Protocol Title

Awareness Enhancing Interventions (AWEI)

Study Protocol & Statistical Analysis Plan

NCT04683510

March 31, 2024

Michelle Martin, PhD, Principal Investigator
University of Tennessee Health Science Center
Maria Pisu, PhD, Principal Investigator
University of Alabama at Birmingham
Birmingham, AL 35294

Increasing recruitment of underrepresented cancer survivors with awareness enhancing interventions

(AWEI)

Principal Investigator: Michelle Martin, PhD, Maria Pisu, PhD

Sponsor: National Cancer Institute

National Clinical Trial (NCT) Identified Number: NCT04683510

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STATEMENT OF COMPLIANCE

The trial is conducted in accordance with International Conference on Harmonisation Good Clinical Practice (ICH GCP) and applicable United States (US) Code of Federal Regulations (CFR). The Principal Investigator assures that no deviation from, or changes to, the protocol will take place without prior documented approval from the Institutional Review Board (IRB), except where necessary to eliminate an immediate hazard(s) to the trial subjects. All personnel involved in the conduct of this study have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent form(s), recruitment materials, and all subject materials are submitted to the local Institutional Review Board (IRB) for review and approval. Approval of both the protocol was obtained before any subject was enrolled. Any amendment to the protocol required review and approval by the IRB before the changes were implemented to the study.

1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Title:	Increasing recruitment of underrepresented cancer survivors with awareness enhancing interventions (AWEI)
Study Description:	This study aims to investigate whether increasing awareness and, thus, enhancing positive attitudes about research, prior to recruitment attempts, will increase participation in cancer clinical research among African American (AA) cancer survivors Specifically, we investigate if interventions to raise awareness about research can increase the recruitment of African American cancer survivors to a web-based diet and physical activity interventions trial, known as the Adapting MultiPLe behavior Interventions that eFfectively Improve (AMPLIFI) Cancer Survivor Health trial (NCT04000880). The study will use a factorial trial design to test the effectiveness of the Awareness and Willingness to Engage in Research Intervention (AWEI) versus the original AMPLIFI recruitment strategy.
Objectives:	To determine if interventions to raise awareness about research can increase the recruitment of African American cancer survivors to the AMPLIFY web-based diet and physical activity trial
Endpoints:	– Reached = whether the AMPLIFI recruiter was able to reach the potential participant over the phone – Screened if reached = whether the survivor who was reached by the recruiter was willing to consider the study and to be screened to ascertain eligibility for the AMPLIFI trial

	– Consented if eligible = whether the survivor who was screened and found eligible to participate in the AMPLIFI trial agreed and consented to participate in the AMPLIFI trial
Study Population:	Adult (age ≥50 years old) African American cancer survivors who were eligible for enrollment into the AMPLIFI trial - Within 1-5 years from a diagnosis of loco-regional cancers of the colorectum, female breast, prostate, endometrium, localized kidney or ovarian cancer, thyroid cancer, multiple myeloma and non-Hodgkin's lymphoma
Phase:	2
Description of Study Intervention:	The AWEI interventions were educational interventions that varied by: - delivery channel, i.e., education through a brochure vs. a research educator 'navigator' - research emphasis, i.e., highlighting the importance of participating in AMPLIFI vs. in research in general - perspective, i.e., the information reflected the voice of a cancer survivor vs. that of an expert researcher
Study Duration:	3 years
Subject Duration:	15 days

2 INTRODUCTION

2.1 STUDY RATIONALE

African American cancer survivors are often underrepresented in clinical trials, which can limit the generalizability of research findings. This study seeks to address this gap by testing an intervention designed to increase awareness and willingness to participate in a web-based diet and physical activity trial.

2.2 BACKGROUND

As highlighted in the 2022 National Academies of Medicine report on improving representation in clinical trials and research, the lack of representation of diverse groups has many consequences including hindering innovation and new discoveries, generalizability of research findings, access to effective medical interventions, and trust in research and medicine. Inadequate representation in research means we have limited information and opportunity to advance knowledge to reduce the cancer burden

and to understand underlying causes of disparate outcomes across different groups. This is highly significant for African Americans who have the highest death rates of all racial and ethnic groups for about half of the most common cancers.

Increasing awareness among cancer survivors about the importance of research and study participation may be a key, yet often overlooked approach to achieving more racially/ethnically diverse trials. Many questions exist about the best ways to convey the relevant information to potential participants. For example, while lay navigator interventions are promising, they are also costly: whether more economical interventions, e.g., using brochures conveying the same information, are effective is unknown. Other questions are related to whether it would be more effective to raise awareness about the specific study recruiting participants or about the importance of research in general, and whether this should be done conveying the information from the perspective of the survivor or the researchers.

2.3 RISK/BENEFIT ASSESSMENT

2.3.1 KNOWN POTENTIAL RISKS

Risks and discomforts from participation in project activities for the AWEI trial are no greater than those associated with day-to-day living. No medical tests or procedures will be conducted, and no social, legal or other risks are anticipated.

2.3.2 KNOWN POTENTIAL BENEFITS

Survivors participating in this project may benefit from increasing their awareness about research, and better understanding the importance of participating. They will be better able to make an informed decision about the opportunity to participate in the AMPLIFI trial. The findings will benefit the research community as evidence for recruitment methods are scarce especially for increasing the recruitment of minorities.

3 STUDY DESIGN

3.1 OVERALL DESIGN

This is a prospective interventional study using a randomized factorial trial design. Participants will be randomized to one of 8 combinations of the AWEI intervention or to the control group (no AWEI) (Table 1). The AWEI intervention varies by type of delivery channel (Research Educator [RE] and Brochure), information emphasis (research general information vs. AMPLIFI study specific information), and type of perspective (information presented from a researcher or a survivor perspective).

Table 1: AWEI study design and randomized control trial (RCT) arms

	Features			AWEI combination
	Delivery channel	**Information emphasis**	**Perspective**	
Awareness Enhancing Interventions (AWEI)	Research Educator	Research general	Researcher	1
			Survivor	2
		Study specific	Researcher	3
			Survivor	4
	Brochure	Research general	Researcher	5
			Survivor	6
		Study specific	Researcher	7
			Survivor	8
No AWEI	--	--	--	

4 STUDY POPULATION

4.1 INCLUSION CRITERIA

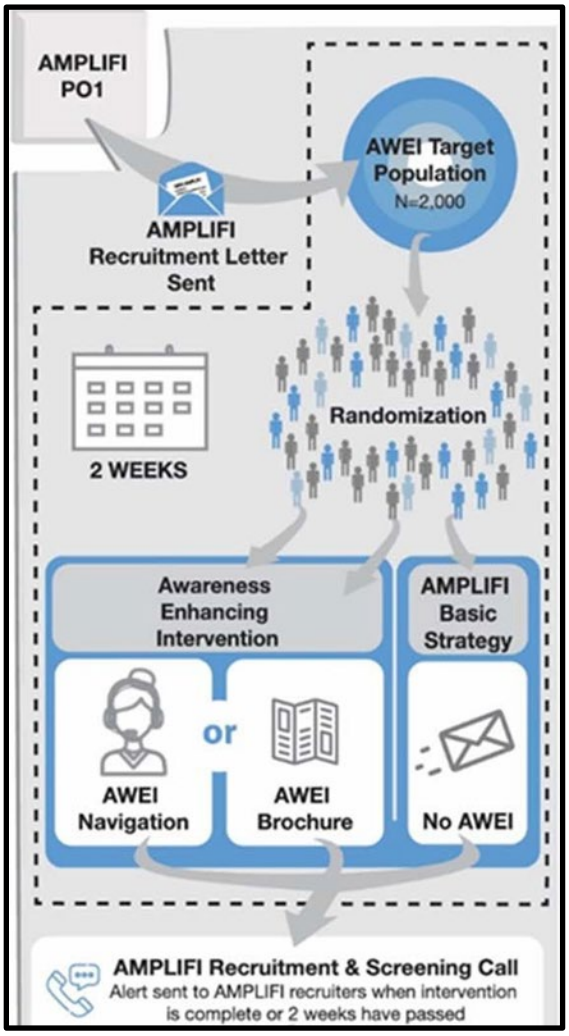
African American cancer survivors who were eligible for enrollment into the AMPLIFI trial

- adults (age ≥50 years old)
- within 1-5 years from a diagnosis of loco-regional cancers of the colorectum, female breast, prostate, endometrium, localized kidney or ovarian cancer, thyroid cancer, multiple myeloma and non-Hodgkin's lymphoma

4.2 EXCLUSION CRITERIA

- Not identified for recruitment to AMPLIFI trial

4.3 STRATEGIES FOR RECRUITMENT AND RETENTION



The AWEI trial was embedded into the AMPLIFI trial's recruitment process.[2] To identify the list of eligible survivors, AMPLIFI collaborated with the Alabama Statewide Cancer Registry (ASCR) and the North Carolina Registry (NCR), and followed their protocols for the release of contact information to the AMPLIFI research team. The AMPLIFI process started with survivors receiving a recruitment letter informing them about the study and of the possibility of receiving a call from an AMPLIFI recruiter. Survivors were also given the team's contact information to opt-out from the study if they so wished.

The AWEI trial randomization occurred once the recruitment letter was sent. No retention strategies were necessary since participation in the AWEI trial lasted 15 days. Outcomes were assessed as part of the AMPLIFY trial.

5 STUDY INTERVENTION

5.1 STUDY INTERVENTION(S) ADMINISTRATION

5.1.1 STUDY INTERVENTION DESCRIPTION

AWEI interventions were educational interventions delivered through a research educator or a brochure.

5.1.2 DOSING AND ADMINISTRATION

In the AWEI-Research Educator (RE) arm, one of four REs attempted to contact survivors by phone starting 5 days after the letter was sent (7 attempts over 10 days) and deliver the content of the intervention following a script. Each RE was trained on the

script of one of the AWEI-RE combinations differing by Information Emphasis and Perspective to avoid contamination across AWEI groups. If the survivor did not receive the recruitment letter, the RE would give more information about the purpose of the call and offer to resend the letter.

In the AWEI-Brochure arm, one of 4 brochures according to AWEI combination was sent 4 days after the recruitment letter was sent. The same content was delivered in the AWEI-RE and AWEI-Brochure arms.

5.2 MEASURES TO MINIMIZE BIAS: RANDOMIZATION

All participants were randomized to the AWEI (the intervention group) and no AWEI (control group) using permuted block randomization. Those who were randomized to the AWEI arm were simultaneously randomized to one of 8 combinations using the same method (Table 1).

6 STUDY INTERVENTION DISCONTINUATION AND SUBJECT DISCONTINUATION/WITHDRAWAL

6.1 DISCONTINUATION OF STUDY INTERVENTION

Not applicable

6.2 SUBJECT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

Not applicable

6.3 LOST TO FOLLOW-UP

Not applicable

7 STUDY ASSESSMENTS AND PROCEDURES

7.1 STUDY ASSESSMENTS

AWEI study outcomes are tracked and recorded by AMPLIFI recruiters who are blind to the AWEI random assignment. No other assessments are conducted.
To allow for the AWEI interventions to be delivered, we allow 15 days from the time from when the recruitment letter was sent to when the AMPLIFY recruitment call occurred.

To further ensure that AMPLIFY recruiters remain blind to study assessment, AWEI participants, including those in the no AWEI control arm, are "released" to the recruiters in a random fashion over the 15 days AWEI period starting at day 8. For the AWEI RE arm, survivors are released after the RE call is completed or the RE completed all 7 attempts to deliver the intervention.

Survivors reached by AMPLIFY recruiters are given more information about the study and given the option to be screened for participation to verify additional inclusion (e.g., completed primary treatment) and exclusion criteria (e.g., conditions that would make unsupervised exercise unsafe). If they screen eligible and are interested in joining AMPLIFY, they would undergo the informed consent process and enroll in AMPLIFY.

7.2 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

Risks and discomforts from participation in project activities for the AWEI trial are no greater than those associated with day-to-day living. No medical tests or procedures will be conducted, and no social, legal or other risks are anticipated.

Given this low risk there is no independent Data Safety and Monitoring Board (DSMB) for the AWEI trial, but will rely on the DSMB established for the AMPLIFI.

7.3 UNANTICIPATED PROBLEMS

7.3.1 DEFINITION OF UNANTICIPATED PROBLEMS (UP)

The Office for Human Research Protections (OHRP) considers unanticipated problems involving risks to subjects or others to include, in general, any incident, experience, or outcome that meets **all** of the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents; and (b) the characteristics of the subject population being studied;
- Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and,
- Suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

7.3.2 UNANTICIPATED PROBLEM REPORTING

To minimize the risk of **breach of confidentiality**, we will take the following precautions:

1. Investigators, recruiters, interviewers, the navigator and other study personnel, are, or will be, HIPAA and IRB certified prior to the handling of any personal data from study participants and must maintain current HIPAA and IRB certification as a requirement for continued employment.

2. Data on potential participants will be obtained from AMPLIFI. Identifiable data (name, addresses, phone numbers, emails) will be imported in Studytrax. Studytrax is an Electronic Data Capture system designed for clinical trials (Phase I – IV), observational studies and patient registries. Studytrax tracks subject enrollment and captures data elements via a secure web portal, and facilitates the transfer of data into statistical packages for analysis. Studytrax uses MS SQL Server as the back end relational database. In compliance with HIPAA privacy rules and HIPAA security rules, database security features target multiple levels including the data element (e.g., restricted access to fields), user (e.g., password authentication access), application (e.g., role-based access to features, access audit trails), and hosting services (e.g., firewall, secure sockets layer). Some of the most important features related to data security include: SSL enforced access, Strong authentication, All passwords are individually salted and hashed, Account locking after 5 failed attempts, Inactive user session time out, Role-based security, and User activity auditing. These features ensure access control, audit control, data integrity, user authentication, and transmission security.

The investigator will report unanticipated loss of confidentiality problems to the Institutional Review Board (IRB) of the University of Alabama at Birmingham (relying IRB) and the University of Tennessee Health Science Center. The report will include the following information:

- Protocol identifying information: protocol title and number, PI's name, and the IRB project number;
- A detailed description of the loss of confidentiality event;
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the loss of confidentiality event.

To satisfy the requirement for prompt reporting, loss of confidentiality events will be reported within 10 working days of the investigator becoming aware of the problem.

8 STATISTICAL CONSIDERATIONS

8.1 STATISTICAL HYPOTHESES

- Primary Efficacy Endpoint(s):

Recruitment yield assessed by:

1) Consented if eligible: Binary indicator of whether the survivor who is screened and found eligible to participate in the AMPLIFY trial agrees and consents to participate in the AMPLIFY trial.

- Secondary Efficacy Endpoint(s):

Interest in participating in the AMPLFY study and returned their consent assessed by:

Same as recruitment yield.

Post Hoc Outcomes:

1) Reached: Binary indicator of whether the AMPLIFY recruiter is able to reach the potential participant over the phone, regardless of whether the survivor is willing to receive information about AMPLIFY

2) Screened if reached: Binary indicator of whether the survivor who is reached by the recruiter is willing to consider the study and to be screened to ascertain eligibility for the AMPLIFY trial

8.2 SAMPLE SIZE DETERMINATION

Hypothesis 1: AWEI (any combination) will have a significantly higher recruitment yield than the basic AMPLIFI recruitment strategy (no AWEI control group).

With a minimum of 1,600 in the AWEI intervention group, and 400 in the no AWEI control group, a two-sided chi-square test (for unequal sample sizes), and a 5% significance level, we will have > 95% power to detect a statistically significant difference in recruitment yield of 10% vs. 20%.

Hypothesis 2 - Delivery channel: AWEI-Research Educator will have a significantly higher recruitment yield than AWEI-brochure

Hypothesis 3 - Information emphasis: Education content with study-specific emphasis will have a significantly higher recruitment yield than with research general emphasis

Hypothesis 4 - Perspective: Education content delivered from the survivor perspective will have a significantly higher recruitment yield than education content delivered from the researcher perspective.

For these hypotheses, with a minimum of 800 per group, a two-sided chi-square test, and a 5% significance level, we will have > 95% power to detect a statistically significant difference in recruitment yield of 10% vs. 20%.

Hypothesis 5: AWEI-Research Educator with study-specific emphasis and cancer survivor perspective (combination #3, Table 1) will be the most efficacious.

The same sample size calculation applies to the comparison of any two combinations. With a minimum of 200 per group, a two-sided chi- square test, and a 5% significance level, we will have 80% power to detect a statistically significant difference in recruitment yield of 10% vs. 20%.

Calculations were performed using nQuery Advisor + nTerim, version 3.0.

Thus, the trial is fully powered with a sample of 2,000 survivors, 200 in each AWEI combination, and 400 in the no AWEI arm. However, we will randomize all survivors identified from the cancer registries. If these are less than 2000, we will expand to other

cancer registries (estimated numbers from these registries exceed 2000 survivors). If these are more than 2000, we will randomize all.

8.3 STATISTICAL ANALYSES

8.3.1 GENERAL APPROACH

An intent-to-treat approach is used for statistical analyses. Descriptive statistics, including frequencies and proportions, are obtained for study variables. Differences between the group and sub-group proportions are examined using the chi-square test; if the assumptions for the chi-square test are not satisfied, Fisher's exact test is used. Logistic regression compared outcomes for three groups: Control, AWEI Brochure and AWEI Research Educator. Future analyses will include logistic regression analysis to test hypotheses 3, 4, and 5. Odds ratios and their corresponding 95% confidence intervals are obtained. Statistical tests are two-sided, and a significance level of 0.05 is assumed for all tests.

8.3.2 ANALYSIS OF THE PRIMARY EFFICACY ENDPOINT(S)

Imbalances in randomization groups if any will be adjusted in analysis.

Outcome variables are categorical. We will logistic to test for differences in outcomes across the randomized groups.

Hypothesis 1 will be tested using all randomized individuals. We will test differences in outcomes for 2 groups: AWEI (any combination) vs. no AWEI (control group).

Hypothesis 2 will be tested within the AWEI group. We will test differences in outcomes for 2 groups: AWEI-Research Educator vs. AWEI-brochure.

Exact 95% confidence intervals based on the binomial distribution will be determined for each proportion.

All statistical analyses will be conducted using SAS, version 9.4 (SAS Institute, Cary, NC).

8.3.3 ANALYSIS OF THE SECONDARY ENDPOINT(S)

We will use the same statistical approach for secondary endpoints.

8.3.4 SAFETY ANALYSES

None

8.3.5 BASELINE DESCRIPTIVE STATISTICS

We will first conduct descriptive analyses to describe the study population and verify that the randomization groups are balanced in age, gender, cancer type and stage, time since diagnosis, and rural/urban status.

9 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

9.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

9.1.1 INFORMED CONSENT PROCESS

9.1.1.1 CONSENT/ASSENT AND OTHER INFORMATIONAL DOCUMENTS PROVIDED TO SUBJECTS

A waiver of informed consent and documentation is approved by the IRB for this trial, given that the purpose is to test recruitment strategies before enrollment in a study (before consent to a study occurs).

9.1.1.2 CONSENT PROCEDURES AND DOCUMENTATION

Not applicable

9.1.2 STUDY DISCONTINUATION AND CLOSURE

Given this low risk there is no independent Data Safety and Monitoring Board (DSMB) for the AWEI trial, but will rely on the DSMB established for the AMPLIFI. The AMPLIFI DSMB may temporarily suspend or prematurely terminate the trial if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to regulatory authorities. If the study is prematurely terminated or suspended, the Principal Investigators will promptly inform the IRB, and will provide the reason(s) for the termination or suspension.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Demonstration of efficacy that would warrant stopping
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination of futility

Study may resume once concerns are addressed, and satisfy the IRB.

9.1.3 CONFIDENTIALITY AND PRIVACY

Subject confidentiality and privacy is strictly held in trust by the participating investigators and their staff. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the Principal Investigator.

All research activities will be conducted in as private a setting as possible.

IRB representatives may inspect all documents and records required to be maintained by the investigators. The clinical study site will permit access to such records.

The study subject's contact information will be securely stored for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB and/or Institutional policies.

Study subject research data, which is for purposes of statistical analysis and scientific reporting, will be stored at UAB. This will not include the subject's contact or identifying information. Rather, individual subjects and their research data will be identified by a unique study identification number. The study data entry and study management systems used by research staff will be secured and password protected.

9.1.4 QUALITY ASSURANCE AND QUALITY CONTROL

We reviewed recruitment report weekly to ensure that recruitment was done as planned. We provided ongoing training to interventionists to ensure that we the intervention was delivered as planned and appropriately documented. We oversaw that the intervention was delivered as planned (e.g., brochure mailed on the prespecified schedule). We had a detailed manual of operations specifying procedures.

The site will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and inspection by local and regulatory authorities.

9.1.5 DATA HANDLING AND RECORD KEEPING

9.1.5.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the Principal Investigators. The Principal Investigators are responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data.

9.1.5.2 STUDY RECORDS RETENTION

Study documents should be retained for a minimum of 3 years after the completion of the study. These documents should be retained for a longer period, however, if required by local regulations.

9.1.6 PROTOCOL DEVIATIONS

A protocol deviation is any noncompliance with the clinical trial protocol requirements. The noncompliance may be either on the part of the subject, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

It is the responsibility of the Principal Investigator to use continuous vigilance to identify and report deviations within 10 working days of identification of the protocol deviation. Protocol deviations must be sent to the reviewing Institutional Review Board (IRB) per their policies. The

Principal Investigator is responsible for knowing and adhering to the reviewing IRB requirements.

9.1.7 CONFLICT OF INTEREST POLICY

The independence of this study from any actual or perceived influence is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial.

9.2 ABBREVIATIONS

AE	Adverse Event
ANCOVA	Analysis of Covariance
CFR	Code of Federal Regulations
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
DHHS	Department of Health and Human Services
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
ICH	International Conference on Harmonisation
ICMJE	International Committee of Medical Journal Editors
IRB	Institutional Review Board
LSMEANS	Least-squares Means
NCT	National Clinical Trial
NIH	National Institutes of Health
OHRP	Office for Human Research Protections
PI	Principal Investigator
QA	Quality Assurance
QC	Quality Control
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SOA	Schedule of Activities
SOP	Standard Operating Procedure
UP	Unanticipated Problem
US	United States