ECOG-ACRIN cancer research group
Reshaping the future of patient care

E1Q11

EROS: Engendering Reproductive Health within Oncologic Survivorship

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Version Date: March 17, 2021

Rev. 5/17 ***STUDY PARTICIPANTS FOR PATIENT ENROLLMENT***

Rev. Add7 *Limited to invited and selected sites (including affiliate sites) that*
Rev. Add8 *agree to participate from the following:*

RevAdd11 ***MU NCORP*** */ NCORP Minority Underserved sites:*
BAPTIST */ Baptist Memorial Health Care / Mid-South MU NCORP (ECOG-ACRIN)*
RevAdd10 ***GACARES*** */ Georgia Cares MU NCORP (ECOG-ACRIN) (COG)*
GULFSOUTH */ Gulf South MU NCORP (ECOG-ACRIN)*
HAWAII */ Hawaii MU NCORP (Alliance, SWOG, NRG)*
MONTEFIORE */ Montefiore Medical Center MU NCORP (ECOG-ACRIN)*
MUSC */ Medical University of South Carolina MU NCORP (ECOG-ACRIN)*
NEWMEXICO */ New Mexico MU NCORP (Alliance, SWOG, NRG)*
RevAdd12 ***TXPED*** */ Texas Pediatric MU NCORP (COG)*
STROGER */ Stroger Hospital of Cook County MU NCORP (ECOG-ACRIN)*
VCU */ VCU Massey Cancer Center MU NCORP (ECOG-ACRIN)*
NCORP */ NCORP sites:*
AURORA */* Aurora *NCORP (ECOG-ACRIN)*
CARLE / Carle Cancer Center NCORP (ECOG-ACRIN)
WESTERN / Western States Cancer Research NCORP *(ECOG-ACRIN)*
COLUMBUS / Columbus NCORP *(ECOG-ACRIN)*
RevAdd12 **CORA /** Catholic Health Initiatives NCORP *(ECOG-ACRIN)*
FLPED / Florida Pediatric NCORP *(COG)*
GEORGIA / Georgia NCORP *(ECOG-ACRIN)*
METROMIN / Metro Minnesota NCORP *(ECOG-ACRIN)*
NCFR / Nevada Cancer Research Foundation NCORP
RevAdd10 *(ECOG-ACRIN)*
NEMOURS / NEMOURS NCORP *(COG)*
PCRC / Pacific Cancer Research Consortium NCORP *(ECOG-ACRIN)*
SCOR */* Southeast Clinical Oncology Research Consortium NCORP *(SWOG)*
UPSTATE / Upstate Carolina Consortium Community Oncology Research Program NCORP (ECOG-ACRIN)
RevAdd12 **MAINE / MaineHealth Cancer Care Network** (ALLIANCE/NRG/COG)

ACTIVATION DATE
September 30, 2015

PRE-ACTIVATION DATE
September 17, 2014
Addendum #1 – Incorporated Prior to Activation
Addendum #2 – Incorporated Prior to Activation
Addendum #3 – Incorporated Prior to Activation
Addendum #4 – 11/16
Addendum #5 – 5/17
Addendum #6 – 11/17
Addendum #7
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Addendum #13

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CANCER TRIALS SUPPORT UNIT (CTSU) CONTACT INFORMATION

To submit site registration documents:	**For patient enrollments:**	**Data collection will be performed exclusively in Medidata Rave. :**
Regulatory documentation must be submitted to the CTSU via the Regulatory Submission Portal: Regulatory Submission Portal (Sign in at www.ctsu.org, and select the Regulatory Submission sub-tab under the Regulatory tab.) RevAdd13 Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately at 1-866-651-2878 to receive further instruction and support. Contact the CTSU Regulatory Help Desk at 1-866-651-2878 for regulatory assistance.	Please refer to the patient enrollment section of the protocol for instructions on using the Oncology Patient Enrollment Network (OPEN) which can be accessed at . https://www.ctsu.org/OPEN_SYSTEM/ or https://OPEN.ctsu.org. Contact the CTSU Help Desk with any OPEN-related questions at ctsucontact@westat.com.	Data collection for this study will be done exclusively through Medidata Rave. Please see the data submission section of the protocol for further instructions. Do not submit study data or forms to CTSU Data Operations. Do not copy the CTSU on data submissions.
The most current version of the **study protocol and all supporting documents** must be downloaded from the protocol-specific Web page of the CTSU Member Web site located at https://www.ctsu.org. Access to the CTSU members' website is managed through the Cancer Therapy and Evaluation Program - Identity and Access Management (CTEP-IAM) registration system and requires user log on with CTEP-IAM username and password. RevAdd13 Permission to view and download this protocol and its supporting documents is restricted and is based on person and site roster assignment housed in the CTSU Regulatory Support System (RSS).		
For clinical questions (i.e., patient eligibility) Contact the Study PI of the Lead Protocol Organization.		
For non-clinical questions (i.e., unrelated to patient eligibility or data submission) contact the CTSU Help Desk by phone or e-mail: CTSU General Information Line – 1-888-823-5923, or ctsucontact@westat.com. All calls and correspondence will be triaged to the appropriate CTSU representative.		
The CTSU Web site is located at https://www.ctsu.org		

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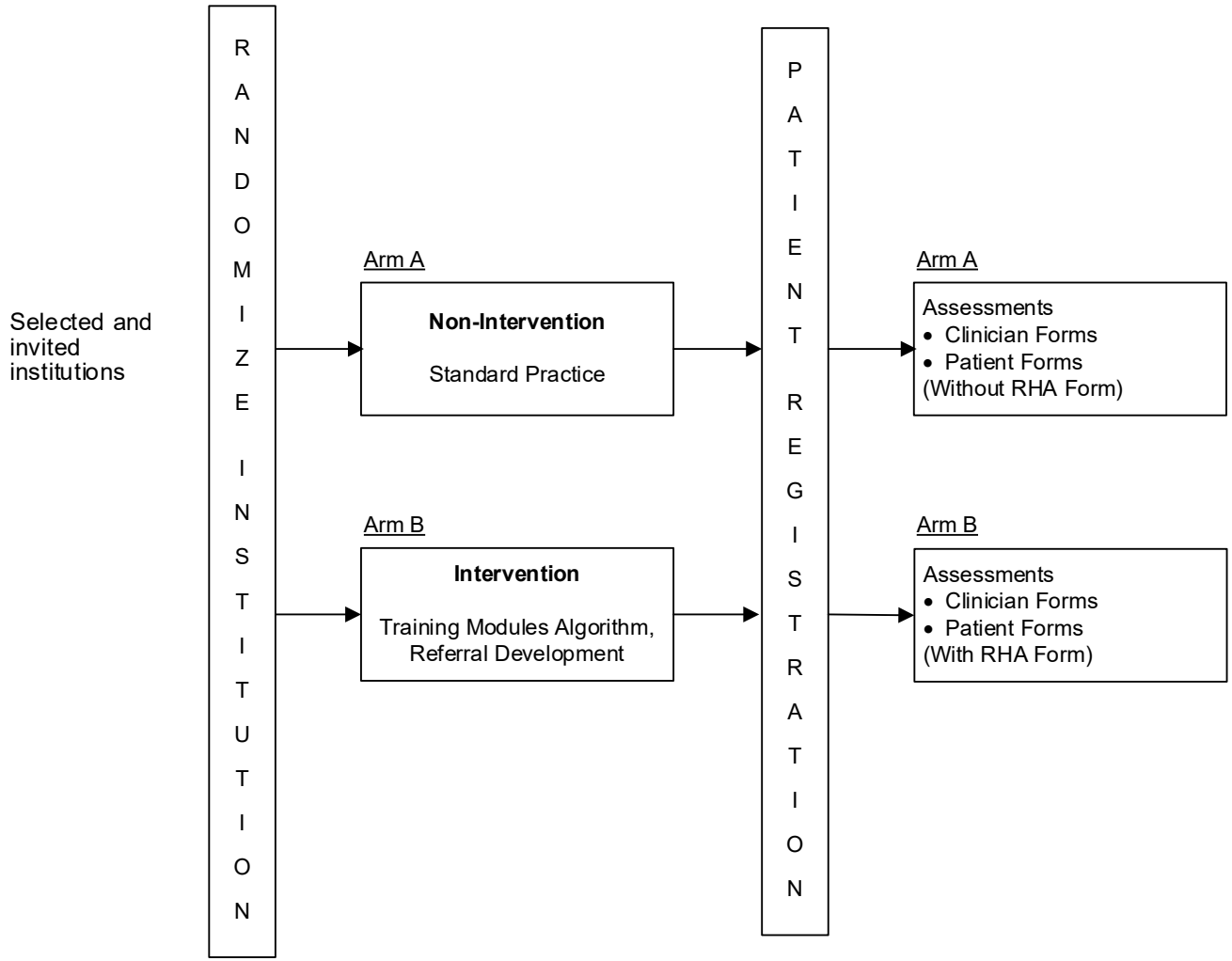
Schema



Total Accrual Goal: 425

1. Introduction

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1.1 Study Foundation

Reproductive health goals of females with cancer in the 15-55-year age range are poorly understood and overlooked. Reproductive health issues that include oncofertility, oncocontraception and sexuality are important to females regardless of cancer diagnosis. Evaluation and treatment of cancer should include an assessment of goals for fertility and family planning in order to optimize a patient's cancer treatment and her future reproductive health.

1.2 Study Overview

We propose the EROS trial "Engendering Reproductive Health within Cancer Survivorship." The primary study is a cluster randomized controlled trial examining an intervention of a reproductive health assessment and algorithm to improve the adoption of appropriate reproductive health management. Two important secondary objectives are to (1) examine reproductive health related endocrine disruption through longitudinal study of endocrine markers during the first five years after cancer diagnosis and (2) perform longitudinal study of sexual function during the first five years after cancer diagnosis.

1.3 Study Aims

This study will add valuable interventional and observational data to this largely unexplored area of research and could have a tremendous impact on the care of young cancer survivors to maintain tenable reproductive health goals. Additionally, tools validated from this study may be utilized by the National Cancer Institute (NCI) to assist clinicians navigating through reproductive health issues in the context of cancer care.

1.4 Hypotheses

1.4.1 The reproductive health needs for females with cancer are not adequately assessed and addressed by cancer care providers.

1.4.2 The implementation of the proposed reproductive health assessment and algorithm will optimize the reproductive health objectives of females with cancer.

1.4.3 Patients and clinicians have different perspectives regarding reproductive health objectives of females with cancer.

1.4.4 There are certain clinical, demographic, healthcare delivery, and socioeconomic factors that affect patients with regards to adequacy of reproductive health management.

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1.5 Background

In 2009, approximately 719,000 females in the United States were newly diagnosed with various types of cancer.[1] Nearly 17% of these new cancer cases were diagnosed in reproductive age females.[1] The most common cancers diagnosed in females of childbearing age are breast and cervical carcinoma, melanoma, non-Hodgkin's lymphoma, leukemia and colon cancer.[2-4] Of these, breast is the most common malignancy site for females and is the second leading cause of cancer-related deaths in females.

Approximately 4 in 100 adults today is a cancer survivor.[5] With the recent advancements in cancer detection and treatment, survival rates are increasing for cancer patients. Over the past 30 years, the number of cancer survivors in the United States has increased to almost 14 million.[5] As a result; there is a tremendous focus on improvement of quality of life in cancer survivors. When a female is diagnosed with cancer, particularly a young female, issues regarding survival are paramount; however, the magnitude of reproductive health and quality of life issues cannot be neglected.[6]

The definition of reproductive health is widely accepted as "the state of complete physical, mental and social well-being, and not merely the absence of reproductive disease or infirmity."[7] The components that define reproductive health are broad and not well defined in the literature. For the purpose of this proposal, we define the components of reproductive health as it pertains to females with cancer as oncofertility, oncocontraception, and sexuality. The initial period of cancer diagnosis and treatment is fraught with much uncertainty regarding reproductive health issues related to prognosis of disease, iatrogenic loss of fertility, endocrine disruption, and exposure to teratogenic treatment agents.

Fertility preservation for young cancer survivors has obtained research and public interest; however, reproductive health is not only limited to fertility preservation but also includes sexuality and family planning, ranging from oncocontraception, preconception counseling, and optimization of present or future pregnancy.[8] The full scope of reproductive health is often omitted from the discussion of cancer treatment planning.

While organizations, such as the American Cancer Society (ACS) and American Society of Clinical Oncologists (ASCO) have recommendations regarding reproductive health in cancer, ASCO states that there is a paucity of literature in the area of reproductive health particularly randomized controlled trials, as well as information that relates to diverse populations and socioeconomic groups.[3]

Our proposal is a cluster randomized controlled trial design to address aspects of reproductive health in cancer care. An integrated cancer management and reproductive health plan will be developed and implemented for females in this study. Success of the reproductive health plan will be evaluated. Outcomes to be investigated are contraceptive utilization, pregnancy outcomes, and attention to sexuality related issues. Since this study will accrue patients with cancer of the colon/rectum, breast, lung, and others, a secondary analysis of the previously stated objectives will also be conducted to study the differences and similarities among these patients with respect to their disease sites. Study sites will be sought to include patients from across the country with diversity of ethnicity and sociodemographics. The sample size was constructed to allow for the evaluation of the success of the reproductive health programming among females aged between 15-55 years old with initial diagnosis of any form of cancer.

1.6 Summary and Rationale for Proposed Study

Uncertainties regarding future fertility, pregnancy and cancer survival are intricate and challenging for a patient and a cancer care team. The goals of comprehensive reproductive health care at times may come in conflict with the primary objective of cancer care. However, with appropriate counseling and preventive measures, this conflict can be absolved to unify objectives. Work from

this study should inform leading organizations in cancer care and treatment to improve guidelines and to include a reproductive health assessment for all young females with cancer. It would also aid informed decision making and management plans.

This interventional study involves an initial assessment of reproductive health for females with cancer. Various modalities will provide data on the prevalence of reproductive health care needs during the course of cancer care. Based on this reproductive health assessment, a management plan pertaining to reproductive and sexual health is developed in conjunction with the cancer management plan. Measurable outcomes pertaining to management and treatment implementation and modification are the cornerstones of this study. Study tools have been tested by our research group at four institutions and are feasible for administration.

As this is a behavior study, details pertaining to the intervention are included in addendum I and are only accessible to those sites randomized to receive the intervention. It is requested that the details of the intervention remain confidential to maintain the integrity of the randomized cluster-controlled design. If local IRBs have questions or concerns regarding the intervention, they are instructed to contact ECOG-ACRIN or the study team directly.

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1.7 Reproductive Health Related Endocrine Disruption in Cancer Care

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We propose a 2-year observational study following tumor markers for fertility status and endocrine disruption of the first 200 individuals who agree to participate.

Primary Hypothesis

At least 80% of females will have significant endocrine disruption during chemotherapy.

Background

The sequelae of endocrine disruption may include loss of fertility. Although some cancer therapy modalities induce amenorrhea, many patients undergoing treatment remain fertile. After a short period of chemotherapy-induced amenorrhea, 50% of females younger than 35 years resume menstruation, whereas in older females the risk of amenorrhea is increased due to reduced follicular reserve.[9] The absence of menstruation does not necessarily indicate lack of ovarian function. Additionally, the possibility of spontaneous recovery of ovarian function has been observed, particularly in cases of ovarian germ cell cancer. A study by Fossa found that cisplatin-based chemotherapy is followed by a recovery of ovarian function in almost all patients.[9]

For patients on chemotherapy who desire fertility, ovarian function should be reassessed periodically. Since menstrual activity is not a reliable index to assess ovarian function, various tests like FSH level, inhibin A or B levels or antimullerian hormone (AMH) and vaginal ultrasonography assessment for number of antral follicles can be used.[10]

Knowledge of the functional ovarian reserve may benefit females with cancer prior to making important decisions regarding treatment, fertility preservation, and contraception. An ideal marker for fertility status has not yet been identified. Recent literature (2009) indicates the best biochemical indicators of ovarian reserve are serum FSH levels, AMH and Inhibin B.[11] In the reproductive

endocrinology literature, AMH is emerging as the optimal marker to determine ovarian reserve and subsequent pregnancy success.[12] Experience with AMH in cancer survivors is limited, however this marker has potential as an indicator of ovarian function post chemotherapy.[11,13] FSH as a marker may be less reliable as it is ovulatory cycle dependent and affected by tamoxifen and other hormonal therapies.[13]

Additionally alterations in thyroid function have been noted in females with breast cancer with a baseline rate of autoimmune thyroid disease 2-3 times the general population.[14] Thyroid function may be affected by chemotherapy and radiation treatment, particularly when treatment is localized to the vicinity of the thyroid.[15] Such disruption may lead to symptoms that may affect quality of life indicators related to sexuality and sexual health. Repercussions of these effects remain an important aspect of research within oncology care. Given the available data, many questions remain unanswered; therefore, the laboratory ancillary included in this proposal would provide important data during the course of our primary study.

This data will provide a foundation for future research to aid prediction of fertility status throughout the course of cancer care and treatment.

This analysis will be performed at Quest Diagnostics.

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1.8 Quality of Life (QOL) Assessment: Longitudinal Study of Sexuality in Females with Newly Diagnosed Cancer

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We propose a prospective observational study performing interval sexuality surveys for reproductive aged females throughout 2 years post diagnosis of cancer.

Hypothesis

Primary Hypothesis: Cancer survivors' sexual function decreases during initial cancer treatment then increases with time after treatment completion.

Secondary Hypothesis: Cancer survivors have lower levels of satisfaction with their sex lives compared to the age-matched general population at baseline.

Background

Sexuality remains an important aspect of reproductive health that is greatly influenced by cancer diagnosis and treatment. The extent of impact of cancer diagnosis and treatment is poorly understood. Sexuality encompasses gender roles, patterns of affection, social and family roles, and genital sex, and affects a survivor physically, psychologically, and emotionally.[16] It should be understood that sexuality is "an ever-changing, lived experience affecting the way in which people view themselves, their body and their ability to intimately connect with significant others throughout life, rather than limiting it to fertility status or capacity for sexual intercourse."[17]

In a study of females post-trachelectomy for cervical cancer, it was observed that many patients' fears of intercourse and dyspareunia were reported prior to surgery.[18] Furthermore, information suggests that females with gynecologic cancers may have a higher risk of psychological distress.[19] In a review by Fossa, the diagnosis of cancer affects sexual life more so in females than in males, and was found to strongly influence emotional aspects of partnership.[9]

Hordern and Street analyzed the quality of discussions regarding sexuality between patients and healthcare providers. Not only did they find that patients felt their needs were unmet, but there were also "mismatched expectations.[17] Among the barriers are clinician embarrassment, lack of time, and inexperience. These can be addressed with proper training, thereby increasing comfort with these conversations.

The National Institutes of Health (NIH) established the Patient-Reported Outcomes Measurement Information System (PROMIS) Network with the goal of developing a comprehensive, standardized, and efficient means of measuring patient–reported outcomes in persons with chronic diseases. As one of the 7 original research sites, Duke University led the development of 2 domains of measurement for patients with cancer, including sexual function. The first phase of PROMIS supported research toward the development of the sexual function domain for cancer populations. Early testing suggests the PROMIS Sexual Function Brief Profile v1.0 - Female is superior to alternative patient-reported outcomes measures in terms of understandability, comprehensiveness, and appropriateness for many types of people. Sexual functioning and intimacy were considered important to quality of life. While most effects of cancer were considered negative, many participants identified improvements to intimacy after cancer.[20] We propose conducting an observational study as part of this trial to gain valuable data on the trajectory of sexual function among females (15-55 years of age) with cancer using the PROMIS Sexual Function Brief Profile v1.0 - Female.

The incorporation of NIH PROMIS Sexual Function Brief Profile v 1.0 - Female within this study will leverage NIH-funded advances in measurement science while contributing to the ongoing development of this measure. The ongoing evaluation psychometric properties of the NIH Sexual Function Brief Profile v 1.0 - Female is a research aim for the NIH PROMIS network. Through collaborating with PROMIS investigators, we will support the attainment of this aim by collecting longitudinal data on the NIH PROMIS Sexual Function Brief Profile v 1.0 - Female from trial participants. Questions from the NIH PROMIS Sexual Function Brief Profile v1.0 – Female have been incorporated into the E1Q11 Sexual Function Survey.

2. Objectives

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2.1 Primary Objective

The primary objective of this study is to evaluate the success of the implementation of reproductive health programming (Didactics, EROS Reproductive Health Assessment and EROS Trial Algorithm) among reproductive aged females (15-55) with cancer.

2.2 Secondary Objectives

2.2.1 To assess the degree of discrepancy between patients and their clinicians in estimates of significance of the reproductive health goals for the patient

2.2.2 To evaluate baseline and follow-up reproductive health assessments for trends in reproductive health choices relating to oncofertility, oncocontraception and pregnancy over the 2 year study period

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2.2.3 To identify clinical and demographic factors that predict the adequacy of reproductive health care management

2.3 Correlative Objective

2.3.1 To perform a longitudinal study following endocrine markers of fertility in a cohort of the first 200 registered EROS trial patients who agree to participate

2.4 Quality of Life Objective

2.4.1 To perform a longitudinal study of sexual function using the PROMIS sexual function survey in all subjects participating in the EROS Trial

3. Selection of Patients

Each of the criteria in the checklist that follows must be met in order for a patient to be considered eligible for this study. Use the checklist to confirm a patient's eligibility. For each patient, this checklist must be photocopied, completed and maintained in the patient's chart.

In calculating days of tests and measurements, the day a test or measurement is done is considered Day 0. Therefore, if a test is done on a Monday, the Monday four weeks later would be considered Day 28.

ECOG-ACRIN Patient No. _____

Patient's Initials (L, F, M) _____

Physician Signature and Date _____

NOTE: All questions regarding eligibility should be directed to the study chair or study chair liaison.

NOTE: Institutions may use the eligibility checklist as source documentation if it has been reviewed, signed, and dated prior to registration by the treating physician.

3.1 Eligibility Criteria

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_____ 3.1.1 Female patients presenting with initial diagnosis of any type of cancer, including patients with DCIS.

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_____ 3.1.2 Patients must not have initiated chemotherapy, radiation therapy or endocrine therapy prior to registration to this study.

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_____ 3.1.3 Patients must not have had a prior hysterectomy, bilateral oophorectomy or sterilization of any method.

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_____ 3.1.4 Patients must be pre-menopausal patients within the reproductive age range of 15-55 years.

Please note, pre-menopausal will be defined as females meeting the following criteria:

- Patients not currently on hormonal contraception with the presence of menses in the past 6 months.
- If no menstruation in the past 6 months, without hormonal manipulation, then confirmed FSH < 23mIU/mL

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- If age < 47 years and on hormonal contraception, then patient will be eligible regardless of menstrual history

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- If age ≥ 47 years and on hormonal contraception, then FSH confirmed < 23mIU/mL

_____ 3.1.5 Pregnant females are eligible to participate in this study.

_____ 3.1.6 Patients must have the cognitive ability to participate in the study.

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4. CTEP Registration Procedures

Food and Drug Administration (FDA) regulations and National Cancer Institute (NCI) policy require all individuals contributing to NCI-sponsored trials to register and to renew their registration annually. To register, all individuals must obtain a Cancer Therapy Evaluation Program (CTEP) Identity and Access Management (IAM) account (https://ctepcore.nci.nih.gov/iam). In addition, persons with a registration type of Investigator (IVR), Non-Physician Investigator (NPIVR), or Associate Plus (AP) must complete their annual registration using CTEP's web-based Registration and Credential Repository (RCR) (https://ctepcore.nci.nih.gov/rcr).

RCR utilizes five person registration types.

- IVR — MD, DO, or international equivalent;
- NPIVR — advanced practice providers (e.g., NP or PA) or graduate level researchers (e.g., PhD);
- AP — clinical site staff (e.g., RN or CRA) with data entry access to CTSU applications (e.g., Roster Update Management System (RUMS), OPEN, Rave,);
- Associate (A) — other clinical site staff involved in the conduct of NCI-sponsored trials; and
- Associate Basic (AB) — individuals (e.g., pharmaceutical company employees) with limited access to NCI-supported systems.

RCR requires the following registration documents:

Documentation Required	IVR	NPIVR	AP	A	AB
FDA Form 1572	✓	✓			
Financial Disclosure Form	✓	✓	✓		
NCI Biosketch (education, training, employment, license, and certification)	✓	✓	✓		
GCP training	✓	✓	✓		
Agent Shipment Form (if applicable)	✓				
CV (optional)	✓	✓	✓		

An active CTEP-IAM user account and appropriate RCR registration is required to access all CTEP and CTSU (Cancer Trials Support Unit) websites and applications. In addition, IVRs and NPIVRs must list all clinical practice sites and IRBs covering their practice sites on the FDA Form 1572 in RCR to allow the following:

- Added to a site roster
- Assigned the treating, credit, consenting, or drug shipment (IVR only) tasks in OPEN
- Act as the site-protocol PI on the IRB approval

In addition, all investigators act as the Site-Protocol PI, consenting/treating/drug shipment, or as the CI on the DTL must be rostered at the enrolling site with a participating organization (i.e., Alliance). Additional information can be found on the CTEP website at <https://ctep.cancer.gov/investigatorResources/default.htm>. For questions, please contact the RCR ***Help Desk*** by email at <RCRHelpDesk@nih.gov>.

CTSU Registration Procedures

This study is supported by the NCI Cancer Trials Support Unit (CTSU).

IRB Approval:

For CTEP and Division of Cancer Prevention (DCP) studies open to the National Clinical Trials Network (NCTN) and NCI Community Oncology Research Program (NCORP) Research Bases after March 1, 2019, all U.S.-based sites must be members of the NCI Central Institutional Review Board (NCI CIRB). In addition, U.S.-based sites must accept the NCI CIRB review to activate new studies at the site after March 1, 2019. Local IRB review will continue to be accepted for studies that are not reviewed by the CIRB, or if the study was previously open at the site under the local IRB. International sites should continue to submit Research Ethics Board (REB) approval to the CTSU Regulatory Office following country-specific regulations.

Sites participating with the NCI CIRB must submit the Study Specific Worksheet for Local Context (SSW) to the CIRB using IRBManager to indicate their intent to open the study locally. The NCI CIRB's approval of the SSW is automatically communicated to the CTSU Regulatory Office, but sites are required to contact the CTSU Regulatory Office at CTSURegPref@ctsu.coccg.org to establish site preferences for applying NCI CIRB approvals across their Signatory Network. Site preferences can be set at the network or protocol level. Questions about establishing site preferences can be addressed to the CTSU Regulatory Office by emailing the email address above or calling 1-888-651-CTSU (2878).

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In addition, the Site-Protocol Principal Investigator (PI) (i.e., the investigator on the IRB/REB approval) must meet the following criteria to complete processing of the IRB/REB approval record:

- Holds an Active CTEP status;
- Rostered at the site on the IRB/REB approval (applies to US and Canadian sites only) and on at least one participating roster;
- If using NCI CIRB, rostered on the NCI CIRB Signatory record;
- Includes the IRB number of the IRB providing approval in the Form FDA 1572 in the RCR profile; and
- Holds the appropriate CTEP registration type for the protocol.

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Additional Requirements

Additional requirements to obtain an approved site registration status include:

- An active Federal Wide Assurance (FWA) number;
- An active roster affiliation with the Lead Protocol Organization (LPO) or a Participating Organization (PO); and
- Compliance with all protocol-specific requirements (PSRs).

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4.1 Selection and Randomization of Sites

To ensure patient diversity in this study, all Minority/Underserved National Cancer Institute Community Oncology Research Programs (MU NCORP) sites will be invited to participate. The remainder of sites will be filled by NCORPs.

All MU NCORPS and selected NCORPs will receive an invitation letter from the Group Chair together with the study chair including a brief description of the study. Potential sites will be asked to respond to several questions related to site

characteristics, including patient volume and possible accrual and reproductive-related services available in the areas of each site, to determine feasibility of utilizing the site for trial recruitment and the site's level of interest in serving as a study site. Information from sites that respond will be reviewed by the study chair and the study team. Sites that express interest in participating and that report adequate patient volume to meet the protocol accrual goal will be sent a formal invitation to participate in this study. Depending on the number of participating MU NCORPs, other NCORPs will be randomly selected to participate in this study. Once sites have been selected, they will be randomized to the intervention or non-intervention arm. Sites randomized to the intervention arm will receive access to additional materials and information specific to the intervention including the intervention content.

A notice of randomized intervention assignment will be forwarded by the ECOG-ACRIN Operations Office - Boston. Each participating institution will be sent a notice confirming the assignment of the intervention or non-intervention arm.

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4.2 Registration of Patients

This study is supported by the NCI Cancer Trials Support Unit (CTSU).

Prior to the recruitment of a patient for this study, investigators must be registered members of a Cooperative Group. Each investigator must have an NCI investigator number and must maintain an "active" investigator registration status through the annual submission of a complete investigator registration packet (FDA Form 1572 with original signature, current CV, Supplemental Investigator Data Form with signature, and Financial Disclosure Form with original signature) to the Pharmaceutical Management Branch, CTEP, DCTD, NCI. These forms are available on the CTSU Web site (enter credentials at https://www.ctsu.org; then click on the Register tab) or by calling the PMB at 240-276-6575 Monday through Friday between 8:30 a.m. and 4:30 p.m. Eastern time.

Each investigator or group of investigators at a clinical site must obtain IRB approval for this protocol and submit IRB approval and supporting documentation to the CTSU Regulatory Office before they can enroll patients. Study centers can check the status of their registration packets by querying the Regulatory Support System (RSS) site registration status page of the CTSU member web site by entering credentials at https://www.ctsu.org.

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Submitting Regulatory Documents

Once your site is authorized to begin the IRB approval process, please apply to the CIRB for participation approval and follow local IRB submission requirements as outlined by your institution. If local IRBs have questions or concerns regarding the intervention, they are instructed to contact ECOG-ACRIN or the study team directly. Once approval is received, you may move forward with study initiation if you are randomized to Arm A (control). If you are randomized to Arm B (intervention), you are required to submit all intervention materials (addendum I) to your IRB, if you have not already done so, for the next phase of approval before moving forward with study initiation.

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Before an Institution may enter patients, protocol specific documents must be submitted to the CTSU Regulatory Office. Submit required forms and documents to the CTSU Regulatory Office via the Regulatory Submission Portal on the CTSU website.

To access the Regulatory Submission Portal log on to the CTSU members' website → Regulatory → Regulatory Submission

Institutions with patients waiting that are unable to use the Regulatory Submission Portal should alert the CTSU Regulatory Office immediately at 1-866-651-2878 in order to receive further instruction and support.

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Checking Your Site's Registration Status:

Site registration status may be verified on the CTSU members' website.

- Click on the *Regulatory* at the top of the screen;
- Click on the *Site Registration*; and
- Enter the sites 5-character CTEP Institution Code and click on Go
- Additional filters are available to sort by Protocol, Registration Status, Protocol Status, and/or IRB Type

NOTE: The status shown only reflects institutional compliance with site registration requirements as outlined within the protocol. It does not reflect compliance with protocol requirements for individuals participating on the protocol or the enrolling investigator's status with NCI or their affiliated networks.

Downloading Site Registration Documents:

Download the site registration forms from the protocol-specific page located on the CTSU members' website. Permission to view and download this protocol and its supporting documents is restricted based on person and site roster assignment. To participate, the institution and its associated investigators and staff must be associated with the LPO or a PO on the protocol.

- Log on to the CTSU members' website https://www.ctsu.org using your CTEP-IAM username and password
- Click on the Protocols in the upper left of your screen
- Either enter the protocol # in the search field at the top of the protocol tree, or
- Click on the By Lead Organization folder to expand
- Click on the ECOG-ACRIN link to expand, then select trial protocol #E1Q11
- Click on Documents, select the Site Registration, and download and complete the forms provided.

  NOTE: For sites under the CIRB initiative, IRB data will load automatically to the CTSU as described above.)

Required Protocol Specific Regulatory Documents

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1. Copy of IRB Informed Consent Document.

   NOTE: Any deletion or substantive modification of information concerning risks or alternative procedures contained in the sample informed consent document must be justified in writing by the investigator and approved by the IRB.

2. A. CTSU IRB Certification Form.
   Or
   B. Signed HHS OMB No. 0990-0263 (replaces Form 310).
   Or
   C. IRB Approval Letter

NOTE: The above submissions must include the following details:

- Indicate all sites approved for the protocol under an assurance number.
- OHRP assurance number of reviewing IRB
- Full protocol title and number
- Version Date
- Type of review (full board vs. expedited)
- Date of review
- Signature of IRB official

4. E1Q11 Study Participation Interest and Feasibility Form (See Section 4.7.4)
5. Site Signature Log and Delegation of Responsibilities (ECOG-ACRIN website)
6. Site Training Record (ECOG-ACRIN website)-**Required only for Arm B sites**
7. Site Referral Network Form (ECOG-ACRIN website) **– Required only for Arm B sites**

Patients must not start protocol prior to registration.

Patient registration can occur only after eligibility criteria have been met, and the study site is listed as 'approved' in the CTSU RSS. Patients must have signed and dated all applicable consents and authorization forms.

The Oncology Patient Enrollment Network (OPEN) is a web-based registration system available on a 24/7 basis. OPEN is integrated with CTSU regulatory and roster data and with the Lead Protocol Organization (LPOs) registration/randomization systems or Theradex Interactive Web Response System (IWRS) for retrieval of patient registration/randomization assignment. OPEN will populate the patient enrollment data in NCI's clinical data management system, Medidata Rave.

Requirements for OPEN access:

- A valid CTEP-IAM account;
- To perform enrollments or request slot reservations: Be on a LPO roster, ETCTN Corresponding roster, or PO roster with the role of Registrar. Registrars must hold a minimum of an AP registration type;
- Have an approved site registration for a protocol prior to patient enrollment.

To assign an Investigator (IVR) or Non-Physician Investigator (NPIVR) as the treating, crediting, consenting, drug shipment (IVR only), or receiving investigator for a patient transfer in OPEN, the IVR or NPIVR must list the IRB number used on the site's IRB approval on their Form FDA 1572 in RCR.

Prior to accessing OPEN site staff should verify the following:

- All eligibility criteria have been met within the protocol stated timeframes.

- All patients have signed an appropriate consent form and HIPAA authorization form (if applicable).

Access requirements for OPEN:

- Site staff will need to be registered with CTEP and have a valid and active CTEP-IAM account and a 'Registrar' role on either the LPO or participating organization roster. This is the same account (user id and password) used for the CTSU members' web site.
- To perform registrations, the site user must have been assigned the 'Registrar' role on the relevant Group or CTSU roster and hold a minimum of an AP registration type.
- To perform registrations on protocols for which you are a member of the Lead Group, you must have an equivalent 'Registrar' role and hold an account of AP or higher on the Lead Group roster. Role assignments are handled through the Groups in which you are a member
- To perform registrations to trials accessed via the CTSU mechanism (i.e., non-Lead Group registrations) you must have the role of Registrar on the CTSU roster and hold a minimum of an AP registration type.

NOTE: The OPEN system will provide the site with a printable confirmation of registration. Please print this confirmation for your records.

Access OPEN at https://open.ctsu.org or from the OPEN link on the CTSU members' website. Further instructional information is provided on the OPEN tab of the CTSU members' side of the CTSU website at https://www.ctsu.org or at https://open.ctsu.org. For any additional questions contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

The following information will be requested

4.3 Protocol Number

4.4 Investigator Identification

4.4.1 Institution and affiliate name (Institution CTEP ID)

4.4.2 Investigator's name (NCI number)

4.4.3 Cooperative Group Credit

4.4.4 Credit Investigator

4.4.5 Protocol specific contact information

4.5 Patient Identification

4.5.1 Patient's initials (first and last)

4.5.2 Patient's Hospital ID and/or Social Security number

4.5.3 Patient demographics

4.5.3.1 Gender

4.5.3.2 Birth date

4.5.3.3 Race

4.5.3.4 Ethnicity

4.5.3.5 Nine-digit ZIP code

4.5.3.6 Method of payment

4.5.3.7 Country of residence

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4.6 Eligibility Verification

4.6.1 Patients must meet all of the eligibility requirements listed in Section 3.

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4.7 COG Patient Registration Enrollment Information

For COG Credited Enrollments ONLY: Prior to enrollment on this study, patients enrolling must be assigned a COG patient ID number. This number is obtained via the Patient Registry module in OPEN once authorization for the release of protected health information (PHI) has been obtained. The COG patient ID number is used to identify the patient in all future interactions with COG. If you have problems with the registration, please refer to the online help. For additional help or information, please contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com. See Appendix IV for the Information Sheet for teens from 15 through 17 years of age.

4.8 Additional Requirements

4.8.1 Patients and clinicians must provide a signed and dated, written informed consent form.

NOTE: Copies of the consent are not collected by the ECOG-ACRIN Operations Office -Boston.

4.8.2 Blood samples for the endocrine markers should be submitted as outlined in Section 9 per patient consent.

NOTE: ECOG-ACRIN requires that biological samples submitted from patients participating in E1Q11 be entered and tracked via the online ECOG Sample Tracking System (STS). See Section 9.5.

NOTE: Institutions must complete and submit the Quest Diagnostics Sub-Account Information Sheet (Appendix III) to create their study-specific account number in order to obtain supplies and arrange for courier service for the blood sample collections.

4.8.3 Medidata Rave

Medidata Rave is a clinical data management system being used for data collection for this trial/study. Access to the trial in Rave is controlled through the CTEP-IAM system and role assignments.

Requirements to access Rave via iMedidata:

- A valid CTEP-IAM account; and
- Assigned a Rave role on the LPO or PO roster at the enrolling site of: Rave CRA, Rave Read Only, Rave CRA (LabAdmin), Rave SLA, or Rave Investigator.

- Rave role requirements:
  - Rave CRA or Rave CRA (Lab Admin) role must have a minimum of an Associate Plus (AP) registration type;
  - Rave Investigator role must be registered as an Non-Physician Investigator (NPIVR) or Investigator (IVR); and
  - Rave Read Only role must have at a minimum an Associates (A) registration type.

  Refer to https://ctep.cancer.gov/investigatorResources/default.htm for registration types and documentation required.

Upon initial site registration approval for the study in RSS, all persons with Rave roles assigned on the appropriate roster will be sent study invitation e-mail from iMedidata. To accept the invitation, site users must log into the Select Login (https://login.imedidata.com/selectlogin) using their CTEP-IAM user name and password, and click on the "accept" link in the upper right-corner of the iMedidata page. Please note, site users will not be able to access the study in Rave until all required Medidata and study specific trainings are completed. Trainings will be in the form of electronic learnings (eLearnings), and can be accessed by clicking on the link in the upper right pane of the iMedidata screen. If an eLearning is required and has not yet been taken, the link to the eLearning will appear under the study name in iMedidata instead of the Rave EDC link; once the successful completion of the eLearning has been recorded, access to the study in Rave will be granted, and a Rave EDC link will display under the study name.

Users that have not previously activated their iMedidata/Rave accounts will also receive a separate invitation from iMedidata to activate their account. Account activation instructions are located on the CTSU website, Rave tab under the Rave resource materials (Medidata Account Activation and Study Invitation Acceptance). Additional information on iMedidata/Rave is available on the CTSU website under the Rave tab at http://www.ctsu.org/RAVE/ or by contacting the CTSU Help Desk at 1-888-823-5923 or by e-mail at ctsucontact@westat.com.

Provider data collection will be done in the PROMIS Assessment Center, a web-based application.

4.8.4 Site Credentialing

Sites interested in participating in E1Q11 must have an active CTEP ID number. Site staff who do not have a CTEP ID number must first register with the Pharmaceutical Management Branch (PMB, CTEP) at https://eapps-ctep.nci.nih.gov/iam/. For additional information on obtaining a CTEP ID number and joining ECOG, go to http://ecog-acrin.org/about-us/membership/how-to-join. If you have any questions, please contact ecog.membership@jimmy.harvard.edu.

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To express interest in participating, sites must email e1q11interest@jimmy.harvard.edu with the following information:

First and Last Name of the Primary Contact at your Institution

Email address for Primary Contact

Site Name

CTEP Site ID

Street Address

City, State, Zip

NOTE: The person identified as the Primary Contact will be the person responsible for data entry in Rave.

The Primary Contact will receive an email letting them know their site has been registered in Rave and that they can access the "E1Q11 Study Participation and Feasibility" study to complete the Study Participation and Feasibility Interest Form in Medidata Rave. (Please note that only the Primary Contact at each NCORP group will need to complete the E1Q11 Study Participant and Feasibility Interest Form. It will not be necessary for each affiliate to complete the form.)

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4.8.5 Data Quality Portal

The Data Quality Portal (DQP) provides a central location for site staff to manage unanswered queries and form delinquencies, monitor data quality and timeliness, generate reports, and review metrics.

The DQP is located on the CTSU members' website under Data Management. The Rave Home section displays a table providing summary counts of Total Delinquencies and Total Queries. DQP Queries, DQP Delinquent Forms and the DQP Reports modules are available to access details and reports of unanswered queries, delinquent forms, and timeliness reports. Review the DQP modules on a regular basis to manage specified queries and delinquent forms.

The DQP is accessible by site staff that are rostered to a site and have access to the CTSU website. Staff that have Rave study access can access the Rave study data using a direct link on the DQP.

To learn more about DQP use and access, click on the Help icon displayed on the Rave Home, DQP Queries, and DQP Delinquent Forms modules.

NOTE: Some Rave protocols may not have delinquent form details or reports specified on the DQP. A protocol must have the Calendar functionality implemented in Rave by the Lead Protocol Organization (LPO) for delinquent form details and reports to be available on the DQP. Site staff should contact the LPO Data Manager for their protocol regarding questions about Rave Calendaring functionality.

5. Methodology

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5.1 Randomization

Participating sites will be randomized to standard practice (Arm A) or intervention (Arm B). Due to logistical challenges of having both intervention and non-intervention programs within a single institution, the unit of randomization will be the institution (i.e., a cluster randomized approach) rather than individual patient. Institutions (i.e., the NCORP groups) participating in the study will be randomized to one of the two arms: Arm A without intervention and Arm B with intervention. Upon registration to this study, patients will be assigned to a study arm depending on the institutional assignment. Training for those randomized to Arm B will be offered at ECOG-ACRIN Group meetings and/or through a webinar on the ECOG website to enhance feasibility of site participation. Trainings specific to the intervention will be provided only to Arm B sites.

5.2 Study Arms and Intervention

5.2.1 Arm A – Non-intervention

Sites randomized to non-intervention will function with usual standard practice related to reproductive health.

5.2.2 Arm B – Intervention

Sites randomized to the intervention will receive training and intervention materials. Information specific to the intervention can be found in Addendum I.

5.3 Provider Survey Administration Instructions - Using Assessment Center™

5.3.1 Electronic administration of the Provider Surveys will be done using the study's website in the PROMIS Assessment Center. http://www.assessmentcenter.net/ac1/Assessments/E1Q11.

5.3.2 Prior to accessing the website, each provider will need to know his/her own physician's CTEP ID and site name/site CTEP ID.

5.3.3 User-friendly instructions will then be shown on the screen.

5.3.4 For providers who complete assessments using the Assessment Center, sites will log completion of these assessments in Medidata Rave. If the provider needed assistance or was unable to complete assessments at a given timepoint, the reason or type of assistance should be provided.

5.3.5 For sites with troubleshooting inquiries regarding the use of Assessment Center, the following steps should be followed: 1) All sites should direct troubleshooting inquiries directly to the E1Q11 Data Associate; 2) ECOG-ACRIN will forward unresolved inquiries to Northwestern University research staff; 3) Research staff at Northwestern University may forward unresolved inquiries to Assessment Center for final resolution. NOTE: Assessment Center should not receive any troubleshooting inquiries directly from sites.

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5.4 Patient Recruitment

Patients from oncology clinics with newly diagnosed cancer are possible candidates for the study. Complete eligibility criteria are included in Section 3. After the diagnosis of cancer is given to the patient, the primary provider will refer the patient to the study personnel for initial contact. The primary provider is defined as the clinician (MD, nurse practitioner, PA-C) that is clinically assessing the oncology patient. Subjects must enroll prior to initiation of chemotherapy or radiation, if applicable.

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Institutions will identify a clinical research nurse (CRN)/CRA that will be responsible for all aspects of this study. The designated (CRN)/CRA from each institution will be available to work with physicians during the clinical session to identify and recruit patients. This person will discuss the details of this study with appropriate care and thoughtfulness as she has recently received the diagnosis of a cancer. If the patient agrees, she will be screened for study eligibility at that time or at a subsequent visit as deemed appropriate by study personnel. This person will also be available to answer any questions regarding the study.

Patients will either be enrolled in the study or listed on the "Patient Log" (Appendix II), which requires a reason for the patient's decision not to participate. Please keep a copy of the Patient Log in patient chart at institution.

5.5 Data Collection

Patients will be followed over time and all surveys will be administered as described in Table 1 (Section 7).

5.5.1 Following site randomization and local IRB approval, a consent form will be given to each provider (oncology staff, i.e. MD, nurse practitioner or PA-C, that clinically assesses the patient). A signed provider consent form is required for participation.

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5.5.2 Upon site study activation a delegation of responsibility log should be completed and submitted to CTSU prior to enrolling the first patient

5.5.3 Patients will be recruited to participate at their scheduled provider appointment. Study staff will approach patients who are possible candidates to determine interest. If interested, eligibility will be confirmed (Section 3).

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5.5.4 A consent form will be given to interested and eligible patients. The consent form should be completed on the same day eligibility is confirmed, however, it must be signed prior to treatment initiation (See Section 7 Patient-specific timeline).

5.5.5 Patient will have the baseline provider visit, complete baseline surveys and be registered to the trial on the same day of consent. If this is not feasible, then all baseline requirements (including registration) must be completed within one week of patient consent. Baseline provider visits, completion of baseline surveys and study registration must be completed on same day. (Table 1).

5.5.6 The designated research staff person (CRN or CRA) from each institution will administer questionnaires and assist with the completion of form(s) at the baseline and follow-up visits, as necessary. A CRN or CRA must review form(s) for completeness as

soon as the patient finishes them to ensure all items have been marked appropriately.

5.5.7 The scheduled study tools must be completed during the visit.

5.5.8 Completed clinician and patient form(s) will be entered into Medidata Rave within 7 days of collection.

5.6 Administration Instructions

5.6.1 The forms must be administered at the time points noted in Table 1 (Section 7).

5.6.2 The CRA should read the instructions at the beginning of each questionnaire and administer to the patient unless the patient chooses to complete the survey on her own. The patient should be instructed to respond to questions in terms of her experience during the time frame specified on the form. It is permissible to assist the patient with completion of the forms, as long as the staff person does not influence the patient's response.

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5.6.3 The completed forms must be reviewed by the designated CRN or CRA, as soon as the patient completes them, to ensure all items were marked appropriately. If more than one answer was marked, the patient should be asked to choose the answer which best reflects how she is feeling. If a question was not answered, the patient should be asked if she would like to answer it. The patient should always have the option to refuse. If the patient refuses, it should be indicated on the form that she declined to answer the item.

5.6.4 If the patient cannot complete the baseline form properly, the reason should be noted on the Assessment Compliance Form. If a patient cannot complete the follow-up questionnaire because she is too sick AND the CRN/CRA learns of it, it will be documented on the Assessment Compliance Form.

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5.6.5 The clinician responsible for filling out the **Provider Reproductive Health Values Surveys (Specific to Patient)** may be the treating MD, the nurse practitioner, or PA-C involved in the clinical care of the patient. This will be determined per patient by the CRA/CRN.

5.6.6 If overlap occurs between the patient study follow-up visit and chemotherapy/radiation treatment visit, the Patient Follow-up Interviews should be completed rather than the Patient Follow-up Interview During Chemotherapy.

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5.7 On-Study and Follow Up Assessment Schedule

5.7.1 Provider Assessment Schedule

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Providers (oncology staff, i.e. MD, nurse practitioner or PA-C, that clinically assesses the patient) from both arms will complete two surveys, the **Provider Reproductive Health Values Survey (General)** and the **Provider Reproductive Health Values Survey (Specific to Patient)**. The general survey consists of 18 questions which assess provider opinion regarding reproductive health and cancer care and referral practices. The patient specific survey

consists of 8 questions assessing provider opinion regarding the reproductive health care needs of a specific patient.

Providers will complete the **Provider Reproductive Health Values Survey (General)** at the following two timepoints. This survey will take approximately 5 minutes to complete.

1. Pre-Study (0 months)
2. 30 months from site initiation

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Additionally, the provider will complete the **Provider Reproductive Health Values Survey (Specific to Patient)** at the following eight timepoints:

1. Baseline - (0 months)
2. 3 Months from Baseline Visit
3. 6 Months from Baseline Visit
4. 12 Months from Baseline Visit
5. 24 Months from Baseline Visit

Study Staff will complete forms according to the following schedule:

Medical Record Abstraction Form - Baseline

1. Baseline

Medical Record Abstraction Form – Follow-up

NOTE: The term 'regimen' is defined as anytime a patient starts a new course of medical treatment.

1. Within one week prior to the start of each chemotherapy regimen for patients undergoing chemotherapy or every four weeks of RT for patients undergoing radiation therapy alone
2. 3 Months from Baseline Visit
3. 6 Months from Baseline Visit
4. 12 Months from Baseline Visit
5. 24 Months from Baseline Visit

5.7.2 Patient Reported Outcomes Assessment Schedule

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If a patient is eligible to participate in this study and the physician approves, the study is further discussed with the patient. Patients providing consent will be registered on trial. Participants will complete a total of 8 assessment visits (including baseline). Structured interviews will be administered to participants at the timepoints listed below. At each time point, two questionnaires will be administered by a study team member. Completion of these forms on a given visit should take about 10-20 minutes. Patient interviews are designed to assess the patient's reproductive health history, management and goals at baseline and as they progress through cancer treatment. Additionally, the Sexual Function Survey, which includes the PROMIS Sexual Function Brief Profile v1.0 – Female, is designed to assess sexual health at diagnosis and throughout treatment.

Patients will be assessed according to the following schedule:

Patient Baseline Interview (51 Questions)

Baseline

Patient Follow-Up Interview (34 Questions)

1. 3 Months from Baseline Visit
2. 6 Months from Baseline Visit

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3. 12 Months from Baseline Visit
4. 24 Months from Baseline Visit

Patient Interview - During Chemotherapy/Radiation Treatment (11 Questions)

In addition to the above forms, each patient will complete the **Patient Interview During Chemo/Radiation Treatment** as well according to the following schedule:

Within one week prior to the start of each chemotherapy regimen for patients undergoing chemotherapy or every four weeks of RT for patients undergoing radiation therapy alone

Sexual Function Survey (16 Questions)

1. Baseline
2. Within one week prior to the start of each chemotherapy regimen for patients undergoing chemotherapy or every four weeks of RT for patients undergoing radiation therapy alone
3. 3 Months from Baseline Visit
4. 6 Months from Baseline Visit
5. 12 Months from Baseline Visit
6. 24 Months from Baseline Visit

5.8 Provision of Appropriate Care for Patients

The clinical management of all patients (regardless of symptom severity) will be determined by the treating physician.

5.9 Reproductive Health Related Endocrine Disruption in Cancer Care

This part of the study will be conducted on the first 200 patients enrolled in the EROS study who agree to participate. Blood samples will be drawn and laboratory tests (AMH, FSH, Thyroperoxidase antibody and TSH) will be evaluated to assess fertility status and endocrine disruption at baseline and at 3,

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6,12, and 24 months from Baseline Visit.

5.10 Quality of Life (QOL) Assessment

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The Sexual Function Survey will be administered to all patients recruited for the EROS study over the 2 year study period (as specified in Table 1). The PROMIS Sexual Function Brief Profile v1.0 - Female measures are included in the Sexual Function Survey.

5.11 Duration of Study

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Patients will participate on this study for 24 months from registration.

Patient will complete surveys in this study unless:

- Extraordinary Medical Circumstances: If at any time the constraints of this protocol are detrimental to the patient's health, administration of protocol surveys should be discontinued. In this event submit data through Medidata Rave according to the schedule in the E1Q11 Forms Completion Guidelines.
- Patient withdraws consent.

5.12 Duration of Follow-up

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For this protocol, all patients, including those who discontinue study participation early, will be followed for survival for 2 years from the date of registration.

6. Measures

6.1 Study Tools

Forms completed by clinical staff:

6.1.1 The EROS Trial: Engendering Reproductive Health Within Oncologic Survivorship Provider Reproductive Health Values Survey (General*).

6.1.2 The EROS Trial: Engendering Reproductive Health Within Oncologic Survivorship Provider Reproductive Health Values Survey (Specific to Patient*).

6.1.3 The EROS Trial: Engendering Reproductive Health Within Oncologic Survivorship Medical Record Abstraction Form – Baseline.

6.1.4 The EROS Trial: Engendering Reproductive Health Within Oncologic Survivorship Medical Record Abstraction Form – Follow-up.

6.1.5 The EROS Trial: Engendering Reproductive Health Within Oncologic Survivorship Pregnancy Supplement Form.

6.1.6 The EROS Trial: Engendering Reproductive Health Within Oncologic Survivorship Reproductive Health Assessment. (for intervention sites only)

Semi-Structured Interviews to be administered to study participants:

6.1.7 The EROS Trial: Engendering Reproductive Health Within Oncologic Survivorship Patient Baseline Interview.

6.1.8 The EROS Trial: Engendering Reproductive Health Within Oncologic Survivorship Sexual Function Survey.

6.1.9 The EROS Trial: Engendering Reproductive Health Within Oncologic Survivorship Patient Interview – During Chemotherapy/Radiation Treatment.

6.1.10 The EROS Trial: Engendering Reproductive Health Within Oncologic Survivorship Patient Follow-up Inter*view*.

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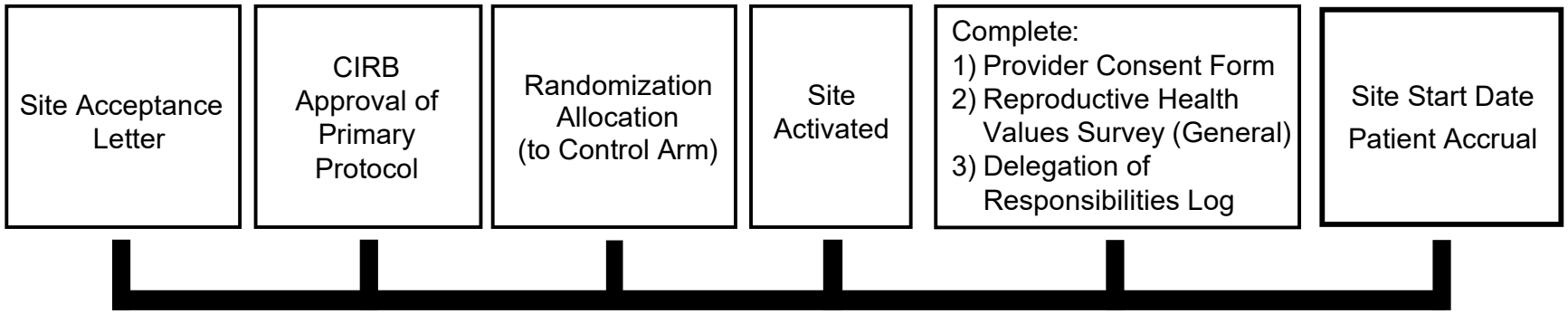
***Providers (oncology staff, i.e. MD, nurse practitioner or PA-C, that clinically assesses the patient) are required to review, sign, and submit a Provider Consent Form prior to site initiation of this study.**

7. Study Parameters (For Arm A only)

NOTE: THE ASSESSMENT SCHEDULE FOR THE INTERVENTION ARM B (WITH SOME EXTRA ITEMS) IS AVAILABLE IN ADDENDUM I.

Site Specific Timeline



Subject Specific Timeline

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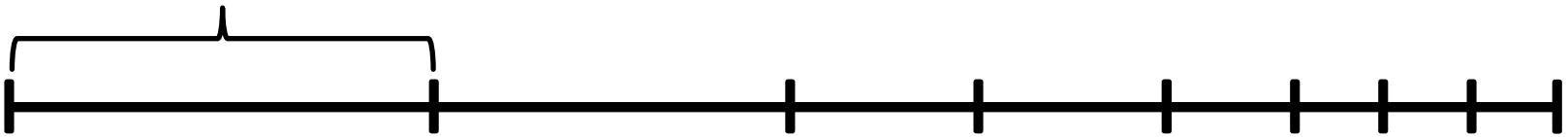
Recruitment Timeframe
Prior to initiation of cancer treatment



Patient Recruitment

1) CRA/CRN approach preliminarily eligible patient to determine interest
2) If interested, confirm eligibility (Section 3)

Patient Baseline

1) Consent Signed
2) Baseline visit with provider
3) Baseline surveys completed after visit
4) Patient registered

Baseline provider visit, baseline surveys and registration should be completed on the same day as consent, if this is not feasible baseline visit, baseline forms, and registration must be completed on the same day, within 1 week of consent and before treatment initiation.

3 Month Visit

6 Month Visit

12 Month Visit

24 Month Visit

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Table 1. Non-Intervention (Arm A) Engendering Reproductive Health within Oncologic Survivorship: Data Collection

For Intervention Arm (Arm B) data collection table includes four additional items located in Addendum I

NOTE: The term 'regimen' is defined as anytime a patient starts a new course of medical treatment.

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	Pre-study[1]	Baseline[4]	0 and 30 Months from Site Initiation	Within one week prior to start of each Chemotherapy Regimen or Every Four Weeks during RT[10,11]	At the end of 3, 6, 12, 24 Months from Baseline Visit[11,12]
SITE[2]					
Provider Consent Form	X				
Delegation of Responsibilities Log	X				
CLINICIAN					
Provider Reproductive Health Values Survey (General)[3]	X		X		
Provider Reproductive Health Values Survey (Specific to Patient)[5]		X			X
Medical Record Abstraction Form – Baseline[6]		X			
Rev. Add11 Medical Record Abstraction Form – Follow-up[6,13]				X	X
Pregnancy Test[7]		X		X	X
Pregnancy Supplemental Form[8]		X		X	X
PATIENT					
Patient Baseline Interview[9]		X			
Sexual Function Survey		X		X	X
Rev. Add10 Patient Interview - During Chemotherapy/Radiation Treatment[10]				X	
Patient Follow-up Interview[11, 12]					X

1. Pre-Study documents should be completed prior to participant recruitment.
2. These documents need to be updated based on staffing and provider changes over the course of this study. We define provider as the clinician (MD, nurse practitioner or PA-C) that clinically assesses the oncology patient.
3. Rev. 11/16 Each primary clinician should complete this form once at 0 (Prior to Study Training) and 30 months from site initiation. It is not necessary to fill out the form for each patient at each of these time points. As staffing changes over the course of this study new clinicians will complete this form

Rev. Add8 upon signing provider consent and at 30 months from site initiation. The date for site initiation is defined as the time when the site is approved to enroll patients into this study.

Rev. Add10 4. Patient will have the baseline provider visit, complete baseline surveys and be registered to the trial on the same day of consent. If this is not feasible, then all baseline requirements (including registration) must be completed within one week of patient consent and before treatment initiation as part of their standard of care (i.e., chemotherapy or radiation therapy). Baseline provider visits, completion of baseline surveys and study registration must be completed on same day.

5. This form should be completed by the primary clinician after each office visit (as determined by the CRN/CRA)

6. Complete the medical record abstraction forms from the medical chart of each eligible participant after visit with the patient. Form must be completed and entered electronically in Medidata Rave within one week of patient visit.

7. Pregnancy Test requirements. All patients must be counseled about pregnancy precautions, risks of fetal exposure and other risk as per standard of care. Pregnancy tests should be administered at Baseline, 3, 6, 12, and 24 months from Baseline Visit and within one (1) week prior to each chemotherapy regimen. For patients on radiation therapy (RT) alone, pregnancy tests should be administered within one (1) week prior

Rev. Add10 to the initiation of radiation therapy then every four (4) weeks until the end of radiation treatment. For patients who aged past 55 after enrollment may discontinue pregnancy tests if menopause is confirmed FSH < 23mIU/mL. Patients who have had a hysterectomy after enrollment may also discontinue pregnancy tests. Pregnant patients may discontinue pregnancy tests until delivery

8. If patient is pregnant or has been pregnant since her last study visit, one Pregnancy Supplement Form should be completed for each pregnancy.

9. Interview done after visit with the provider.

10. Study surveys should be completed at the beginning of each regimen of cancer treatment. For patients undergoing chemotherapy, surveys should be administered within one (1) week prior to each chemotherapy regimen. For patients on radiation therapy (RT) alone, surveys should be administered within one (1) week prior to the initiation of radiation therapy then every four (4) weeks until the end of radiation treatment. Patients receiving both chemotherapy and RT must follow the chemotherapy reporting schedule; if patient's treatment overlaps (+/- 2 weeks), the questionnaires do not have to be repeated.

Rev. Add10 11. Sites must complete the study surveys within the following windows:
- 3-month visit: +/- one month
- 6-month visit: +/- one month
- starting from 12-month visits: +/- 2 months

12. If there is an overlap (+/- 2 weeks) of visits at 3, 6, 12, and 24 months and visits relating to chemotherapy or RT, the Medical Record Abstraction-Follow up, Patient Follow-up Interview, the Sexual Function Survey and the Pregnancy Test only need to be completed once at the 3, 6, 12, and 24 month visits and not at the chemotherapy or RT visits.

13. The term ‘regimen’ is defined as anytime a patient starts a new course of medical treatment

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Table 2. Biological Sample Submissions

NOTE: **Effective March 10, 2021 the endocrine marker sub-study is closed to further accrual. This sub study has met its targeted accrual goal.**

Serum specimens should continue to be collected from previously enrolled patients that have consented to provide serum specimens at the time points outlined below.

Do not submit serum specimens from patients registered to E1Q11 after March 10, 2021.

NOTE: THIS SECTION APPLIES TO BOTH STUDY ARMS.

Blood samples should be submitted for the endocrine markers as outlined in Section 9. Submit only from patients who have given written consent to participate in the optional laboratory studies.

NOTE: It is required that biological sample submissions be logged into the ECOG-ACRIN Sample Tracking System (STS) for purposes of monitoring compliance.

NOTE: Institutions must complete and submit the Quest Diagnostics Sub-Account Information Sheet (Appendix III) to create their study specific account number in order to obtain supplies and arrange for courier service for the collection of the blood samples. See Section 9 for further instructions.

Biological Materials	Day of Registration [prior to treatment][1]	Within One Week Prior to Start of Each Chemotherapy Regimen or Every Four Weeks during RT[1]	At the end of 3, 6, 12, 24 Months from Baseline Visit
From Patients Who Answer *"Yes"* to *"I agree to participate in the laboratory research studies that are being done as part of this clinical trial."*[3]			
Serum (one 7.5mL red top tube)[2,3,4]	X	X	X
Serum, SST (one 7.5mL red/black top tube)[2,3,4]	X	X	X

1. For patients undergoing chemotherapy, blood samples will also be collected in conjunction with chemotherapy within one (1) week prior to the start of each chemotherapy regimen. For patients undergoing radiation therapy (RT) alone, blood samples will be collected within one (1) week prior to the initiation of radiation therapy and every four (4) weeks until the end of radiation treatment.
2. When possible, blood draws will be timed with the collection of blood draws for routine clinical purposes thus minimizing participant burden.
3. Ship blood samples to Quest Diagnostics as outlined in Section 9.
4. Supplies are available for the collection of the blood samples.

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8. Statistical Considerations

The primary objective of this study is to evaluate the success of implementation of the reproductive health programming among females aged between 15-55 years old with initial diagnosis of any form of cancer (before chemotherapy or radiation has started). Secondary objectives include (1) assessing the degree of discrepancy between patients and their clinicians in estimates of significance of the reproductive health goals for the patient, (2) evaluating baseline and follow-up reproductive health assessments for trends in reproductive health choices relating oncofertility, oncocontraception, and pregnancy over the 2 year study period, (3) identifying clinical and demographic factors that predict the adequacy of reproductive health management.

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Rev. 11/17 E1Q11 is a cluster randomized trial (CRT) with patients in one site all receiving the same intervention. This study was originally designed with a paired-matching cluster randomization, paired mainly by the type of institution (MU NCORP vs. NCORP) and geographical region (Northeast vs. Midwest vs. South vs. West). However, this design falls apart as some sites originally invited to participate in this study dropped from the study (at various time points). Consequently, the study design is now changed to a parallel cluster randomization (i.e., with clusters randomized to one of treatment arms). To have a manageable number of patients in this study and have this study completed in a reasonable timeline, the sample size was re-calculated based mainly on the primary endpoint of the primary objective (instead of the important secondary endpoint of the primary objective) and the patient's age limit was lowered to 15 years. Due to an oversight in previous sample size calculations, the sample size was re-calculated in amendment 13.

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8.1 Design and Randomization

In this study, the patient population will include all female patients initially diagnosed with any form of cancer and within the reproductive age of 15-55 years old. All enrolled female patients will be categorized into one of the four strata (Figure 1) – Stratum 1 with patients who are not pregnant, sexually active, and have not completed childbearing, Stratum 2 with patients who are not pregnant, sexually active, and have completed childbearing, Stratum 3 with patients who are not pregnant and not sexually active, and Stratum 4 with pregnant females and females who are interested in becoming pregnant within one year of study enrollment.

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Given that E1Q11 adopts a cluster randomized design, the details of endpoints can be found in the statistical analysis plan (located in Addendum II) in order to avoid contaminating control sites and to preserve the integrity of the intervention.

To evaluate the success of the intervention, appropriate reproductive health management will be used as the primary endpoint and the sample size will be calculated based on this endpoint. It is expected that the intervention can increase appropriate reproductive health management from 50% to 80% (across all four strata). The baseline rate of 50% was determined by Pilot Study 1 data.[21,22] In the "Reproductive Health Algorithm," 100% of females had appropriate reproductive health management after the intervention.[23] Therefore, with this study, we expect to detect an improvement from 50% to 80%.

For the secondary endpoint of LTC, it is hypothesized that for patients in Stratum 1, intervention will increase the contraception usage rate from 1% to 22% (based on Pilot Study 1). For patients in Stratum 2, the intervention will increase the

contraception usage rate from 20% to 60% (based on Pilot Study 1 and the "Reproductive Health Algorithm")[23,21,22]. Stratum 3 and Stratum 4 are observational groups and no specific hypothesis is given for them.

Institutions will be selected and invited to participate in this study. Because of the logistical difficulties of having both intervention and no intervention programs within a single institution, the unit of randomization will be the institution (i.e., a cluster randomized approach) rather than the individual patient. Thus, institutions participating in the study will be randomized to one of the two arms, Arm A without intervention and Arm B with intervention. Patients being accrued to the study, regardless of stratum, will be assigned to one of the two arms depending on the institutional assignment.

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Figure 1. Patient Strata

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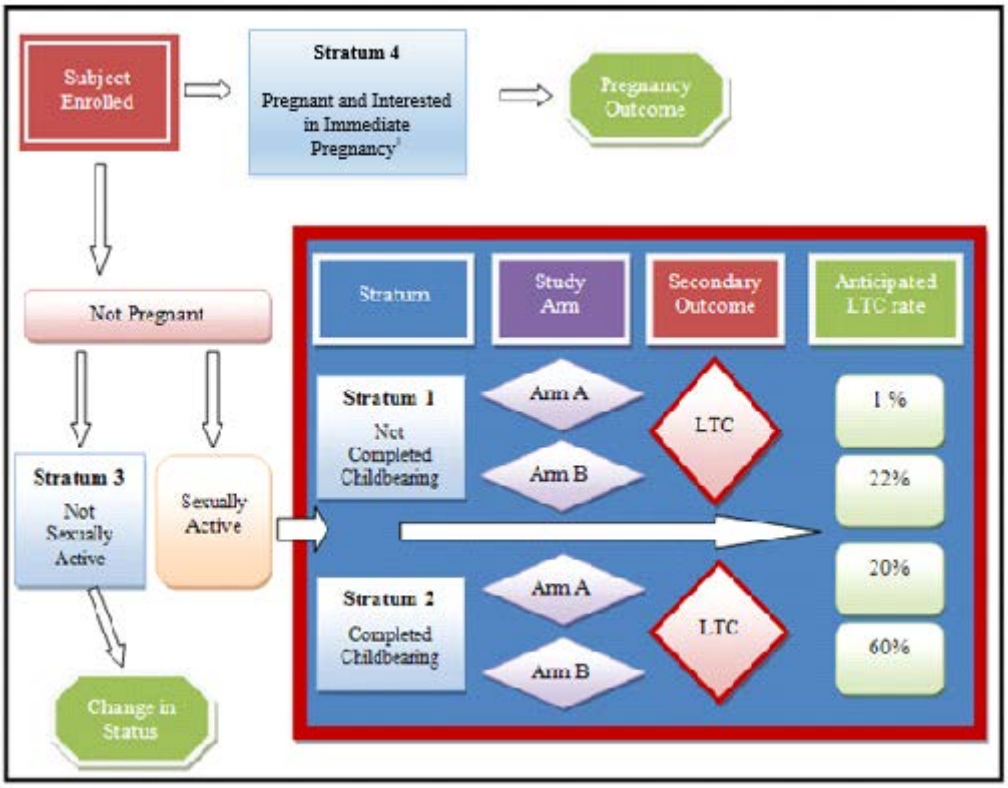

1. Defined as within one year from study enrollment) for the phrase "Immediate Pregnancy.

8.2 Selection of Participating Clinics

To ensure patient diversity in this study, all NCI MU NCORPs will be invited to participate in this study. Once participating MU NCORPs have been identified, the remainder of sites will be filled by NCORPS. All institutions will be equally randomized to either the non-intervention group (Arm A) or the intervention group (Arm B). Each institution will have patients enrolled in one of the four strata depending on the patient's pregnancy status, sexual activity status, and/or her birth intention.

8.3 Sample Size

To have a manageable number of patients in this study, the sample size is re-calculated based on the primary endpoint. For a cluster randomized trial, we must take into account the similarity among responses within a cluster (known as the intracluster correlation coefficient (ICC); ICC=0 indicating individuals completely independent; ICC=1 indicating individuals completely dependent), the required number of clusters per arm (denoted as k), and the number of patients per cluster (denoted as *m*) for the sample size calculations. To account for the possibility of variable cluster size in real accrual, coefficient of variation (CV) of cluster sizes (defined as the ratio of standard deviation of cluster sizes to mean of cluster sizes) was considered in sample size calculations as well. In this section, the power is computed assuming equal enrollment per arm. As of January 4, 2021, though, 66% (268/406) of the enrollment is from sites on the control arm and 34% from sites in the intervention group (with recent accrual closer to 50% in each group, due to site accrual caps). The number of intervention arm cases needed under equal enrollment will then be used to determine the overall sample size under the enrollment proportions seen in this study. The actual power should then be higher than stated, given the additional enrollment on the control arm.

To detect an increase from 50% to 80% (across all four strata) in the adoption of appropriate reproductive health management within 3 months consistent with patient's initial reproductive health goals (the primary endpoint),Table 1 shows the power with respect to various parameter values (including intra-cluster correlation coefficient, number of clusters, coefficient of variation, and mean cluster size), assuming an exchangeable within-cluster correlation structure, t-distribution, and type I error rate (α) at 0.10 (two-sided). The sample size and power calculations were conducted using the Shiny CRT Calculator, a web-based tool (https://clusterrcts.shinyapps.io/rshinyapp/)[24,25].

Table 1: Power for Various Plausible Parameter Values (assuming an exchangeable within-cluster correlation structure, t-distribution, and α=0.10)

Number of Clusters (k, per arm)	Coefficient of Variation (CV)	Mean Cluster Size (m)	ICC		
			0.05	0.10	0.15
8	0.0	11	0.96	0.90	0.84
	0.5	14	0.97	0.90	0.82
	0.6	16	0.97	0.90	0.81
	0.7	20	0.98	0.90	0.81
	0.8	15	0.95	0.85	0.75
	0.8	27	0.98	0.90	0.80
9	0.0	9	0.95	0.90	0.85
	0.5	11	0.96	0.90	0.83
	0.6	12	0.96	0.90	0.82
	0.7	14	0.97	0.90	0.82
	0.8	17	0.97	0.90	0.81
10	0.0	8	0.96	0.91	0.87
	0.5	9	0.96	0.90	0.84

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Number of Clusters (k, per arm)	Coefficient of Variation (CV)	Mean Cluster Size (m)	ICC		
			0.05	**0.10**	**0.15**
	0.6	10	0.96	0.90	0.84
	0.7	11	0.97	0.90	0.83
	0.8	12	0.97	0.90	0.81

Based on the results in the Verma and Lê's study[26], it is estimated that the intra-cluster correlation coefficient for the primary endpoint is 0.10. As of January 4, 2021, 9 Arm A sites and 8 Arm B sites have had enrolled patients for the EROS trial (n=268 for Arm A and 138 for Arm B) with CV=0.78 (=23.9/18.6). Assuming ICC=0.10, 16 institutions in total (i.e., 8 clusters per arm) and CV=0.8, Table 1 indicates an average of 27 eligible patients per cluster can detect an improvement from 50% to 80% while keeping 0.10 two-sided type I error rate and 90% power. Due to the slow accrual in Arm B, the study power was lowered to 85% with an average of 15 eligible patients per cluster, keeping the other parameters constant. In this case, this study requires 240 eligible patients in total enrolled into this study (average of 15 per cluster, 120 per arm) in order to keep 0.10 type I error rate and 85% chance of detecting the proposed 50% to 80% improvement on the primary endpoint. Assuming a 5% ineligibility rate and an additional 15% of attrition rate at 3 months (based on the fourth interim analysis with data pulled in July 2019), the sample size for the primary endpoint of this study is inflated to 298 patients in total (149 patients per arm, across the four strata), under equal enrollment on the two arms. To obtain 149 intervention arm cases, total enrollment will need to be 425 patients (see below).

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8.4 Accrual Goal and Accrual Period

To help safeguard 10 enrolling sites per intervention group (as originally proposed), we have invited more than 20 MU NCORPs/NCORPs to participate in this study (as listed on the cover page of the protocol). To further help accrual, we lowered the age limit to 15 years in Addendum 9 (effective from February 6, 2019). Besides the original participating MU NCORPs/NCORPs, interested pediatric MU NCORPs/NCORPs are allowed to participate in the EROS trial as well.

To have adequate power to detect the difference from 50% to 80% in the primary endpoint, the accrual goal of this study was re-calculated to ensure 149 patients in the intervention arm, assuming 16 sites enrolling patients for this trial (8 to the non-intervention group (Arm A) and the other 8 to the intervention group (Arm B)). Patients from each site will be enrolled into one of the four strata depending on the patient's pregnancy status, sexual activity status, and/or her birth intention. Given some sites accrue much faster than the others, a NCORP accrual cap of 45 patients was implemented per Addendum 8.

As of January 4, 2021, 268 patients from 9 Arm A sites and 138 patients from 8 Arm B sites have had been enrolled to this trial. As this is a comparative study, the trial will continue accrual for both arms until Arm B meets its accrual goal of 149 patients which is projected to take another 5 months. Taking into account the site accrual up to January 4, 2021 and the accrual rate in the past three months (i.e., the last three months of 2020, with the top three accrual sites met the accrual cap of 45 patients and closed accrual to Arm A), the final accrual of this study, thus, is expected to be 425 patients (276 from Arm A and 149 from Arm

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B). The mean cluster size is projected to be 25 patients assuming 17 enrolling sites in total (~30 patients per cluster for Arm A and ~18 patients per cluster for Arm B). As suggested by Table 1, this study is equipped with more power if the cluster size is larger than the average of 18-19 patients per cluster and/or if the number of clusters per arm is greater than the stated 8 sites per arm in the sample size calculations. The additional patients and sites in Arm A imply the power of this study will be a little larger than stated (i.e., 85% power) to detect a change from 50% to 80% on the primary endpoint with the projected final accrual of 425 patients.

Based on E5103, PACT1, E4599, and E4402, it is projected that the accrual rate for this patient population (female patients initially diagnosed with any form of cancer within the reproductive age of 15-55) is 50 patients per month. Since only limited institutions will be invited to participate in this study, it is further assumed that 13 patients per month will be accrued via these institutions for this study.

8.5 Power for the Important Second Endpoint (the LTC Usage at 6 Month Assessment)

8.5.1 Stratum 1 with patients who are not pregnant, sexually active, and have not completed childbearing.

It is expected that intervention can increase the LTC usage rate at 6 months after baseline visit from 1% (without intervention) to 22% for patients in Stratum 1.

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Table 2 shows the power with various parameter values to detect such an improvement, assuming ICC=0.10, an exchangeable within-cluster correlation structure, t-distribution, and type I error rate at 0.10 (two-sided). As indicated in Table 2, this study needs an average of 10 eligible patients enrolled into stratum 1 per cluster in order to have 84% power to detect an improvement in the LTC usage rate at 6 months from 1% to 22%, assuming ICC=0.10, 8 institutions per arm, and CV=0.8. The power drops to 47% if an average of 3 eligible patients is enrolled into stratum 1 per cluster, keeping all other parameters constant.

Results from the fourth interim analysis suggest that approximately 20% of eligible patients can be categorized into Stratum 2 and the 6-month attrition rate is approximately 20%. With the stated 15 eligible patients to detect a change from 50% to 80% on the primary endpoint (assuming 8 sites per arm), the projected average cluster size is 2-3 eligible patients in stratum 1 (=15x0.2x0.80). Thus, the new study design is not adequately powered to detect the proposed difference in LTC usage rate in Stratum 1.

Table 2: Power for Various Plausible Parameter Values (assuming improvement from 1% to 22%, ICC=0.10, an exchangeable within-cluster correlation structure, t-distribution, and α=0.10).

Number of Clusters (k, per arm)	Coefficient of Variation (CV)	Mean Cluster Size (m)	Power
8	0.5	3	0.50
	0.5	4	0.65

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Number of Clusters (k, per arm)	Coefficient of Variation (CV)	Mean Cluster Size (m)	Power
	0.5	5	0.73
	0.5	10	0.89
	0.8	3	0.47
	0.8	4	0.61
	0.8	5	0.69
	0.8	10	0.84
10	0.5	3	0.59
	0.5	5	0.82
	0.5	10	0.94
	0.8	3	0.56
	0.8	5	0.77
	0.8	10	0.90

8.5.2 Stratum 2 with patients who are not pregnant, sexually active, and have completed childbearing

It is expected that intervention can increase the LTC usage rate at 6 months after baseline visit from 20% (without intervention) to 60% for patients in Stratum 2. Table 3 summarizes the power with various parameter values, assuming ICC=0.10, an exchangeable within-cluster correlation structure, t-distribution, and type I error rate at 0.10 (two-sided). As indicated in Table 3, this study needs an average of 5 eligible patients enrolled into stratum 2 per cluster in order to have 85% power to detect an improvement in the LTC usage rate at 6 months from 20% to 60%, assuming ICC=0.10, 8 institutions per arm, and CV=0.8.

Results from the fourth interim analysis suggest that approximately 40% of eligible patients can be categorized into Stratum 2 and the 6-month attrition rate is approximately 20%. With the stated 15 eligible patients to detect a change from 50% to 80% on the primary endpoint (assuming 8 sites per arm), the projected average cluster size is expected to be 4-5 eligible patients in stratum 2 (=15x0.4x0.8). Consequently, the new study design has at least 80% power to detect an increase from 20% to 60% in the LTC usage rate at 6 month between the two arms.

Table 3: Power for Various Plausible Parameter Values (assuming improvement from 20% to 60%, ICC=0.10, an exchangeable within-cluster correlation structure, t-distribution, and α=0.10)

Number of Clusters (k, per arm)	Coefficient of Variation (CV)	Mean Cluster Size (m)	Power
8	0.5	3	0.71
	0.5	4	0.84
	0.5	5	0.89

Number of Clusters (k, per arm)	Coefficient of Variation (CV)	Mean Cluster Size (m)	Power
	0.5	10	0.97
	0.8	3	0.67
	0.8	4	0.80
	0.8	5	0.86
	0.8	10	0.95
10	0.5	3	0.79
	0.5	5	0.94
	0.5	10	0.99
	0.8	3	0.76
	0.8	5	0.92
	0.8	10	0.98

8.5.3 Stratum 3 with patients who are not pregnant and not sexually active

Stratum 3 is an observational group and no specific hypothesis is proposed for it.

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8.5.4 Stratum 4 with pregnant patients and patients who are interested in becoming pregnant within one year of study enrollment.

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Stratum 4 is an observational group and no specific hypothesis is proposed for it.

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8.6 Analysis Plan

8.6.1 Plan for the primary objective

With a cluster randomized design, the generalized estimating equations (GEEs) method will be used to evaluate the intervention effect. The GEEs method can be used to construct an extension of standard logistic regression[27]. For the primary endpoint, appropriate reproductive health management, a GEE model with an exchangeable correlation structure (i.e., assuming every patient within a cluster is equally correlated with every other patient from that cluster) and registering institution as the cluster variable will be fitted to compare the rates between the intervention group and the no intervention group by combining patients in all strata. The appropriate reproductive health management rate at each time point will be summarized, by arm, with frequency and percentage along with its 95% confidence interval. This rate in the non-intervention arm will indicate whether reproductive health needs are adequately addressed (Hypothesis 1, Section 1.4.1). Whether the intervention can improve reproductive health care (Hypothesis 2, Section 1.4.2) can be determined by comparing this rate between the non-intervention arm and the intervention arm.

The same method will be used to evaluate the intervention effect on contraception usage for Stratum 1 and Stratum 2, separately. Since it is expected that contraception usage will be influenced by the number

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of children (0, 1-2, >2), type of treatment (chemo vs. RT vs. surgery vs. combination), and disease stage (nonmetastatic vs. metastatic) as well, these factors will be included in the model as covariates. The contraception usage rate at each time point will be reported with frequency and percentage along with its 95% confidence interval. Similar analysis method will be applied to the proportion of patients with pregnancy by the end of 2 years after baseline visit on the study. The analysis will be applied to patients by stratum for each of these secondary endpoints.

8.6.2 Plan for secondary objectives

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Objective 1: To assess the degree of discrepancy between patients and their clinicians in estimates of significance of the reproductive health goals for the patient.

Assume the rating (1-10) on the reproductive health value questions is on a continuous scale. For each question, mean and standard deviation in terms of rating will be computed by arm for patients and their clinicians, respectively. The difference in ratings between the patient and his/her clinician will also be computed and summarized with descriptive statistics. The ratings between patients and clinicians will be compared using a linear mixed-effect model. Only data available from both the patient and his/her clinician will be included in this part of analysis. This analysis can address Hypothesis 3 that patients and clinicians have different perspectives regarding reproductive health objectives of females with cancer (Section 1.4.3).

Objective 2: To evaluate baseline and follow-up reproductive health assessments.

Frequency/percentage will be used to summarize results collected at each time point. Longitudinal analysis will be applied when appropriate.

Objective 3: To identify clinical and demographic factors predictive of the adequacy of reproductive health management.

To identify clinical and demographic factors predictive of the adequacy of reproductive health management (Hypothesis 4, Section 1.4.4), the GEE method will be used.

8.6.3 Plan for Endocrine Disruption in Cancer Care

A longitudinal observational study is proposed to examine reproductive health biomarkers in a subgroup of participants (first 200 subjects who agree to participate in this part of study) in the EROS

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Trial. Participants will be asked to provide blood samples for laboratory correlates (AMH, FSH, TSH, TPO), indicating reproductive health, fertility status, and endocrine disruption. Blood samples will be obtained at baseline and periodically at 3, 6, 12, and 24 months from baseline visit on the study, which totals 8 blood draws. In addition, blood samples will be acquired in conjunction with chemotherapy (within one week of each regimen, prior to chemotherapy) or radiation therapy (within one week prior to the initiation of radiation therapy then every four weeks until the end of radiation treatment). This will increase the number of samples for that population as we attempt to

assess impact of chemotherapy on endocrine function. The hormonal levels at each measurement point will be summarized (by median and range) and plotted across time by marker. All analysis will be performed for patients with chemotherapy and without chemotherapy separately. To assess the impact of chemotherapy on endocrine function, a linear mixed-effect model will be used to make comparisons between the two groups with respect to each marker.

To determine the percent of females having significant endocrine disruption during chemotherapy, Table 7 below summarizes the abnormal level for each marker.

Table 7: Endocrine Markers and Associated Threshold Values for Endocrine Disruption

Marker	Age Range	Abnormal Range
FSH	15-55	≥ 23.0 mIU/mL
TPO	15-55	< 35 IU/mL
TSH	≤ 19	0.50-4.30 mIU/mL
	≥ 20	0.40-4.50 mIU/mL
AMH	≤ 19	0.76 – 11.34 ng/mL
	20-29	0.76- 11.34 ng/mL
	30-39	< 9.24 ng/mL
	40-49	< 4.50 ng/mL
	≤ 50	< 0.45 ng/mL

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Quest Diagnostics Laboratory reference ranges

For each marker, the patient with the observed lab value falling into the abnormal range is considered to represent a case with endocrine disruption. Frequency and percentage (along with its 95% confidence interval) will be used to summarize patients with endocrine disruption during chemotherapy for each marker.

8.6.4 Plan for Longitudinal Study of Sexuality

Measurement of PROMIS Sexual Function Survey Brief Profile v1.0 - Female will be used to evaluate the hypotheses that (1) cancer survivors' sexual function decreases during primary cancer treatment then increases after treatment completion and (2) cancer survivors have lower levels of satisfaction with their sex lives compared to the age-matched general population at baseline. All patients recruited for the EROS study will be included in this part of analysis. Data collected in PROMIS Sexual Function Survey Brief Profile v1.0 - Female in the EROS study will be summarized and plotted across time with respect to each of the subdomains (global satisfaction with sex life, interest in sexual activity, lubrication, vaginal discomfort, and orgasm). A linear mixed-effect model will be used to study changes in each of the subdomain scores of PROMIS Sexual Function Survey Brief Profile v1.0 - Female over time, with institution as the random effect (by stratum and across all patients if there is no difference between strata). For the secondary hypothesis, our comparative group is the

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age-matched population of non-cancer females in the reproductive age range surveyed by the Duke Clinical Research Institute. The collaborator at Duke Clinical Research Institute will provide summary data on age-matched non-cancer patients. The PROMIS study uses a *T* score method with a mean of 50 and a standard deviation of 10. Results from the Sexual Function Survey in the EROS trial will be transformed into T scores as well then comparison between the groups will be performed using the two-sample t test.

8.7 Randomization Scheme

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Institutions that are selected to participate will be randomly assigned (with a 1:1 allocation ratio) to either the non-intervention arm or the intervention arm.

8.8 Monitoring Plan

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Study Progress and Safety Reports are prepared twice yearly for all ECOG-ACRIN studies. Reports of these analyses are sent to the ECOG-ACRIN Principal Investigator or Senior Investigator at the participating institutions. The ECOG-ACRIN Data Safety Monitoring Committee (DSMC) will semi-annually review this randomized trial as well.

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An interim analysis plan is proposed to monitor study progress instead of early stopping for efficacy or futility.

The survey compliance rates (considering both Medical Record Abstraction Form and Patient Interview Form are completed), considering both baseline/3 months and baseline/6 months will be reported separately in each of the interim analysis, starting after every 100 patients enrolled on this study and synchronizing with the DSMC meeting. The proportion of patients who adopts appropriate reproductive health management within 3 months from baseline visit (the primary endpoint, across all evaluable patients) will also be reported in the interim analysis, together with the 90% confidence interval. All these results will be presented to the DSMC.

8.9 Race and Ethnicity

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Patients in this study will be females only. The slow accrual in Arm B led to over-accrual in Arm A (n=268, as of January 4, 2021) with respect to the new accrual goal (n=149 per arm). Taking into account the site accrual up to January 4, 2021 and the accrual rate in the past three months (i.e., the last three months of 2020), the final accrual of this study is projected to be approximately 425 patients in total when Arm B meets its accrual goal. According to historic data for ECOG studies (E5103, PACT1, E4599, E4402, and E1A11), the anticipated accrual in subgroups defined by ethnicity and race is as follows:

Racial Categories	Not Hispanic/Latino		Hispanic/Latino		Total
	Female	Male	Female	Male	
American Indian/Alaska Native	2	0	0	0	2
Asian	14	0	0	0	14
Native Hawaiian or Other Pacific Islander	2	0	0	0	2
Black or African American	43	0	2	0	45
White	315	0	47	0	362
Total	376	0	49	0	425

The accrual targets in individual cells are not large enough for definitive comparisons to be made within these subgroups. Therefore, overall accrual to the study will not be extended to meet individual subgroup targets.

8.10 Handling Missing Data

The primary analysis will treat missing data as missing at random then analyze cases with complete data. The method of multiple imputation will be used to handle missing data if more than 20% of the cases have missing data in the variables of interest. If so, sensitivity analysis will be performed to compare results from the complete case analysis and imputation analysis. In case of discrepancies, possible explanations will be discussed. For longitudinal data, given the expected high level of missingness in these data, data will be analyzed according to the methods described in Schluchter and in Schluchter, Greene, and Beck[28,29]. These methods take into account the possibility of informative missingness by jointly modeling the longitudinal response and the time to dropout.

9. Correlative Studies

NOTE: Effective March 10, 2021 the endocrine marker sub-study is closed to further accrual. This sub study has met its targeted accrual goal.

Serum specimens should continue to be collected from previously enrolled patients that have consented to provide serum specimens at the time points outlined below.

Do not submit serum specimens from patients registered to E1Q11 after March 10, 2021.

NOTE: THIS SECTION APPLIES TO BOTH STUDY ARMS.

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NOTE: ECOG-ACRIN requires that all biological samples submitted be entered and tracked via the online ECOG-ACRIN Sample Tracking System. An STS shipping manifest form must be generated and shipped with the sample submissions. See Section 9.4.

NOTE: An informed consent must be signed prior to the submission of any samples for laboratory studies. Samples for the optional laboratory studies should be submitted only from patients who have given written consent for the use of their samples for these purposes.

9.1 Study-Specific Account Set Up for Quest Diagnostics

The following steps should be completed prior to consenting or registering patients to the study, as account creation and initial supply delivery takes about two (2) weeks.

- Institutions must complete and submit the Quest Diagnostics Sub-Account Information Sheet (Appendix III) to create their study-specific account number.
- E-mail the completed form to Andrea.P.Pogue@questdiagnostics.com or Fax to (855) 848-4237.
- Quest will provide each institution with a study-specific account name and number and ship an initial allocation of supplies (collection tubes, specimen labels, specimen transport bags, serum transport vials/caps, pre-printed custom requisitions forms) using the contact information listed on Account Set Up Information section of the Sub-Account Information Sheet (Appendix III). The study-specific account number will be included on a laminated form with the initial supplies shipment.
- Upon receipt of the study-specific account number, institutions should contact Quest at (866) 697-8378 to obtain courier and pick-up details for their institution. Institutions will be given a specific cut-off time for calling in to receive same day pick-up and to determine if Saturday service is available (if needed). The courier service will provide dry ice. If your institution is not eligible for Quest courier pick-up Quest will provide supplies for shipping via FedEx.
- To order additional supplies contact Quest Diagnostics at (866) 226-8046 or e-mail DGXNational@QuestDiagnotics.com. Supplies will be shipped via ground delivery to arrive within three to five working days.

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9.2 Sample Submission Schedule

Blood samples are being collected for the correlative studies outlined in Section 1.7 and analyzed by Quest Diagnostics.

NOTE: Results of these laboratory tests will not be returned to the institutions or reported to the patient.

NOTE: Blood samples should be collected as outlined in the table and sections below.

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Biological Materials	Day of Registration [prior to treatment][1]	Within One Week Prior to Start of Each Chemotherapy Regimen or Every Four Weeks during RT[1]	At the end of 3, 6, 12, 24 Months from Baseline Visit
From Patients Who Answer *"Yes"* to *"I agree to participate in the laboratory research studies that are being done as part of this clinical trial."*[3]			
Serum (one 7.5mL red top tube)[2]	X	X	X
Serum, SST (one 7.5mL red/black top)[2]	X	X	X

1. For patients undergoing chemotherapy, blood samples will also be collected in conjunction with chemotherapy within one (1) week prior to the start of each chemotherapy regimen. For patients undergoing radiation therapy (RT) alone, blood samples will be collected within one (1) week prior to the initiation of radiation therapy and every four (4) weeks until the end of radiation treatment.
2. When possible, blood draws will be timed with the collection of blood draws for routine clinical purposes thus minimizing participant burden.

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9.3 Sample Preparation Guidelines

If you have any questions concerning sample collection and shipment, please contact Quest Diagnostics National Clinical Call Center at (866) 226-8046 or DGXNational@QuestDiagnostics.com Monday-Friday 7AM-7PM CST, please have your national account number ready when calling.

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9.3.1 Red Top Tube Collection

1. Draw 7.5mL of blood into the Red Top tube.
2. Invert tube gently no more than eight (8) times to mix the blood with the clot activator.
3. Do not remove stopper at any time. Do not centrifuge immediately after drawing blood. Allow the blood to coagulate in an upright position at room temperature for at least 30 minutes, but no longer than one (1) hour before centrifugation.
4. Centrifuge tube for at least 15 minutes at speeds between 2200 and 2500rpm within one (1) hour of collection.
5. Separate serum from clot and dispense at least 1mL of serum into the plastic transport screw cap vial.

6. Screw the cap to the vial securely and freeze at ≤ -20°C immediately until pick-up.

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9.3.2 SST Tube Collection

1. Draw 7.5mL of blood into the SST tube.
2. Invert tube gently no more than eight (8) times to mix the blood with the clot activator.
3. Do not remove stopper at any time. Do not centrifuge immediately after drawing blood. Allow the blood to coagulate in an upright position at room temperature for at least 30 minutes, but no longer than one (1) hour before centrifugation.
4. Centrifuge tube for at least 15 minutes at speeds between 2200 and 2500rpm within one (1) hour of collection.
5. Store at ambient temperature until pick-up.

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9.3.3 Labeling and Custom Test Requisition Form Completion

All specimens should be labeled at the time of collection with at least two patient identifiers.

Each tube must be clearly labeled in ball point pen to include:

- ECOG-ACRIN Five-Digit Patient Sequence Number (required, if not available at baseline visit Patient Initials must be used)
- Patient Gender

The tubes must also be labeled with the specimen labels from the test requisition forms. See packaging guidelines below.

Specimens must be accompanied by custom paper test requisition forms. Custom test requisition forms will be included with the supplies. Two pre-printed test requisition forms must be submitted with the blood samples (one for each tube type).

Complete the patient information section on the requisition and select the tests to be performed. Please be sure to keep a copy of each test requisition form within the patient's chart.

The tests to be ordered with corresponding codes are as follows:

Frozen Red Top Tube

- Anti-Mullerian Hormone AssessR [#37227]

Ambient SST Tube

- Thyroid Peroxidase Antibodies (TPO) [#5081]
- TSH [#899]
- FSH [#470]

The requisition should contain the following patient information:

- ECOG-ACRIN Five-Digit Sequence Number (enter under Patient ID#) (if not available at baseline visit Patient Initials must be used)
- Do NOT write in the patient's name
- Sex
- Name of Insured/Responsible Party (enter as ECOG-ACRIN)

- Name and Address of Physician Ordering the Test
- Tests Requested (see codes above)
- Date and Time of Specimen Collection
- Fasting or Non Fasting

Please do NOT fill out information related to results reporting, patient social security number and date of birth, patient phone number and street address.

9.3.4 Packaging Guidelines

1. Ensure that all specimen container caps and lids are properly tightened to prevent leakage.
2. Complete the test requisition forms, one for the frozen blood sample in the transport tube and one for the blood sample in the SST tube.
3. Collect the specimens and transfer to a proper transport container, if needed.
4. Double check the specimen container to ensure that the device is not beyond its stated expiration date.
5. Remove a self-stick label from the bottom of the pre-printed paper test requisition and securely affix this label to the specimen transport container. Fold the top copy (original) of the test requisition in half widthwise (top to bottom) with the bar code facing out. Retain the second copy for your files.
6. The specimen transport bag has two pouches. Place the specimen containers in the front pocket. Insert the test requisition into the rear pocket with the bar code visible in the bottom corner of the bag.
7. Frozen specimens should be transported in plastic screw--cap containers only. Frozen specimens must be placed in a separate specimen bag along with a separate test requisition.
8. Remove the protective strip and seal the specimen bag. The protective strip must not obstruct the bar code. This will protect the test requisition from leakage and help ensure that the patient information can be entered directly into the laboratory computer by scanning of the bar code.

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9.3.5 Quest Courier Service

The blood samples should be transported using the Quest Diagnostics courier service. Please contact Quest Diagnostics at (866) 697-8378 to schedule the courier pick-up **within 24 hours of the blood draw**. You will be given a specific cut-off time for calling in to receive same day pick-up, if calls are made past this time, the pick-up will be scheduled for the following day. Please provide your account number when calling. If courier service is not available in your location, FedEx air bill labels will be provided to you with your supplies, be sure to request two FedEx air bill labels for each of the tube shipments.

9.4 ECOG-ACRIN Sample Tracking System

It is **required** that all samples submitted on this trial be entered and tracked using the ECOG-ACRIN Sample Tracking System (STS). The software will allow the use of either 1) an ECOG-ACRIN user-name and password previously assigned (for those already using STS), or 2) a CTSU username and password.

When you are ready to log the collection and/or shipment of the samples required for this study, please access the Sample Tracking System software by clicking https://webapps.ecog.org/Tst

Important: Please note that the STS software creates pop-up windows, so you will need to enable pop-ups within your web browser while using the software. A user manual and interactive demo are available by clicking this link: http://www.ecog.org/general/stsinfo.html Please take a moment to familiarize yourself with the software prior to using the system.

An STS shipping manifest form must be generated and shipped with all sample submissions.

Please direct your questions or comments pertaining to the STS to ecog.tst@jimmy.harvard.edu

9.4.1 Study Specific Notes

An ECOG-ACRIN Generic Specimen Submission Form (#2981) will be required only if STS is unavailable at the time of sample submission. Indicate the appropriate Lab ID # on the submission form:

- 0169 = Quest Diagnostics

  NOTE: Quest Diagnostics will not be utilizing the STS; therefore blood samples submitted will not be marked as received in STS.

Retroactively enter all collection and shipping information when STS is available.

9.5 Banking

The blood samples submitted will be used for the embedded laboratory research studies as outlined in Section 9. No residuals will be stored for future research studies.

9.6 Sample Inventory Submission Guidelines

Inventories of all samples submitted from institutions will be tracked via the ECOG-ACRIN STS and receipt and usability verified by the receiving laboratory. Inventories of samples forwarded and utilized for approved laboratory research studies will be submitted by the investigating laboratories to the ECOG-ACRIN Operations Office - Boston on a monthly basis in an electronic format defined by the ECOG-ACRIN Operations Office - Boston.

9.7 Lab Data Transfer Guidelines

The data collected on the above mentioned laboratory research studies will be submitted electronically using a secure data transfer to the ECOG–ACRIN Operations Office – Boston by the investigating laboratories on a quarterly basis or per joint agreement between ECOG-ACRIN and the investigator.

10. Electronic Data Capture

Please refer to the E1Q11 Forms Completion Guidelines for the forms submission schedule. Data collection will be performed exclusively in Medidata Rave.

This study will be monitored by the CTEP Data Update System (CDUS) version 3.0. Cumulative CDUS data will be submitted quarterly from the ECOG-ACRIN Operations Office-Boston to CTEP by electronic means.

11. Patient Consent and Peer Judgment

Current FDA, NCI, state, federal and institutional regulations concerning informed consent will be followed.

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EROS: Engendering Reproductive Health within Oncologic Survivorship

Appendix I

Patient Thank You Letter

We ask that the physician use the template contained in this appendix to prepare a letter thanking the patient for enrolling in this trial. The template is intended as a guide and can be downloaded from the web site at http://www.ecog.org. As this is a personal letter, physicians may elect to further tailor the text to their situation.

This small gesture is a part of a broader program being undertaken by ECOG-ACRIN and the NCI to increase awareness of the importance of clinical trials and improve accrual and follow-through. We appreciate your help in this effort.

[PATIENT NAME] [DATE]

[PATIENT ADDRESS]

Dear [PATIENT SALUTATION],

Thank you for agreeing to take part in this important research study. Many questions remain unanswered in cancer. With the participation of people like you in clinical trials, we will improve treatment and quality of life for those with your type of cancer.

We believe you will receive high quality, complete care. I and my research staff will maintain very close contact with you. This will allow me to provide you with the best care while learning as much as possible to help you and other patients.

On behalf of ***[INSTITUTION]*** and the ECOG-ACRIN, we thank you again and look forward to helping you.

Sincerely,

[PHYSICIAN NAME]

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Appendix II

Patient Log

INSTITUTION: Use this form to record the oncology out-patients who have been asked and elected **not** to participate in this study.

Institution:_____ CRA:_____

Patient Initials (L, F)	Date Approached (M/D/Y)	Reason Given for Not Participating
1._____	_____/_____/____	_____
2._____	_____/_____/____	_____
3._____	_____/_____/____	_____
4._____	_____/_____/____	_____
5._____	_____/_____/____	_____
6._____	_____/_____/____	_____
7._____	_____/_____/____	_____
8._____	_____/_____/____	_____
9._____	_____/_____/____	_____
10._____	_____/_____/____	_____
11._____	_____/_____/____	_____
12._____	_____/_____/____	_____
13._____	_____/_____/____	_____
14._____	_____/_____/____	_____
15._____	_____/_____/____	_____

Page _____ of _____'s Patient Log
Institution/site name

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Appendix III
Quest Diagnostics Sub-Account Information Sheet

All of the information requested below is required to set-up a new sub-account for an existing NCTS client.

Account Set-Up Information:

Account Name	
Attn	
Address City, State, Zip	
Phone	
Fax	ECOG-ACRIN Fax: 617-589-0914 (all results to ECOG-ACRIN via Care360)
Rep Name and Sales ID	Andi Pogue/AH24
RSM Name and Sales ID	Dave Stella/DS16
Ordering Physician (Name, License Number and State, UPIN Number, NPI)	
National ID Code	NEFS
If existing accounts are group billed, what is the Group Bill Number?	97513507

Billing Information:

(Bill to the following statement address, complete only if different from information above)

Bill To Name	ECOG-ACRIN E1Q11
Attn	Chris Schleyer
Address City, State, Zip	ECOG-ACRIN Medical Research Foundation 1818 Market Street, Suite #1100 Philadelphia, PA 19103

Reporting Options:

Final Reports or Partial Reports – Final Reports

Fax Final (faxed report only, no mailed copy) – Care360 (All Results for Sub-Account to go back to ECOG-ACRIN)

Care360 – LO&R or Physician Portal

The Secure Fax letter must be filled out for either option, signed and faxed to Quest Diagnostics.

If Care 360, user request forms must be completed and authorized by ordering physician.

All information must be complete before submitting.

Email Completed Form to Andrea.P.Pogue@questdiagnostics.com or Fax to (855) 848-4237.

What Custom Panels (if any) are to be activated for this account?

INTERNAL INFORMATON ONLY: Use Account #

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Appendix IV

INFORMATION SHEET REGARDING RESEARCH STUDY E1Q11 (for teens from 15 through 17 years of age)

A study about reproductive health care needs for female patients who are treated for cancer

1. We have been talking with you about your cancer and the side effects of cancer treatment, including possible effects on reproductive health.
2. We are asking you to take part in a research study because you are receiving treatment for cancer. A research study is when doctors work together to try out new ways to help people who are sick. The purpose of this study is to learn more about how female patients are usually being helped with their reproductive health needs during cancer treatment. This study will also look at tools and information that could be added to help more.
3. You do not have to be in this study. No one will be disappointed in or angry with you if you decide not to join after learning about the details of the study. If, after understanding the nature of the study, you decide to join today you can change your mind later. Once you read, discuss, and understand the study, and if you and your parent/guardian agree, you will be asked to sign your name on this form. You will be given a copy of this form to keep.
4. The study staff will talk with you and your parent/guardian about this study and answer your questions, as needed.
5. Teens who are part of this study will be asked to complete questionnaires at about eight to ten time points during their regular medical visits. The questions will be about your reproductive health interests. Each time, a study team member will give you questionnaires and ask you the questions listed. This will be done in private, without anyone else besides the study team member with you in the room. The questions should take about 10-15 minutes at each visit.
6. Sometimes good things can happen to people when they are in a research study. These good things are called “benefits.” We hope that a benefit to you of being part of this study is that communication between you and your doctor will better help treatment planning fit your future reproductive health goals. We hope the information learned from this study will benefit other cancer patients in the future. But we don’t know for sure if there is any benefit of being part of this study.
7. Sometimes bad things can happen to people when they are in a research study. These bad things are called “risks.” The risks to you from this study are that some of the questions or topics that come up during this study may cause you to feel embarrassed, or may upset you. You can choose to fill in the survey questions in private or to not answer questions. Other things may happen to you that we don’t yet know about.
8. Your family can choose to be part of this study or not. Your family can also decide to stop being in this study at any time once you start. There may be other options that your doctor can tell you about. Make sure to ask your doctors any questions that you have.
9. We are asking your permission to collect additional blood. We want to study changes to reproductive hormone levels that may happen throughout and after treatment. Researchers will perform tests on the blood in order to look at how chemotherapy impacts the endocrine (hormone) system. These samples would be taken when other standard blood tests are being performed, so there should not be any extra blood sticks

beyond your usual care. You can still be a part of this study even if you don't allow us to collect the extra blood samples for research.