

AWARD NUMBER: W81XWH-15-1-0268

Log Number: BC141141

TITLE: Randomized Trial of Aspirin as Adjuvant Therapy for Node-Positive Breast Cancer

PRINCIPAL INVESTIGATOR: Eric Winer

RECIPIENT: Dana-Farber Cancer Institute, Inc.

REPORT DATE: OCTOBER 2020

TYPE OF REPORT: Annual

**PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012**

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REPORT DOCUMENTATION PAGE

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OMB No. 0704-0188

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1. REPORT DATE OCTOBER 2020			2. REPORT TYPE Annual		3. DATES COVERED 9/15/2019 - 9/14/2020	
4. TITLE AND SUBTITLE Randomized Trial of Aspirin as Adjuvant Therapy for Node-Positive Breast Cancer					5a. CONTRACT NUMBER W81XWH-15-1-0268	
					5b. GRANT NUMBER	
					5c. PROGRAM ELEMENT NUMBER	
6. AUTHOR(S) Eric Winer Wendy Chen E-Mail: Eric.Winer@dfci.harvard.edu ; Wendy.Chen@dfci.harvard.edu					5d. PROJECT NUMBER	
					5e. TASK NUMBER	
					5f. WORK UNIT NUMBER	
7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES) Dana-Farber Cancer Institute 450 Brookline Avenue Boston, MA 02215-5450					8. PERFORMING ORGANIZATION REPORT NUMBER	
9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES) U.S. Army Medical Research and Materiel Command Fort Detrick, Maryland 21702-5012					10. SPONSOR/MONITOR'S ACRONYM(S)	
					11. SPONSOR/MONITOR'S REPORT NUMBER(S)	
12. DISTRIBUTION / AVAILABILITY STATEMENT Approved for Public Release; Distribution Unlimited						
13. SUPPLEMENTARY NOTES						
14. ABSTRACT In the United States, more than 3 million women are living after a breast cancer diagnosis. There is great need for additional breast cancer adjuvant treatments that are low-cost and low toxicity. These would not only save thousands of lives, but offer improved quality of life for those who do not tolerate current treatments, and treatment options to women in developing countries who currently get none. We will enroll 3000 women with node-positive HER2 negative Stage II or III breast cancer with a 1:1 randomization to aspirin 325 mg daily versus placebo. Primary endpoint is invasive disease-free survival (including local and distant). Secondary endpoints include recurrence-free interval (local and distant), overall survival, cardiovascular disease, toxicity, and adherence. We will exclude those at high risk of bleeding complications with aspirin (\geq age 70, history of prior stroke, significant gastrointestinal bleeding, anticoagulation) or those with indications for taking aspirin (history of myocardial infarction or atrial fibrillation) Breast cancer advocates will be involved in the creation of all recruitment letters, consent forms, and information sheets. We would conduct the trial in a multi-center collaboration of the Brigham and Women's Hospital, Dana Farber Harvard Cancer Institute, and the Alliance for Clinical Trials in Oncology. The research infrastructure, long-standing leadership roles in clinical trials, and ability to rapidly accrue subjects make the assembled research team ideal to lead a US trial within the proposed time frame.						
15. SUBJECT TERMS Breast cancer, adjuvant treatment, aspirin, randomized controlled trial						
16. SECURITY CLASSIFICATION OF:				17. LIMITATION OF ABSTRACT Unclassified	18. NUMBER OF PAGES 17	19a. NAME OF RESPONSIBLE PERSON USAMRMC
a. REPORT Unclassified	b. ABSTRACT Unclassified	c. THIS PAGE Unclassified	19b. TELEPHONE NUMBER (include area code)			

ABSTRACT

In the United States, more than 3 million women are living after a breast cancer diagnosis. There is great need for additional breast cancer adjuvant treatments that are low-cost and low toxicity. These would not only save thousands of lives, but offer improved quality of life for those who do not tolerate current treatments, and treatment options to women in developing countries who currently get none.

We will enroll 2936 women with HER2 negative non-metastatic breast cancer with a 1:1 randomization to aspirin 300 mg daily versus placebo. Primary endpoint is invasive disease-free survival (including local and distant). Secondary endpoints include recurrence-free interval (local and distant), overall survival, cardiovascular disease, toxicity, and adherence. We will exclude those at high risk of bleeding complications with aspirin (>age 70, history of prior stroke, significant gastrointestinal bleeding, anticoagulation) or those with indications for taking aspirin (history of myocardial infarction or atrial fibrillation) Breast cancer advocates will be involved in the creation of all recruitment letters, consent forms, and information sheets. We would conduct the trial in a multi-center collaboration of the Brigham and Women's Hospital, Dana Farber Harvard Cancer Institute, and the Alliance for Clinical Trials in Oncology. The research infrastructure, long-standing leadership roles in clinical trials, and ability to rapidly accrue subjects make the assembled research team ideal to lead a US trial within the proposed time frame.

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- 1. INTRODUCTION:** Narrative that briefly (one paragraph) describes the subject, purpose and scope of the research.

There is great need for additional breast cancer adjuvant treatments that are low-cost and low toxicity. We believe aspirin holds great promise, and propose a randomized controlled trial to test that promise. There is compelling epidemiologic, in-vitro, and in-vivo, evidence of aspirin's potential. We will enroll 2936 women with HER2 negative non-metastatic breast cancer with a 1:1 randomization to aspirin 300 mg daily versus placebo. Primary endpoint is invasive disease-free survival (including local and distant). Secondary endpoints include recurrence-free interval (local and distant), overall survival, cardiovascular disease, toxicity, and adherence. We hypothesize that breast cancer survivors randomized to aspirin will have fewer recurrences and longer recurrence-free survival than those on placebo.

- 2. KEYWORDS:** Provide a brief list of keywords (limit to 20 words).

Breast cancer, adjuvant treatment, aspirin, randomized controlled trial

- 3. ACCOMPLISHMENTS:** The PI is reminded that the recipient organization is required to obtain prior written approval from the awarding agency Grants Officer whenever there are significant changes in the project or its direction.

What were the major goals of the project?

List the major goals of the project as stated in the approved SOW. If the application listed milestones/target dates for important activities or phases of the project, identify these dates and show actual completion dates or the percentage of completion.

The goals and milestones listed below pertain to months 49-60 in the approved SOW:

Specific Aims 1 & 2: Clinical Trial

- Screen subjects and consent eligible subjects to study (months 6-30) – Began December 2016, ongoing
- Assign participants to one of two randomized groups study (months 6-30) – Began December 2016, ongoing
- Distribute study medication for the first 6 months study (months 6-30) – Began December 2016, ongoing
- Review accrual statistics to ensure that accrual goals will be met (every 6 months) – This is actually done every month. Began December 2016 and occurs on weekly basis
- Assess participants every 6 months while on study (months 12-30) – Began December 2016, ongoing
- Assess for toxicity and adverse events (ongoing) – Began December 2016, ongoing
- Assess for need for dose reduction (ongoing) – Began December 2016, ongoing
- Assess for need for proton pump inhibitor (ongoing) – Began December 2016, ongoing
- Assess compliance with study drug (months 12-60) Began December 2016, ongoing
- Coordinate with sites and data for data collection (months 6-60) – Began December 2016, ongoing
- Data cleaning (months 54-55)

- Perform data analysis (months 55-58)
- Present data at Alliance and national oncology meetings (months 59-60)
- *Milestone achieved: Meet accrual goal for subjects (month 30)* -Prior to the COVID19 pandemic, the accrual goal of 100 subjects had been met. As expected, accrual significantly declined in April and May 2020, but has gradually been increasing since and most recently has averaged 75 subjects per month for the past 3 months. – see Section 5: Changes, Problems
- *Milestone Achieved: Report findings from characteristics of baseline population (month 30-32)*) - This was not achieved due to delay in subject accrual – see Section 5: Changes, Problems
- *Milestone Achieved: Report findings from Study (month 60)* This was not achieved due to delay in subject accrual – see Section 5: Changes, Problems.

Specific Aim 3: Creation of biospecimen and epidemiologic biobank

- Collection of tumor specimens at baseline (months 6-30) – Began December 2016, ongoing
- Collection of blood and urine specimens at baseline (months 6-30) – Began December 2016, ongoing
- Storage and cataloguing of specimens (months 6-60) – Began December 2016, ongoing
- Collection of covariate data on sleep, stress, BMI, etc. (months 6-60) – Began December 2016, ongoing
- *Milestone Achieved: Complete biospecimen collection and creation of a biospecimen repository (month 60)*. This is ongoing and not completed due to delay in subject accrual.
- *Milestone Achieved: Submit research grants on correlative works using biospecimens and epidemiologic data (months 50-60)* A sub-study evaluating changes in mammographic density among triple negative breast cancer patients enrolled on the aspirin stud was activated through the Alliance and is accruing subjects. The funding for the sub-study is through the National Cancer Institute

What was accomplished under these goals?

For this reporting period describe: 1) major activities; 2) specific objectives; 3) significant results or key outcomes, including major findings, developments, or conclusions (both positive and negative); and/or 4) other achievements. Include a discussion of stated goals not met. Description shall include pertinent data and graphs in sufficient detail to explain any significant results achieved. A succinct description of the methodology used shall be provided. As the project progresses to completion, the emphasis in reporting in this section should shift from reporting activities to reporting accomplishments.

Referring to the SOW:

Specific Aims 1 & 2: Clinical Trial

- We began enrollment on Dec. 8, 2016. This included screening, randomization, distribution of study medication, collection of biospecimens, collection of epidemiologic data, collection of information on toxicity and adverse events, need for dose reduction, and need for proton pump inhibitor. The Alliance Data Safety and Monitoring Board last

met on May 15, 2020 and did not find any issues regarding adverse events or efficacy. Specifically, there were no grade 3 or 4 adverse events attributed to study drug. No interventions were recommended.

- We have assessed enrollment monthly
- As of September 9, 2020, 1191 sites have registered and approved to enroll subjects.
- As of October 12, 2020, 2811 subjects have registered and been randomized.
- Prior to the COVID19 pandemic, the trial had met its accrual goal of 100 subjects per month. In April and May 2020, accrual significantly declined, but now has rebounded. Over the past 3 months, accrual has averaged 75 subjects per month.

Specific Aim 3: Biorepository

- As of September 26, 2020, 72% have submitted biospecimens (blood and/or tumor) and 90% have submitted a lifestyle questionnaire
- A sub-study evaluating changes in mammographic density among triple negative breast cancer patients enrolled on the aspirin stud was activated through the Alliance and is accruing subjects. The funding for the sub-study is through the National Cancer Institute

Additional Achievements, not in the SOW

- The first External Advisory Board meeting was held 11/21/16 . A trials in progress poster was presented at the semi-annual Alliance for Clinical Trials Oncology meeting in May 2017 at the annual American Society for Clinical Oncology meeting in June 2017. Our Patient Advocates publicized the study at the National Advocate Leadership Summit for the National Breast Cancer Coalition in May 2017.
- The second External Advisory Board meeting was held on 11/13/17. During the meeting we discussed slow accrual. The advice was given to liberalize the inclusion criteria (please see Section 5 Problems and Changes to document what was suggested). A trials in progress poster was presented at the semi-annual Alliance for Clinical Trials Oncology meeting in November 2017 and May 2018 and at the annual American Society of Clinical Oncology meeting in June 2018. The advocates publicized the work at the San Antonio Breast Symposium in December 2017.
- December 2018 Patient Advocate Maggie Carvan publicized the trial at the San Antonio Breast Cancer Conference. The External Advisory Board met on December 10, 2018 and members were updated on study progress and protocol amendments. A trials in progress poster was presented at the annual American Society of Clinical Oncology meeting in June 2019
- The External Advisory Board met on February 3, 2020. A trials in progress poster was presented at the annual American Society of Clinical Oncology meeting in June 2020.

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

If the project was not intended to provide training and professional development opportunities or there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe opportunities for training and professional development provided to anyone who worked on the project or anyone who was involved in the activities supported by the project. "Training" activities are those in which individuals with advanced professional skills and experience assist others in attaining greater proficiency. Training activities may include, for

example, courses or one-on-one work with a mentor. “Professional development” activities result in increased knowledge or skill in one’s area of expertise and may include workshops, conferences, seminars, study groups, and individual study. Include participation in conferences, workshops, and seminars not listed under major activities.

Nothing to report

How were the results disseminated to communities of interest?

If there is nothing significant to report during this reporting period, state “Nothing to Report.”

Describe how the results were disseminated to communities of interest. Include any outreach activities that were undertaken to reach members of communities who are not usually aware of these project activities, for the purpose of enhancing public understanding and increasing interest in learning and careers in science, technology, and the humanities.

Nothing to report

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

If this is the final report, state “Nothing to Report.”

Describe briefly what you plan to do during the next reporting period to accomplish the goals and objectives.

We should complete accrual within the next few months based upon current accrual. The statistical power is driven by the number of cancer events as well as total enrollment. More time will be needed to await occurrence of cancer events, so a no cost extension was requested and approved. Please see Section 5: Problems and Changes for these details.

4. **IMPACT:** Describe distinctive contributions, major accomplishments, innovations, successes, or any change in practice or behavior that has come about as a result of the project relative to:

What was the impact on the development of the principal discipline(s) of the project?

If there is nothing significant to report during this reporting period, state “Nothing to Report.”

Describe how findings, results, techniques that were developed or extended, or other products from the project made an impact or are likely to make an impact on the base of knowledge, theory, and research in the principal disciplinary field(s) of the project. Summarize using language that an intelligent lay audience can understand (Scientific American style).

Nothing to report.

What was the impact on other disciplines?

If there is nothing significant to report during this reporting period, state “Nothing to Report.”

Describe how the findings, results, or techniques that were developed or improved, or other products from the project made an impact or are likely to make an impact on other disciplines.

Nothing to report

What was the impact on technology transfer?

If there is nothing significant to report during this reporting period, state “Nothing to Report.”

Describe ways in which the project made an impact, or is likely to make an impact, on commercial technology or public use, including:

- *transfer of results to entities in government or industry;*
- *instances where the research has led to the initiation of a start-up company; or*
- *adoption of new practices.*

Nothing to report

What was the impact on society beyond science and technology?

If there is nothing significant to report during this reporting period, state “Nothing to Report.”

Describe how results from the project made an impact, or are likely to make an impact, beyond the bounds of science, engineering, and the academic world on areas such as:

- *improving public knowledge, attitudes, skills, and abilities;*
- *changing behavior, practices, decision making, policies (including regulatory policies), or social actions; or*
- *improving social, economic, civic, or environmental conditions.*

Nothing to report

5. **CHANGES/PROBLEMS:** The Project Director/Principal Investigator (PD/PI) is reminded that the recipient organization is required to obtain prior written approval from the awarding agency Grants Officer whenever there are significant changes in the project or its direction. If not previously reported in writing, provide the following additional information or state, “Nothing to Report,” if applicable:

Changes in approach and reasons for change

Describe any changes in approach during the reporting period and reasons for these changes. Remember that significant changes in objectives and scope require prior approval of the agency.

Nothing to report

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

Describe problems or delays encountered during the reporting period and actions or plans to resolve them.

At the beginning of the current reporting period, we achieved our target accrual of 100 patients per month. We were on target to finish accrual in summer 2020 (end of year 5), however would need extra time for analysis and thus requested a 1 year no cost extension which was granted in June 2020.

However in early 2020, the COVID-19 pandemic engulfed the entire United States and severely impacted the US health care system. Some hospitals suspended enrollment in clinical trials and/or decreased the number of clinical trials enrolling. Furthermore, many patients postponed their routine follow up appointments for physicians. Consequently, our accrual decreased to a nadir of 21 subjects in April 2020 and 28 subjects in May 2020. In April 2020, we had an amendment approved to allow remote consenting and telehealth visits, since telemedicine has become a routine part of healthcare now. This is important for two reasons: to ensure new subjects continue to enroll, but also to maintain follow up of subjects already on study. Shipping of study drug to participants had already been allowed per protocol. Over the past 3 months (July-September 2020), we have average 75 subjects per month. We are currently at 96% of our target accrual (2811/2936). We are confident that we can reach our full accrual by the end of 2020. Because of the further delay by the pandemic, we may need a second no cost extension year for additional follow up time since power to achieve results is driven by number of cancer events, as well as reaching target accrual.

During the prior reporting period, our patient accrual had lagged behind what we had anticipated. In response to this and reported barriers to accrual, we implemented several changes in the eligibility criteria including: 1) inclusion of high risk node negative (T2-3N0 triple negative breast cancers), 2) decrease the washout periods for regular aspirin use, and 3) allow subjects within 10 years of diagnosis for hormone positive node positive subjects and within 18 months for triple negative cancers. Sample size and power were unchanged since the risks of recurrence for HER2 negative breast cancers are linear within these time frames. These changes resulted in a significant increase in accrual.

Furthermore, the study remains open in the other cooperative groups including ECOG, SWOG, CCTG, and Health Canada. The study is promoted at all of the cooperative group meetings by the study champions. We have also engaged our advocates and their network to maintain accrual. In addition, the trial is presented on the monthly Alliance breast conference calls and the biannual meetings and the American Society of Clinical Oncology annual meetings.

Changes that had a significant impact on expenditures

Describe changes during the reporting period that may have had a significant impact on expenditures, for example, delays in hiring staff or favorable developments that enable meeting objectives at less cost than anticipated.

A major cost of the trial is the \$1400 per patient enrollment fee paid to the Alliance. As accrual was behind, these expenditures took longer than expected. We are now catching up with patient enrollment and expenditures.

Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents

Describe significant deviations, unexpected outcomes, or changes in approved protocols for the use or care of human subjects, vertebrate animals, biohazards, and/or select agents during the reporting period. If required, were these changes approved by the applicable institution committee (or equivalent) and reported to the agency? Also specify the applicable Institutional Review Board/Institutional Animal Care and Use Committee approval dates.

Significant changes in use or care of human subjects

Due to the COVID-19 pandemic, an amendment to allow remote consenting and telehealth visits was approved on April 3, 2020

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:** List any products resulting from the project during the reporting period. If there is nothing to report under a particular item, state “Nothing to Report.”

Publications, conference papers, and presentations

Report only the major publication(s) resulting from the work under this award.

Journal publications. *List peer-reviewed articles or papers appearing in scientific, technical, or professional journals. Identify for each publication: Author(s); title; journal; volume; year; page numbers; status of publication (published; accepted, awaiting publication; submitted, under review; other); acknowledgement of federal support (yes/no).*

Nothing to report

Books or other non-periodical, one-time publications. *Report any book, monograph, dissertation, abstract, or the like published as or in a separate publication, rather than a periodical or series. Include any significant publication in the proceedings of a one-time*

conference or in the report of a one-time study, commission, or the like. Identify for each one-time publication: Author(s); title; editor; title of collection, if applicable; bibliographic information; year; type of publication (e.g., book, thesis or dissertation); status of publication (published; accepted, awaiting publication; submitted, under review; other); acknowledgement of federal support (yes/no).

Nothing to report

Other publications, conference papers, and presentations. *Identify any other publications, conference papers and/or presentations not reported above. Specify the status of the publication as noted above. List presentations made during the last year (international, national, local societies, military meetings, etc.). Use an asterisk (*) if presentation produced a manuscript.*

Chen WY, Winer EP, Ballman KV, Partridge AH, Carey LA, Openshaw TH, Visvanathan K, Symington B, Matyka C, Carvan M, Holmes MD. ABC trial (AO11502) A randomized phase III double blinded placebo controlled trial of aspirin as adjuvant therapy for breast cancer. 2020 Annual meeting of the American Society for Clinical Oncology.

Website(s) or other Internet site(s)

List the URL for any Internet site(s) that disseminates the results of the research activities. A short description of each site should be provided. It is not necessary to include the publications already specified above in this section.

<http://abctrial.org/>

This is the website for general information about the trial, for interested patients and clinicians. There are no results to disseminate yet.

- **Technologies or techniques**

Identify technologies or techniques that resulted from the research activities. In addition to a description of the technologies or techniques, describe how they will be shared.

Nothing to report

- **Inventions, patent applications, and/or licenses**

Identify inventions, patent applications with date, and/or licenses that have resulted from the research. State whether an application is provisional or non-provisional and indicate the application number. Submission of this information as part of an interim research performance progress report is not a substitute for any other invention reporting required under the terms and conditions of an award.

Nothing to report

• **Other Products**

Identify any other reportable outcomes that were developed under this project. Reportable outcomes are defined as a research result that is or relates to a product, scientific advance, or research tool that makes a meaningful contribution toward the understanding, prevention, diagnosis, prognosis, treatment, and/or rehabilitation of a disease, injury or condition, or to improve the quality of life. Examples include:

- *data or databases;*
- *biospecimen collections;*
- *audio or video products;*
- *software;*
- *models;*
- *educational aids or curricula;*
- *instruments or equipment;*
- *research material (e.g., Germplasm; cell lines, DNA probes, animal models);*
- *clinical interventions;*
- *new business creation; and*
- *other.*

Nothing to report

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

Provide the following information for: (1) PDs/PIs; and (2) each person who has worked at least one person month per year on the project during the reporting period, regardless of the source of compensation (a person month equals approximately 160 hours of effort). If information is unchanged from a previous submission, provide the name only and indicate “no change.”

Example:

Name: Mary Smith
Project Role: Graduate Student
Researcher Identifier (e.g. ORCID ID): 1234567
Nearest person month worked: 5
Contribution to Project: Ms. Smith has performed work in the area of combined error-control and constrained coding.
Funding Support: The Ford Foundation (Complete only if the funding support is provided from other than this award).

Name:	Eric Winer
Project Role:	Principal Investigator (DFCI)
Nearest person-month worked:	No change
Contribution to project:	Dr. Winer has had multiple meetings and conference class with both the National Cancer Institute and Alliance for Clinical Trials

	in Oncology to secure approval for the protocol at both the NCI and Alliance. He has provided key input on the protocol and study design and has been a key liaison across the partnering organizations.
Name: Project Role: Nearest person-month worked: Contribution to project:	Wendy Chen Co-Investigator (DFCI) No change Dr. Chen serves as study chair for the clinical trial at the Alliance for Clinical Trials in Oncology and has been in charge of writing and revising the protocol and securing approval through the Alliance and NCI. She oversees trial conduct including review of eligibility criteria and ongoing study procedures and follow up. She works closely with Dr. Holmes and participates in regular conference calls regarding all aspects of this project.

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

If there is nothing significant to report during this reporting period, state “Nothing to Report.”

If the active support has changed for the PD/PI(s) or senior/key personnel, then describe what the change has been. Changes may occur, for example, if a previously active grant has closed and/or if a previously pending grant is now active. Annotate this information so it is clear what has changed from the previous submission. Submission of other support information is not necessary for pending changes or for changes in the level of effort for active support reported previously. The awarding agency may require prior written approval if a change in active other support significantly impacts the effort on the project that is the subject of the project report.

Nothing to report

What other organizations were involved as partners?

If there is nothing significant to report during this reporting period, state “Nothing to Report.”

Describe partner organizations – academic institutions, other nonprofits, industrial or commercial firms, state or local governments, schools or school systems, or other organizations (foreign or domestic) – that were involved with the project. Partner organizations may have provided financial or in-kind support, supplied facilities or equipment, collaborated in the research, exchanged personnel, or otherwise contributed.

Provide the following information for each partnership:

Organization Name:

Location of Organization: (if foreign location list country)

Partner’s contribution to the project (identify one or more)

- *Financial support;*
- *In-kind support (e.g., partner makes software, computers, equipment, etc., available to project staff);*
- *Facilities (e.g., project staff use the partner’s facilities for project activities);*

- *Collaboration (e.g., partner's staff work with project staff on the project);*
- *Personnel exchanges (e.g., project staff and/or partner's staff use each other's facilities, work at each other's site); and*
- *Other.*

Bayer Pharma AG, Mullerstr 178, 13353 Berlin, Germany is supplying both aspirin and placebo for this trial at no cost to the trial. We have executed a contract with them to do so on May 13, 2016.

8. SPECIAL REPORTING REQUIREMENTS

COLLABORATIVE AWARDS: For collaborative awards, independent reports are required from BOTH the Initiating PI and the Collaborating/Partnering PI. A duplicative report is acceptable; however, tasks shall be clearly marked with the responsible PI and research site. A report shall be submitted to <https://ers.amedd.army.mil> for each unique award.

QUAD CHARTS: If applicable, the Quad Chart (available on <https://www.usamraa.army.mil>) should be updated and submitted with attachments.

- 9. APPENDICES:** Attach all appendices that contain information that supplements, clarifies or supports the text. Examples include original copies of journal articles, reprints of manuscripts and abstracts, a curriculum vitae, patent applications, study questionnaires, and surveys, etc.