HRP-592 - Protocol for Human Subject Research with Use of Test Article(s)

Protocol Title:

Provide the full title of the study as listed in item 1 on the "Basic Information" page in CATS IRB (http://irb.psu.edu).

Digital intervention to promote physical activity and improve cardiovascular health among cancer survivors exposed to cardiotoxic treatments

Principal Investigator:

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Version Date:

Provide the date of this submission. This date must be updated each time the submission is provided to the IRB office with revisions.

April 29th, 2019

Clinicaltrials.gov Registration #:

Provide the registration number for this study, if applicable.

This study will be registered as a clinical trial on clinicaltrial.gov within 21 days of enrolling the first participant.

Important Instructions for Using This Protocol Template:

1. Add this completed protocol template to your study in CATS IRB (http://irb.psu.edu) on the "Basic Information" page, item 7.
2. This template is provided to help investigators prepare a protocol that includes the necessary information needed by the IRB to determine whether a study meets all applicable criteria for approval.
3. **Type your protocol responses below the gray instructional boxes of guidance language. If the section or item is not applicable, indicate not applicable.**
4. **For research being conducted at Penn State Hershey or by Penn State Hershey researchers only, delete the instructional boxes from the final version of the protocol prior to upload to CATS IRB (http://irb.psu.edu). For all other research, do not delete the instructional boxes from the final version of the protocol.**
5. When making revisions to this protocol as requested by the IRB, please follow the instructions outlined in the Study Submission Guide available in the Help Center in CATS IRB (http://irb.psu.edu) for using track changes.

If you need help…	
University Park and other campuses: Office for Research Protections Human Research Protection Program The 330 Building, Suite 205 University Park, PA 16802-7014 Phone: 814-865-1775	**College of Medicine and Hershey Medical Center:** Human Subjects Protection Office 90 Hope Drive, Mail Code A115, P.O. Box 855 Hershey, PA 17033 (Physical Office Location: Academic Support Building Room 1140) Phone: 717-531-5687

Fax: 814-863-8699 Email: irb-orp@psu.edu	Fax number: 717-531-3937 Email: irb-hspo@psu.edu

Table of Contents

1.0 Objectives

1.1 Study Objectives

Describe the purpose, specific aims or objectives. State the hypotheses to be tested. Describe the treatment that is considered standard of care (i.e., indicate how patients would be treated in a non-investigational setting). Indicate if the study test article(s) is available to patients without taking part in the study.

This application involves testing the effects of a low burden, inexpensive, and scalable digital tool on motivation, physical activity (PA) and cardiovascular health in cancer survivors exposed to cardiotoxic treatments. We hypothesize that evaluative conditioning of PA with pleasure can be used to enhance motivation and increase PA resulting in improved cardiovascular health in post-treatment cancer survivors.

1.2 Primary Study Endpoints

State the primary endpoints to be measured in the study. Clinical trials typically have a primary objective or endpoint. Additional objectives and endpoints are secondary. The endpoints (or outcomes), determined for each study subject, are the quantitative measurements required by the objectives. Measuring the selected endpoints is the goal of a trial (examples: response rate and survival).

Change in total physical activity volume from baseline to 3 and 6 month as measured by the Actigraph GT3XP-BTLE (total activity counts).

1.3 Secondary Study Endpoints

State the secondary endpoints to be measured in the study.

1. Total PA Volume: Fitbit Charge 2 HR (step counts) worn from baseline to 3 months
2. MVPA: Actigraph GT3XP-BTLE (bout frequency & duration)
3. Automatic affective evaluations of PA: Single-Category Implicit Association Test in lab
4. Reflective affective judgments of PA: Physical Activity Enjoyment Scale; Behavioral Regulations in Exercise Questionnaire-2+ via self-reports in lab
5. Cardiac reserve; fitness capacity: 3-min step test; predicted VO2max
6. Cycle ergometer
7. Cardiovascular health: Cardiometabolic panel via phlebotomy (15 mL serum sampling)
8. Macrovascular function: Brachial artery flow-mediated vasodilation
9. Microvascular function: Cutaneous microcirculatory assessment of NO-mediated vasodilation acetycholine dose-response with/without NO-synthase inhibition (L-NAME)

2.0 Background

2.1 Scientific Background and Gaps

Describe the scientific background and gaps in current knowledge.

Many common cancers, including breast cancer, leukemia and lymphoma, involve treatment with cardiotoxic anthracyclines. These treatments have long-term cardiovascular side effects. PA is one of the most effective behaviors for preserving cardiovascular health and is therefore critical for this survivor population. Unfortunately, most survivors do not engage in sufficient PA either before or after a cancer diagnosis. Even modest increases in PA among this population may be sufficient to improve cancer-related outcomes by increasing aerobic capacity (a robust indicator of cardiac reserve) and improving vascular function (an early indicator of cardiovascular disease).

2.2 Previous Data

Describe any relevant preliminary data.

In a preliminary study, we found that people activate their smartphones over 40 times/day, hence they have over 40 micro-exposures to evaluative conditioning stimuli every day. Although brief, these micro-exposures accumulate and rapidly exceed doses used in lab-based evaluative conditioning interventions. Over 8 weeks, a sample of healthy adults using the HeartPhone app increased intrinsic motivation (d=0.82), enjoyment (d=0.68), and total PA volume (d=0.75). It is presently unclear whether the intervention is feasible for delivery to an at-risk population of cancer survivors and whether the behavior change is clinically significant. Thus, we propose to evaluate the effects of the HeartPhone app on PA, fitness, and functional indices of vascular function in survivors.

2.3 Study Rationale

Provide the scientific rationale for the research.

PA is an important lifestyle behavior for all cancer survivors, and especially for those treated with cardiotoxic agents. Technological advances over the past decade have increased the reach of PA interventions for cancer survivors. For this application, we seek to evaluate a new digital tool to increase PA and improve cardiovascular health in survivorship.

3.0 Inclusion and Exclusion Criteria

Create a numbered list below in sections 3.1 and 3.2 of criteria subjects must meet to be eligible for study enrollment (e.g., age, gender, diagnosis, etc.). Indicate specifically whether you will include any of the following vulnerable populations: (You may not include members of these populations as subjects in your research unless you indicate this in your inclusion criteria.) Review the corresponding checklists to ensure that you have provided the necessary information.

- **Adults unable to consent**
  - Review "CHECKLIST: Cognitively Impaired Adults (HRP-417)" to ensure that you have provided sufficient information. HRP-417 can be accessed by clicking the Library link in CATS IRB (http://irb.psu.edu).
- **Individuals who are not yet adults (infants, children, teenagers)**
  - If the research involves persons who have not attained the legal age for consent to treatments or procedures involved in the research ("children"), review the "CHECKLIST: Children (HRP-416)" to ensure that you have provided sufficient information. HRP-416 can be accessed by clicking the Library link in CATS IRB (http://irb.psu.edu).
- **Pregnant women**
  - Review "CHECKLIST: Pregnant Women (HRP-412)" to ensure that you have provided sufficient information. HRP-412 can be accessed by clicking the Library link in CATS IRB (http://irb.psu.edu).
- **Prisoners**
  - Review "CHECKLIST: Prisoners (HRP-415)" to ensure that you have provided sufficient information. HRP-415 can be accessed by clicking the Library link in CATS IRB (http://irb.psu.edu).
- **Neonates of uncertain viability or non-viable neonates**
  - Review "CHECKLIST: Neonates (HRP-413)" or "CHECKLIST: Neonates of Uncertain Viability (HRP-414)" to ensure that you have provide sufficient information. HRP-413 and HRP-414 can be accessed by clicking the Library link in CATS IRB (http://irb.psu.edu).

3.1 Inclusion Criteria

List the criteria that define who will be included in your study.

1) Age 18-65 years

2) Diagnosis of breast cancer, leukemia, or lymphoma <15 yrs
3) Completed chemotherapy with cardiotoxic anthracycline-based agents 1+ year ago
4) English-proficiency
5) Own & use smartphone with Android operating system

The same inclusion criteria will apply to those in the ancillary study.

3.2 Exclusion Criteria

List the criteria that define who will be excluded in your study.

Main Study and Ancillary Study Exclusion Criteria:
1) Currently receiving curative treatment for cancer
2) 90+ min/week moderate (or greater) intensity PA
3) Any medical contraindications on the Physical Activity Readiness Questionnaire
4) Require an assistive device for mobility or has any other condition that may limit or prevent participation in moderate-intensity physical activity
5) Current smoker
6) Pregnant or planning to become pregnant in the next 6 mos/breastfeeding
8) Taking metformin
9) Allergy to test substances
10) Allergy to latex

Ancillary Study:
7) Current medications that could conceivably alter the cardiovascular or thermoregulatory control or responses (e.g. beta blockers, calcium channel blockers, angiotensin receptor blockers)

Note: excluding participants may also be at the discretion of the researchers

3.3 Early Withdrawal of Subjects

3.3.1 Criteria for removal from study

Insert subject withdrawal criteria (e.g., safety reasons, failure of subject to adhere to protocol requirements, subject consent withdrawal, disease progression, etc.).

Research is optional, and participants have the right to withdraw their consent at any time throughout the study. When withdrawing from the study, the participant should let the research team know that he/she wishes to withdraw. Participants may provide the research team with the reason(s) for leaving the study but are not required to provide their reason. Refusal to take part in or withdraw from this study will involve no penalty or loss of benefits one would receive otherwise.

If participants have a recurrence of cancer during the study period and initiate a new round of treatment they will be removed from the study, consistent with the study's exclusion criteria.

3.3.2 Follow-up for withdrawn subjects

Describe when and how to withdraw subjects from the investigational product or study; the type and timing of the data to be collected for withdrawal of subjects; whether and how subjects are to be replaced; the follow-up for subjects withdrawn from investigational treatment.

Not applicable.

4.0 Recruitment Methods

4.1 Identification of subjects

Describe the methods that will be used to identify potential subjects or the source of the subjects. If not recruiting subjects directly (e.g., database query for eligible records or samples) state what will be queried, how and by whom.

StudyFinder: If you intend to use StudyFinder (http://studyfinder.psu.edu) for recruitment purposes, please indicate this in section 4.1 along with any other methods for identifying subjects. Note that information provided in this protocol should be consistent with information provided on the StudyFinder page in your CATS IRB study.

For Penn State Hershey submissions using Enterprise Information Management (EIM) for recruitment, attach your EIM Design Specification form on the Basic Information page in CATS IRB (irb.psu.edu). See HRP-103 Investigator Manual, "What is appropriate for study recruitment?" for additional information.

Participants will be recruited through community advertisements and word of mouth. Participants who have participated in a related study (Study #00011146), who indicated they wish to be contacted about similar studies in the future will be contacted about participating in this study.

4.2 Recruitment process

Describe how, where and when potential subjects will be recruited (e.g., approaching or providing information to potential subjects for participation in this research study).

Potential participants will be recruited from the greater State College area. Methods of recruitment in State College will include fliers, StudyFinder, HHD listserv, social media (Facebook) or local newspapers, and information provided from participants of an ongoing study (Study #00011146) who indicated they wish to be contacted about other related studies.

Participants from the Partnering to Prevent and Control Cancer (PPCC; STUDY6779; PI: Dr. S Mama) study who consented to allow contact about future research studies will be contacted by Dr. Scherezade Mama with information about this study. Dr. Mama is on the research team for both the PPCC protocol and the present protocol. She will mail a letter introducing the study to participants she previously worked with and providing contact information for them to reach us if they are interested in learning more and possibly enrolling.

4.3 Recruitment materials

List the materials that will be used to recruit subjects. Add recruitment documents to your study in CATS IRB (http://irb.psu.edu) on the "Consent Forms and Recruitment Materials" page. For advertisements, upload the final copy of printed advertisements. When advertisements are taped for broadcast, attach the final audio/video tape. You may submit the wording of the advertisement prior to taping to preclude re-taping because of inappropriate wording, provided the IRB reviews the final audio/video tape.

StudyFinder: If you intend to use StudyFinder (http://studyfinder.psu.edu) for recruitment purposes, you do not need to upload a separate recruitment document for information placed on the STUDYfinder site to your study in CATS IRB. Necessary information will be captured on the StudyFinder page in your CATS IRB study.

Copies of the recruitment script, screening materials, and study fliers are included as an appendix.

A copy of the recruitment letter that will be sent out to consenting participants from STUDY6779 who indicated they wished to be contacted about future research studies has been included in the recruitment materials.

4.4 Eligibility/screening of subjects

If potential subjects will be asked eligibility questions before obtaining informed consent, describe the process. Add the script documents and a list of the eligibility questions that will be used to your study in CATS IRB (http://irb.psu.edu) on the "Consent Forms and Recruitment Materials" page.

StudyFinder: If you intend to use StudyFinder (http://studyfinder.psu.edu) for recruitment purposes, any scripts (phone, email, or other) used when contacting StudyFinder participants as well as any eligibility screening questions must be added to your study in CATS IRB (http://irb.psu.edu) on the "Consent Forms and Recruitment Materials" page.

If an individual is interested in participating in the study, the person may call us or e-mail us. A research team member will speak with the prospective participant to provide information about the study and conduct a screening for eligibility (script attached), including questions from the PAR-Q. Provisionally eligible participants will undergo a week of activity monitoring to ensure they engage in <90 mins of moderate or greater intensity activity/week. Prospective participants who are eligible will be scheduled for a lab visit to enroll. If the individual declines participation or ineligible for the study, they will be thanked for their time and interest.

5.0 Consent Process and Documentation

Refer to "SOP: Informed Consent Process for Research (HRP-090)", for information about the process of obtaining informed consent from subjects. HRP-090 can be accessed by clicking the Library link in CATS IRB (http://irb.psu.edu).

5.1 Consent Process

5.1.1 Obtaining Informed Consent

5.1.1.1 Timing and Location of Consent

Describe where and when the consent process will take place.

Informed consent will be a multi-step process. Informed consent for the screening will take place when interested participants contact the researchers about the study using the screening consent form and verbal consent will be sought. If eligible to participate based on the screening questions, participants will move into the second screening portion of the study. For this part of the study, we will mail out accelerometers to participants to confirm they engage in <90 mins of moderate-to-vigorous physical activity in a given week. We will describe the nature of the screening and what we are asking from participants. At this time, we will ask for verbal consent for this portion of the study. When mailing out the accelerometers we will also include a copy of the consent form.

Following the run-in period whereby participants will wear the accelerometer for a week to determine if they engage in <90 minutes of moderate-to-vigorous physical activity in a week, further consent will be sought regarding the fasting procedures. For those that are eligible, the researchers will call the participant to inform them they are eligible to participate in the study and will read the script regarding the fasting procedures and request verbal consent.

Eligible participants will be provided with a copy of the informed consent document during the first lab visit to 17 Rec Hall. Participants will provide written informed consent after the research assistant describes the studies and answers any questions. If participants are qualified and are willing to participate, they can sign two copies of the consent form.

Additional consent will be sought for those in the ancillary study. Participants will receive a separate consent form and the researcher will describe the procedures and answer any questions. Participants will sign two copies of this consent form.

5.1.1.2 Coercion or Undue Influence during Consent

Describe the steps that will be taken to minimize the possibility of coercion or undue influence in the consent process.

Participants will be assured that their participation is completely voluntary, they are free to withdraw from the study at any time, and there will be no impact from the decision. The copy of the informed consent form that participants retain will also provide information regarding voluntary participation and that they are free to drop out of the study whenever they like.

5.1.2 Waiver or alteration of the informed consent requirement

If you are requesting a waiver or alteration of consent (consent will not be obtained, required information will not be disclosed, or the research involves deception), describe the rationale for the request in this section. If the alteration is because of deception or incomplete disclosure, explain whether and how subjects will be debriefed. Add any debriefing materials or document(s) to your study in CATS IRB (http://irb.psu.edu) on the "Supporting Documents" page. NOTE: Review the "CHECKLIST: Waiver or Alteration of Consent Process (HRP-410)" to ensure you have provided sufficient information for the IRB to make these determinations. HRP-410 can be accessed by clicking the Library link in CATS IRB (http://irb.psu.edu).

We are not requesting a waiver or alteration of consent.

5.2 Consent Documentation

5.2.1 Written Documentation of Consent

Refer to "SOP: Written Documentation of Consent (HRP-091)" for information about the process to document the informed consent process in writing. HRP-091 can be accessed by clicking the Library link in CATS IRB (http://irb.psu.edu).

If you will document consent in writing, describe how consent of the subject will be documented in writing. Add the consent document(s) to your study in CATS IRB (http://irb.psu.edu) on the "Consent Forms and Recruitment Materials" page. Links to Penn State's consent templates are available in the same location where they are uploaded and their use is required.

Participants will receive a signed copy of the written consent documents and the researcher will keep a signed copy of written consent. Participants in the ancillary study will receive a signed copy of both consent forms.

5.2.2 Waiver of Documentation of Consent (Implied consent, Verbal consent, etc.)

If you will obtain consent (verbal or implied), but not document consent in writing, describe how consent will be obtained. Add the consent script(s) and/or information sheet(s) to your study in CATS IRB (http://irb.psu.edu) on the "Consent Forms and Recruitment Materials" page. Links to Penn State's consent templates are available in the same location where they are uploaded and their use is required. Review "CHECKLIST: Waiver of Written Documentation of Consent (HRP-411)" to ensure that you have provided sufficient information. HRP-411 can be accessed by clicking the Library link in CATS IRB (http://irb.psu.edu).

If your research presents no more than minimal risk of harm to subjects and involves no procedures for which written documentation of consent is normally required outside of the research context, the IRB will generally waive the requirement to obtain written documentation of consent.

The written script of the information will be presented orally (verbal consent) prior to the commencement of the screening process and all written information contains the required and appropriate elements of consent (see attached verbal consent for screening document). The waiver of consent is requested as the research presents no more than minimal risk of harm to subjects. The research involves no procedures for which written consent is normally required outside of the research context. Eligible participants taking part in the accelerometer portion of the screening will also have a copy of the consent form mailed out in their packet.

5.3 Consent – Other Considerations

5.3.1 Non-English Speaking Subjects

Indicate what language(s) other than English are understood by prospective subjects or representatives.

If subjects who do not speak English will be enrolled, describe the process to ensure that the oral and written information provided to those subjects will be in that language. Indicate the language that will be used by those obtaining consent.

Indicate whether the consent process will be documented in writing with the long form of the consent documentation or with the short form of the consent documentation. Review the "SOP: Written Documentation of Consent (HRP-091)" and the "Investigator Manual (HRP-103)" to ensure that you have provided sufficient information. HRP-091 and HRP-103 can be accessed by clicking the Library link in CATS IRB (http://irb.psu.edu).

Individuals who do not read and speak English will not be included in the study.

5.3.2 Cognitively Impaired Adults

Refer to "CHECKLIST: Cognitively Impaired Adults (HRP-417)" for information about research involving cognitively impaired adults as subjects. HRP-417 can be accessed by clicking the Library link in CATS IRB (http://irb.psu.edu).

5.3.2.1 Capability of Providing Consent

Describe the process to determine whether an individual is capable of consent.

Individuals who suffer from diagnosed cognitive impairments will not be included in the study.

5.3.2.2 Adults Unable To Consent

Describe whether and how informed consent will be obtained from the legally authorized representative. Describe who will be allowed to provide informed consent. Describe the process used to determine these individual's authority to consent to research.

For research conducted in the state, review "SOP: Legally Authorized Representatives, Children and Guardians (HRP-013)" to be aware of which individuals in the state meet the definition of "legally authorized representative". HRP-013 can be accessed by clicking the Library link in CATS IRB (http://irb.psu.edu).

For research conducted outside of the state, provide information that describes which individuals are authorized under applicable law to consent on behalf of a prospective subject to their participation in the procedure(s) involved in this research. One method of obtaining this information is to have a legal counsel or authority review your protocol along with the definition of "children" in "SOP: Legally Authorized Representatives, Children, and Guardians (HRP-013)." HRP-013 can be accessed by clicking the Library link in CATS IRB (http://irb.psu.edu).

Individuals who suffer from diagnosed cognitive impairments will not be included in the study.

5.3.2.3 Assent of Adults Unable to Consent

Describe the process for assent of the subjects. Indicate whether assent will be required of all, some or none of the subjects. If some, indicate which subjects will be required to assent and which will not.

If assent will not be obtained from some or all subjects, provide an explanation of why not.

Describe whether assent of the subjects will be documented and the process to document assent. The IRB allows the person obtaining assent to document assent on the consent document and does not routinely require assent documents and does not routinely require subjects to sign assent documents.

Not applicable.

5.3.3 Subjects who are not yet adults (infants, children, teenagers)

5.3.3.1 Parental Permission

Describe whether and how parental permission will be obtained. If permission will be obtained from individuals other than parents, describe who will be allowed to provide permission. Describe the process used to determine these individual's authority to consent to each child's general medical care.

For research conducted in the state, review "SOP: Legally Authorized Representatives, Children and Guardians (HRP-013)" to be aware of which individuals in the state meet the definition of "children". HRP-013 can be accessed by clicking the Library link in CATS IRB (http://irb.psu.edu).

For research conducted outside of the state, provide information that describes which persons have not attained the legal age for consent to treatments or procedures involved in the research, under the applicable law of the jurisdiction in which research will be conducted. One method of obtaining this information is to have a legal counsel or authority review your protocol along with the definition of "children" in "SOP: Legally Authorized Representatives, Children, and Guardians (HRP-013)." HRP-013 can be accessed by clicking the Library link in CATS IRB (http://irb.psu.edu).

Not applicable.

5.3.3.2 Assent of subjects who are not yet adults

Indicate whether assent will be obtained from all, some, or none of the children. If assent will be obtained from some children, indicate which children will be required to assent. When assent of children is obtained describe whether and how it will be documented.

Not applicable.

6.0 HIPAA Research Authorization and/or Waiver or Alteration of Authorization

This section is about the access, use or disclosure of Protected Health Information (PHI). PHI is individually identifiable health information (i.e., health information containing one or more 18 identifiers) that is transmitted or maintained in any form or medium by a Covered Entity or its Business Associate. A Covered Entity is a health plan, a health care clearinghouse or health care provider who transmits health information in electronic form. See the "Investigator Manual (HRP-103)" for a list of the 18 identifiers. HRP-103 can be accessed by clicking the Library link in CATS IRB (http://irb.psu.edu).

If requesting a waiver/alteration of HIPAA authorization, complete sections 6.2 and 6.3 in addition to section 6.1. The Privacy Rule permits waivers (or alterations) of authorization if the research meets certain conditions. Include only information that will be accessed with the waiver/alteration.

6.1 Authorization and/or Waiver or Alteration of Authorization for the Uses and Disclosures of PHI

Check all that apply:

☒ **Not applicable, no identifiable protected health information (PHI) is accessed, used or disclosed in this study.** *[Mark all parts of sections 6.2 and 6.3 as not applicable]*

☐ **Authorization will be obtained and documented as part of the consent process.** *[If this is the only box checked, mark sections 6.2 and 6.3 as not applicable]*

☐ **Partial waiver is requested for recruitment purposes only (Check this box if patients' medical records will be accessed to determine eligibility before consent/authorization has been obtained).** *[Complete all parts of sections 6.2 and 6.3]*

☐ **Full waiver is requested for entire research study (e.g., medical record review studies).** *[Complete all parts of sections 6.2 and 6.3]*

☐ **Alteration is requested to waive requirement for written documentation of authorization (verbal authorization will be obtained).** *[Complete all parts of sections 6.2 and 6.3]*

6.2 Waiver or Alteration of Authorization for the Uses and Disclosures of PHI

6.2.1 Access, use or disclosure of PHI representing no more than a minimal risk to the privacy of the individual

6.2.1.1 Plan to protect PHI from improper use or disclosure

Include the following statement as written – DO NOT ALTER OR DELETE unless this section is not applicable because the research does not involve a waiver of authorization. If the section is not applicable, remove the statement and indicate as not applicable.

Not applicable.

6.2.1.2 Plan to destroy identifiers or a justification for retaining identifiers

Describe the plan to destroy the identifiers at the earliest opportunity consistent with the conduct of the research. Include when and how identifiers will be destroyed. If identifiers will be retained, provide the legal, health or research justification for retaining the identifiers.

Not applicable.

6.2.2 Explanation for why the research could not practicably be conducted without access to and use of PHI

Provide an explanation for why the research could not practicably be conducted without access to and use of PHI.

Not applicable.

6.2.3 Explanation for why the research could not practicably be conducted without the waiver or alteration of authorization

Provide an explanation for why the research could not practicably be conducted without the waiver or alternation of authorization.

Not applicable.

6.3 Waiver or alteration of authorization statements of agreement

By submitting this study for review with a waiver of authorization, you agree to the following statement – DO NOT ALTER OR DELETE unless this section is not applicable because the research does not involve a waiver or alteration of authorization. If the section is not applicable, remove the statement and indicate as not applicable.

Not applicable.

7.0 Study Design and Procedures

7.1 Study Design

Describe the type/design of trial to be conducted (e.g., double-blind, placebo controlled, parallel design, etc.). Provide a schematic diagram of study design, procedures and stages, if appropriate.

We propose a single-group pre-post behavioral intervention trial (N=30) with an ancillary lab study on a sub-sample (n=10) to gather mechanistic data on changes in microvascular function.

7.2 Study Procedures

Provide a description of all research procedures being performed and when they are being performed (broken out by visit, if applicable), including procedures being performed to monitor subjects for safety or minimize risks. Include any long-term follow-up procedures and data collection, if applicable.

Describe where or how you will be obtaining information about subjects (e.g., medical records, school records, surveys, interview questions, focus group topics, audio or video recordings, data collection forms, and collection of specimens through invasive or non-invasive procedures to include the amount to be collected and how often). Add any data collection instruments that will be seen by subjects to your study in CATS IRB (http://irb.psu.edu) in the "Supporting Documents" page.

7.2.1 Screening

Provide a description as defined above and format accordingly.

Screening for this study is a multi-step process. Interested participants may contact the researchers to determine their eligibility for the study. During the initial screening process, participants will be asked a number of questions to determine their eligibility (re: inclusion/exclusion criteria) as well as respond to the items of the PAR-Q which will be assessed over the phone. From there, interested and provisionally-eligible participants will be mailed an Actigraph accelerometer with a 1-week wear log (to verify <90 min/week of moderate or greater intensity PA) and a research assistant will call these participants to provide training on how to wear the device. After wearing the accelerometer for 1 week, provisionally-eligible participants will return the accelerometer via mail. Eligible participants (those that completed <90 min/week of moderate or greater intensity PA) will be contacted and scheduled for a lab visit. Those that are not eligible will be contacted and told they are not eligible to participate and thanked for their time. Eligible participants will be instructed prior to arriving for testing to drink water but to fast for 12 hours, no caffeine, and not to engage in exercise for 24 hours before.

7.2.2 Lab Visit 1 (Month 0)

During the lab visit 1, participants will provide informed consent to participate in the study by permitting their data to be used for research purposes. As the first step, participants will be asked to complete a baseline assessment which includes demographic questions, anthropometrics (height, weight), questions assessing motivation and enjoyment of PA and usual engagement in physical activity (international physical activity questionnaire). Participants will also complete a timed sorting task on a lab computer. Following this, approved research staff will install an application, HeartPhone, onto the participants' smartphone and instruct them on how to use the app. The research assistant will provide the participant with a Fitbit activity monitor and will load the Fitbit app on the participant's phone. Participants will provide permission to share their Fitbit data with the research team. Participants will not be told to increase their physical activity while enrolled in the study. Rather, a primary aim of the intervention is to examine whether the app is associated with any changes in their physical activity.

The HeartPhone application alters the background of a splash screen that appears when participants activate their screens. The background has images of physical activity and pleasant stimuli (example screen shots included as appendix). The app records the duration between turning the smartphone on and advancing to the next screen, date and time, and the number of attempts before the correct password is entered. These data are transmitted to a server maintained by the research team.

Dr. Conroy has been working with Chris Greiner in HHD regarding the app. We do not believe that there will be an issue with our app as it utilizes a vendor hosted solution for data (no Penn State security issues) and there is no personally identifiable information stored on the server (our participant privacy/security will not be compromised). We have contacted Chris and in the event that he believes that we need to submit to OIS, we will do so

Participants will then be escorted over to Noll lab for assessments of:

a. heart rate (HR)
b. blood pressure (BP)
c. oral temperature
d. blood draw
e. macrovascular function
f. microvascular function (only for those in the ancillary study)Participants will also complete two fitness tests including the YMCA step test and a cycle ergometer test to assess aerobic function.

The nurse draws about 30 ml (2 Tbsp) of blood from a vein in the subject's arm. We send the blood to labs for some analyses. If the subject takes thyroid hormone, we draw an extra 3.5 ml (0.2 Tbsp) to check the level of thyroid hormone. Screening tests performed on blood: CBC, Lipid panel, and blood chemistry, Interleukin Panel (IL), folic acid and B12, homocysteine, oxidized LDL, total antioxidant capacity. We do not perform genetic analyses on the blood nor look for presence of disease (e.g. HIV).

Macrovascular Function: Flow Mediated Dilation (FMD)

FMD is an assessment of conduit vessel endothelial function. A blood pressure cuff is placed on the forearm, gel on the upper arm just above the elbow, and a Doppler ultrasound probe on the gel. The ultrasound measures vessel size and blood velocity. After a 3-minute "resting" measurement, we inflate the cuff for 5 minutes to occlude forearm blood flow. After deflating the cuff, we perform a second reading.

Microvascular Function: Microdialysis (MD)

The MD experiment directly quantifies nitric oxide-mediated vasodilation in the microcirculation. Subjects undergo MD at baseline. They repeat MD 3 and 6 months after the baseline experiment.

Preparation for all MD experiments:
Women of childbearing potential undergo a urine pregnancy test.
The participant washes a ventral forearm with antimicrobial soap.
The participant washes a ventral forearm with antimicrobial soap.

Microdialysis probe insertion:
A tight band is placed around the participant's arm to visualize veins.
For each MD site, a pair of pen-marks is made on the arm 2.5 cm (1 inch) apart and away from veins. The tight band is removed. The MD tubing enters and exits the skin at the marks.
The participant's ventral forearm is cleaned with povidone iodine and alcohol, and an ice bag is placed on the arm for 5 minutes to numb the skin. Then a thin needle is inserted into the skin at each entry mark. The needle's tip travels between the layers of skin for 2.5 cm (1 inch) and exits the skin at the matching exit mark. The MD tubing is threaded through the needle, and then the needle is withdrawn leaving the tubing in the skin. Any hyperemia related to the insertion subsides in about 60 minutes.

We place a cuff on the upper arm sans the MD probes to measure BP.

We apply a local skin heater and laser Doppler probe over each MD site.
We measure local skin temperature and skin blood flow (SkBF) throughout the MD experiments.
We also measure BP every 5-7 minutes (brachial osculation and/or Cardiocap).

Acetylcholine (ACh) Dose Response:
Two MD probes are inserted (see above)

Probe 1: Lactated Ringer's
Probe 2: Lactated Ringer's + LNAME (15mM)

Hyperemia associated with the probe insertion is allowed to subside for ~60 minutes.
Baseline SkBF data are collected for ~10 minutes.
The first concentration of ACh is added to the perfusate at sites 1 and 2.
Sites 1 and 2 receive 11 increasing concentrations of ACh (10^{-11} to 10^{-1} mM) over 75 minutes.
As SkBF stabilizes with the addition of each concentration of ACh, the next concentration of ACh is added to the perfusates.
After the last concentration of ACh, the perfusates at both sites are switched to Lactated Ringer's + SNP (28mM), and holders are heated to 43°C (109.4°F) at a rate of 0.5°C/5 seconds. Heating + SNP perfusion elicits maximum vasodilation.
SkBF stabilizes after ~20 minutes.
MD tubing is removed from the skin and sterile bandages are placed over the sites. If the participant desires, a bag of ice is placed on the MD sites for 10 minutes to reduce bruising that may occur.

Equipment

Laser Doppler Flowmetry: The Laser Doppler Flowmeter (Moor Instruments, Inc.) non-invasively provides a qualitative measure of skin blood flow to a depth of about 1 mm in the skin using a weak laser light. This measure is a dimensionless value called "flux" that reflects the speed and number of blood cells moving through the microvasculature in an area of skin. The flowmeter continuously measures skin blood flow using a fiber optic probes that fit into holders taped to the skin. *approved by the FDA*

Blood Pressure, ECG (Heart rate): The CardioCap 5 (General Electric – GE) critical care monitor measures blood pressure via a cuff inflated every 5-7 minutes on the upper arm and heart rate via 3-lead ECG probes taped to the skin of the chest. *approved by the FDA*

Flow Mediated Dilation (FMD): FMD measures the health of blood vessels. The researchers place a blood pressure cuff around the forearm. They put gel on the upper arm just above the elbow. Then they place a Doppler ultrasound probe on the gel. The ultrasound makes sound waves to measure the size of blood vessels and the speed of the blood. They make a "resting" measurement before they inflate the cuff. Then they inflate the cuff for 5 minutes to stop blood flowing to and from the forearm. After they deflate the cuff, they perform a second reading for 3 minutes. ATL HDI 5000 SonoCT (Ultrasound) *FDA 510 (k) approved by the FDA*

Fitness tests:
YMCA step test: For the YMCA step test, we will have people stepping onto a 12 inch step. They will be stepping up and down, alternating steps to a metronome set to 96 bpm, which would be stepping at a rate of 24 steps per minute. They will step up and down at that rate for 3 minutes. After the 3 minutes, the participant will immediately sit down and have their heart rate recorded for the min following the test. Participants will wear a heart rate monitor on their chest to monitor their heart rate.

YMCA cycle ergometer tests: For the cycle ergometer test, participants will wear a chest worn heart rate monitor and will cycle at a rate of 50 rpm (repetitions/minute) for two to four 3-minute stages of continuous exercise. Their heartrate response would dictate how much we increase work by and then we can use that data to extrapolate what their maximum HR response would be and their fitness (i.e., Vo2 max).

7.2.3 Intervention Period

Provide a description as defined above and format accordingly.

During the first 3-month intervention period, participants will be asked to use the Heartphone app in the field continuously. The application runs automatically, so participants will not be asked to do anything other than install and use the app for the next three months and to wear their Fitbit activity monitor.

7.2.4 Lab Visit 2 (Month 3)

Three months following the baseline visit, participants will be asked to return to the lab to repeat measures taken during the baseline assessment. The researcher will remove the HeartPhone app from the participant's phone. Participants will be set up with an Actigraph accelerometer and given a 1-week wear log to record their activity for one week. Participants will then mail the accelerometer back at the end of the week.

A modification is proposed to include additional questions in the questionnaire pertaining to the acceptability of the Heartphone app. We will also engage in a brief semi-structured interview with the participants at this time to further gauge their experience using the HeartPhone app. The additional questions to be included in the questionnaire and semi-structured interview guide have been uploaded in the Other Attachments section of the Local Site Documents.

7.2.5 Lab Visit 3 (Month 6)

Participants will then be asked to come back into the lab one final time approximately 6 months following their initial baseline visit. All measures taken at baseline and 3 months will again be taken at 6 months.

7.3 Duration of Participation

Describe the duration of an individual subject's participation in the study.

It is anticipated that participation in the study will take approximately two hours each visit for those enrolled in the main study. Participation in the ancillary study will take approximately 7 hours total (2 hours for all the main study assessments plus an additional 5 hours for the ancillary study assessments). Participants enrolled in the ancillary study will be given the option to complete the main study protocol and the ancillary study protocol on separate days if they wish.

7.4 Test Article(s) (Study Drug(s) and/or Study Device(s))

7.4.1 Description

Provide a brief description of all test articles (drugs (including any foods and dietary supplements), devices and/or biologics used in the research including the purpose of their use and their approval status with the Food and Drug Administration (FDA). Include information about the form of the drug product (e.g., tablets, capsules, liquid).

Acetylcholine	ACh	Form: Solid

Role in Current Study: Local heating combined with the local perfusion of endothelial agonist, acetylcholine, specifically examines the attenuated endothelium-dependent vasodilation (eNOS-derived NO) associated with vascular pathologies.
Concentration: 10^-11 to 10^-1M

LNAME N^G-nitro-L-arginine methyl ester Form: Solid
Role in current study: A nitric oxide synthase inhibitor. L-NAME is an analog to the amino acid, L-arginine. L-NAME is a non-specific inhibitor for nitric oxide synthases, thereby inhibiting the production of nitric oxide (NO) that causes vasodilation. We deliver small doses of LNAME to a nickel-sized area of the skin.
Concentration: 15mM

Sodium Nitroprusside SNP Form: Solid
Role in Current Study: SNP, acting an NO donor, dilates blood vessels maximally thereby achieving maximal SkBF. Maximal SkBF is a reference point for other measures of SkBF.
Concentration: 28mM

Lactated Ringer's Ringer's Form: Liquid
Role in current study: Lactated Ringer's acts as the vehicle for the investigative substances and as a flush.

7.4.2 Treatment Regimen

Describe dose, route of administration and treatment duration. Include information about dose adjustments.

Investigative Substances: Microdialysis
The following is a table of the research agents used with intradermal microdialysis

Drug	Concentration (mM)	Treatment Duration (min)	Dose (14% Delivery, mg)
ACH	1.00E-01	5	2.54E-02
ACH	1.00E-02	5	2.54E-03
ACH	1.00E-03	5	2.54E-04
ACH	1.00E-04	5	2.54E-05
ACH	1.00E-05	5	2.54E-06
ACH	1.00E-06	5	2.54E-07
ACH	1.00E-07	5	2.54E-08
ACH	1.00E-08	5	2.54E-09
ACH	1.00E-09	5	2.54E-10
ACH	1.00E-10	5	2.54E-11
ACH	1.00E-11	5	2.54E-12
L-NAME	1.50E-02	85	0.96E-01
SNP	2.80E-02	30	7.00E-02

7.4.3 Method for Assigning Subject to Treatment Groups

Describe the randomization process and how the associated treatment assignment will be made.

Not applicable.

7.4.4 Subject Compliance Monitoring

Insert the procedures for monitoring subject compliance.

Not applicable.

7.4.5 Blinding of the Test Article

Describe how the test article is blinded.

Not applicable.

7.4.6 Receiving, Storage, Dispensing and Return

7.4.6.1 Receipt of Test Article

Describe how the test article will be obtained and from what source. Describe how the study test article will be packaged along with amounts (e.g., number of tablets/capsules or volume of liquid) and labeling. If drug kits are used, describe all the contents of the kit and associated labeling.

Investigative Substances: Microdialysis
The containers of the substances are dated upon receipt and when opened.

Research Agent	Source(s)
ACh	USP
L-NAME	EMD, Tocris
SNP	USP
Lactated Ringer's	McKesson, Owens and Minor

A license from the CRC physician, the nurse manager, or the overseeing physician is filed with vendors (e.g. VWR, McKesson, Moore Medical) requiring the documentation for the purchase of some investigative agents (e.g. Lactated Ringer's). The investigative agents are shipped to Noll Lab or picked up from the pharmacy by lab personnel. Copies of the prescriptions and orders are maintained in Dr. Alexander's laboratory files.

7.4.6.2 Storage

Describe the plans to store, handle the test article so they will be used only on subjects and only by authorized investigators. Describe storage temperature requirements and how temperature will be monitored and recorded.

Drugs used with microdialysis:
The room temperatures are recorded daily during weekdays. The temperature of the room is also monitored by the Central Control System of the Environmental Systems at PSU.

The drugs used with microdialysis in their solid form are stored under environmental conditions according to manufacturer's instructions in cabinets, refrigerators, or freezers located in room 224A or 228 Noll Laboratory. Opened drugs in their solid form are discarded after one year. The rooms are locked when unoccupied.

All of the chemicals are purchased in solid form and are stable for years when stored according to manufacturer's instructions. All of the chemicals are purchased in small vials that are exhausted within one to several weeks. Once mixed, stock solutions of substances are used within one week of stored in the refrigerator and within 6 months if stored in the freezer. Final dilutions of solutions that are prepared for an experiment are used within a couple of minutes to hours of preparation.

7.4.6.3 Preparation and Dispensing

Describe how the test article will be assigned to each subject and dispensed. Describe the steps necessary to prepare the test article. Include where the test article preparation will be done and by whom. Fully describe how the study treatment is to be administered and by whom.

None of the microdialysis drugs are dispensed to the subject; rather they are used in the experiments. All subjects will receive all test articles. A physician provides medical oversight for the preparation and administration of investigational agents via intradermal microdialysis (See Physician Oversight SOP).

<u>Preparation of the Microdialysis Perfusates</u>
Test article preparation will occur in Noll Lab.
When mixing the perfusates, the lab personnel performing microdialysis washes their hands, wears protection (e.g. gloves, lab coat), and uses glassware that has been washed with cleanser (Alconox, designed for use with healthcare instruments, pharmaceutical process equipment, tissue culture apparatus, etc.), and rinsed multiple times in tap water and then doubly-distilled water and air-dried. The solid investigational agents are weighed on a microbalance and then mixed with sterile pharmaceutical-grade lactated Ringer's solution to the desired concentration (See **Treatment Regimen**). The solution is drawn into a syringe through a 0.2 µm filter. Prior to injecting a solution into or withdrawing a solution from a sterile container through a sterile hypodermic needle, the stopper of the sterile container is cleaned thoroughly with alcohol. The final dilutions of the perfusates are drawn into sterile syringes through 0.2 µm filters within minutes or hours of their use in the experiment.

The lab personnel performing microdialysis will use the study treatments in the microdialysis experiments.

7.4.6.4 Return or Destruction of the Test Article

Describe the procedures for final reconciliation of the test article supply at the end of the study and whether the test article is to be shipped back to a source or destroyed on site.

Investigative substances are usually consumed in the experiments. Investigative substances not consumed by the experiments are disposed of in accordance with the policies of Environmental Health and Safety of Penn State. Some substances (e.g. protein or peptide-based) are autoclaved prior to disposal.

7.4.6.5 Prior and Concomitant Therapy

Describe what prior and/or concomitant medical therapy will be collected. Describe which concomitant medicines/therapies are permitted during the study. Describe which concomitant medicines are not permitted during the study.

Not applicable.

8.0 Subject Numbers and Statistical Plan

8.1 Number of Subjects

Indicate the total number of subjects to be accrued.

If applicable, distinguish between the number of subjects who are expected to be enrolled and screened, and the number of subjects needed to complete the research procedures (i.e., numbers of subjects excluding screen failures.)

For the main study, a total of 30 survivors of either leukemia/lymphoma or breast cancer will be enrolled. The ancillary lab study will enroll 10 breast cancer survivors from the main study (i.e., from the 30 participants already enrolled).

8.2 Sample size determination

If applicable, provide a justification of the sample size outlined in section 8.1 – to include reflections on, or calculations of, the power of the study.

Assuming a 5% type-1 error rate, this sample size affords 80% power for detecting pre-post changes in the primary outcome of d=0.47 (one tailed)/d=0.53 (two-tailed). Effect sizes for secondary outcomes will be used to inform planning for a future clinical trial.

8.3 Statistical methods

Describe the statistical methods (or non-statistical methods of analysis) that will be employed.

Descriptive statistics will be calculated for all variables. Paired-samples t-tests (under intent to treat principles) will be used to test for differences from baseline-3 mos and 3-6 mos in motivation and physical activity (Aim 1) and fitness and vascular function (Aim 2). Given the lack of a control group, effect sizes (standardized mean differences) will be emphasized when interpreting data. Sensitivity analyses will be conducted using patients with/without radiation therapy.

9.0 Confidentiality, Privacy and Data Management

For research being conducted at Penn State Hershey or by Penn State Hershey researchers only, the research data security and integrity plan is submitted using "HRP-598 – Research Data Plan Review Form Application Supplement", which is available in the Library in CATS IRB (http://irb.psu.edu). Refer to Penn State College of Medicine IRB's "Standard Operating Procedure Addendum: Security and Integrity of Human Research Data", which is available on the IRB's website. **In order to avoid redundancy, for this section state "See the Research Data Plan Review Form" in section 9.0 if you are conducting Penn State Hershey research and move on to section 10.**

For all other research, in the sections below, describe the steps that will be taken to secure the data during storage, use and transmission.

9.1 Confidentiality

9.1.1 Identifiers associated with data and/or specimens

List the identifiers that will be included or associated with the data and/or specimens in any way (e.g., names, addresses, telephone/fax numbers, email addresses, dates (date of birth, admission/discharge dates, etc.), medical record numbers, social security numbers, health plan beneficiary numbers, etc.).

If no identifiers will be included or associated with the data in any way, whether directly or indirectly, please indicate this instead.

Data collected from participants will be linked to each other by an alphanumeric code at the date that data collection begins. During data collection, the alphanumeric code will be temporarily linked with participants' names and email address for data management purposes but this key will be stored on a password-protected lab computer and destroyed at the end of data collection. The principal investigator will enter that code when initializing the app and Qualtrics survey during each visit.

9.1.1.1 Use of Codes, Master List

If identifiers will be associated with the data and/or specimens (as indicated in section 9.1.1 above), describe whether a master record or list containing a code (i.e., code number, pseudonyms) will be used to separate the data collected from identifiable information, where that master code list will be stored, who will have access to the master code list, and when it will be destroyed.

If identifiers are included or associated with the data as described in section 9.1.1 above, but no master record or list containing a code will be used, it will be assumed by the IRB that the investigator plans to directly link the identifiers with the data.

Alphanumeric codes matching the lab-generated email accounts will be used to identify participants (e.g., psuaim101). A master list containing the alphanumeric codes will be used to separate the data collected from identifiable information (the names, email addresses and phone numbers of the participants). This list that matches the names and contact information along with the code numbers will be stored in the locked file cabinet of the locked office of the research project manager (18A Rec Hall). Only the study team members responsible for consent and subject compliance monitoring calls will have access to that list. The list will be destroyed upon completion of the study.

9.1.2 Storage of Data and/or Specimens

Describe where, how and for how long the data (hardcopy (paper) and/or electronic data) and/or specimens will be stored. NOTE: Data can include paper files, data on the internet or websites, computer files, audio/video files, photographs, etc. and should be considered in the responses. Refer to the "Investigator Manual (HRP-103)" for information about how long research records must be stored following the completion of the research prior to completing this section. HRP-103 can be accessed by clicking the Library link in CATS IRB (http://irb.psu.edu).

Please review Penn State's Data Categorization Project for detailed information regarding the appropriate and allowable storage of research data collected according to Penn State Policy

AD71. Although the IRB can impose greater confidentiality/security requirements (particularly for sensitive data), the IRB cannot approve storage of research data in any way or using any service that is not permissible by Penn State Policy AD71.

Data from three cloud servers (a lab server for HeartPhone app data, Qualtrics server for questionnaire data, and the Fitabase server for the Fitbit data) will be linked in this study. Data collected from the HeartPhone application will be stored on the server while the study is in progress. This cloud-based dataset will include the serial number that will be given to each participant at the beginning of the study but no PHI. Data collected from Qualtrics questionnaires will be stored on Qualtrics' servers temporarily, and right after the study finishes they will be downloaded and stored on lab computers; data on Qualtrics' database will be then deleted from the Qualtrics' server. Data will be linked via the serial number which will be entered into the app and the Qualtrics questionnaire during the first lab visit by the principal investigator. As soon as data collection is completed, all data stored will be downloaded and deleted from the cloud servers. The integrated data file will be stored on a password protected computer in 17 Rec Hall (a locked room).

All data collected in Noll Lab is kept in the laboratory in locked cabinets, on a password-protected folder on the secured PSU server, and on password-protected computers maintained in a locked room. Only authorized personnel have access. Coded data shared with unauthorized persons cannot be traced to individuals. The list linking code numbers to participants is not shared with unauthorized persons and destroyed when project is completed and published.

Biological specimens are stored at University Park and Quest Labs, (Chantilly, VA). At University Park, the specimens are stored in a -80°C freezer in Noll first floor hallway. All specimens not exhausted upon analysis are maintained no longer than 5 years after publication.

9.1.3 Access to Data and/or Specimens

Identify who will have access to the data and/or specimens. This information should not conflict with information provided in section 9.1.1.1 regarding who has access to identifiable information, if applicable.

The principal investigators and approved research staff will have access to the data.

9.1.4 Transferring Data and/or Specimens

If the data and/or specimens will be transferred to and/or from outside collaborators, identify the collaborator to whom the data and/or specimens will be transferred and how the data and/or specimens will be transferred. This information should not conflict with information provided in section 9.1.1.1 regarding who has access to identifiable information, if applicable.

Some specimens are mailed or transported by lab members or couriers to outside labs for analysis. The outside labs are the Biomarker Core Lab (PSU, University Park) and Quest Diagnostics (Chantilly, VA). All specimens are coded and do not contain identifiers. We do not share the code with unauthorized persons.

9.2 Subject Privacy

This section must address subject privacy and NOT data confidentiality.

Indicate how the research team is permitted to access any sources of information about the subjects.

Describe the steps that will be taken to protect subjects' privacy interests. "Privacy interest" refers to a person's desire to place limits on whom they interact with or to whom they provide personal information.

Describe what steps you will take to make the subjects feel at ease with the research situation in terms of the questions being asked and the procedures being performed. "At ease" does not refer to physical discomfort, but the sense of intrusiveness a subject might experience in response to questions, examinations, and procedures.

During the lab visits, participants will complete an online questionnaire in the lab and a computer task. Participants will complete both the computer task and questionnaires in a private room in the lab without others present. Further, the exercise tests will be done in a private room in Noll Lab with only the investigator present. On occasion (e.g. educational visit, visiting colleague, site visit) participants may give permission for visitors to observe a procedure or experiment.

10.0 Data and Safety Monitoring Plan

This section is required when research involves more than Minimal Risk to subjects. As defined in "SOP: Definitions (HRP-001)", available in the Library in CATS IRB (http://irb.psu.edu), Minimal Risk is defined as the probability and magnitude of harm or discomfort anticipated in the research that are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests. For research involving prisoners, Minimal Risk is the probability and magnitude of physical or psychological harm that is normally encountered in the daily lives, or in the routine medical, dental, or psychological examination of healthy persons. **Please complete the sections below if the research involves more than minimal risk to subjects OR indicate as not applicable.**

10.1 Periodic evaluation of data

Describe the plan to periodically evaluate the data collected regarding both harms and benefits to determine whether subjects remain safe.

Not applicable.

10.2 Data that are reviewed

Describe the data that are reviewed, including safety data, untoward events, and efficacy data.

Not applicable.

10.3 Method of collection of safety information

Describe the method by which the safety information will be collected (e.g., with case report forms, at study visits, by telephone calls and with subjects).

Not applicable.

10.4 Frequency of data collection

Describe the frequency of data collection, including when safety data collection starts.

Not applicable.

10.5 Individuals reviewing the data

Identify the individuals who will review the data. The plan might include establishing a data and safety monitoring committee and a plan for reporting data monitoring committee findings to the IRB and the sponsor.

Not applicable.

10.6 Frequency of review of cumulative data

Describe the frequency or periodicity of review of cumulative data.

Not applicable.

10.7 Statistical tests

Describe the statistical tests for analyzing the safety data to determine whether harms are occurring.

Not applicable.

10.8 Suspension of research

Describe any conditions that trigger an immediate suspension of research.

Not applicable.

11.0 Risks

List the reasonably foreseeable risks, discomforts, hazards, or inconveniences to the subjects related the subjects' participation in the research. For each potential risk, describe the probability, magnitude, duration, and reversibility. Consider all types of risk including physical, psychological, social, legal, and economic risks. If applicable, indicate which procedures may have risks to the subjects that are currently unforeseeable. If applicable, indicate which procedures may have risks to an embryo or fetus should the subject be or become pregnant. If applicable, describe risks to others who are not subjects.

Please keep in mind that loss of confidentiality is a potential risk when conducting human subject research and should be addressed as such.

All downloaded data of the study will be stored on a password protected computer in 17 Rec Hall (a locked room) on the University Park campus, and only approved and trained personnel (research staff who completed the CITI training) will have access to the data. Thus, the loss of confidentiality may be minimized. Finally, participants are made aware that they can skip any question(s) they are not comfortable answering.

Physical discomfort may result from the aerobic tests performed in the study. It is possible that subjects may experience faintness, fatigue, muscle pain, chest pain, or a musculoskeletal injury during the exercise tests. These possible side effects are inherent in activities that require physical exertion. Study personnel will monitor subjects for the duration of the protocol and exercise will be submaximal to minimize risk. There is an AED in Noll Lab. In any emergency, 911 will be called immediately.

Further, discomfort arising from increasing physical activity is possible if participants rapidly increase their level of physical activity; however, any discomfort is expected to decrease as they adapt to the increased activity over the course of the study.

General note about the vascular function assessments: The research group's members administering the drugs and drawing blood are trained and competent in their duties. The group, led by Dr. Alexander, evaluates the effectiveness and safety of protocols and procedures in an ongoing fashion. They discuss the protocol with candidates, invite questions, and offer tours of the laboratory. Candidates read and sign informed consent forms detailing protocols, procedures, risks, sensations, compensation, etc. The researchers give candidates witnessed copies of the signed consent forms. After accepting participants into the study, the researchers discuss and review the procedures and protocols with them generally and at each step throughout the project. They frequently remind participants of the option to withdraw from the study at any time. Restricting access to

experiments, data, and coding to authorized personnel maintains confidentiality. The Noll Lab's electronics technician certifies the electrical devices for human use. Lists of emergency numbers remain by lab telephones. At least one cell phone is present at each experiment. A hospital and emergency medical services are within 1-2 miles of the lab. An AED hangs nearby in the hallway.

Microdialysis: The researchers insert a 25 g needle horizontally into and then out of the layers of the skin of the ventral forearm. The needle's entry and exit are about 2.5 cm (1 inch) apart. They thread the microdialysis "probe," comprising a tube of membrane (320 µm OD) with tubing attached at both ends (650 µm OD), through the needle. Then they withdraw the needle leaving the membrane under the skin. They perfuse the probe with sterile saline using a syringe pump.

Cutaneous microdialysis commonly causes some pain and bruising similar to that experienced during venipuncture. There is usually no pain after the probe is in place. The participant may experience mild pain while the researchers remove the probe. Minor bleeding may occur. As with routine venipuncture, a participant who is nervous about needles could have increased heart rate and blood pressure, become lightheaded or nauseated, or could faint.

As with venipuncture or any event that breaks the skin, infection is possible. However, no participants in any of the researchers' experiments have reported infection. The researchers place a sterile bandage on the site after the experiment. Although rare, if the membrane should break in half during removal, the researcher removes the remaining half by gently pulling the attached tubing. This presents no additional risk to the participant. In the unlikely event in which the membrane breaks during removal leaving an isolated piece of membrane under the skin, they treat the piece of membrane in a manner similar to that for a splinter in the skin. In this case, they have to make a superficial incision for removal.

Perfusate: Lactated Ringer's solution flows through the microdialysis probes. An allergic reaction to this physiological saline solution, although possible, is highly unlikely.

All substances added to the fluid perfusing the microdialysis probes (*ACh, L-NAME, SNP*) have been used previously clinically and/or in research in humans.

Microdialysis delivers small amounts of the substances to a nickel-sized area of the skin. The small quantities used and the extremely localized administration during microdialysis does not produce systemic effects. There are no reports of long- or short-term side effects of these substances administered through microdialysis. The chance of adverse reactions to these substances is extremely small given the minute amount delivered to a very small area of skin, the lack of adverse reactions to similar amounts delivered via MD in many other studies, and the lack of adverse effects in human cell cultures. There is a slight chance of allergic reaction to these substances that could produce redness, itching, rash, and/or swelling. A severe reaction (anaphylactic shock) could also cause fever, difficulty in breathing, changes in pulse, convulsions, and/or loss of consciousness.

The perfusate is sterile. The researchers prepare the perfusate in their laboratory using sterile techniques and supplies commonly used for this purpose in research laboratories. The Ringer's solution is sterile as purchased. They add other solutions aseptically to the sterile bag of Ringer's solution through 0.2 µm Gelman Sterile Acrodisc syringe filters. They mix the perfusate for same-day use and discard excess perfusate after the experiment. During the IND application process, the FDA accepted the researchers' technique for preparing perfusates. Although unlikely, in the case of a severe reaction to the perfusate, the researchers call 911.

Laser Doppler Flowmetry: The probe attaches to the skin with double-sided tape and measures skin blood flow in a 1 mm^3 volume of skin. Weak lasers can hurt the eye if one should stare into the light for a long time. The red light seen on the surface of the skin is harmless. The researchers do not turn on the laser until they tape the probes to a surface. They remove the tape afterward carefully. The researchers have used this technique in their lab with IRB approval for many years without incident.

Blood Pressure (manual, CardioCap 5): The manual method and CardioCap5 use a cuff that inflates on the upper arm. The cuff slowly deflates while the researchers listen to pulse-sounds at the inside of the elbow with a stethoscope, or the CardioCap 5 takes a measurement. The inflated cuff may make the arm feel tingly and numb, and the cuff may temporarily bruise the arm. Efficient and competent measurement technique minimizes the duration of cuff inflation. These techniques are unlikely to produce lasting ill effects.

Povidone Iodine: Hospitals and researchers use povidone iodine to clean and sterilize the skin. Participants could be allergic to iodine. An allergic reaction could cause redness, itching, rash, and/or swelling. A worse reaction could also cause fever, breathing problems, changes in pulse and/or blood pressure, convulsions, shock, and/or loss of consciousness. Staff use only alcohol on participants with iodine allergy as identified during screening.

Blood draw: Blood draws can cause anxiety (with increased heart rate and blood pressure), mild pain, swelling, nausea, lightheadedness, fainting, or bleeding. There is a slight chance of infection. A competent nurse performs blood draws using standard venipuncture procedure and techniques that minimize the chance of infection. Participants may recline for the procedure.

Tape and adhesive disks: Subjects could be sensitive to the adhesive of the tape and double-sided adhesive discs used in the study causing redness, rash, tenderness, and/or itching. The researchers remove the tape and adhesive discs carefully. Ointment is available, if needed.

ECG: The researchers attach three to twelve electrodes to the participant's chest and then attach the electrode wires to an ECG machine. The machine records the electrical activity of the heart. There are no adverse effects from this measure. A subject may be shy about electrodes applied to the chest. The staff carefully remove the tape afterward. They conduct the test professionally and privately.

Local Heating: The local heating control unit (Moor Instruments) precisely controls and monitors the temperature of the heated probe holders used with the laser Doppler flowmeter. To determine the maximal SkBF, the researchers increase the temperature of the heating units slowly (about 0.1°C every 1 second). The skin feels very warm but not painful. Local heating causes temporary redness of the skin that subsides within several hours. This technique is very unlikely to produce long-term ill effects. The local heating controllers (Moor Instruments) precisely control and monitor the temperature of the heated probe holders. The system has programmed maximal temperature limits. This technique is unlikely to cause long-term ill effects.

Latex: Some gloves and medical materials are made of latex rubber. Some people may be sensitive to latex. Screening identifies and excludes candidates having a known latex allergy.

Flow-mediated Vasodilation (FMD Test)/Doppler Ultrasound: There is a small chance the probe could irritate the skin. Placing the probe on the arm's skin may cause temporary minor redness. The inflated cuff may cause the participant's arm to feel numb or tingly, and the skin's color to change slightly. The cuff could cause mild bruising. The gel is the same as that used with medical ultrasound tests. The gel may feel cool or cold on the skin. A bad reaction to the gel is highly unlikely. The cuff inflates for a minimal amount of time. The temporary redness from the probe is unlikely to have lasting ill effects. The participant may decline the test.

12.0 Potential Benefits to Subjects and Others

12.1 Potential Benefits to Subjects

Describe the potential benefits that individual subjects may experience from taking part in the research. If there is no direct benefit to subjects, indicate as such. Compensation is not considered a benefit. Compensation should be addressed in section 14.0.

Participants may increase their physical activity and experience increased physiological and psychological health benefits accordingly.

12.2 Potential Benefits to Others

Include benefits to society or others.

Results from this study may lead to new intervention approaches for lifestyle changes.

13.0 Sharing Results with Subjects

Describe whether results (study results or individual subject results, such as results of investigational diagnostic tests, genetic tests, or incidental findings) will be shared with subjects or others (e.g., the subject's primary care physicians) and if so, describe how it will be shared.

Participants will not receive individual results. They may request a copy of any publications summarizing results from the research.

14.0 Subject Stipend (Compensation) and/or Travel Reimbursements

Describe the amount and timing of any subject stipend/payment or travel reimbursement here. If there is no subject stipend/payment or travel reimbursement, indicate as not applicable.

If course credit or extra credit is offered to subjects, describe the amount of credit and the available alternatives. Alternatives should be equal in time and effort to the amount of course or extra credit offered.

If an existing, approved student subject pool will be used to enroll subjects, please indicate as such and indicate that course credit will be given and alternatives will be offered as per the approved subject pool procedures.

Participant compensation is requested and will be allocated separately for the main study (n = 30; 3 visits X $20/visit) and ancillary laboratory study (n = 10; 3 visits X $100/visit). Participants will also keep the Fitbit activity monitor worn throughout the study. In sum, participants in the main study (n = 30), will receive $60 for completing the study. Those in the ancillary study (n = 10), will receive an additional $300 for completing all portions of the ancillary study as well as $60 for their participation in the main study for a total of $360).

15.0 Economic Burden to Subjects

15.1 Costs

Describe any costs that subjects may be responsible for because of participation in the research.

Up to 6 megabyte (MB) may be deducted from participants' mobile data plan or charged for the use of the application as a result of study participation (approximately 30 to 60 cents over the course of the entire study). Participants will be responsible for any travel costs related to transportation to and from the lab.

15.2 Compensation for research-related injury

If the research involves more than Minimal Risk to subjects, describe the available compensation in the event of research related injury.

If there is no sponsor agreement that addresses compensation for medical care for research subjects with a research-related injury, include the following text as written - DO NOT ALTER OR DELETE:

It is the policy of the institution to provide neither financial compensation nor free medical treatment for research-related injury. In the event of injury resulting from this research, medical treatment is available but will be provided at the usual charge. Costs for the treatment of research-related injuries will be charged to subjects or their insurance carriers.

For sponsored research studies with a research agreement with the sponsor that addresses compensation for medical care for research-related injuries, include the following text as written - DO NOT ALTER OR DELETE:
It is the policy of the institution to provide neither financial compensation nor free medical treatment for research-related injury. In the event of injury resulting from this research, medical treatment is available but will be provided at the usual charge. Such charges may be paid by the study sponsor as outlined in the research agreement and explained in the consent form.

In the unlikely event a participant becomes injured as a result of participation in this study, medical care is available. It is the policy of the institution to provide neither financial compensation nor free medical treatment for research-related injury. In the event of injury resulting from this research, medical treatment is available but will be provided at the usual charge. Costs for the treatment of research-related injuries will be charged to participants or their insurance carriers.

16.0 Resources Available

16.1 Facilities and locations

Identify and describe the facilities, sites and locations where recruitment and study procedures will be performed.

If research will be conducted outside the United States, describe site-specific regulations or customs affecting the research, and describe the process for obtaining local ethical review. Also, describe the principal investigator's experience conducting research at these locations and familiarity with local culture.

This research will be conducted in the Penn State University at the University Park campus. The lab sessions will be carried out in 17 Rec Hall and in the Noll Laboratory. The Noll laboratory is a 4-floor (35,000 sq. ft.) free-standing building devoted to basic, clinical, and applied physiological research. Biochemistry laboratories are available for sample processing and analyses. Available equipment includes centrifuges, critical care monitors, sonicator, microbalances, laser doppler flowmeters, mini-syringe pumps/ controllers, hospital beds, ECG analysis system, Finipres, refrigerators, pharmaceutical refrigerator, -20 C and -80 C freezers, local skin cooling/ heating systems, blood pressure monitors, metabolic cart, gas sterilization equipment, treadmills, bikes, semi-recumbent cycle ergometer, and autoclave facilities. In addition to ample office and laboratory laptop or desktop computers for research and student use, and a trunk line connection to the University's mainframe computer system. Internal, office and laboratory computers are linked. The laboratory has four PC-based data acquisition systems (DAQ) equipped with Dataq-based DAQ system driven by Windaq software or a PowerLab, DAQ system. A Clinical Research Center (CRC) is contiguous to the Noll Laboratory in the 14,000 sq. ft. Elmore wing. The CRC is readily available for research support.

16.2 Feasibility of recruiting the required number of subjects

Indicate the number of potential subjects to which the study team has access. Indicate the percentage of those potential subjects needed for recruitment.

Based on available data in the Centre County region, the average annual incidence rate per 100,000 people is 108 for breast cancer, 32 for lymphoma, and 20 for leukemia each year. Nationally, the

incidence rate for breast cancer is 124.7, 18.9 for lymphoma and 13.6 for leukemia each year. Based on those annual estimates and the possible age range of participants (18-65) and a diagnosis within the past 15 years, we will need to recruit approximately 0.01% of eligible individuals (based on national estimates) to meet our sample size of 30 cancer survivors.

16.3 PI Time devoted to conducting the research

Describe how the PI will ensure that a sufficient amount of time will be devoted to conducting and completing the research. Please consider outside responsibilities as well as other on-going research for which the PI is responsible.

Dr. Conroy has 5% of his time protected by the Department of Kinesiology for the purpose of performing this research study. Dr. Alexander has 5% of her time protected by the Department of Kinesiology for the purpose of performing this research study. Sufficient study personnel and resources exist to facilitate the completion of the study when he must be absent.

16.4 Availability of medical or psychological resources

Describe the availability of medical or psychological resources that subject might need as a result of their participation in the study, if applicable.

Participants will be monitored for the duration of the protocol by study personnel. There is an AED in Noll Lab. In any emergency, 911 will be called immediately.

16.5 Process for informing Study Team

Describe the training plans to ensure members of the research team are informed about the protocol and their duties, if applicable.

The investigator and research team members involved in the study have completed their required Collaborative IRB Training Initiative (CITI) in the protection of Human Research Subjects. Study staff delegated to conduct specific study procedures will be trained on these procedures individually or in a group format by the PIs.

17.0 Other Approvals

17.1 Other Approvals from External Entities

Describe any approvals that will be obtained prior to commencing the research (e.g., from cooperating institutions, community leaders, schools, external sites, funding agencies).

We have prepared an IND application to the FDA that includes all drugs used with microdialysis in this research. This application was submitted 12/14/18. We are waiting for the FDA to assign an IND number. We will add the number to CATS when we receive it.

17.2 Internal PSU Committee Approvals

Check all that apply:

☐ Anatomic Pathology – Hershey only – Research involves the collection of tissues or use of pathologic specimens. Upload a copy of HRP-902 - Human Tissue For Research Form on the "Supporting Documents" page in CATS IRB. This form is available in the CATS IRB Library.

☐ Animal Care and Use – All campuses – Human research involves animals and humans or the use of human tissues in animals

X Biosafety – All campuses – Research involves biohazardous materials (human biological specimens in a PSU research lab, biological toxins, carcinogens, infectious agents, recombinant viruses or DNA or gene therapy).

☐ Clinical Laboratories – Hershey only – Collection, processing and/or storage of extra tubes of body fluid specimens for research purposes by the Clinical Laboratories; and/or use of body fluids that had been collected for clinical purposes, but are no longer needed for clinical use. Upload a copy of HRP-901 - Human Body Fluids for Research Form on the "Supporting Documents" page in CATS IRB. This form is available in the CATS IRB Library.

X Clinical Research Center (CRC) Advisory Committee– All campuses – Research involves the use of CRC services in any way.

☐ Conflict of Interest Review – All campuses – Research has one or more of study team members indicated as having a financial interest.

☐ Radiation Safety – Hershey only – Research involves research-related radiation procedures. All research involving radiation procedures (standard of care and/or research-related) must upload a copy of HRP-903 - Radiation Review Form on the "Supporting Documents" page in CATS IRB. This form is available in the CATS IRB Library.

X IND/IDE Audit – All campuses – Research in which the PSU researcher holds the IND or IDE or intends to hold the IND or IDE.

☐ Scientific Review – Hershey only – All investigator-written research studies requiring review by the convened IRB must provide documentation of scientific review with the IRB submission. The scientific review requirement may be fulfilled by one of the following: (1) external peer-review process; (2) department/institute scientific review committee; or (3) scientific review by the Clinical Research Center Advisory committee. NOTE: Review by the Penn State Hershey Cancer Institute Scientific Review Committee is required if the study involves cancer prevention studies or cancer patients, records and/or tissues. For more information about this requirement see the IRB website at: http://www.pennstatehershey.org/web/irb/home/resources/investigator

18.0 Multi-Site Research

If this is a multi-site study (i.e., the study will be conducted at other institutions each with its own principal investigator) and you are the lead investigator, describe the processes to ensure communication among sites in the sections below.

18.1 Communication Plans

Describe the plan for regular communication between the overall study director and the other sites to ensure that all sites have the most current version of the protocol, consent document, etc. Describe the process to ensure all modifications have been communicated to sites. Describe the process to ensure that all required approvals have been obtained at each site (including approval by the site's IRB of record). Describe the process for communication of problems with the research, interim results and closure of the study.

Not applicable.

18.2 Data Submission and Security Plan

Describe the process and schedule for data submission and provide the data security plan for data collected from other sites. Describe the process to ensure all engaged participating sites will safeguard data as required by local information security policies.

Not applicable.

18.3 Subject Enrollment

Describe the procedures for coordination of subject enrollment and randomization for the overall project.

Not applicable.

18.4 Reporting of Adverse Events and New Information

Describe how adverse events and other information will be reported from the clinical sites to the overall study director. Provide the timeframe for this reporting.

Not applicable.

18.5 Audit and Monitoring Plans

Describe the process to ensure all local site investigators conduct the study appropriately. Describe any on-site auditing and monitoring plans for the study.

Not applicable.

19.0 Adverse Event Reporting

19.1 Adverse Event Definitions

For drug studies, incorporate the following definitions into the below responses, as written:	
Adverse event	Any untoward medical occurrence associated with the use of the drug in humans, whether or not considered drug related
Adverse reaction	Any adverse event caused by a drug
Suspected adverse reaction	Any adverse event for which there is a reasonable possibility that the drug caused the adverse event. Suspected adverse reaction implies a lesser degree of certainty about causality than "adverse reaction". • *Reasonable possibility.* For the purpose of IND safety reporting, "reasonable possibility" means there is evidence to suggest a causal relationship between the drug and the adverse event.
Serious adverse event or Serious suspected adverse reaction	Serious adverse event or Serious suspected adverse reaction: An adverse event or suspected adverse reaction that in the view of either the investigator or sponsor, it results in any of the following outcomes: Death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.
Life-threatening adverse event or	An adverse event or suspected adverse reaction is considered "life-threatening" if, in the view of either the Investigator (i.e., the study site

life-threatening suspected adverse reaction	principal investigator) or Sponsor, its occurrence places the patient or research subject at immediate risk of death. It does not include an adverse event or suspected adverse reaction that had it occurred in a more severe form, might have caused death.
Unexpected adverse event or Unexpected suspected adverse reaction.	An adverse event or suspected adverse reaction is considered "unexpected" if it is not listed in the investigator brochure, general investigational plan, clinical protocol, or elsewhere in the current IND application; or is not listed at the specificity or severity that has been previously observed and/or specified.

For device studies, incorporate the following definitions into the below responses, as written:	
Unanticipated adverse device effect	Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or IDE application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

19.2 Recording of Adverse Events

Address the frequency and process for eliciting adverse event information from research subject, e.g., "Research subjects will be routinely questioned about adverse events at study visits."

In the response, incorporate the following as written:
All adverse events (serious or non-serious) and abnormal test findings observed or reported to study team believed to be associated with the study drug(s) or device(s) will be followed until the event (or its sequelae) or the abnormal test finding resolves or stabilizes at a level acceptable to the investigator.

An abnormal test finding will be classified as an adverse event if one or more of the following criteria are met:

- The test finding is accompanied by clinical symptoms
- The test finding necessitates additional diagnostic evaluation(s) or medical/surgical intervention; including significant additional concomitant drug treatment or other therapy
  NOTE: Simply repeating a test finding, in the absence of any of the other listed criteria, does not constitute an adverse event.
- The test finding leads to a change in study drug dosing or discontinuation of subject participation in the clinical research study
- The test finding is considered an adverse event by the investigator.

Research subjects will be routinely questioned about adverse events (e.g., musculoskeletal injuries, cardiovascular events) at study visits and monitored carefully during laboratory procedures.

In the case of untoward events, those lab members present during the event are included in a debriefing and notes of the meeting are taken. The participant involved in an untoward event is interviewed in person or via telephone concerning the event and the responses are included into the notes for that event.

All adverse events (serious or non-serious) and abnormal test findings observed or reported to study team believed to be associated with the study drug(s) or device(s) will be followed until the event (or its sequelae) or the abnormal test finding resolves or stabilizes at a level acceptable to the investigator.

An abnormal test finding will be classified as an adverse event if one or more of the following criteria are met:

- The test finding is accompanied by clinical symptoms
- The test finding necessitates additional diagnostic evaluation(s) or medical/surgical intervention; including significant additional concomitant drug treatment or other therapy
  NOTE: Simply repeating a test finding, in the absence of any of the other listed criteria, does not constitute an adverse event.
- The test finding leads to a change in study drug dosing or discontinuation of subject participation in the clinical research study
- The test finding is considered an adverse event by the investigator.

19.3 Causality and Severity Assessments

By submitting this study for review, you agree to the following statement – DO NOT ALTER OR DELETE:

The investigator will promptly review documented adverse events and abnormal test findings to determine 1) if the abnormal test finding should be classified as an adverse event; 2) if there is a reasonable possibility that the adverse event was caused by the study drug(s) or device(s); and 3) if the adverse event meets the criteria for a serious adverse event.

If the investigator's final determination of causality is "unknown and of questionable relationship to the study drug(s) or device(s)", the adverse event will be classified as associated with the use of the study drug(s) or device(s) for reporting purposes. If the investigator's final determination of causality is "unknown but not related to the study drug(s) or device(s)", this determination and the rationale for the determination will be documented in the respective subject's case history.

19.4 Reporting of Adverse Reactions and Unanticipated Problems to the FDA

19.4.1 Written IND/IDE Safety Reports

For a drug study under an IND, incorporate the following from 21 CFR 312.32 as written – DO NOT ALTER OR DELETE:
The Sponsor-Investigator will submit a written IND Safety Report (i.e., completed FDA Form 3500A) to the responsible new drug review division of the FDA for any observed or volunteered adverse event that is determined to be a serious and unexpected, suspected adverse reaction. Each IND Safety Report will be prominently labeled, "IND Safety Report", and a copy will be provided to all participating investigators (if applicable) and sub-investigators.

Written IND Safety Reports will be submitted to the FDA as soon as possible and, in no event, later than 15 calendar days following the Sponsor-Investigator's receipt of the respective adverse event information and determination that it meets the respective criteria for reporting.

For each written IND Safety Report, the Sponsor-Investigator will identify all previously submitted IND Safety Reports that addressed a similar suspected adverse reaction experience and will provide an analysis of the significance of newly reported, suspected adverse reaction in light of the previous, similar report(s) or any other relevant information.

Relevant follow-up information to an IND Safety Report will be submitted to the applicable review division of the FDA as soon as the information is available and will be identified as such (i.e., "Follow-up IND Safety Report").

If the results of the Sponsor-Investigator's follow-up investigation show that an adverse event that was initially determined to not require a written IND Safety Report does, in fact, meet the requirements for reporting; the Sponsor-Investigator will submit a written IND Safety Report as soon as possible, but in no event later than 15 calendar days, after the determination was made.

For a device study under an IDE, incorporate the following from 21 CFR 812.150 as written – DO NOT ALTER OR DELETE:
The Sponsor-Investigator will submit a completed FDA Form 3500Ato the FDA's Center for Devices and Radiological Health for any observed or volunteered adverse effect that is determined to be an unanticipated adverse device effect. A copy of this completed form will be provided to all participating sub-investigators.

The completed FDA Form 3500Awill be submitted to the FDA as soon as possible and, in no event, later than 10 working days after the Sponsor-Investigator first receives notice of the adverse effect.

If the results of the Sponsor-Investigator's follow-up evaluation show that an adverse effect that was initially determined to not constitute an unanticipated adverse device effect does, in fact, meet the requirements for reporting; the Sponsor-Investigator will submit a completed FDA Form 3500Aas soon as possible, but in no event later than 10 working days, after the determination was made.

For each submitted FDA Form 3500A, the Sponsor-Investigator will identify all previously submitted reports that that addressed a similar adverse effect experience and will provide an analysis of the significance of newly reported adverse effect in light of the previous, similar report(s).

Subsequent to the initial submission of a completed FDA Form 3500A, the Sponsor-Investigator will submit additional information concerning the reported adverse effect as requested by the FDA.

The Sponsor-Investigator will submit a written IND Safety Report (i.e., completed FDA Form 3500A) to the responsible new drug review division of the FDA for any observed or volunteered adverse event that is determined to be a serious and unexpected, suspected adverse reaction. Each IND Safety Report will be prominently labeled, "IND Safety Report", and a copy will be provided to all participating investigators (if applicable) and sub-investigators.

Written IND Safety Reports will be submitted to the FDA as soon as possible and, in no event, later than 15 calendar days following the Sponsor-Investigator's receipt of the respective adverse event information and determination that it meets the respective criteria for reporting.

For each written IND Safety Report, the Sponsor-Investigator will identify all previously submitted IND Safety Reports that addressed a similar suspected adverse reaction experience and will provide an analysis of the significance of newly reported, suspected adverse reaction in light of the previous, similar report(s) or any other relevant information.

Relevant follow-up information to an IND Safety Report will be submitted to the applicable review division of the FDA as soon as the information is available and will be identified as such (i.e., "Follow-up IND Safety Report").

If the results of the Sponsor-Investigator's follow-up investigation show that an adverse event that was initially determined to not require a written IND Safety Report does, in fact, meet the requirements for reporting; the Sponsor-Investigator will submit a written IND Safety Report as soon as possible, but in no event later than 15 calendar days, after the determination was made.

19.4.2 Telephoned IND Safety Reports – Fatal or Life-threatening Suspected Adverse Reactions

For a drug study under an IND, incorporate the following from 21 CFR 312.32 into the response, as written:
In addition to the subsequent submission of a written IND Safety Report (i.e., completed FDA Form 3500A), the Sponsor-Investigator will notify the responsible review division of the FDA by telephone or facsimile transmission of any unexpected, fatal or life-threatening suspected adverse reaction.

The telephone or facsimile transmission of applicable IND Safety Reports will be made as soon as possible but in no event later than 7 calendar days after the Sponsor-Investigator's receipt of the respective adverse event information and determination that it meets the respective criteria for reporting.

In addition to the subsequent submission of a written IND Safety Report (i.e., completed FDA Form 3500A), the Sponsor-Investigator will notify the responsible review division of the FDA by telephone or facsimile transmission of any unexpected, fatal or life-threatening suspected adverse reaction.

The telephone or facsimile transmission of applicable IND Safety Reports will be made as soon as possible but in no event later than 7 calendar days after the Sponsor-Investigator's receipt of the respective adverse event information and determination that it meets the respective criteria for reporting.

19.5 Reporting Adverse Reactions and Unanticipated Problems to the Responsible IRB

By submitting this study for review, you agree to the following statement – DO NOT ALTER OR DELETE:

In accordance with applicable policies of The Pennsylvania State University Institutional Review Board (IRB), the investigator will report, to the IRB, any observed or reported harm (adverse event) experienced by a subject or other individual, which in the opinion of the investigator is determined to be (1) unexpected; and (2) probably related to the research procedures. Harms (adverse events) will be submitted to the IRB in accordance with the IRB policies and procedures.

19.6 Unblinding Procedures

Describe the procedures for unblinding study therapy on a subject, including documentation of this in the subject's source document. Include example(s) here why someone might unblind a study. In most cases, the unblinding will be part of managing a serious adverse reaction and will be reported with the serious adverse event. However, in cases where unblinding was not associated with a serious adverse event, such actions should be reported in a timely manner.

Not applicable

19.7 Stopping Rules

In studies with a primary safety endpoint or studies with high risk to study subjects, provide the rules that define the circumstances and procedures for interrupting or stopping the study. If an independent Data and Safety Monitoring (DSMB) or Committee (DSMC) is set up for the study, the same stopping rules should be incorporated into the safety analysis plan as well.

There are no stopping rules for the behavioral component of the intervention.

Stopping rules are in place for the laboratory portion of the study. Although such events are extremely unlikely to occur, we are prepared to immediately stop experiments and seek medical assistance if the subjects should experience the more serious reactions described in the informed consents, and IRB applications such as signs and symptoms of an allergic reaction, anaphylactic shock, etc. As always, our subjects are reminded throughout the protocol that they may stop the experiment at any time. Also, we exercise the discretion to end a subject's participation if the subject should engage in behavior that could jeopardize his/her own health and well-being or that of others.

We end the experiments if the subject experiences:

- Systolic or diastolic blood pressures exceed 220 or 110 mmHg, respectively, or
- Systolic or diastolic blood pressures are less than 90 or 50 mmHg, respectively or
- Heartrate <40 bpm or > 120 bpm.

20.0 Study Monitoring, Auditing and Inspecting

20.1 Study Monitoring Plan

20.1.1 Quality Assurance and Quality Control

Include this section if FDA regulations apply to this study (see "WORKSHEET: Drugs (HRP-306)" and "WORKSHEET: Devices (HRP-307)". HRP-306 and HRP-307 can be accessed by clicking the Library link in CATS IRB (http://irb.psu.edu).

Describe how you will ensure that this study is conducted and that the data are generated, documented (recorded) and reported in compliance with this protocol, with institutional and IRB policies, with Good Clinical Practice guidelines and any other applicable regulatory requirements.

Indicate who is responsible for monitoring the conduct of the study and specify how often the study will be monitored.

For single-site studies with low risk, it may be appropriate for the principal investigator to monitor the study.

For multi-center studies or single site studies involving significant risk, an independent monitor may be required (e.g., monitoring by the staff of the PSU quality assurance program office(s) or by a clinical research organization).

The project coordinator (Dr. Gilchrist) will provide weekly reports to Dr. Conroy and Dr. Alexander who will monitor the study to ensure that the data are generated, documented (recorded) and reported in compliance with this protocol, with institutional and IRB policies, with Good Clinical Practice guidelines and any other applicable regulatory requirements.

20.1.2 Safety Monitoring

Include this section if FDA regulations apply to this study (see "WORKSHEET: Drugs (HRP-306)" and "WORKSHEET: Devices (HRP-307)". HRP-306 and HRP-307 can be accessed by clicking the Library link in CATS IRB (http://irb.psu.edu).

Indicate the process for identifying, recording and reporting adverse events.

Specify roles for adverse event recording and monitoring. Indicate each staff member's role in the adverse event reporting process. Include the following if applicable:

The **Principal Investigator** will confirm that all adverse events (AE) are correctly entered into the AE case report forms by the coordinator; be available to answer any questions that the

coordinators may have concerning AEs; and will notify the IRB, FDA, sponsor and/or DSMB of all applicable AEs as appropriate. All assessments of AEs will be made by a licensed medical professional who is an investigator on the research.

The **Research Coordinator** will complete the appropriate report form and logs; assist the PI to prepare reports and notify the IRB, FDA and/or DSMB of all Unanticipated Problems/SAE's.

The **Monitor** will confirm that the AEs are correctly entered into the case report forms. The Monitor will also confirm that the adverse events are consistent with the source documents and are reported to the appropriate regulatory bodies as required.

The Principal Investigators will confirm that all adverse events (AE) are correctly entered into the AE case report forms by the coordinator; be available to answer any questions that the coordinators may have concerning AEs; and will notify the IRB, FDA, sponsor and/or DSMB of all applicable AEs as appropriate. All assessments of AEs will be made by a licensed medical professional who is an investigator on the research.

The Research Coordinator will complete the appropriate report form and logs; assist the PI to prepare reports and notify the IRB, FDA and/or DSMB of all Unanticipated Problems/SAE's.

21.0 Future Undetermined Research: Data and Specimen Banking

If this study is collecting identifiable data and/or specimens that will be banked for future undetermined research, please describe this process in the sections below. This information should not conflict with information provided in section 9.1.1 regarding whether or not data and/or specimens will be associated with identifiers (directly or indirectly).

21.1 Data and/or specimens being stored

Identify what data and/or specimens will be stored and the data associated with each specimen.

Not applicable.

21.2 Location of storage

Identify the location where the data and/or specimens will be stored.

Not applicable.

21.3 Duration of storage

Identify how long the data and/or specimens will be stored.

Not applicable.

21.4 Access to data and/or specimens

Identify who will have access to the data and/or specimens.

Not applicable.

21.5 Procedures to release data or specimens

Describe the procedures to release the data and/or specimens, including: the process to request a release, approvals required for release, who can obtain data and/or specimens, and the data to be provided with the specimens.

Not applicable.

21.6 Process for returning results

Describe the process for returning results about the use of the data and/or specimens.

Not applicable.

22.0 References

List relevant references in the literature which highlight methods, controversies, and study outcomes.

Not applicable.