to Mail to Potential Women**

| Referring Site Name | City | Referring to | # of Mailings | Enrollments |
|---|---|---|---|---|
| Diagnostic and Wellness | Torrance, CA | Cedars/LA Biomed | 1100 | 24 |
| BDI | Torrance, CA | LA Biomed/Cedars | 2300 | 70 |
| Advanced Imaging | Orange City, FL | Daytona Beach | 451 | 2 |
| CVMG | Beverly Hills, CA | Cedars/LA Biomed | 600 | 6 |
| Bayview Imaging | Tampa, FL | Tampa | 800 | |
| Advent Health Imaging-cath | Tampa, FL | Tampa | 5641 | 14 |
| Precision Imaging Center | Jacksonville Beach, FL | Jacksonville | On hold | |
| Carlisle Imaging Center | Clearwater, FL | Tampa | | |
| Twin Lakes Imaging | Daytona Beach, FL | Daytona Beach | | |
| HCA Memorial Hospital | Tampa, FL | Tampa | 143 | |
| Radiology Regional Center | Fort Myers, FL | Naples/Fort Myers | | |
| Jack Bodker | Phoenix, AZ | Pending site | 685 | |
| POC | Las Vegas, NV | Parilak site | 500 | |
| Clearwater Cardiovascular | Clearwater | Tampa sites | 150 | |

**Potential Impact**

The initial referring CTA imaging centers were focused on the Los Angles sites, and these have been moderately successful with over 100 of the participants enrolling at LA Biomed and Cedars coming from imaging center referrals. Imaging centers for other areas of the country have overall not been successful.

However, with the modification of the protocol to allow for reimbursement of a coronary CTA in women who meet all study criteria but lack a current, objective assessment of CAD may improve the level of participation from imaging centers. Assessment of this additional component will take place in the first quarter of 2020. Currently there are 7 women who are pending scheduling coronary CTA for documentation for inclusion.

The contacting of imaging centers has resulted in additional sites requesting information about becoming new recruiting sites for WARRIOR. There were 26 site referrals from the mailings with 8 who are in the process of contracting/regulatory approval.

**Additional Recruitment Strategies in Place**

The DCC continues to focus additional efforts to increase WARRIOR Trial awareness to women through:

- Social media
    - Advertising
    - Education
- Site hospital EMR platforms such as “MyChart”
- Site recruitment services
- Direct to consumer
    - Mailings
    - Billboards
    - Radio ads

## Section 4- Revised Design - Recruitment and Power

Recruitment remains below original projections due to multiple factors that have been presented in detail in the prior report. The Executive Committee has examined the delayed recruitment of sites/subjects in detail and will increase sites from the originally planned 51 to 75 to complete recruitment and have sufficient follow up to achieve the originally specified MACE outcomes. Original site recruitment was planned to be 50 sites enrolling 4 patients per month for a total enrollment of 89 patients per center over 15 months. Currently site recruitment ranges from 1-11 patients per month. Revised patient recruitment was based on currently active sites continuing to recruit at current rates and revised rates as noted below. Figures 3-6 illustrate the different patient accrual projections. Based on this data, revised power calculations were performed and are detailed in **Tables 6-10**

**Figure 3** summarizes the original recruitment plan (blue), and 3 alternate strategies to match the power below:

A. Conservative enrollment (orange - 2 subjects/month for new sites, and existing recruitment rates for currently enrolling sites for a total of 57 sites)
B. Conservative expanded 75 site model (gray – 2 subjects/month for new sites, and existing recruitment rates for a total of 75 sites)
C. Aggressive model (yellow - 4 subjects/month for new sites and existing recruitment rates for currently enrolling sites for a total of 75 sites)

**Figure 3. WARRIOR Recruitment Projection Original and 3 Alternative Estimates**

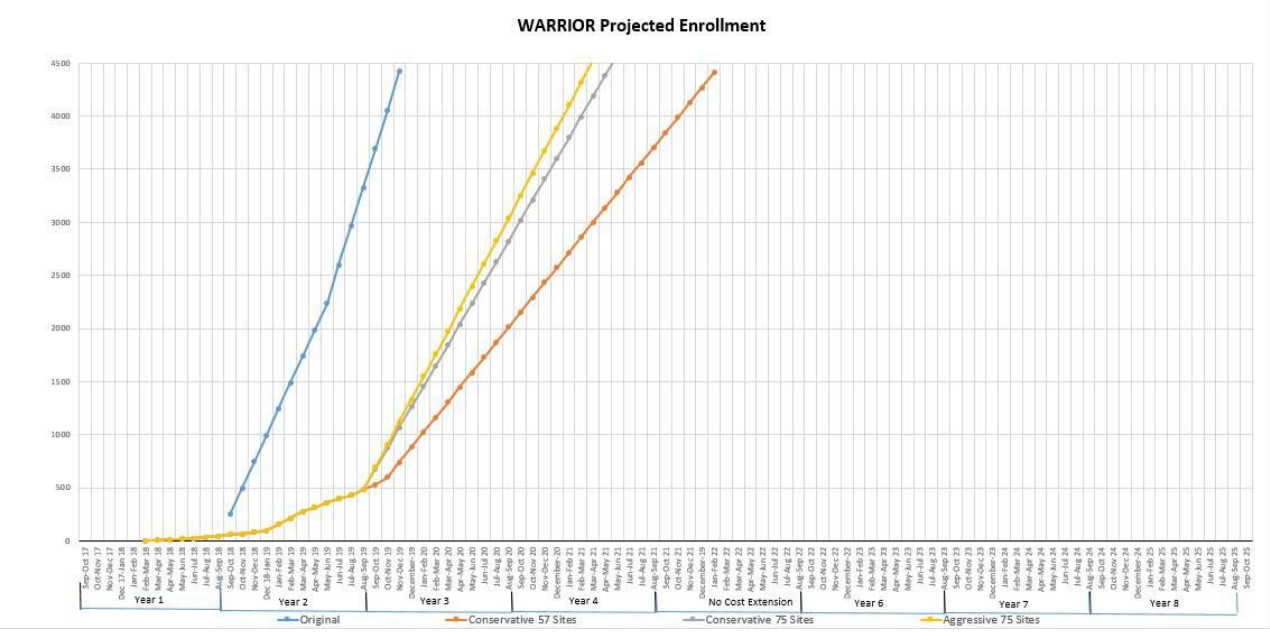
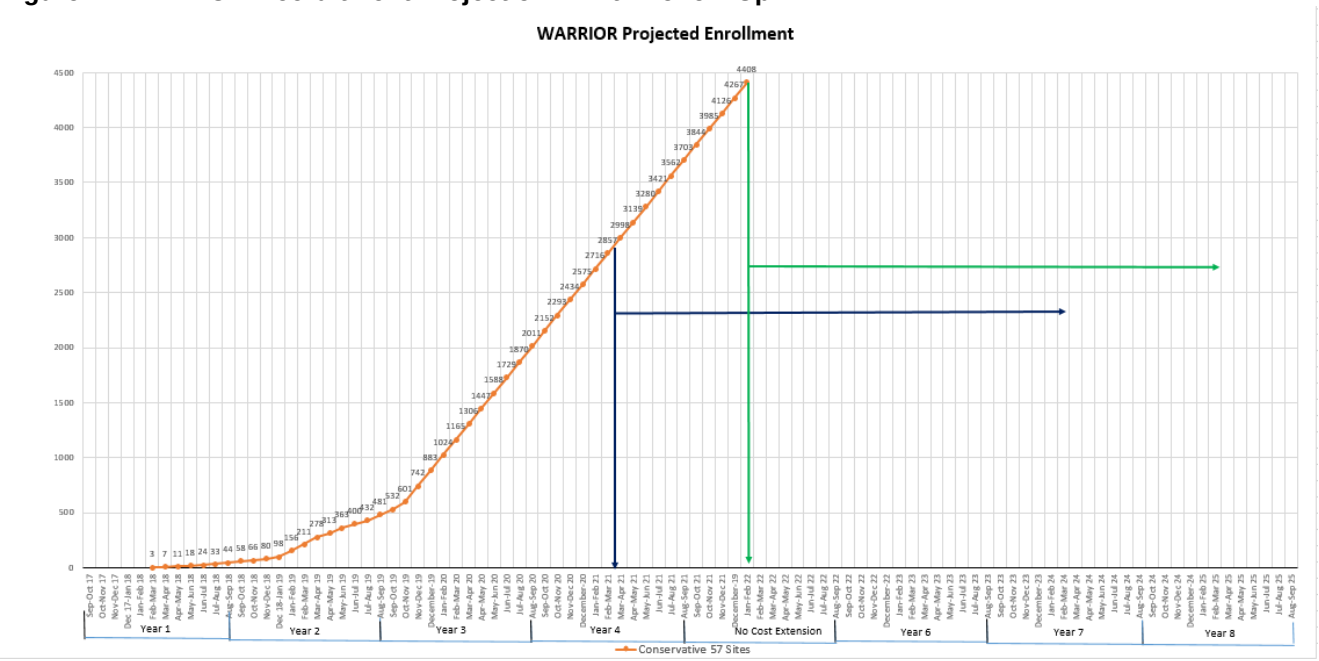


**Figure 4. WARRIOR Recruitment Projection A with Follow Up**




## Follow up with Conservative 57 Site Projection

In this model, conservative recruitment by 57 sites who will all be activated by November 2019. Blue arrows reflect a 10 point total MACE. Covers SAQ-7: max sample size of 2800, and lower boundary for 5 point total MACE. Mean follow-up would be 26.55 months. Green reflects full enrollment and mean follow-up would be 20.69 months.

**Figure 5. WARRIOR Recruitment Projection B with Follow up**

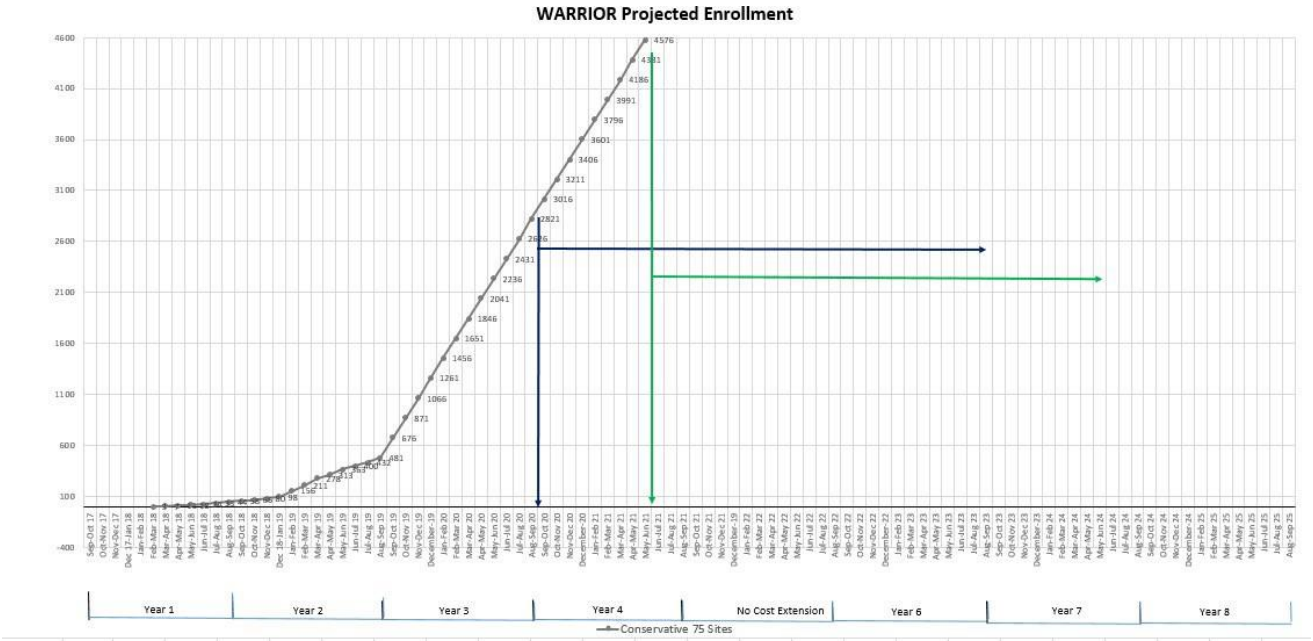



**Figure 5** represents conservative recruitment by 75 sites who will all be activated by January 2019. Blue arrows reflect a 10 point total MACE. Covers SAQ-7: max sample size of 2800, and lower boundary for 5 point total MACE. Mean follow-up would be 29.40 months. Green reflects full enrollment and mean follow-up would be 25.19 months.

**Figure 6. WARRIOR Recruitment Projection C and Follow up**

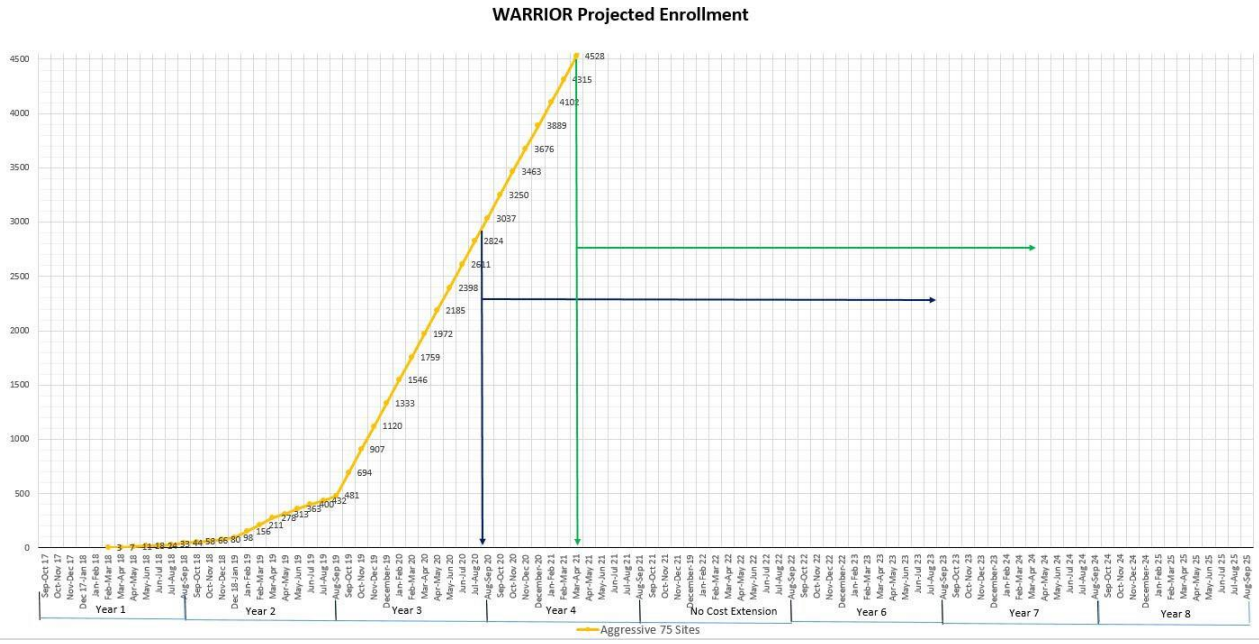



**Figure 6** represents aggressive recruitment by 75 sites who will all be activated by January 2019. Blue arrows reflect a 10 point total MACE. Covers SAQ-7: max sample size of 2800, and lower boundary for 5 point total MACE. Mean follow-up would be 29.71 months. Green reflects full enrollment and mean follow-up would be 26.03

Based on these projections, additional time is needed to carry out this trial to capture sufficient MACE events to answer the proposed question. We have obtained a letter of commitment from our Project Officer Rahul G. Thakar, Ph.D. (Appendix C). Revised power calculations are summarized below.

**Power Calculations**

Power considerations are presented in the original study protocol (Section E.10.i), where Table 3 lists the design assumptions and Table 4 summarizes the study power considerations. To compare the original design with the Revised Designs, we present, as a reference, the power achieved with the following assumptions from the original design:

10% Drop-out
2% Loss to follow-up
Contamination = 30%, and
Total Follow-up = 42 months (3.5 years).

In the **Revised Designs**, accrual will be extended into years 3,4 and 5, and follow-up will be extended to different total follow up times of 4,5 or 6 years. In order to reach 80% power, the study will need to be extended to have a total follow up of more than 5 years.

| Table 6 Power Assumptions |
|---|
| Accrual Rate see below |
| Total Sample Size n = 4422 |
| Randomized 1:1 IMT vs UC |
| Drop-out rate 10% |
| Effective Sample Size 3984 |
| Contamination UC to IMT 30% |
| Contamination IMT to UC 30% |
| Type I error (2-sided) 0.05 |
| Minimum follow-up 24 months |
| Lost to follow-up 2% |

We considered three enrollment scenarios: A, B, and C, consistent with the 3 alternate strategies above, and described below:

In **Scenario A**, 4422 patients are enrolled with constant accrual (141/month) from 57 sites into year 5 (month 53). Power calculations are provided in Table 7.

**Table 7. Power calculation: Rates of MACE for UC and IMT groups with 30% contamination, conservative 57 sites accrual, increasing total study follow up to 5 or 6 years**

| **Estimated cumulative incidence of MACE at 3 years** | | **Power to detect difference in MACE rates at end total follow up** | | |
|---|---|---|---|---|
| **UC** | **IMT** | **48 months** | **60 months** | **72 months** |
| **0.15** | 0.12 | - | 0.52 | 0.60 |
| **0.20** | 0.16 | - | 0.66 | 0.75 |
| **0.25** | 0.20 | - | 0.78 | **0.86** |
| **0.30** | 0.24 | - | 0.86 | 0.93 |
| **0.35** | 0.28 | - | 0.93 | 0.97 |

In **Scenario B**, 4422 patients are enrolled with constant accrual (195/month) at 75 sites until month 45. Power calculations are provided in Table 8.

| **Table 8. Power calculation: : Rates of MACE for UC and IMT groups with 30% contamination, conservative 75 sites accrual, increasing total study follow up to 4, 5 or 6 years** | | | | |
|---|---|---|---|---|
| **Estimated cumulative incidence of MACE at 3 years** | | **Power to detect difference in MACE rates at end total follow up** | | |
| **UC** | **IMT** | **48 months** | **60 months** | **72 months** |
| **0.15** | 0.12 | 0.37 | 0.51 | 0.60 |
| **0.20** | 0.16 | 0.48 | 0.65 | 0.74 |
| **0.25** | 0.20 | 0.59 | 0.77 | **0.85** |
| **0.30** | 0.24 | 0.69 | 0.86 | 0.93 |
| **0.35** | 0.28 | 0.77 | 0.92 | 0.97 |

In **Scenario C**, 4422 patients are enrolled with constant accrual (213/month) at 75 sites until month 43. Power calculations are provided in Table 9.

| **Table 9 Power calculation: Rates of MACE for UC and IMT groups with 30% contamination, aggressive 75 sites accrual, increasing total study follow up to 4, 5 or 6 years** | | | | |
|---|---|---|---|---|
| **Estimated cumulative incidence of MACE at 3 yrs** | | **Power to detect difference in MACE rates at end total follow up** | | |
| **UC** | **IMT** | **48 months** | **60 months** | **72 months** |
| **0.15** | 0.12 | 0.38 | 0.52 | 0.60 |
| **0.20** | 0.16 | 0.49 | 0.66 | 0.75 |
| **0.25** | 0.20 | 0.60 | 0.78 | **0.86** |
| **0.30** | 0.24 | 0.70 | 0.86 | 0.93 |
| **0.35** | 0.28 | 0.79 | 0.93 | 0.97 |

The power values to be compared with the original design reference are highlighted in yellow in Tables 7,8,9. One can see that according to the **Revised Design**, all the highlighted values are above 80% for 6 years of total follow up. Therefore, the **Revised Design** will provide adequate power comparable to the original design if total follow up is extended.

**Grant Extension**

We have obtained a letter of commitment from our Project Officer Rahul G. Thakar, Ph.D., Senior Science Officer, Congressionally Directed Medical Research Programs via Tunnell Government Services United States Army Medical Research Development Command (USAMRDC) for no-cost extensions (see Appendix C). No cost extension for an additional year is a standard part of the existing award and given the current conduct of the trial and assuming the project remains in compliance and progress toward reaching the study aims are on target there is extremely high likelihood of getting a second year no-cost extension.

## Section 5 - BASELINE DEMOGRAPHICS OF PARTICIPANTS

The database was locked on 8/1/19. Demographics for 506 participants are summarized in Appendix B.

## Section 6 - ADVERSE EVENTS

Site-reported and Adjudicated Events are summarized in Appendix B.

## Section 7 - Contingency planning

Contingency planning as summarized in our prior DSMB report and is supplied in the previous meeting report. A no cost extension has been discussed and was endorsed by the DoD Project Officer.

## Section 8 - WARRIOR Biorepository

Funding was awarded from DoD to collect baseline samples and store in a biorepository. Supplemental funding has been awarded from the McJunkin Family Foundation to initiate sample analysis. Preliminary data on sample from the initial 50 women enrolled was analyzed to obtain preliminary data on mechanisms to be included in the NHLBI Ancillary Studies R01 reapplication. An initial report of activity from this effort is attached in Appendix D.

## APPENDIX A. CURRENT STATUS OF ALL WARRIOR SITES

**Table 1. WARRIOR Site Status- All Sites**

| Site Name | Contracting Status | Activation/IRB Status |
|---|---|---|
| WAR38: Tripler Army Medical Center | Contracted | Waiting on IRB Documents |
| WAR39: Brooks Army Medical Center | Contracted | Waiting on IRB Documents |
| WAR40: Walter Reed | Contracted | Waiting on IRB Documents |
| WAR41: University of Florida: Jacksonville | Contracted | Waiting on IRB Documents |
| WAR42:Jamacia Hospital | Contracted | Ready to Submit to the IRB |
| WAR43: Essentia Health | Pending | Ready to Submit to the IRB |
| WAR44: Midwest Heart and Vascular | Pending | Ready to Submit to the IRB |
| WAR45: Baptist Health Miami | Pending | Waiting on IRB Documents |
| WAR46: Tampa VA | Pending | Waiting on IRB Documents |
| WAR47: Heart Center Research | Pending | Waiting on IRB Documents |
| WAR48: Central Florida Cardiovascular Institute | Pending | Waiting on IRB Documents |
| WAR49: TriCity Cardiology | Pending | Waiting on IRB Documents |
| WAR50: Aventura Hospital | Pending | Waiting on IRB Documents |
| WAR51: Ballad Health | Pending | Waiting on IRB Documents |
| WAR52: Central Research Associates | Pending | Waiting on IRB Documents |
| WAR53: Community Hospital | Pending | Waiting on IRB Documents |
| WAR54: East Tennessee State | Pending | Waiting on IRB Documents |
| WAR55: Indiana University | Pending | Waiting on IRB Documents |
| WAR56: North Dallas Research | Pending | Waiting on IRB Documents |
| WAR57: Parkview | Pending | Waiting on IRB Documents |
| WAR58: Permanente Medical | Pending | Waiting on IRB Documents |
| WAR59: Sentara Health | Pending | Waiting on IRB Documents |
| WAR60: University of Vermont | Pending | Waiting on IRB Documents |

| | | |
|---|---|---|
| WAR61: Wisconsin University | Pending | Waiting on IRB Documents |
| WAR62: Minneapolis Heart Institute | Pending | Waiting on IRB Documents |
| WAR63: Citrus Cardiology | Pending | Waiting on IRB Documents |
| WAR64: Presbyterian Heart Group | Sent CDA | Sent Regulatory Package |
| WAR65: University of Southern California | Sent CDA | Sent Regulatory Package |
| WAR66: Washington Hospital Center | Sent CDA | Sent Regulatory Package |
| WAR67: Munson Med Center | Sent CDA | Sent Regulatory Package |
| WAR68: Mercy General Hospital | Sent CDA | Sent Regulatory Package |
| WAR69: Baylor Hamilton Heart and Vascular | Sent CDA | Sent Regulatory Package |
| WAR70: Washington University St. Louis | Sent CDA | Sent Regulatory Package |
| WAR71: St. John Hospital and Medical Center | Sent CDA | Sent Regulatory Package |
| WAR72: Rhode Island Hospital | Sent CDA | Sent Regulatory Package |
| WAR73: St. Mary's Medical Center | Sent CDA | Sent Regulatory Package |
| WAR74: Indiana Heart Hospital | Sent CDA | Sent Regulatory Package |
| WAR75: Sr. Johns Mercy Medical Research Center | Sent CDA | Sent Regulatory Package |
| WAR76: Saint Francis Hospital | Sent CDA | Sent Regulatory Package |
| WAR77: St. Elizabeth's Hospital | Sent CDA | Sent Regulatory Package |
| WAR78: New Hanover Regional Med Center | Sent CDA | Sent Regulatory Package |
| WAR79: Henry Ford Hospital | Sent CDA | Sent Regulatory Package |
| WAR80: Fletcher Allen Health Care | Sent CDA | Sent Regulatory Package |
| WAR81: Virginia Commonwealth University | Sent CDA | Sent Regulatory Package |
| WAR82: Albert Einstein Med Center | Sent CDA | Sent Regulatory Package |
| WAR83: Memorial Medical Center | Sent CDA | Sent Regulatory Package |
| WAR84: University of Texas Southwestern Med Center | Sent CDA | Sent Regulatory Package |
| WAR85: Bryan LGH Heart Center | Sent CDA | Sent Regulatory Package |
| WAR86: St. John Health | Sent CDA | Sent Regulatory Package |

## APPENDIX B. BASELINE DEMOGRAPHICS OF PARTICIPANTS AND ADVERSE EVENTS

**Table 1. WARRIOR Eligibility Criteria**

| | Group 1 (n=253) | Group 2 (n=253) | Total (n=506) |
|---|---|---|---|
| **Eligibility Criteria** | | | |
| **Symptoms/Signs of ischemia** | **253** (100%) | **253** (100%) | **506** (100%) |
| **Chest pain above waist** | **209** (82.6%) | **221** (87.4%) | **430** (85%) |
| **Abnormal ECG** | **38** (15%) | **33** (13%) | **71** (14%) |
| **Abnormal stress test** | **27** (10.7%) | **28** (11.1%) | **55** (10.9%) |
| **Abnormal troponin** | **12** (4.7%) | **14** (5.5%) | **26** (5.1%) |
| **Shortness of breath/breathlessness** | **140** (55.3%) | 127 (50.2%) | **267** (52.8%) |
| **Cardiac catheterization showing non-obstructive CAD** | **148** (58.5%) | **151** (59.7%) | **299** (59.1%) |
| **Fraction flow reserve >0.8, n=299** | **8** (5.4%) | **8** (5.3%) | **16** (5.4%) |
| **Coronary CTA showing non-obstructive CAD** | **112** (44.3%) | **109** (43.1%) | **221** (43.7%) |
| **Intolerance or allergy to ACE inhibitors** | **4** (1.6%) | **2** (0.8%) | **6** (1.2%) |
| **Intolerance or allergy to statins** | **1** (0.4%) | **2** (0.8%) | **3** (0.6%) |

**Table 2. WARRIOR Demographics**

| | Group 1 (n=253) | | | | | | Group 2 (n=253) | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **N** | **Mean** | **Std Dev** | **Min** | **Med** | **Max** | **N** | **Mean** | **Std Dev** | **Min** | **Med** | **Max** |
| **Age, years** | **253** | 60.43 | 12.26 | 21.03 | 61.45 | 89.19 | **253** | 60.25 | 11.65 | 23.19 | 61.14 | 93.34 |
| **Height, inches** | **251** | 64.15 | 3.48 | 45 | 64 | 78 | **246** | 63.95 | 3.25 | 48 | 64 | 78 |
| **Weight, lbs** | **251** | 185.92 | 53.03 | 94 | 177 | 402 | **246** | 186.35 | 50.45 | 89 | 177.4 | 440 |
| **BMI** | **251** | 31.81 | 8.76 | 16.13 | 29.95 | 66.9 | **246** | 32.06 | 8.28 | 15.02 | 30.58 | 70.39 |
| **Systolic BP, mmHg** | **249** | 124.61 | 15.23 | 83 | 122 | 164.5 | **246** | 124.85 | 15.5 | 88 | 123 | 173 |
| **Diastolic BP, mmHG** | **249** | 75.23 | 10.34 | 52 | 74 | 112 | **246** | 75.87 | 10.3 | 51 | 76 | 125.5 |
| **Pulse rate, b/min** | **251** | 72.11 | 11.34 | 49.5 | 71 | 126 | **246** | 72.15 | 11.77 | 445 | 70.5 | 104 |
| **Total cholesterol, mg/dL** | **158** | 180.26 | 35.75 | 95 | 178.5 | 296 | **147** | 185.68 | 48.85 | 82 | 182 | 343 |
| **HDL, mg/dL** | **158** | 56.09 | 14.76 | 30 | 53 | 109 | **147** | 59.99 | 18.5 | 27 | 57 | 141 |
| **LDL, mg/dL** | **154** | 100.45 | 30.19 | 36 | 96.5 | 190 | **144** | 102.4 | 39.32 | 32 | 98.5 | 235 |
| **Triglycerides, mg/dL** | **158** | 137.12 | 95.61 | 27 | 111.5 | 797 | **147** | 131.16 | 82.89 | 41 | 104 | 593 |
| **Hemoglobin a1c, %** | **148** | 5.89 | 1.13 | 4.5 | 5.6 | 11.4 | **142** | 5.82 | 1.14 | 4.6 | 5.55 | 12.3 |
| **Glucose, mg/dL** | **54** | 94.78 | 36.5 | 45 | 94.5 | 213 | **13** | 76.69 | 23.75 | 50 | 69 | 143 |
| **Creatinine, mg/dL** | **56** | 0.81 | 0.15 | 0.39 | 0.8 | 1.19 | **16** | 0.91 | 0.19 | 0.6 | 0.84 | 1.23 |

**Table 3. WARRIOR Medical History**

| | Group 1 (n=253) | Group 2 (n=253) | Total (n=506) |
|---|---|---|---|
| **Angina** | **210** (83%) | **216** (85.4%) | **426** (84.2%) |
| **Atrial fibrillation** | **20** (7.9%) | **21** (8.3%) | **41** (8.1%) |
| **Cancer** | **29** (11.5%) | **38** (15%) | **67** (13.2%) |
| **Cardiomyopathy** | **4** (1.6%) | **11** (4.4%) | **15** (3%) |
| **Heart failure** | **13** (5.1%) | **9** (3.6%) | **22** (4.4%) |
| **Diabetes** | **55** (21.7%) | **49** (19.4%) | **104** (20.6%) |
| **GERD** | **87** (34.4%) | **84** (33.2%) | **171** (33.8%) |
| **Heart attack** | **25** (9.9%) | **31** (12.3%) | **56** (11.1%) |
| **Heart surgery** | **4** (1.6%) | **4** (1.6%) | **8** (1.6%) |
| **High blood pressure** | **162** (64%) | **161** (63.6%) | **323** (63.8%) |
| **High cholesterol** | **153** (60.5%) | **138** (54.6%) | **291** (57.5%) |
| **High triglycerides** | **39** (15.4%) | **35** (13.8%) | **74** (14.6%) |
| **Kidney disease** | **8** (3.2%) | **4** (1.6%) | **12** (2.4%) |
| **Peripheral artery disease** | **6** (2.4%) | **4** (1.6%) | **10** (2%) |
| **Polycystic ovary disease** | **14** (5.5%) | **12** (4.7%) | **26** (5.1%) |
| **Stroke** | **14** (5.5%) | **13** (5.1%) | **27** (5.3%) |
| **Thyroid disease** | **49** (19.4%) | **42** (16.6%) | **91** (18%) |
| **Family history of heart disease** | **179** (71%) | **183** (73.2%) | **362** (72.1%) |
| **Current tobacco use or smoking** | **27** (10.7%) | **35** (14%) | **62** (12.4%) |
| **Current alcohol use** | **76** (30.2%) | **77** (30.8%) | **153** (30.5%) |
| **Natural menstruation has stopped** | **207** (82.1%) | **208** (83.2%) | **415** (82.7%) |
| **Oral contraception use:** | | | |
| **Currently** | **7** (2.8%) | **7** (2.8%) | **14** (2.8%) |
| **In the past** | **156** (61.9%) | **140** (56%) | **296** (59%) |
| **Never** | **89** (35.3%) | **103** (41.2%) | **192** (38.3%) |
| **Ever used hormone replacement therapy:** | | | |
| **Currently** | **21** (8.3%) | **12** (4.8%) | **33** (6.6%) |
| **In the past** | **46** (18.3%) | **47** (18.8%) | **93** (18.5%) |
| **Never** | **185** (73.4%) | **191** (76.4%) | **376** (74.9%) |

**Table 4. WARRIOR Baseline Medications**

| | Group 1 (n=253) | Group 2 (n=253) | Total (n=506) |
|---|---|---|---|
| **Statin** | **159** (62.9%) | **164** (64.8%) | **323** (63.8%) |
| **ACE** | **71** (28.1%) | **76** (30%) | **147** (29.1%) |
| **ARB** | **57** (22.5%) | **49** (19.4%) | **106** (21%) |
| **Aspirin** | **135** (53.4%) | **136** (53.8%) | **271** (53.6%) |
| **Antiarrhythmic agent** | **16** (6.4%) | **14** (5.7%) | **30** (6%) |
| **Antiplatelet agent, other than aspirin** | **15** (6%) | **15** (6.1%) | **30** (6%) |
| **Anticoagulent** | **23** (9.2%) | **24** (9.7%) | **47** (9.4%) |
| **Beta blocker** | **88** (35.1%) | **93** (37.7%) | **181** (36.4%) |
| **Ca channel blocker** | **60** (23.9%) | **60** (24.3%) | **120** (24.1%) |
| **Diuretic** | **67** (26.7%) | **67** (27.1%) | **134** (26.9%) |
| **Nitrate** | **43** (17.1%) | **48** (19.4%) | **91** (18.3%) |
| **Ranolazine** | **10** (4%) | **8** (3.2%) | **18** (3.6%) |
| **Selective estrogen modulator** | **2** (0.8%) | **4** (1.6%) | **6** (1.2%) |
| **Vasodilators or others** | **14** (5.6%) | **11** (4.5%) | **25** (5%) |

**Table 5. WARRIOR Baseline History- Characteristics by Eligibility with Catheterization, CTA or both:**

| | Both (n=14) | CTA (n=207) | Cath (n=285) | Fisher's Exact Test p-value |
|---|---|---|---|---|
| **Ethnicity not Hispanic or Latino** | **12** (85.7%) | **171** (83%) | **257** (90.5%) | 0.0378 |
| **Race white** | **12** (85.7%) | **153** (73.9%) | **204** (71.6%) | 0.5109 |
| **Angina** | **10** (71.4%) | **158** (76.3%) | **258** (90.5%) | <0.0001 |
| **Atrial fibrillation** | **0** | **9** (4.4%) | **32** (11.2%) | 0.0131 |
| **Cancer** | **2** (14.3%) | **31** (15%) | **34** (11.9%) | 0.617 |
| **Cardiomyopathy** | **2** (14.3%) | **3** (1.5%) | **10** (3.5%) | 0.027 |
| **Heart Failure** | **0** | **5** (2.4%) | **17** (6%) | 0.164 |
| **Diabetes** | **1** (7.1%) | **47** (22.7%) | **56** (19.7%) | 0.3824 |
| **GERD** | **2** (14.3%) | **71** (34.3%) | **98** (34.4%) | 0.3335 |
| **Heart attack** | **5** (35.7%) | **10** (4.8%) | **41** (14.4%) | <0.0001 |
| **Heart surgery** | **0** | **1** (0.5%) | **7** (2.5%) | 0.3195 |
| **High blood pressure** | **7** (50%) | **124** (59.9%) | **192** (67.4%) | 0.1256 |
| **High cholesterol** | **8** (57.1%) | **112** (54.1%) | **171** (60%) | 0.4156 |
| **High triglycerides** | **2** (14.3%) | **32** (15.5%) | **40** (14%) | 0.911 |
| **Kidney disease** | **0** | **4** (1.9%) | **8** (2.8%) | 0.8354 |
| **Peripheral artery disease** | **0** | **3** (1.5%) | **7** (2.5%) | 0.6462 |
| **Polycystic ovary disease** | **2** (14.3%) | **14** (6.8%) | **10** (3.5%) | 0.0715 |
| **Stroke** | **0** | **12** (5.8%) | **15** (5.3%) | 0.9277 |
| **Thyroid disease** | **4** (28.6%) | **36** (17.4%) | **51** (17.9%) | 0.5033 |
| **Family history of heart disease** | **10** (71.4%) | **135** (65.2%) | **217** (77.2%) | 0.0127 |
| **Current tobacco use or smoking** | **0** | **30** (14.5%) | **32** (11.4%) | 0.2628 |
| **Current alcohol use** | **11** (78.6%) | **69** (33.3%) | **73** (26%) | 0.0001 |
| **Natural menstruation has stopped** | **7** (50%) | **172** (83.1%) | **236** (84%) | 0.0107 |
| | | | | **ANOVA p-value** |
| **Age** | **53** ± 13 | **58** ± 12 | **62** ± 11 | 0.0002 |
| **BMI** | **31** ± 10 | **32** ± 9 | **32** ± 8 | 0.635 |
| **SBP** | **123** ± 18 | **124** ± 16 | **125** ± 15 | 0.8273 |
| **DBP** | **75** ± 10 | **76** ± 11 | **75** ± 10 | 0.3154 |
| **HR** | **70** ± 10 | **73** ± 11 | **72** ± 12 | 0.5162 |
| **HDL** | **72** ± 18 | **59** ± 19 | **57** ± 15 | 0.1357 |
| **Triglycerides** | **123** ± 38 | **145** ± 115 | **128** ± 72 | 0.3006 |
| **LDL** | **85** ± 10 | **108** ± 35 | **98** ± 35 | 0.0412 |
| **Total Cholesterol** | **179** ± 15 | **192** ± 45 | **178** ± 41 | 0.0183 |

**Table 6. WARRIOR Smoking Status Post Baseline**

| Group 1 | | | | |
|---|---|---|---|---|
| **Visit** | **Current Smoking Status (pace assessment)** | | | |
| | **Never smoker** | **Ex-smoker** | **Current smoker** | **Total** |
| **Baseline** | 149 | 80 | 21 | 250 |
| | 59.6% | 32% | 8.4% | |
| **Follow-up Month 3** | 100 | 50 | 11 | 161 |
| | 62.11% | 31.06% | 6.83% | |
| **Follow-up Month 6** | 54 | 23 | 9 | 86 |
| | 62.79% | 26.74% | 10.47% | |
| **Follow-up Month 12** | 14 | 6 | 2 | 22 |
| | 63.64% | 27.27% | 9.09% | |
| **Follow-up Month 18** | 2 | 0 | 0 | 2 |
| | 100% | 0% | 0% | |
| | | | | |
| **Group 2** | | | | |
| **Visit** | **Current Smoking Status (pace assessment)** | | | |
| | **Never smoker** | **Ex-smoker** | **Current smoker** | **Total** |
| **Baseline** | 147 | 71 | 31 | 249 |
| | 59.04% | 28.51% | 12.45% | |
| **Follow-up Month 3** | 96 | 46 | 12 | 154 |
| | 62.34% | 29.87% | 7.79% | |
| **Follow-up Month 6** | 51 | 21 | 12 | 84 |
| | 60.71% | 25% | 14.29% | |
| **Follow-up Month 12** | 10 | 1 | 5 | 16 |
| | 62.5% | 6.25% | 31.25% | |
| **Follow-up Month 18** | 3 | 0 | 0 | 3 |
| | 100% | 0% | 0% | |

**Table 7. WARRIOR Contamination Report by Group**

| | Group 1 (n=253) | Group 2 (n=253) | Total (n=506) |
|---|---|---|---|
| **At recommended Statin and ACE/ARB dosage** | **104** (41.1%) | **16** (6.3%) | **120** (23.7%) |
| **Statin** | **192** (75.9%) | **150** (59.3%) | **342** (67.6%) |
| **Low Intensity Statin** | **29** (35.6%) | **85** (74.3%) | **114** (54.9%) |
| **High Intensity Statin** | **163** (64.4%) | **65** (25.7%) | **228** (45.1%) |
| **At recommended ACE dosage** | **68** (26.9%) | **35** (13.8%) | **103** (20.4%) |
| **At recommended ARB dosage** | **61** (24.1%) | **13** (5.1%) | **74** (14.6%) |
| **At recommended ACE or ARB dosage** | **129** (51%) | **48** (19%) | **177** (35%) |
| **RAS Blocker** | **172** (68%) | **70** (27.7%) | **242** (47.8%) |
| **Aspirin** | **142** (56.1%) | **133** (52.6%) | **275** (54.4%) |

**Table 8. WARRIOR MACE EVENTS**

| | Adjudicated | | In Adjudication Process | | |
|---|---|---|---|---|---|
| **MACE TYPE** | **Group 1** | **Group 2** | **Group 1** | **Group 2** | **Total** |
| **Death** | 0 | 0 | 0 | 0 | **0** |
| **Non-Fatal MI** | 2 | 0 | 1 | 0 | **3** |
| **Stroke/TIA** | 0 | 1 | 1 | 0 | **2** |
| **Hospitalization/ ED >24 Hours for Chest Pain** | 1 | 2 | 2 | 4 | **9** |
| **Hospitalization for Heart Failure** | 0 | 0 | 0 | 0 | **0** |
| **Total:** | **3** | **3** | **4** | **4** | **14** |
| **Total MACE for Group 1:** 7<br>**Total MACE for Group 2:** 7 | | | | | |

**Table 9. WARRIOR Hospitalization and Emergency Department Visits for Chest Pain**

| | Group 1 | Group 2 | Total |
|---|---|---|---|
| **Hospitalization** | 3 | 6 | **9** |
| **ED > 24 Hours** | 0 | 0 | **0** |
| **ED < 24 Hours** | 16 | 14 | **30** |
| **Total:** | **19** | **20** | **39** |

Definitions from the WARRIOR CEC charter:

Patients who are hospitalized for management of chest pain will be classified into stable/atypical angina, unstable angina, worsening chest pain, non-cardiac chest pain, or indeterminate.

**Worsening angina:** A chest pain pattern consistent with unstable angina but does not meet the above criteria (eg admission within 24 hours of most recent change in symptoms, accelerating pattern of chest pain that occurs with a lower activity threshold, considered to be myocardial ischemia upon final diagnosis, and requiring an escalation of anti-anginal therapy) (nitrates, beta-blockers, calcium antagonists, or ranolazine or a coronary revascularization procedure. Classification of worsening angina will be subclassified into (i) primary cause (believed due to change in coronary anatomy) or (ii) secondary (eg hypertensive urgency or emergency, severe anemia, or other well-known causes of demand ischemia like tachyarrhythmia) or (iii) primary or secondary cause cannot be determined.

**Escalation of Therapy:** Escalation of therapy is defined as an increase in prevention medication (statin/ACE/ARB) dose, addition of a prevention medication (statin/ACE/ARB), and/or addition or increase of antianginal therapy, or scheduled for a PCI or CABG.

**Table 10. WARRIOR Adjudicated MACE Narratives**

| Adjudicated | | | | | | |
|---|---|---|---|---|---|---|
| **Event** | **Group** | **Site-Participant ID** | **Date of SAE** | **Serious** | **Related to Study Procedure** | **Resolution Date** |
| Worsening Chest Pain, ED <24 Hours | 1 | 1-2 | 2/20/19 | Yes | Unrelated | 02/21/19 |
| **Narrative:** 44yo in ED <24hrs for chest pain. Admission BP 146/90, troponins neg., EKG showed no ischemic changes. Discharged with instructions to it take easy and continue taking her home medications including Isordil and with follow-up with PCP | | | | | | |
| Worsening Chest Pain, ED <24 Hours | 1 | 1-23 | 11/16/18 | Yes | Unrelated | 11/16/18 |
| **Narrative:** 59yo in ED <24hrs for chest pain. ECG was abnormal. No changes to therapy. Discharged with follow-up with PCP. | | | | | | |
| Worsening Chest Pain, ED <24 Hours | 1 | 5-13 | 10/18/18 | Yes | Unrelated | 10/19/18 |
| **Narrative:** 41yo in ED <24hrs for chest pain, BP 135/72, troponin neg., borderline ECG, chest x-ray was done with no acute finding. No changes to therapy. Discharged to follow up with PCP within 1-2 days. | | | | | | |
| Worsening Chest Pain, ED <24 Hours | 1 | 5-15 | 10/26/18 | Yes | Unrelated | Resolving |
| **Narrative:** 54yo in ED <24hr. for chest pain. BP 115/77, troponin neg., chest x-ray was done no acute airspace opacities are seen, EKG NSR 91. Did not meet acute STEMI criteria. Relief of chest pain with SL nitro. No changes to therapy. Discharged. | | | | | | |
| Stroke | 2 | 1-15 | 07/25/18 | Yes | Unrelated | 08/01/18 |
| **Narrative:** 69yo Stroke/TIA. Pt likely had reversible cerebral vasoconstriction syndrome but with residual hemiparesis on day 5 and tPA administration in the setting of new onset AF and PFO. Ischemic stroke highly probable. | | | | | | |
| MI | 1 | 14-14 | 01/25/19 | Yes | Unrelated | 01/29/19 |
| **Narrative:** 74yo hospitalized for non-fatal MI. Patient had chest pain, MI cTn profile and significant drop in EF. MI complicated by HF. ECG: LBBB. No cath done. Prior cath showed non-obstructive CAD. Type 2 MI. | | | | | | |
| MI | 1 | 5-13 | 10/10/2018 | Yes | Unrelated | 10/19/2018 |
| **Narrative:** 41yo ED visit, admitted to hospital. Stay >24hrs for non-fatal-MI. BP103/50, troponins neg., ECG demonstrated no significant abnormality. Discharged with follow-up with PCP. | | | | | | |
| Worsening Chest Pain, Hospitalization | 2 | 1-22 | 06/28/18 | Yes | Unrelated | 07/02/18 |
| **Narrative:** 61 yo with known variant angina hospitalized for chest pain. BP 84/56. cTn x3 neg. ECG T inversion anterior, old according to med records, no cath this admin but prior cath normal coronaries with vasospasm. | | | | | | |
| Worsening Chest Pain, Hospitalization | 1 | 1-16 | 06/21/18 | Yes | Unrelated | 06/22/19 |

| | | | | | | |
|---|---|---|---|---|---|---|
| **Narrative:** 59 yo hospitalized. Sharp atypical CP and SOB worse with respiration, BNP, cTn normal. EKG with NSST changes. CXR mild congestion but CT chest negative. No changes to therapy. Discharged with follow-up with PCP. | | | | | | |
| Worsening Chest Pain, Hospitalization | 2 | 14-3 | 04/01/19 | Yes | Unrelated | 04/01/19 |
| **Narrative:** 37 yo hospitalized >24hr. for chest pain. Atypical chest pain on and off for 1 week. CXR and troponin normal x4, EKG abnormal but no signs of ischemia. Discharged with follow up with follow-up with PCP. | | | | | | |

**Table 11. WARRIOR Pending Adjudication MACE Narratives**

| **Pending Adjudication** | | | | | | |
|---|---|---|---|---|---|---|
| **Event** | **Group** | **Site-Participant ID** | **Date of SAE** | **Serious** | **Related to Study Procedure** | **Resolution Date** |
| Worsening Chest Pain, ED <24 Hours | 1 | 2-1 | 08/13/18 | Yes | Unrelated | 08/13/18 |
| **Narrative:** 56 yo. in ED <24hrs for chest pain. BP175/85, troponin normal, CT neg., EKG show no ST elevation or depression. No changes to therapy. Discharged with follow-up with PCP. | | | | | | |
| Worsening Chest Pain, ED <24 Hours | 1 | 5-13 | 12/27/18 | Yes | Unrelated | 12/28/18 |
| **Narrative:**41yo in ED <24hrs. for chest pain, troponins neg., discharged to see PCP within a week | | | | | | |
| Worsening Chest Pain, ED <24 Hours | 2 | 11-2 | 12/25/18 | Yes | Unrelated | 12/26/18 |
| **Narrative:** 55yo in ED <24hr. for chest pain. BP 139/74, troponin<0.01ng/mL, chest x-ray normal. Symptoms improved. Discharged with follow-up with PCP. | | | | | | |
| Worsening Chest Pain, ED <24 Hours | 1 | 14-2 | 01/05/19 | Yes | more likely than not | 01/05/19 |
| **Narrative:** 54 yo. in ED <24hr. for chest pain. BP 101/71, trop neg., EKG normal. Study medication withdrawn. Patient discharged with follow up with PCP. | | | | | | |
| Stroke | 1 | 1-59 | 03/25/19 | Yes | Unrelated | 03/30/19 |
| **Narrative:** Went to ED then admitted for Embolic Stroke, PFO. BP 112/69, CT scan was neg., but did receive tPA. Discharged with follow up in 2-3 weeks | | | | | | |
| MI | 1 | 14-14 | 02/17/19 | Yes | Unrelated | 02/22/19 |

| | | | | | | |
|---|---|---|---|---|---|---|
| **Narrative:** 74 yo hospitalized for Non-fatal MI. Cardiac cath did not demonstrate significant CAD, patient most likely had TAKOTSUBO SYNDROME. Patient has not had any further CP or SOB since being in the hospital. Patient stable for discharge to home. | | | | | | |
| Worsening Chest Pain, Hospitalization | 1 | 1-29 | 01/24/19 | Yes | Unrelated | 01/27/19 |
| **Narrative:** 66 yo hospitalized for chest pain. BP 145/77, troponin neg., admitted for CP, CT angiogram did not show CAD. No change to therapy. Discharged with follow-up with PCP. | | | | | | |
| Worsening Chest Pain, Hospitalization | 2 | 5-42 | 05/06/19 | Yes | Unrelated | 05/07/19 |
| **Narrative:** 52 yo hospitalized for chest pain. EKG nl, troponin neg., and chest X-ray nl. BP 136/88. Chronic chest pain likely secondary to uncontrolled blood pressure, to follow-up with primary cardiologist. | | | | | | |
| Worsening Chest Pain, Hospitalization | 2 | 11-2 | 06/30/19 | Yes | Unrelated | 07/01/19 |
| **Narrative:** 57 yo hospitalized for chest pain. BP 123/67, chest x-ray nl, exercise test normal, ACS ruled out by criteria, discharged for outpatient follow-up. | | | | | | |
| Worsening Chest Pain, Hospitalization | 2 | 11-10 | 05/01/19 | Yes | Unrelated | 05/02/19 |
| **Narrative:** 75 yo hospitalized for chest pain. BP 124/50, troponin neg. Atrial fibrillation, converted spontaneously, discharged to follow up with cardiologist in 1 week. | | | | | | |
| Worsening Chest Pain, Hospitalization | 2 | 14-18 | 02/07/19 | Yes | Unrelated | 04/18/19 |
| **Narrative:** 64 yo hospitalized for chest pain. Troponin neg., BP 107/52, small inferior and apical reversible ischemic area on stress nuclear imaging. Given 3 nitros with no relief. Pending discharge notes and final adjudication. | | | | | | |
| Worsening Chest Pain, Hospitalization | 1 | 14-47 | 04/15/19 | Yes | Unrelated | 04/16/19 |
| **Narrative:** 47yo hospitalized for chest pain. BP 104/76, Serial troponin and EKG negative, BNP WNL. Discharge stable for discharge on home medications. Scheduled for outpatient TTE and EECP. | | | | | | |

**Table 12. WARRIOR Secondary Outcomes**

| Group 1 | N | Mean | Std Dev | Min | Med | Max | | Group 2 | N | Mean | Std Dev | Min | Med | Max |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **SAQ physlim** | 237 | **63.57** | 26.67 | 0 | 66.67 | 100 | | **SAQ physlim** | 232 | **67.13** | 26.75 | 0 | 69.44 | 100 |
| **SAQ angfreq** | 247 | **73.04** | 22.78 | 0 | 80 | 100 | | **SAQ angfreq** | 242 | **75.74** | 21.38 | 10 | 80 | 100 |
| **SAQ angstab** | 247 | **46.05** | 23.79 | 0 | 50 | 100 | | **SAQ angstab** | 242 | **51.55** | 25.97 | 0 | 50 | 100 |
| **SAQ trtsat** | 247 | **75.25** | 26.44 | 0 | 81.25 | 100 | | **SAQ trtsat** | 242 | **73.96** | 28.13 | 0 | 81.25 | 100 |
| **SAQ qol** | 247 | **52.11** | 26.1 | 0 | 50 | 100 | | **SAQ qol** | 242 | **55.11** | 26.23 | 0 | 58.33 | 100 |
| **SAQ-7overall** | 247 | **63.05** | 21.9 | 0 | 64.17 | 100 | | **SAQ-7overall** | 242 | **66.6** | 22.57 | 6.11 | 69.17 | 100 |
| **DASI score** | 253 | **5.42** | 4.97 | 0 | 4.4 | 16.7 | | **DASI score** | 253 | **5.74** | 5.19 | 0 | 3.9 | 16.7 |
| **PCL5 sum** | 251 | **14.6** | 15.64 | 0 | 9 | 80 | | **PCL5 sum** | 249 | **15.89** | 15.75 | 0 | 11 | 80 |
| **PCL5 cluster B** | 251 | **3.94** | 4.98 | 0 | 2 | 20 | | **PCL5 cluster B** | 249 | **4.47** | 4.81 | 0 | 3 | 20 |
| **PCL5 cluster C** | 251 | **1.82** | 2.38 | 0 | 1 | 8 | | **PCL5 cluster C** | 249 | **1.95** | 2.37 | 0 | 1 | 8 |
| **PCL5 cluster D** | 251 | **4.29** | 6.03 | 0 | 2 | 28 | | **PCL5 cluster D** | 249 | **4.39** | 5.5 | 0 | 2 | 28 |
| **PCL5 cluster E** | 251 | **4.54** | 4.26 | 0 | 4 | 24 | | **PCL5 cluster E** | 249 | **5.08** | 4.89 | 0 | 4 | 24 |

**Table 13. WARRIOR Non-Serious Adverse Events Unrelated**

| | Grade 1 Mild or Grade 2 Moderate | | Grade 4 Life-threatening consequences: |
|---|---|---|---|
| | Randomized Group | | Randomized Group |
| | 1 | 2 | 2 |
| | N | | |
| **Cardiac** | | | |
| **Dyspnea** | 3 | 2 | . |
| **Hypotension** | 0 | 1 | . |
| **Chest pain, worsening** | 14 | 18 | . |
| **Non-cardiac** | | | |
| **Cough** | 2 | 1 | . |
| **Edema, pedal** | 1 | . | . |
| **Gastrointestinal bleeding** | | 1 | |
| **Headache** | 0 | 2 | . |
| **Hyperkalemia** | 0 | 1 | . |
| **Hypokalemia** | 3 | 0 | . |
| **Lightheadedness** | 1 | 0 | . |
| **Myositis (Myalgia plus CPK elevation >10x normal reference range)** | 1 | 1 | . |
| **Other** | 63 | 53 | 1 |
| **Total** | 89 | 80 | 1 |

**Table 14. WARRIOR Non-Serious Adverse Events Unrelated- Other**

| | Grade 1 Mild or Grade 2 Moderate | | Grade 4 Life-threatening consequences: |
|---|---|---|---|
| | Randomized Group | | Randomized Group |
| | 1 | 2 | 2 |
| | N | | |
| **Cardiac** | | | |
| **Hypertension** | 1 | 3 | . |
| **Hypertrophic cardiomyopathy** | 1 | . | . |
| **Left subclavian occlusion** | 1 | . | . |
| **Palpitations** | 2 | . | . |
| **Paroxysmal atrial fibrillation** | 1 | . | . |
| **Premature ventricular contractions** | 1 | . | . |
| **Syncope/near syncope** | 3 | 1 | . |
| **Tachycardia** | 1 | 1 | . |
| **Non-cardiac** | | | |
| **Abdominal pain** | 1 | 1 | . |
| **Abdominal wall hematoma** | . | 1 | . |
| **Abdominal pain, upper** | 1 | . | . |
| **Acute left ankle pain** | 1 | . | . |
| **Acute cystitis** | . | 1 | . |
| **Acute flank pain** | 1 | . | . |
| **Acute kidney injury** | 1 | . | . |
| **Allergy** | . | 1 | . |
| **Ankle sprain** | . | 1 | . |
| **Bacterial pneumonia** | . | 1 | . |
| **Bilateral hand pain** | . | 1 | . |
| **Bladder biopsy for hematuria** | 1 | . | . |
| **Knee surgery** | . | 1 | |
| **Pelvic pain** | 2 | . | . |
| **Pilonidal cyst** | . | 1 | . |
| **Pneumothorax, right** | 1 | . | . |
| **Poor libido** | . | 1 | . |
| **Post-operative bleeding** | . | 1 | . |
| **Post op pain** | . | 1 | . |
| **Pyelitis** | 1 | . | . |
| **Respiratory virus** | . | 1 | . |
| **Right facial numbness** | . | 1 | . |
| **Rotator cuff tear, partial** | 1 | . | . |
| **Shortness of breath, nausea** | . | 2 | . |
| **Shoulder pain** | 1 | . | . |
| **Sinus Infection** | . | 1 | . |
| **Spot on lung** | 1 | . | . |
| **Status migrainosus** | . | 1 | . |
| **Tinea unguium with skin ulceration right 3rd toe** | . | 1 | . |
| **Toe pain** | 1 | . | . |
| **Upper respiratory infection** | 2 | . | . |
| **Urinary tract infection** | 1 | 3 | . |
| **Urticarial Rash** | . | 1 | . |
| **Vaginal bleeding** | 1 | . | . |
| **Vertigo** | . | 1 | . |
| **Vomiting** | 1 | 2 | . |
| **Total of other events** | 62 | 52 | 1 |

**Table 15. WARRIOR Non-Serious Adverse Event- Related**

| | Grade 1 Mild | | Grade 2 Moderate |
|---|---|---|---|
| | Randomized Group | | Randomized Group |
| | 1 | 2 | 1 |
| | N | | |
| **Cardiac** | | | |
| **Dyspnea** | . | . | 2 |
| **Hypotension** | 1 | . | 2 |
| **Lightheadedness** | 2 | . | 1 |
| **Chest Pain, worsening** | 1 | 1 | . |
| **Non-cardiac** | | | |
| **Cough** | 1 | . | . |
| **Headache** | . | . | 1 |
| **Other (specify below)** | 7 | 1 | 5 |
| **Total** | 12 | 2 | 11 |

**Table 16. WARRIOR Non-Serious Adverse Event Related- Other**

| | Grade 1 Mild | | Grade 2 Moderate |
|---|---|---|---|
| | Randomized Group | | Randomized Group |
| | 1 | 2 | 1 |
| | N | | |
| **Cardiac** | | | |
| **Bradycardia** | 1 | . | . |
| **Non-cardiac** | | | |
| **Back pain** | . | . | 1 |
| **Elevated liver enzymes** | 1 | . | . |
| **Fatigue** | . | . | 1 |
| **Hip pain** | . | . | 1 |
| **Hives** | 1 | . | . |
| **Jaw pain** | 1 | . | . |
| **Left flank pain** | . | 1 | . |
| **Leg pain/cramps** | . | . | 2 |
| **Muscle aches/cramps** | 2 | . | . |
| **Myalgias, No CPK drawn** | 1 | . | . |
| **Total** | 7 | 1 | 5 |

**Table 17. WARRIOR Non-Serious Adverse Events Likely Related**

| | Grade 1 Mild | Grade 2 Moderate |
|---|---|---|
| | Randomized Group | Randomized Group |
| | 1 | 1 |
| | N | |
| **Cardiac** | | |
| **Hypotension** | 1 | . |
| **Lightheadedness** | 1 | 1 |
| **Chest pain, worsening** | 2 | . |
| **Non-cardiac** | | |
| **Cough** | 1 | . |
| **Other (specify below)** | 1 | 1 |
| **Total** | 6 | 2 |

**Table 18. Non Serious Adverse Events Likely Related- Other**

| | Grade 1 Mild | Grade 2 Moderate |
|---|---|---|
| | Randomized Group | Randomized Group |
| | 1 | 1 |
| | N | |
| **Non-cardiac** | | |
| **Heartburn** | . | 1 |
| **Oral, swelling** | 1 | . |
| **Total** | 1 | 1 |

**Table 19. WARRIOR Serious Adverse Events Unrelated- Other Reasons for Hospitalizations**

| Toxicity grade of the adverse event. Please refer to the CTCAE Grade Adverse Event V5.0 | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Grade 1 Mild | | Grade 2 Moderate | | Grade 3 Severe | | Grade 4 Life-Threatening | |
| **Describe other reason for hospitalization:** | | | | | | | | |
| | Group | | Group | | Group | | Group | |
| **Cardiac** | **1** | **2** | **1** | **2** | **1** | **2** | **1** | **2** |
| **Anterior septal myomectomy** | 1 | . | . | . | . | . | | |
| **Embolic stroke (PFO)** | 1 | . | . | . | . | . | | |
| **Frequent PVCs/bigeminy** | 1 | . | . | . | . | . | | |
| **Hypertensive crisis** | 1 | . | . | . | . | . | | |
| **Inappropriate sinus tachycardia** | 1 | . | . | . | . | . | | |
| **NSTEMI** | . | . | . | 1 | . | . | | |
| **Planned PFO Closure** | 1 | . | . | . | . | . | | |
| **Syncope** | . | 1 | . | . | . | . | | |
| **Chest pain, worsening** | . | . | . | . | . | . | 1 | . |
| **Non-cardiac** | | | | | | | | |
| | **1** | **2** | **1** | **2** | **1** | **2** | **1** | **2** |
| **Abdominal pain** | . | 1 | . | . | . | . | | |
| **Acalculous cholecystitis/acute cholecystitis** | . | . | . | . | 1 | . | | |
| **Asthma exacerbation** | . | . | . | . | . | 1 | | |
| **Cellulitis, lower leg** | . | 1 | . | . | . | . | | |
| **Cecal mass** | . | . | . | . | 1 | . | | |
| **Cellulitis of abdominal wall** | 1 | . | . | . | . | . | | |
| **Chronic neck and back pain** | . | 1 | . | . | . | . | | |
| **Dyspnea on exertion** | 1 | . | . | . | . | . | | |
| **Gastroparesis flare-up** | . | 1 | . | . | . | . | | |
| **Left pelvic fracture** | 1 | . | . | . | . | . | | |
| **Migraine** | . | . | . | 1 | . | . | | |
| **Pneumonia** | 1 | . | . | . | . | . | | |
| **Right total knee replacement** | . | 1 | . | . | . | . | | |
| **RS Virus** | 1 | . | . | . | . | . | | |
| **Sacroiliitis** | . | . | . | . | 1 | . | | |
| **Sepsis** | 1 | 2 | . | . | . | . | | |
| **Seziure monitoring** | . | . | 3 | 2 | . | . | | |
| **Status Migrainosis** | . | . | . | . | 1 | . | | |
| **Stills disease flare up** | . | . | . | 1 | 1 | . | | |
| **All** | **12** | **8** | **3** | **5** | **5** | **1** | **1** | **.** |

**Table 20. WARRIOR Serious Adverse Events – Other Reasons for Emergency Department Visits**

| Toxicity grade of the adverse event. Please refer to the CTCAE Grade Adverse Event V5.0 | | | | |
|---|---|---|---|---|
| | Grade 1 Mild | Grade 2 Moderate | | Grade 4 Life-Threatening |
| | Group | Group | | Group |
| | 2 | 1 | 2 | 2 |
| | N | | | |
| Describe other reason for the emergency room visit: | | | | |
| **Cardiac** | | | | |
| Syncope | 1 | 3 | . | . |
| Chest pain, worsening | 1 | . | . | . |
| **Non-cardiac** | | | | |
| Acute left-sided low back pain | . | . | 1 | . |
| Allergic Reaction-Rash | 1 | . | . | . |
| Back spasm | 1 | . | . | . |
| Pneumonia of right lower lobe due to infectious organism | . | . | . | 1 |
| All | 4 | 3 | 1 | 1 |

## APPENDIX C DOD PROJECT OFFIDER EMAIL FOR NO-COST EXTENSION

Hello Dr. Handberg,

I would like to recap the NCE process for CDMRP and USMRAA for the purposes of your upcoming September 24, 2019 DSMB Meeting.

For the first NCE request, it is effectively a formality to request one assuming an award I good standing. Good standing for a clinical trial award refers to all technical reporting requirements being fulfilled. For your project, quarterly reports have been requested. The quarterlies should not be a burden and the key information I need are enrollment numbers, any issues with or related to HRPO or IRB, and any key findings. Any presentations or publication (and IP if applicable) is also welcome. The fourth quarterly is the annual report, which has a higher burden to complete. Here, the year's progress is recapped.

RAA will look to see if there are any outstanding financial issues and both RAA and I look at research overlap. However, you have a clinical trial -- this not really an issue I would worry about (research overlap for your trial, that is).

If these requirements are met, the first NCE is issued quite readily. When the time comes, ~90 days before the end of your award, notify the Contract Specialist and me regarding the request, and you will be sent the following list (below) to help us in processing the request.

1. Notify the USAMRAA Grants Officer or Grants Specialist of your intention to extend your award at least 30 days prior to the expiration date of your award. This notification can be in the form of an email or letter, but must come from the authorized Business Office/Sponsored Projects Office official. Please copy the Grants Officer's Representative/Science Officer assigned to your award on your correspondence.
2. Indicate how much additional time is needed; your request cannot exceed 12 months.
3. Indicate that no additional funds are being requested.
4. Outline the remaining tasks to be completed; all work must be within the scope of the original Statement of Work.
5. Include reasons supporting the extension.
6. Make certain that all financial (SF425) and technical progress reports (quarterly and/or annual) have been submitted.
7. Make certain all human and/or animal protocols and continuing reviews are up to date and that the appropriate approvals are in place 8. If your award has a progress report that is due even while your NCE request is being processed, please submit as the next due Annual rather than the Final report.

If a second NCE is needed, it is a very similar process, except this time, the Science Officer (me) will conduct an assessment of the progress of the work and offer a rationale to Contract Specialist, Program Manager, and Contracts Officer as to why the additional time is necessary. Ultimately, with a clinical trial, the patients' well-being and product the DoD is attempting to fund are key. Unless there is negligence with respect to technical, financial, and patients' outcomes reporting, the second NCE is a good option for all parties involved.

The key thing with both requests is to request additional time only; no additional funds should be requested.

If you have any questions, please contact me directly [below] and I will be happy to resolve any issues the DSMB may have with the DoD's processes.

Thank you.

Rahul
=========
Rahul G. Thakar, Ph.D.
Senior Science Officer, Congressionally Directed Medical Research Programs via Tunnell Government Services United States Army Medical Research Development Command (USAMRDC)

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## APPENDIX D MCJUNKIN

Utilizing McJunkin foundation support preliminary analyses on biorepository specimens from the WARRIOR population have been completed and the pilot data is being utilized to submit for additional AHA, NIH and DoD funding. A brief outline of the two active proposals are summarized below.

***Project 1*- Pilot study quantification of inflammation, efferocytosis and endothelial cell dysfunction in women with coronary microvascular dysfunction**

**Overarching Aim:** to examine associations among CMD, inflammation and endothelial cell biology. Ho: clinical severity of CMD correlates with level of inflammatory mediators, rate of inflammation resolution (efferocytosis), and endothelial cell number and function. Data will be collected from women with CMD and peripheral blood specimens via BE-A-WARRIOR biorepository (IRB201801541). A limited number of reference women will be studied to optimize assays.
1. Plasma samples examined for chronic inflammatory mediators (ELISA/Luminex assay and liquid chromatography-tandem mass spectroscopy-based metabolipidomics.

2. Cellular fraction (buffy coat) of peripheral blood samples examined for concentration of circulating progenitor cells (CD34+, CD34+CD133+, CD34+VEGFR2+, CD34+CD133+VEGFR2+), endothelial cell outgrowth in EGM2 media, and gap closure by scratch assay in endothelial cells.

3. From these same participants, we will also obtain clinical data via the WARRIOR trial.

- Accordingly, we *hypothesized* that inflammation in general, and **ICH** in particular, may be a key factor that explains development of small vessel disease/dysfunction in the heart (and perhaps in other solid organs throughout the body), in some women with chest pain and/or shortness of breath.
- To better understand this-
    - we are studying the ***function and responses*** of circulating peripheral blood mononuclear cells (**PBMC**) from women:
    - in the biorepository, and
    - ***reference subjects*** without chest pain/known heart disease.

**Our preliminary studies to date have:**

- Uncovered remarkable state of **inflammatory cell hyperactivity (ICH)** that can exist under conditions that have been stressful to the body (e.g. emotional, physical, head trauma, etc.).
- This hyper-reactive state has some especially notable features. It:

  1.) P**ersists** for extended periods of time (months or perhaps years), after initial stressor is no longer apparent or presenting obvious difficulty; and
  2.) Is **silent**, in that levels of inflammatory factors present in the bloodstream do not reflect this hyperactivity of the circulating cells.
- Perhaps they are *most clearly hyperactive* after they *are "re-stimulated",* or
- The quantity of inflammatory factors that they produce, while medically significant, is insufficient to be detected when diluted throughout the body.

***Project 2- Assessing inflammatory and immune status in women with microvascular disease.***

**Overarching Aim:** to assess key soluble and cellular factors believed important in defining level of systemic “stress”, due to, and manifested as inflammation that can adversely affect coronary microvascular function in women. To accomplish this, we will perform assays as follows:

- Luminex bead-based assays for multiple protein factors (e.g. TNFa, IL-1, IL-6, IL-10, etc.);

- Flow cytometric assays for leukocyte subset phenotyping, including assessment of typical and regulatory T cells (Tregs), circulating monocytes of M1 (pro-inflammatory) and M2 phenotypic tendencies, and monocyte-derived suppressor cells (MDSC);

- Based on our data about systemic stress-induced inflammation, we will assess secretory profiles of monocyte preparations from women, at baseline and upon stimulation by pro- inflammatory factors. Provides insight into how much ongoing inflammation is present and how much of a “hair-trigger” for worsened inflammation is experienced by each individual. Preliminary data indicates that some individuals, post-stress, are “inflamed” as well as “hyper-responsive” to inflammatory stimuli and;

- ***We have also observed that adipose-derived stem cell secretome suppresses this inflammatory tendency. Thus, we will evaluate whether cells from inflamed women with CMD can be suppressed, with respect to inflammation.***

## APPENDIX D. DSMB Recommendations

**Women's IschemiA TRial to Reduce Events In Non-ObstRuctive CAD (WARRIOR) Trial**
**Data and Safety Monitoring Board (DSMB) Summary Report**
October 3, 2019

Dear WARRIOR Investigators,

The Data Safety Monitoring Board (DSMB) for WARRIOR convened on Tuesday, September 24, 2019 with no safety concerns:

- a review of outcome data, adverse events, and information relating to study performance (e.g., data timeliness, completeness, and quality) across all centers took place
- the observed frequency of adverse events did not exceed what was expected and indicated in the informed consent
- There was no recent literature relevant to the research
- the DSMB recommends that the study continue with a major effort on recruitment

The DSMB would like to commend the trial investigators on their response to queries and would like to request the following:

- An interim report regarding recruitment before the next DSMB
- Review of any protocol amendment
- A review of the consent forms
- Information on vaping added to data forms

Finally, Dr. Wenger would like to reconvene for another full DSMB meeting in six months.

Sincerely,
Kyler Conn
**WARRIOR Executive Secretary**
**Cedars-Sinai Consortium**
kyler.conn@cshs.org

Attendees:

| | | | |
|---|---|---|---|
| ☒Nanette K. Wenger | *DSMB Member (DSMB Chair)* | ☒Carl Pepine | *Executive Committee* |
| ☒Kerry Lee | *DSMB Member (Biostatistician)* | ☒Eileen Handberg | *Executive Committee* |
| ☒Daniel Mark | *DSMB Member* | ☐ Rhonda Cooper-DeHoff | *Executive Committee* |
| ☒Harmony Reynolds | *DSMB Member* | ☒C. Noel Bairey Merz | *Executive Committee* |
| ☒Viviany Taqueti | *DSMB Member* | ☒Andre Rogatko | *Executive Committee* |
| ☒Puja Mehta | *Research Monitor* | ☒Janet Wei | *Executive Committee* |
| | | ☒Bernard Chaitman | *Executive Committee* |
| | | ☐ Dana Leach | *Project Manager* |
| | | ☒Taylor Galloway | *Project Coordinator* |
| | | ☒Kyler Conn | *Executive Secretary* |

**APPENDIX E. 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)
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 (CSC)
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 currentlydivided 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.

# 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** |