

AWARD NUMBER: W81XWH-15-1-0268

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

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Fort Detrick, Maryland 21702-5012

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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 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 (\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					
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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 node-positive Stage II or III 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 1-12 in the approved SOW.

Specific Aims 1 & 2: Clinical Trial

- Submit protocol to Alliance/NCI central review committee for approval (months 1-3) – approved by Alliance month 1, approved by NCI/CTEP month 7
- Submit protocol to Alliance/NCI Internal review board for approval (months 1-3)- Alliance/CIRB approved month 9
- Submit protocol to DoD Internal review Board for approval (months 1-3) – submitted for pre-approval month 5. On August 1, 2016, the DoD HRPO deferred oversight of the Alliance protocol to the Department of Health and Human Services, National Institutes of Health, National Cancer Institute IRB.
- Submit application for exemption of Investigational New Drug (months 1-3)-submitted month 12. Please see section 5, Changes/Problems regarding submission delay.
- Refine eligibility criteria, exclusion criteria, screening protocol (months 1-3)-completed month 5
- Finalize consent form (months 1-3)- approved by CIRB month 12
- Coordinate with other sites for site-specific IRB protocol submission after approval by Alliance IRB (months 3-7)
 - Milestone: Central IRB approval (month 3) – approved by CIRB month 12
 - Milestone: Local IRB approval at sites (month 6) – Will be done on a rolling basis at individual sites.
- Training & review of approval protocol at individual study sites (months 6-7)- Will be done at a rolling basis at individual sites.
- Development of case report forms for subjects on study at individual sites (months 6-7) - completed month 7
 - Milestone: Research staff trained (month 7) – Will be done on a rolling basis at individual sites
- Packaging and labeling of aspirin and placebo (months 1-6) – Will be done by Biologics
 - Screen subjects and consent eligible subjects to study (months 6-30)
 - Assign participants to one of 2 randomized groups (months 6-30)
 - Distribute study medication for first 6 months (months 6-30)

Specific Aim 3: Creation of biospecimen and epidemiologic biobank

- Selection of covariate measures to collect (months 1-6) – completed month 9.

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:

- The National Cancer Institute (NCI) Cancer Therapy Evaluation Program (CTEP) and Division of Cancer Prevention (DCP) have given their scientific approval of the protocol. The protocol and consent form have been approved by the NCI Central IRB (CIRB). Amendments regarding the dose change from 325/81 to 300/100 have been submitted to NCI/CTEP and CIRB. On Sept. 29, 2016, final approval from CTEP and CIRB was obtained.

- A call was arranged with the DoD legal and human subjects experts and NCI officials on how to meet regulatory requirements in as efficient a manner as possible. On August 1, 2016, Laura Brosch of HRPO at DOD stated that human research protection regulatory oversight would be deferred to the Alliance/CTEP/CIRB/NCI.

With the protocol and consent approved on September 29, 2016, the study will be pre-activated by the Alliance. Clinicaltrials.gov registration will be completed. Individual study sites will obtain local IRB approval, train their staff, and start to enroll at individual study sites.

Case report forms for all study sites were completed in April 2016.

- Bayer and Brigham and Women's Hospital (BWH) have executed a contract for Bayer to provide aspirin and placebo. The aspirin dosage has been changed from 325 mg/81 mg to 300 mg/100 mg for cost and supply reasons. The 300/100 mg dose will be supplied by the Bayer Global division at a much lower price and earlier start date than the 325/81 mg from the Bayer US division. The 300/100 mg dose is clinically equivalent to the 325/81mg dose. Because of the dose change, a protocol amendment was submitted and approved by NCI/CIRB.

- Since the protocol has just been approved, training at the sites will be starting soon.

Specific Aim 3 – The subject questionnaires were selected and all study booklets were printed in June 2016.

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 initially submitted the protocol to the DoD Human Research Protection Office in February 2016 for pre-approval. On 1 August 2016, the HRPO deferred oversight of the protocol to the Department of Health and Human Services, National Institutes of Health, National Cancer Institute CIRB since the protocol will be run through the Alliance for Clinical Trials in Oncology .

Final approval from the NCI CIRB and CTEP was obtained on Sept. 29, 2016. The protocol will be activated through the Alliance and begin recruiting and enrolling subjects.

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.

Because of issues related to drug supply, the protocol was amended to change the aspirin dose from 325/81 to 300/100. This required submission of an amended protocol and consent form to NCI/CTEP and CIRB. The amended protocol and consent form were approved by the NCI Central IRB (CIRB) and CTEP on Sept. 29, 2016 and will be activated through the Alliance

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.

In order to maximize accrual by allowing community physicians and the other cancer cooperative groups to participate, approval was also sought through NCI/CTEP. This also means that the NCI CIRB is the IRB of records. The additional approval of NCI/CTEP and CIRB introduced some modest delays of a few months. However, the advantage is that the study will now be broadly available across the United States both in academic setting and community settings which will broaden the reach of the study. The NCI has also provided some additional funds such the enrollment costs that were covered by the DOD budget were less than the funds that were normally be provided for trial enrollment. Therefore, enrolling of study subjects is now anticipated to begin in the 1st quarter of year 2.

The IND submission did not occur until month 12 because the NCI approved the protocol as IND exempt based upon meeting the FDA criteria for IND exemption § 312.2(b). However, in month 12, Bayer informed the study team that the aspirin and placebo could not be shipped until an official letter from the FDA was obtained documenting IND exemption. Therefore, the IND exemption application was filed in month 12, rather than earlier.

A major cost of the trial is the \$1400 per patient enrollment fee paid to The Alliance. As we have yet to enroll any patients, these expenditures are much lower than expected. We expect to catch up with patient enrollment (and expenditures) in coming years.

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

Not applicable

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.*

Nothing to report

- **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.

Nothing to report

- **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

Role: Principal Investigator

1.20 calendar months

Contribution: Dr. Winer has had multiple meetings and conference calls 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: Wendy Chen

Role: Co-Investigator

1.80 calendar months

Contribution: Dr. Chen serves as study chair for the clinical trial at the Alliance for Clinical Trials in Oncology so has been in charge of writing and revising the protocol and securing approval through the Alliance and NCI. She has also been participating in regular conference calls on protocol revisions and approval.

Name: William Barry

Role: Biostatistician

0.6 calendar months

Contribution: Dr. Barry has helped to write the statistical analysis parts of the protocol and has also provided key input on study design. He has also participated in multiple conference calls to address questions about statistical issues relevant to the study.

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 will supply 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.