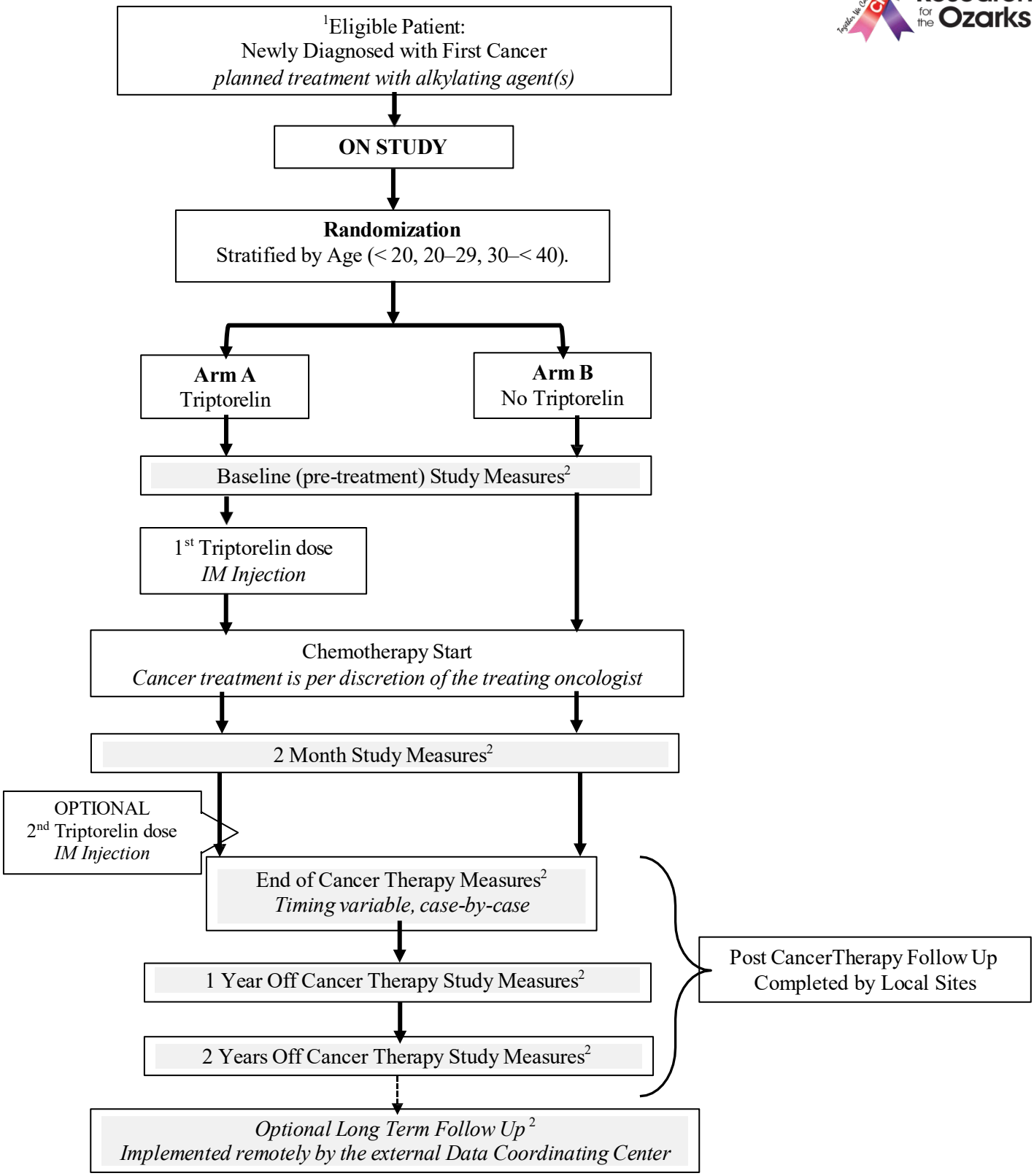
EXPERIMENTAL DESIGN SCHEMA



1. See Section 3.2 for Eligibilty details.
2. See Section 7 for Study Measures

ABSTRACT
Reproductive health outcomes, including the possibility of infertility from cancer treatment, are a major source of distress for adolescent and young adult (AYA) patients from diagnosis through survivorship. The overarching objective of this study is to investigate the impact of the Gonadotropin Releasing Hormone agonist (GnRHa) triptorelin, as a randomized intervention, on the ovarian reserve of newly diagnosed AYA cancer patients (exclusive of breast cancer) treated with alkylating agent chemotherapy. This trial is supported by the NCI Community Oncology Research Program (NCORP), led by the Children's Oncology Group (COG), and is open as a cross network trial to NCORPs and non-NCORP sites. To demonstrate feasibility, in this initial phase, 60 AYA female subjects < 40 years of age will be enrolled. Randomization will be stratified by age (< 20, 20–29, 30–< 40). Once feasibility can be demonstrated, the ultimate goal will be to enroll up to 250 participants in order to assess the effect of triptorelin on the difference in anti-Mullerian hormone (AMH), a biomarker of ovarian reserve, at two years from the completion of alkylating agent therapy between the randomized arms. The overall study will impact future clinical practice by providing a strong evidence base for the utility (or disutility) of GnRHa on ovarian reserve among newly diagnosed AYA cancer patients. In addition to measurements of ovarian reserve, the study will collect relevant patient-reported outcomes, including symptoms and quality of life over time, as differences in these domains may be as important to participants as measurements of ovarian reserve.

1.0 GOALS AND OBJECTIVES (SCIENTIFIC AIMS)

1.1 Primary Aims

1.1.1 Determine the feasibility of conducting a cross network, multi-site, randomized clinical trial of triptorelin among newly diagnosed adolescent and young adult (AYA) female cancer patients age <40 years (exclusive of breast cancer).

1.1.2 Measure ovarian reserve via anti-Mullerian hormone (AMH) at 2-years post completion of alkylating agent-containing chemotherapy among randomized patients.

1.2 Secondary Aims

1.2.1 Collect information on the longitudinal trajectory of change in AMH and other ovarian hormone levels from cancer diagnosis to 2 years post cancer treatment completion among randomized patients.

1.2.2 Determine the feasibility of measuring estrogen deprivation symptoms (i.e., hot flashes, sexual dysfunction) menstrual pattern, and quality of life among randomized patients.

1.3 Exploratory Aim

1.3.1 Establish a unique cohort of female AYA patients treated with alkylating agent chemotherapy and randomized to receive or not receive triptorelin, that can be followed long-term to study reproductive health concerns and outcomes as well as genetic risk factors for premature menopause.

3.2 Patient Eligibility Criteria

Important note: The eligibility criteria listed below are interpreted literally and cannot be waived. All clinical and laboratory data required for determining eligibility of a patient enrolled on this trial must be available in the patient's medical/research record which will serve as the source document for verification at the time of audit.

Inclusion Criteria

3.2.1 Age
< 40 years of age at the time of enrollment

3.2.2 Post-menarchal Menstrual Status
Patient must be a post-menarchal female and report that their initial menstrual period occurred > 6 months prior to enrollment. (Current menstrual status is not part of the inclusion criteria.)

3.2.3 Diagnosis
Newly diagnosed with first cancer, exclusive of breast cancer.

3.2.4 Treatment Plan

3.2.4.1 Planned treatment must include one or more of the following alkylating agents delivered with curative intent: cyclophosphamide, ifosfamide, procarbazine, chlorambucil, carmustine (BCNU), lomustine (CCNU), melphalan, thiotepa, busulfan, nitrogen mustard.

3.2.4.2 For patients < 20 years of age at enrollment, the expected alkylator dose must be ≥ 4 g/m^2 cumulative cyclophosphamide equivalent dose (CED). For patients ≥ 20 years of age at enrollment, any planned alkylator dose is permitted. Eligible patients must receive at least one of the alkylators that contribute to CED.

Equation to calculate cyclophosphamide equivalent dose, CED:
1.0 (cumulative cyclophosphamide dose (mg/m^2)) +
0.244 (cumulative ifosfamide dose (mg/m^2)) +
0.857 (cumulative procarbazine dose (mg/m^2)) +
14.286 (cumulative chlorambucil dose (mg/m^2)) +
15.0 (cumulative carmustine dose (mg/m^2)) +
16.0 (cumulative lomustine dose (mg/m^2)) +
40 (cumulative melphalan dose (mg/m^2)) +
50 (cumulative thiotepa dose (mg/m^2)) +
100 (cumulative nitrogen mustard dose (mg/m^2)) +
8.823 (cumulative busulfan dose (mg/m^2))

Exclusion Criteria

3.2.5 Planned treatment exclusions

3.2.5.1 Any planned radiation to the pelvis; or cranial radiation ≥ 30 Gy to the hypothalamus, inclusive of any total body irradiation (TBI).

3.2.5.2 Planned bilateral oophorectomy.

Note: *A participant's desire to pursue alternative fertility preservation procedures (i.e., embryo, oocyte, or ovarian tissue cryopreservation) will be allowed (and in fact encouraged).*

3.2.6 Pre-existing conditions

3.2.6.1 Congenital syndromes associated with infertility and decreased ovarian reserve at baseline. For example: Turner's Syndrome, Fragile X premutation carriers, Down syndrome, etc.

3.2.6.2 Pre-existing seizure disorder, congenital long QT syndrome, pseudotumor cerebri; history of pulmonary embolism, venous thrombosis, or myocardial infarction.

Note: *Contact study chairs if questions arise about other pre-existing conditions.*

3.2.7 Prior Therapy Exclusions

3.2.7.1 Receipt of long acting (depot) GnRH agonists within 6 months before enrollment. In contrast, subcutaneous GnRH agonist used for oocyte retrieval is not an exclusion; oral and other hormonal contraceptive use is also not an exclusion.

Note: *Please see Section 4.1 for the concomitant therapy restrictions for patients during the study treatment period. See Section 4.5 for information about oral and other hormonal contractive use during the study treatment period.*

3.2.7.2 Prior receipt of systemic chemotherapy. However, steroids and intrathecal chemotherapy are permitted prior to study enrollment.

3.2.7.3 Any prior radiation to the pelvis; or cranial radiation ≥ 30 Gy to the hypothalamus, inclusive of any total body irradiation (TBI).

3.2.8 Pregnancy and Lactation

3.2.8.1 Patients who are pregnant are not eligible. A pregnancy test is required for female patients of childbearing potential.

3.2.8.2 Lactating females who plan to breastfeed their infants for the duration of triptorelin therapy (24 weeks per dose).

3.2.8.3 Sexually active patients of reproductive potential who have not agreed to use an effective contraceptive method for the duration of triptorelin therapy (24 weeks per dose).