

R01

PI:	Title: Ovarian Reserve After Cancer: Longitudinal Effects	
Received: 02/03/2009	FOA: PA07-070	Council: 10/2009
Competition ID: ADOBE-FORMS-A	FOA Title: RESEARCH PROJECT GRANT (PARENT R01)	
	Dual:	Accession Number:
IPF:	Organization:	
Former Number:	Department:	
IRG/SRG:	AIDS: N	Expedited: N
Subtotal Direct Costs (excludes consortium F&A)	Animals: N Humans: Y Clinical Trial: N Current HS Code: 30 HESC: N	New Investigator: Y Early Stage Investigator: Y
Year 1: 396,703		
Year 2: 394,907		
Year 3: 403,886		
Year 4: 451,217		
Year 5: 469,488		
<b>Senior/Key Personnel:</b>		
	<b>Organization:</b>	<b>Role Category:</b>
		PD/PI
		Other (Specify)-Co-Inv./Subcontract PI
		Other (Specify)-Co-Investigator
		Other (Specify)-Co-Investigator

*Appendices*

appendix\_upload\_2, appendix\_upload\_3, appendix\_upload\_1

APPLICATION FOR FEDERAL ASSISTANCE  
SF 424 (R&R)

<b>2. DATE SUBMITTED</b> 02/03/2009		<b>Applicant Identifier</b> [ ]
<b>3. DATE RECEIVED BY STATE</b> [ ]		<b>State Application Identifier</b> [ ]
<b>1. * TYPE OF SUBMISSION</b> <input type="checkbox"/> Pre-application <input checked="" type="checkbox"/> Application <input type="checkbox"/> Changed/Corrected Application		
<b>4. Federal Identifier</b> [ ]		
<b>5. APPLICANT INFORMATION</b> * Organizational DUNS: [ ]		
* Legal Name: [ ]		
Department: [ ]		Division: [ ]
* Street1: [ ]		
Street2: [ ]		
* City: [ ]		County: [ ]
* State: [ ]		Province: [ ]
* Country: [ ] USA: UNITED STATES		* ZIP / Postal Code: 19104-6205
Person to be contacted on matters involving this application		
Prefix: [ ]	* First Name: [ ]	Middle Name: [S]
* Last Name: [ ]	Suffix: [ ]	
* Phone Number: [ ]	Fax Number: [ ]	
Email: [ ]		
<b>6. * EMPLOYER IDENTIFICATION (EIN) or (TIN):</b> [ ]		
<b>7. * TYPE OF APPLICANT:</b> [ ] O: Private Institution of Higher Education		
Other (Specify): [ ]		
Small Business Organization Type <input type="checkbox"/> Women Owned <input type="checkbox"/> Socially and Economically Disadvantaged		
<b>8. * TYPE OF APPLICATION:</b> <input checked="" type="checkbox"/> New <input type="checkbox"/> Resubmission <input type="checkbox"/> Renewal <input type="checkbox"/> Continuation <input type="checkbox"/> Revision		If Revision, mark appropriate box(es). <input type="checkbox"/> A. Increase Award <input type="checkbox"/> B. Decrease Award <input type="checkbox"/> C. Increase Duration <input type="checkbox"/> D. Decrease Duration <input type="checkbox"/> E. Other (specify): [ ]
* Is this application being submitted to other agencies? Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> What other Agencies? [ ]		
<b>9. * NAME OF FEDERAL AGENCY:</b> National Institutes of Health/DHHS		<b>10. CATALOG OF FEDERAL DOMESTIC ASSISTANCE NUMBER:</b> TITLE: Research Project Grant (Parent R01)
<b>11. * DESCRIPTIVE TITLE OF APPLICANT'S PROJECT:</b> [ ]		
<b>12. * AREAS AFFECTED BY PROJECT (cities, counties, states, etc.)</b> N/A	<b>13. PROPOSED PROJECT:</b> * Start Date [ ] * Ending Date [ ]	<b>14. CONGRESSIONAL DISTRICTS OF:</b> a. * Applicant [ ] b. * Project [ ]
<b>15. PROJECT DIRECTOR/PRINCIPAL INVESTIGATOR CONTACT INFORMATION</b>		
Prefix: [ ]	* First Name: [ ]	Middle Name: [R]
* Last Name: [ ]	Suffix: [ ]	
Position/Title: [ ]		
* Organization Name: [ ]		
Department: [ ]		Division: [ ]
* Street1: [ ]		
Street2: [ ]		
* City: [ ]		County: [ ]
* State: [ ]		Province: [ ]
* Country: [ ]		* ZIP / Postal Code: [ ]
* Phone Number: [ ]	Fax Number: [ ]	
* Email: [ ]		

<p><b>16. ESTIMATED PROJECT FUNDING</b></p> <p>a. * Total Estimated Project Funding <input type="text" value="3,246,476.00"/></p> <p>b. * Total Federal &amp; Non-Federal Funds <input type="text" value="3,246,476.00"/></p> <p>c. * Estimated Program Income <input type="text" value="0.00"/></p>	<p><b>17. * IS APPLICATION SUBJECT TO REVIEW BY STATE EXECUTIVE ORDER 12372 PROCESS?</b></p> <p>a. YES <input type="checkbox"/> THIS PREAPPLICATION/APPLICATION WAS MADE AVAILABLE TO THE STATE EXECUTIVE ORDER 12372 PROCESS FOR REVIEW ON: DATE: <input type="text"/></p> <p>b. NO <input checked="" type="checkbox"/> PROGRAM IS NOT COVERED BY E.O. 12372; OR <input type="checkbox"/> PROGRAM HAS NOT BEEN SELECTED BY STATE FOR REVIEW</p>
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**18. By signing this application, I certify (1) to the statements contained in the list of certifications\* and (2) that the statements herein are true, complete and accurate to the best of my knowledge. I also provide the required assurances \* and agree to comply with any resulting terms if I accept an award. I am aware that any false, fictitious, or fraudulent statements or claims may subject me to criminal, civil, or administrative penalties. (U.S. Code, Title 18, Section 1001)**

\* I agree

*\* The list of certifications and assurances, or an Internet site where you may obtain this list, is contained in the announcement or agency specific instructions.*

**19. Authorized Representative**

Prefix:  \* First Name:  Middle Name:

\* Last Name:  Suffix:

\* Position/Title:

\* Organization:

Department:  Division:

\* Street1:

Street2:

\* City:  County:

\* State:  Province:

\* Country:  \* ZIP / Postal Code:

\* Phone Number:  Fax Number:

\* Email:

**\* Signature of Authorized Representative** **\* Date Signed**

**20. Pre-application**

**21. Attach an additional list of Project Congressional Districts if needed.**

OMB Number: 4040-0001  
Expiration Date: 04/30/2008

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**Appendix**

*Number of Attachments in Appendix: 3*

### RESEARCH & RELATED Project/Performance Site Location(s)

#### Project/Performance Site Primary Location

Organization Name:

\* Street1:

Street2:

\* City:  County:

\* State:  Province:

\* Country:  \* ZIP / Postal Code:

#### Project/Performance Site Location 1

Organization Name:

\* Street1:

Street2:

\* City:  County:

\* State:  Province:

\* Country:  \* ZIP / Postal Code:

Additional Location(s)

OMB Number: 4040-0001  
Expiration Date: 04/30/2008

Close Form

Print Page

About

RESEARCH & RELATED Other Project Information

1. \* Are Human Subjects Involved? [X] Yes [ ] No
1.a If YES to Human Subjects
Is the IRB review Pending? [ ] Yes [X] No
IRB Approval Date: 10/30/2008
Exemption Number: [ ] 1 [ ] 2 [ ] 3 [ ] 4 [ ] 5 [ ] 6
Human Subject Assurance Number: [ ]

2. \* Are Vertebrate Animals Used? [ ] Yes [X] No
2.a If YES to Vertebrate Animals
Is the IACUC review Pending? [ ] Yes [ ] No
IACUC Approval Date: [ ]
Animal Welfare Assurance Number [ ]

3. \* Is proprietary/privileged information included in the application? [ ] Yes [X] No
4.a. \* Does this project have an actual or potential impact on the environment? [ ] Yes [X] No
4.b. If yes, please explain: [ ]
4.c. If this project has an actual or potential impact on the environment, has an exemption been authorized or an environmental assessment (EA) or environmental impact statement (EIS) been performed? [ ] Yes [ ] No
4.d. If yes, please explain: [ ]
5.a. \* Does this project involve activities outside the U.S. or partnership with International Collaborators? [ ] Yes [X] No
5.b. If yes, identify countries: [ ]
5.c. Optional Explanation: [ ]

6. \* Project Summary/Abstract abstract.pdf [Add Attachment] [Delete Attachment] [View Attachment]

7. \* Project Narrative projplan.pdf [Add Attachment] [Delete Attachment] [View Attachment]

8. Bibliography & References Cited ref.pdf [Add Attachment] [Delete Attachment] [View Attachment]

9. Facilities & Other Resources Facilities\_Upload.pdf [Add Attachment] [Delete Attachment] [View Attachment]

10. Equipment Major\_Equipment\_Upload.pdf [Add Attachment] [Delete Attachment] [View Attachment]

11. Other Attachments [Add Attachments] [Delete Attachments] [View Attachments] [ ]

OMB Number: 4040-0001
Expiration Date: 04/30/2008

## **ABSTRACT**

Recent diagnostic and therapeutic advances in oncology have led to greater survival rates in children and young adults with malignancies. However, in women, while cancer therapies improve long-term survival, such treatments often lead to premature ovarian failure and infertility related to early ovarian aging. As more young women survive cancer and lead productive lives, these concerns are becoming increasingly important. Nevertheless, it is difficult to predict if and when such problems will arise and what the severity and duration will be. Indeed, there are no early clinical signs of decreased ovarian dysfunction and even young women who maintain cyclic menses after therapy are at high risk of infertility, early menopause, and long-term health problems related to early ovarian failure. While it has recently been observed that hormone and ultrasound measures of ovarian reserve are impaired in long term survivors of cancer, it is not clear whether these measures reflect fertility potential and time to menopause in this population. We have intriguing preliminary data to suggest that childhood and young adult cancer survivors exposed to high risk cancer therapies in their mid 20's have hormone and ultrasound measures of ovarian reserve similar to naturally aging women in their mid 40's. The current proposal represents the first comprehensive and appropriately powered investigation of the acute and long-term reproductive consequences of cancer treatment in adolescent and young women. The proposed aims are 1) to assess acute changes in reproductive function during and after chemotherapy in cancer patients, 2) to assess the long-term reproductive function of women exposed to cancer therapies and make comparisons to similarly aged and late reproductive aged unexposed females and 3) assess for the presence of follicular and luteal dysfunction in cancer survivors by comparing daily urinary hormone metabolites over 2 menstrual cycles between subjects exposed to high dose alkylating agent therapy and 2 unexposed populations of females. The findings of this proposal will help confirm our preliminary findings, and will be critical in estimating the reproductive window in cancer survivors. In addition, this research will expand our knowledge of the effects of cancer therapy and will help to establish a method to predict the impact of chemotherapy prior to treatment. Ultimately, this data will be critical to determine if these measures are useful in predicting the timing and extent of ovarian dysfunction as well as fertility potential in this population and will have a major impact on the quality of life of girls and women who survive cancer.

## **Project Narrative**

Recent diagnostic and therapeutic advances in oncology have led to greater survival rates in children and young adults with malignancies. However, while cancer therapies, especially alkylating agents, improve long-term survival, such treatments often lead to premature ovarian failure and reproductive dysfunction related to early ovarian aging. This proposal will assess the immediate and long-term changes in reproductive function in young females exposed to chemotherapy. The findings of this research will have a major impact on patient counseling and targeting fertility preservation efforts.

## Resources

The clinical programs of the \_\_\_\_\_ are housed in the Hospital of the \_\_\_\_\_, a 760 bed quaternary care center. The \_\_\_\_\_ has dedicated clinical units for outpatient gynecology and obstetrics, family planning, high risk obstetrics and antenatal testing, gynecological oncology, infertility and endocrinology, assisted reproductive technologies and the premenstrual syndrome. The Department has sub-specialist physicians in maternal-fetal medicine, genetics, endocrinology and infertility, and gynecological oncology. Each of these sub-specialty programs has an approved clinical fellowship training program. There are over 40 faculty members within the Department.

The care of women with reproductive/endocrine disorders is centered in the Department's \_\_\_\_\_ and \_\_\_\_\_ marketed under the brand name "\_\_\_\_\_" (\_\_\_\_\_, Director) of which Drs. \_\_\_\_\_ is a member. In the spring of \_\_\_\_\_ Care moved to newly constructed 14,000 sq ft facilities on the campus of the \_\_\_\_\_. This clinical space is complemented and fully integrated with an additional 8,000 sq ft of clinical and laboratory research space. This combined space includes 8 examination rooms, a clinical procedure room equipped with an ultrasound machine, video monitoring and the ability to capture electronic imaging for colposcopy and hysteroscopy. The Division is one of eight members of the NIH-sponsored \_\_\_\_\_ (\_\_\_\_\_, \_\_\_\_\_). Additionally, the Department's Division of \_\_\_\_\_ is an NIH-funded \_\_\_\_\_ and one of the Public Health Service's 6 Centers of Excellence in Women's Health.

The \_\_\_\_\_ Center (\_\_\_\_\_) is a virtual center interacting with faculty and staff via a variety of communication methods including email, phone, shared drives and face to face meetings. The senior staff including Dr \_\_\_\_\_ Director, \_\_\_\_\_, Director of Operations, a Director of Regulator Affairs and an Executive Assistants, are housed in the reproductive research unit (RRU) on the eighth floor of \_\_\_\_\_ adjacent to \_\_\_\_\_. The center interlinks the clinical and translation research with in Department of Obstetrics and Gynecology and is collaborators within other Centers, Institutes and departments with the \_\_\_\_\_. The mission of the \_\_\_\_\_ is to promote collaboration amongst the faculty in the Ob/Gyn Department and around the University to facilitate the conduct of high-quality clinical research in women's health. \_\_\_\_\_ is actively involved as an investigator in the clinical research that occurs in the center. As of 2003, this RRU occupies dedicated space (8000sq ft) adjacent to the clinical and academic offices of the Center for \_\_\_\_\_. The unit also has access to seven transvaginal ultrasound machines used for the purposes of clinical research and patient care at \_\_\_\_\_. In particular, a 5 MHZ real time ultrasound (Sonoline G50, Siemens, Berlin, Germany) is dedicated specifically to clinical research. Clinical researchers within the \_\_\_\_\_ have access to 6 dedicated minus 80 degree freezers, centrifuge, and liquid nitrogen all needed for the processing of clinical specimens. However, we will be requesting resources to be used specifically for this project. The RRU has two Masters-prepared nurse practitioners who specialize in the care of women, 4 full-time research coordinators, a dedicated administrative assistant, and up to 4 additional part-time workers. This dedicated clinical research staff will be available to perform aspects of the project including recruitment, screening, clinical examinations, specimen processing and storage. This staff is also experienced in data management with nine networked, dedicated, PC compatible computers. All computers have internet access. This staff also is experienced in data management. Since its inception, research in the \_\_\_\_\_ has increased dramatically, and more than 1700 women have been recruited into clinical trials. The \_\_\_\_\_ experienced in the collection of clinical specimens from patients to use for research. The \_\_\_\_\_ has conducted more than 35 multi-center trials is currently participating in two NICHD clinical trial networks, (Reproductive Medicine Network and the Contraception Clinical Trials Network) as well 5 NIH sponsored multi-center trials.

The \_\_\_\_\_ of the \_\_\_\_\_ is a national leader in cancer research, patient care, and education. The pre-eminent position of the Cancer Center is reflected in its continuous designation as a Comprehensive Cancer Center by the National Cancer Institute for 30 years, one of 39 such Centers in the United States. The \_\_\_\_\_ is dedicated to innovative and compassionate cancer care. The clinical program, comprised of a dedicated staff of physicians, nurse practitioners, nurses, social workers, physical therapists, nutritionists and patient care coordinators, currently sees over 50,000 outpatient visits, 3400 inpatient admissions, and provides over 24,000 chemotherapy treatments, and more than 65,000 radiation treatments annually.

Several years ago, the \_\_\_\_\_ began the first program in the United States for adult cancer survivors. Its innovative approach to survivorship inspired a multi-year grant from the Lance Armstrong Foundation. The multidisciplinary **LIVESTRONG** Survivorship Center of Excellence at the \_\_\_\_\_ Center of the University of \_\_\_\_\_ is called Living Well After Cancer. This \_\_\_\_\_ program is led by cancer experts who are committed to helping cancer survivors live healthy, productive and happy lives years after a cancer diagnosis. The team is made up of physicians, nurses and other health professionals who work together on clinical, research and education-focused initiatives designed to reduce the long-term physical and emotional effects of cancer and its treatment. \_\_\_\_\_ is the director of this program and is committed to assessing the effects of cancer therapies on the reproductive function of young women in collaboration with the principal investigator,

In addition, the \_\_\_\_\_ is home to the 300 research scientists committed to improving the prevention, diagnosis and treatment of cancer. The Cancer Center enjoys a vibrant, well-funded research base, which continues to grow. The focus of this effort is on reducing cancer incidence, mortality and morbidity in the community while training future cancer researchers and improving our ability to prevent, diagnose and treat cancer. Cancer Center members currently hold over \$145 million in grant funding. Demonstrating the high level of cancer research being conducted at \_\_\_\_\_ the Cancer Center ranks fifth in funding from the National Cancer Institute and fourth in American Cancer Society funding.

**Animal** N/A

### **Computers**

\_\_\_\_\_ office contains PC desktop and laptop computers with Microsoft Office software and internet access. All the computers contain software for databases and statistical analysis. All investigators in the \_\_\_\_\_ Center are on a network allowing local and extramural e-mail communication. A central server provides Medline for literature searches

### **Other**

**The** \_\_\_\_\_ is an NIH funded unit located in the Hospital of the \_\_\_\_\_. Dedicated to facilitating clinical and translational research at \_\_\_\_\_. The \_\_\_\_\_ supports a wide range of clinical research at \_\_\_\_\_ including both inpatient and outpatient clinical research protocols. Apart from the inpatient facilities, a new 2,800 square feet of outpatient space at the \_\_\_\_\_ opened in September 2005. This space is located in \_\_\_\_\_ which is across from the current inpatient \_\_\_\_\_. It includes 5 individual outpatient rooms, exam rooms, and rooms for patient consultation. The \_\_\_\_\_ provides many benefits to investigators who utilize the \_\_\_\_\_ for their protocols including a core laboratory that runs specialized assays for protocols at no additional cost to the investigator. The \_\_\_\_\_ currently supports 152 clinical research protocols under the direction of a total of 74 investigators. The grant that supports the \_\_\_\_\_; the largest NIH grant at the School of Medicine. The \_\_\_\_\_ Core Lab will perform all the serum and urinary assays for this study under the direction of \_\_\_\_\_ the \_\_\_\_\_ is a senior scientist at \_\_\_\_\_ and has set up more than 150 different assays & has published (author or co-author) in more than 70 publications. He has certification from CLIA, State and Federal regulatory agencies. The lab provides full clinical laboratory testing and immunoassays.

The [redacted] ) has been actively involved in clinically- and pharmacologically-oriented research since 1978. As a Type II Center, it is the primary home for epidemiology and biostatistics at the [redacted]. It is an interdisciplinary and interdepartmental program including clinical and non-clinical faculty, fellows, research staff, biostatisticians, and clerical staff. [redacted] core faculty include 27 clinician epidemiologists, 11 non-clinician epidemiologists, 27 biostatisticians, and 1 clinician biostatistician (these totals exclude approximately 120 affiliated faculty). More than 200 full-time research, administrative, and clerical staff support the activities of the faculty. [redacted] research currently receives over \$38M/year in extramural support. Its total budget is approximately \$52M. Many studies in the [redacted] have focused exclusively on women's health issues. The [redacted] and the [redacted] of the [redacted] were awarded an innovative research training program for clinicians in Reproductive Clinical Epidemiology, especially designed to strengthen links between Obstetrics and Gynecology and traditional epidemiology. Dr. [redacted] has been a recipient of this training award and has close ties with the [redacted] as an Associate Scholar.

The [redacted] maintains its research computing environment by using the most current leading-edge technologies available and suitable for its research mission. These technologies are acquired through open-source venues and commercial vendor sources and are maintained in "production quality" configurations. Professional staff at the Clinical Research Computing Unit of the [redacted] have been and will continue to work under the supervision of [redacted] to optimize an adequate database for data entry. The database management and development software that has been standardized for use within the [redacted] for major research projects such as this one is [redacted].

The [redacted] is organized as a Service Center within the Biostatistics Unit of the [redacted] and provides professional MS- and PhD-level biostatistical support for collaborative research projects. The mission of the [redacted] is to provide high quality data analysis for research in the area of health outcomes, clinical trials, genomics, large prescription and diagnostic databases, and observational epidemiological studies. Specifically, these services include: 1) data analysis support, including performing extensive analyses of project data and generating statistical summaries, tables and graphs; 2) statistical programming using various commercially certified statistical software packages such as SAS, S-Plus, Stata, StatXact and SUDAAN; 3) statistical data management support of analytic activities at any stage of a research project, specifically the preparation of analysis files for statistical software packages; and 4) technical report preparation, including the summarization of results and interpretations of statistical analyses of research data. These [redacted] services may stand alone or complement related services provided by biostatistics faculty. As with other service centers, the approved rates for these BAC services are adjusted each year to ensure that there is no accumulating surplus or deficit.

Organizationally, the [redacted] is administered by a three-tier management system. The staff of 16 professionally-trained biostatisticians, 6 SAS programmers, and 2 administrative support staff are directly supervised by Assistant Managers and Technical Group Leaders who also serve as senior biostatisticians on projects. The physical environment of the [redacted] occupies one floor (approximately 5,000 square feet) in the [redacted] complemented by computing hardware and software within the [redacted] computing environment.

In close collaboration with [redacted] a biostatistics faculty member of the [redacted], [redacted] will be responsible for overseeing research analyses for this project.

**Facilities & Other Resources - (Subcontract Site)**

Ample office space and secretarial support are available to \_\_\_\_\_ at The \_\_\_\_\_. There are extensive computer facilities, including state-of-the-art statistical computing software and hardware, and access to patient medical records. The candidate has a private office located in the \_\_\_\_\_ adjacent to both the main \_\_\_\_\_. Her office is equipped with a state-of-the-art computer, printer, and high-speed internet access.

Founded in 1855, \_\_\_\_\_ is the first hospital in the nation, and the second in the world, dedicated solely to the care of children. \_\_\_\_\_ handles more than 15,000 inpatient admissions annually and sees more than 200,000 emergency and outpatient visits each year. The main hospital has 304 beds, 20 percent of which are allocated to intensive care. The Hospital is located on the campus of the \_\_\_\_\_ and is within walking distance of all \_\_\_\_\_ schools, laboratories, and facilities. Although a separate and private entity, \_\_\_\_\_ is an essential and integral component in the university's medical system and is adjacent to \_\_\_\_\_ and the Hospital of the \_\_\_\_\_.

Now named the \_\_\_\_\_ Research Institute, \_\_\_\_\_ has an active and growing research program, with many funded programs and clinical centers for children with special health care needs. \_\_\_\_\_ has the second largest NIH-sponsored research budget among pediatric hospitals in the USA and the seventh largest of any hospital in the country. Annual support for \_\_\_\_\_ investigators totals more than \$46 million, with a substantial amount of the funding coming from the National Institutes of Health.

**Division**

Approximately 400 new patients with cancer or related diseases were admitted to the Unit at \_\_\_\_\_ in 2007. \_\_\_\_\_ treats approximately 80 percent of all children with cancer in the greater \_\_\_\_\_ region. Comprised of a 34-bed inpatient unit, an outpatient clinic and day hospital, three community-based facilities, and a dedicated bone marrow transplant unit, the Division of Oncology is a highly-specialized national and international resource for the care of infants, children and adolescents diagnosed with malignant diseases.

**Cancer Survivorship Program**

\_\_\_\_\_ is one of the largest providers of services for children with cancer. The \_\_\_\_\_, which sees over 500 patients/year, was established to improve the health and well-being of survivors and to educate patients and health care professionals about the long-term effects of cancer treatment. Access to this patient population in an academic, clinical setting allows our program to successfully measure and study the late effects of childhood cancer survivors.

**Office/Computer**

Ample office space and secretarial support are available to \_\_\_\_\_. There are extensive computer facilities, including state-of-the-art statistical computing software and hardware, and access to patient medical records. The PI has a 125 sq. foot office located in the \_\_\_\_\_ adjacent to both the main \_\_\_\_\_ and the Pediatric basic science building. \_\_\_\_\_ office is equipped with a Mac tower computer, laser printer, and high-speed internet access.

**EQUIPMENT****Ultrasounds:**

The Reproductive Research Unit has access to seven ultrasound machines with transvaginal and transabdominal probes used for the purposes of clinical research and patient care at . In particular, a 5 MHZ real time ultrasound (Sonoline G50, Siemens, Berlin, Germany) is dedicated specifically to clinical research. Another ultrasound machine with transvaginal and transabdominal probes (Sonoline G20) has been placed in the Division of at the of the specifically for this study.

**Other Equipment:**

Clinical researchers within the have access to 6 dedicated minus 80 degree freezers, centrifuge, and liquid nitrogen all needed for the processing of clinical specimens.

**CTRC CORE LAB EQUIPMENT**

EQUIPMENT	MAKE	MODEL	SERIAL #
Aggrometer	BioData	PAP-4	70847-01-04
Aggrometer	BioData	PAP-4	71023
Centrifuge	Fisher	6K	50200016
Centrifuge (Refrigerated))	Sorvall	RT7	9803067
Centrifuge (Micro)	Eppendorf	5424	0005275
Coulter	Beckman Coulter	39	Z040263
Flame Photometer	Instrument Laboratory	943	3079
Freezer	Revco	ULT2186-7D12	N29F290300- NF
Freezer	Revco	ULT2186-7DUA	NA 38077B
Freezer	Revco	ULT2186	Z18B130490ZB
Freezer	Revco	ULT1186	017R228920PR
Gamma Counter	LKW Wallac	1272	720706
Glucose Analyzer	YSI	2300	0210051AA
Glucose Analyzer	YSI	1500 Sidekick	94C15778
HPLC	Shimadzu	PDA,EC,Flourance detectors	
Ice maker	Scotsman		
Immulite	DPC	Immulite	J4272
Lyophilizer w/ speed vac	Centrivap	Labcon	239373
Multiplex	Linco	Luminex	LX10004317301
Sample Evaporator	Zymark	TurboVap-LV	TV9853N8552
PCR	Techne	FGENO5TP	104934-02
Plate Reader	BioTek	ELX808	194201
Plate Shaker	IKA	MT 2/4	3230137
Plate Washer	Dynex	MRW	GB3101
Scintillation Counter	Wallac	1409	
Spectrometer	Barnstead	SM110245	1102041237064
Tube Rotator	Glas-col	099A RD4512	381266
Vacuum Manifold	Fisher	60104-233	
Water Bath	Thermo	2835	202411-432

## RESEARCH & RELATED Senior/Key Person Profile (Expanded)

PROFILE - Project Director/Principal Investigator			
Prefix:	* First Name:	Middle Name:	
* Last Name:		Suffix:	
Position/Title:	Department:	- OB-Obstetrics and Gynec	
Organization Name:	Division:		
* Street1:			
Street2:			
* City:	County:		
* State:	Province:		
* Country:	* Zip / Postal Code:		
* Phone Number:	Fax Number:		
* E-Mail:			
Credential, e.g., agency login:			
* Project Role:	Other Project Role Category:		
* Attach Biographical Sketch	Bio_ .pdf	Add Attachment	Delete Attachment View Attachment
Attach Current & Pending Support		Add Attachment	Delete Attachment View Attachment

PROFILE - Senior/Key Person 1			
Prefix:	* First Name:	Middle Name:	
* Last Name:		Suffix:	
Position/Title:	Department:		
Organization Name:	Division:		
* Street1:			
Street2:			
* City:	County:		
* State:	Province:		
* Country:	* Zip / Postal Code:		
* Phone Number:	Fax Number:		
* E-Mail:			
Credential, e.g., agency login:			
* Project Role:	Other (Specify)	Other Project Role Category: Co-Inv./Subcontract PI	
* Attach Biographical Sketch	Bio_DR .pdf	Add Attachment	Delete Attachment View Attachment
Attach Current & Pending Support		Add Attachment	Delete Attachment View Attachment

## RESEARCH & RELATED Senior/Key Person Profile (Expanded)

PROFILE - Senior/Key Person 2			
Prefix:	* First Name:	Middle Name:	
* Last Name:		Suffix:	
Position/Title:	Department:		
Organization Name:	Division:		
* Street1:			
Street2:			
* City:	County:		
* State:	Province:		
* Country:	* Zip / Postal Code:		
* Phone Number:	Fax Number:		
* E-Mail:			
Credential, e.g., agency login:			
* Project Role:	Other (Specify)	Other Project Role Category:	
* Attach Biographical Sketch	Bio	Phd, R	<input type="button" value="Add Attachment"/> <input type="button" value="Delete Attachment"/> <input type="button" value="View Attachment"/>
Attach Current & Pending Support			<input type="button" value="Add Attachment"/> <input type="button" value="Delete Attachment"/> <input type="button" value="View Attachment"/>

PROFILE - Senior/Key Person 3			
Prefix:	* First Name:	Middle Name:	
* Last Name:		Suffix:	
Position/Title:	Department:		
Organization Name:	Division:		
* Street1:			
Street2:			
* City:	County:		
* State:	Province:		
* Country:	* Zip / Postal Code:		
* Phone Number:	Fax Number:		
* E-Mail:			
Credential, e.g., agency login:			
* Project Role:	Other (Specify)	Other Project Role Category:	Co-Investigator
* Attach Biographical Sketch	Bio	ScD_3.pdf	<input type="button" value="Add Attachment"/> <input type="button" value="Delete Attachment"/> <input type="button" value="View Attachment"/>
Attach Current & Pending Support			<input type="button" value="Add Attachment"/> <input type="button" value="Delete Attachment"/> <input type="button" value="View Attachment"/>

ADDITIONAL SENIOR/KEY PERSON PROFILE(S)

	<input type="button" value="Add Attachment"/>	<input type="button" value="Delete Attachment"/>	<input type="button" value="View Attachment"/>
--	---	--	--

Additional Biographical Sketch(es) (Senior/Key Person)

	<input type="button" value="Add Attachment"/>	<input type="button" value="Delete Attachment"/>	<input type="button" value="View Attachment"/>
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Additional Current and Pending Support(s)

	<input type="button" value="Add Attachment"/>	<input type="button" value="Delete Attachment"/>	<input type="button" value="View Attachment"/>
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**BIOGRAPHICAL SKETCH**

Provide the following information for the key personnel and other significant contributors in the order listed on Form Page 2.  
Follow this format for each person. **DO NOT EXCEED FOUR PAGES.**

NAME		POSITION TITLE	
eRA COMMONS USER NAME			
EDUCATION/ TRAINING <i>(Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)</i>			
INSTITUTION AND LOCATION	DEGREE <i>(if applicable)</i>	YEAR(s)	FIELD OF STUDY
	B.A. M.D. M.S.C.E.		Spanish Medicine Clinical Epidemiology

**A. Positions and Honors.**Research and Professional ExperienceAwards and Honors**B. Selected peer-reviewed publications (in chronological order).**

Principal Investigator/Program Director (Last, first, middle):

Principal Investigator/Program Director (Last, first, middle):

Principal Investigator/Program Director (Last, first, middle):

**C. Research Support.**  
**Ongoing Research Support**

**Completed Research Support**

**BIOGRAPHICAL SKETCH**

Provide the following information for the key personnel and other significant contributors in the order listed on Form Page 2.  
Follow this format for each person. **DO NOT EXCEED FOUR PAGES.**

NAME		POSITION TITLE	
eRA COMMONS USER NAME			
EDUCATION/TRAINING <i>(Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)</i>			
INSTITUTION AND LOCATION	DEGREE <i>(if applicable)</i>	YEAR(s)	FIELD OF STUDY
	B.S. M.D.		Biology Medicine

**A. Positions and Honors.**  
**Professional Experience:**

**Fellowships:**

**Honors and Awards:**

**B. Selected peer-reviewed publications (in chronological order).**

Principal Investigator/Program Director (Last, first, middle):

Principal Investigator/Program Director (Last, first, middle):

**C. Research Support**

**Ongoing Research Support**

**BIOGRAPHICAL SKETCH**

Provide the following information for the key personnel in the order listed for Form Page 2.  
Follow the sample format for each person. **DO NOT EXCEED FOUR PAGES.**

NAME	POSITION TITLE
------	----------------

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)*

INSTITUTION AND LOCATION	DEGREE <i>(if applicable)</i>	YEAR(s)	FIELD OF STUDY
	Diploma		Nursing
	BSN		Nursing
	MS		Community Health
	NP Certificate		Adult Oncology
	PhD		Nursing Science/Genetics

**A. Positions and Honors**

Positions and Employment

Principal Investigator/Program Director (Last, first, middle):

**B. Selected peer-reviewed publications (in chronological order-last 10 years).**

Principal Investigator/Program Director (Last, first, middle):

**C. Research Support**  
Other Support

**BIOGRAPHICAL SKETCH**

Provide the following information for the key personnel and other significant contributors in the order listed on Form Page 2.  
 Follow this format for each person. **DO NOT EXCEED FOUR PAGES.**

NAME		POSITION TITLE	
eRA COMMONS USER NAME (credential, e.g., agency login)			
EDUCATION/TRAINING <i>(Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)</i>			
INSTITUTION AND LOCATION	DEGREE <i>(if applicable)</i>	YEAR(s)	FIELD OF STUDY
	BA		Statistics
	MA		Applied Statistics
	Sc.D.		Biostatistics

**A. Positions and Honors.**  
Positions and Employment

Other Experience and Professional Memberships

Honors

Principal Investigator/Program Director (Last, first, middle):

**B. Selected peer-reviewed publications (in chronological order).**

Principal Investigator/Program Director (Last, first, middle):

**C. Research Support.**  
**Ongoing Research Support**

Principal Investigator/Program Director (Last, first, middle):

**RESEARCH & RELATED BUDGET - SECTION A & B, BUDGET PERIOD 1**

\* ORGANIZATIONAL DUNS: [ ]

\* Budget Type:  Project     Subaward/Consortium

Enter name of Organization: [ ]

Delete Entry    \* Start Date: [ ]    \* End Date: [ ]    Budget Period 1

**A. Senior/Key Person**

Prefix	* First Name	Middle Name	* Last Name	Suffix	* Project Role	Base Salary (\$)	Cal. Months	Acad. Months	Sum. Months	* Requested Salary (\$)	* Fringe Benefits (\$)	* Funds Requested (\$)	
1.						190,846.00	3.60			57,254.00	16,718.00	73,972.00	
2.						139,580.00	1.20			13,958.00	4,076.00	18,034.00	
3.						122,048.00	0.24			2,441.00	713.00	3,154.00	
4.													
5.													
6.													
7.													
8.													
<b>9. Total Funds requested for all Senior Key Persons in the attached file</b>													
<b>Additional Senior Key Persons:</b>											<b>Total Senior/Key Person</b>		95,160.00

Add Attachment    Delete Attachment    View Attachment

**B. Other Personnel**

* Number of Personnel	* Project Role	Cal. Months	Acad. Months	Sum. Months	* Requested Salary (\$)	* Fringe Benefits (\$)	* Funds Requested (\$)	
	Post Doctoral Associates							
	Graduate Students							
	Undergraduate Students							
	Secretarial/Clerical							
1	Core Lab Director	1.80			17,104.00	4,994.00	22,098.00	
1	Project Manager	0.90			8,758.00	2,557.00	11,315.00	
1	Research Nurse Coordin	0.00			59,745.00	17,445.00	77,190.00	
4	Technician	13.20			41,512.00	12,122.00	53,634.00	
1	Data Establishment/Ent	0.00			8,000.00	2,336.00	10,336.00	
<b>Total Number Other Personnel</b>							<b>Total Other Personnel</b>	174,573.00
8							<b>Total Salary, Wages and Fringe Benefits (A+B)</b>	269,733.00

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RESEARCH & RELATED BUDGET - SECTION C, D, & E, BUDGET PERIOD 1

\* ORGANIZATIONAL DUNS: [ ]

\* Budget Type:  Project  Subaward/Consortium

Enter name of Organization: [ ]

Delete Entry

\* Start Date: [ ] \* End Date: [ ] Budget Period 1

C. Equipment Description

List items and dollar amount for each item exceeding \$5,000

	Equipment item	* Funds Requested (\$)
1.	Freezer (-80)	7,000.00
2.	[ ]	[ ]
3.	[ ]	[ ]
4.	[ ]	[ ]
5.	[ ]	[ ]
6.	[ ]	[ ]
7.	[ ]	[ ]
8.	[ ]	[ ]
9.	[ ]	[ ]
10.	[ ]	[ ]
11.	Total funds requested for all equipment listed in the attached file	[ ]
	Total Equipment	7,000.00

Additional Equipment: [ ]

Add Attachment

Delete Attachment

View Attachment

D. Travel

Funds Requested (\$)

1.	Domestic Travel Costs ( Incl. Canada, Mexico and U.S. Possessions)	4,000.00
2.	Foreign Travel Costs	[ ]
	Total Travel Cost	4,000.00

E. Participant/Trainee Support Costs

Funds Requested (\$)

1.	Tuition/Fees/Health Insurance	[ ]
2.	Stipends	[ ]
3.	Travel	[ ]
4.	Subsistence	[ ]
5.	Other [ ]	[ ]
[ ]	Number of Participants/Trainees	Total Participant/Trainee Support Costs [ ]

RESEARCH & RELATED Budget {C-E} (Funds Requested)

OMB Number: 4040-0001  
Expiration Date: 04/30/2008

RESEARCH & RELATED BUDGET - SECTION F-K, BUDGET PERIOD 1

\* ORGANIZATIONAL DUNS: [ ]

\* Budget Type:  Project  Subaward/Consortium

Enter name of Organization: [ ]

Delete Entry Start Date: [ ] \* End Date: [ ] Budget Period 1

F. Other Direct Costs	Funds Requested (\$)
1. Materials and Supplies	10,235.00
2. Publication Costs	[ ]
3. Consultant Services	[ ]
4. ADP/Computer Services	[ ]
5. Subawards/Consortium/Contractual Costs	41,051.00
6. Equipment or Facility Rental/User Fees	[ ]
7. Alterations and Renovations	[ ]
8. Other Costs	46,047.00
9. Outpatient Costs	34,733.00
10. [ ]	[ ]
<b>Total Other Direct Costs</b>	<b>132,066.00</b>

G. Direct Costs	Funds Requested (\$)
<b>Total Direct Costs (A thru F)</b>	<b>412,799.00</b>

H. Indirect Costs	Indirect Cost Type	Indirect Cost Rate (%)	Indirect Cost Base (\$)	* Funds Requested (\$)
1.	Research	57.50	355,015.00	204,134.00
2.	[ ]	[ ]	[ ]	[ ]
3.	[ ]	[ ]	[ ]	[ ]
4.	[ ]	[ ]	[ ]	[ ]
<b>Total Indirect Costs</b>				<b>204,134.00</b>

Cognizant Federal Agency [ ] -9  
(Agency Name, POC Name, and POC Phone Number)

I. Total Direct and Indirect Costs	Funds Requested (\$)
<b>Total Direct and Indirect Institutional Costs (G + H)</b>	<b>616,933.00</b>

J. Fee Funds Requested (\$) [ ]

K. \* Budget Justification budget\_justification\_per1.pdf Add Attachment Delete Attachment View Attachment  
(Only attach one file.)

**RESEARCH & RELATED BUDGET - SECTION A & B, BUDGET PERIOD 2**

\* ORGANIZATIONAL DUNS: \_\_\_\_\_

\* Budget Type:  Project     Subaward/Consortium

Enter name of Organization: \_\_\_\_\_

Delete Entry    \* Start Date: \_\_\_\_\_    \* End Date: \_\_\_\_\_    Budget Period 2

A. Senior/Key Person		Prefix	* First Name	Middle Name	* Last Name	Suffix	* Project Role	Base Salary (\$)	Cal. Months	Acad. Months	Sum. Months	* Requested Salary (\$)	* Fringe Benefits (\$)	* Funds Requested (\$)
1.								196,571.00	3.60			58,971.00	17,220.00	76,191.00
2.								143,767.00	1.20			14,377.00	4,198.00	18,575.00
3.								125,709.00	0.24			2,514.00	734.00	3,248.00
4.														
5.														
6.														
7.														
8.														
9. Total Funds requested for all Senior Key Persons in the attached file													Total Senior/Key Person	98,014.00

Additional Senior Key Persons: \_\_\_\_\_    Add Attachment    Delete Attachment    View Attachment

B. Other Personnel		* Number of Personnel	Project Role	Cal. Months	Acad. Months	Sum. Months	* Requested Salary (\$)	* Fringe Benefits (\$)	* Funds Requested (\$)
			Post Doctoral Associates						
			Graduate Students						
			Undergraduate Students						
			Secretarial/Clerical						
1			Core Lab Director	1.80			17,617.00	5,144.00	22,761.00
1			Project Manager	0.90			9,021.00	2,634.00	11,655.00
1			Research Nurse Coordin	0.00			61,537.00	17,969.00	79,506.00
4			Technician	13.20			42,758.00	12,485.00	55,243.00
1			Data Establishment/Ent	0.00			8,240.00	2,406.00	10,646.00
Total Number Other Personnel									179,811.00
Total Salary, Wages and Fringe Benefits (A+B)									277,825.00

RESEARCH & RELATED BUDGET - SECTION C, D, & E, BUDGET PERIOD 2

\* ORGANIZATIONAL DUNS: [ ]

\* Budget Type:  Project  Subaward/Consortium

Enter name of Organization: [ ]

Delete Entry \* Start Date: [ ] \* End Date: [ ] Budget Period 2

C. Equipment Description

List items and dollar amount for each item exceeding \$5,000

	Equipment Item	* Funds Requested (\$)
1.	[ ]	[ ]
2.	[ ]	[ ]
3.	[ ]	[ ]
4.	[ ]	[ ]
5.	[ ]	[ ]
6.	[ ]	[ ]
7.	[ ]	[ ]
8.	[ ]	[ ]
9.	[ ]	[ ]
10.	[ ]	[ ]
11.	Total funds requested for all equipment listed in the attached file	[ ]
	Total Equipment	[ ]

Additional Equipment: [ ] Add Attachment Delete Attachment View Attachment

D. Travel

Funds Requested (\$)

1.	Domestic Travel Costs ( Incl. Canada, Mexico and U.S. Possessions)	4,120.00
2.	Foreign Travel Costs	[ ]
	Total Travel Cost	4,120.00

E. Participant/Trainee Support Costs

Funds Requested (\$)

1.	Tuition/Fees/Health Insurance	[ ]
2.	Stipends	[ ]
3.	Travel	[ ]
4.	Subsistence	[ ]
5.	Other [ ]	[ ]
[ ]	Number of Participants/Trainees	Total Participant/Trainee Support Costs [ ]

RESEARCH & RELATED Budget {C-E} (Funds Requested)

OMB Number: 4040-0001 Expiration Date: 04/30/2008

RESEARCH & RELATED BUDGET - SECTION F-K, BUDGET PERIOD 2

\* ORGANIZATIONAL DUNS: [ ]

\* Budget Type:  Project  Subaward/Consortium

Enter name of Organization: [ ]

Delete Entry Start Date: [ ] \* End Date: [ ] Budget Period 2

F. Other Direct Costs	Funds Requested (\$)
1. Materials and Supplies	4,053.00
2. Publication Costs	[ ]
3. Consultant Services	[ ]
4. ADP/Computer Services	[ ]
5. Subawards/Consortium/Contractual Costs	42,283.00
6. Equipment or Facility Rental/User Fees	[ ]
7. Alterations and Renovations	[ ]
8. Other Costs	47,430.00
9. Outpatient Costs	35,775.00
10. [ ]	[ ]
<b>Total Other Direct Costs</b>	<b>129,541.00</b>

G. Direct Costs	Funds Requested (\$)
<b>Total Direct Costs (A thru F)</b>	<b>411,486.00</b>

H. Indirect Costs	Indirect Cost Type	Indirect Cost Rate (%)	Indirect Cost Base (\$)	* Funds Requested (\$)
1.	Research	57.50	333,427.00	191,720.00
2.	[ ]	[ ]	[ ]	[ ]
3.	[ ]	[ ]	[ ]	[ ]
4.	[ ]	[ ]	[ ]	[ ]
<b>Total Indirect Costs</b>				<b>191,720.00</b>

Cognizant Federal Agency DHHS, Dr. [ ]  
(Agency Name, POC Name, and POC Phone Number)

I. Total Direct and Indirect Costs	Funds Requested (\$)
<b>Total Direct and Indirect Institutional Costs (G + H)</b>	<b>603,206.00</b>

J. Fee Funds Requested (\$) [ ]

K. \* Budget Justification budget\_justification\_per1.pdf Add Attachment Delete Attachment View Attachment  
(Only attach one file.)

Previous Period

RESEARCH & RELATED BUDGET - SECTION A & B, BUDGET PERIOD 3

\* ORGANIZATIONAL DUNS: [ ]

\* Budget Type:  Project  Subaward/Consortium

Enter name of Organization: [ ]

\* Start Date: [ ] \* End Date: [ ] Budget Period 3

Delete Entry

A. Senior/Key Person

Prefix	* First Name	Middle Name	* Last Name	Suffix	* Project Role	Base Salary (\$)	Cal. Months	Acad. Months	Sum. Months	* Requested Salary (\$)	* Fringe Benefits (\$)	* Funds Requested (\$)
1.						196,700.00	3.60			59,010.00	17,231.00	76,241.00
2.						148,080.00	1.20			14,808.00	4,324.00	19,132.00
3.						129,481.00	0.24			2,590.00	756.00	3,346.00
4.												
5.												
6.												
7.												
8.												
<b>Total Senior/Key Person</b>											98,719.00	

9. Total Funds requested for all Senior Key Persons in the attached file

Additional Senior Key Persons: [ ]

Add Attachment

Delete Attachment

View Attachment

B. Other Personnel

* Number of Personnel	* Project Role	Cal. Months	Acad. Months	Sum. Months	* Requested Salary (\$)	* Fringe Benefits (\$)	* Funds Requested (\$)
	Post Doctoral Associates						
	Graduate Students						
	Undergraduate Students						
	Secretarial/Clerical						
1	Core Lab Director	1.80			18,145.00	5,298.00	23,443.00
1	Project Manager	0.90			9,291.00	2,713.00	12,004.00
1	Research Nurse Coordin	0.00			63,384.00	18,508.00	81,892.00
4	Technician	13.20			44,040.00	12,860.00	56,900.00
1	Data Establishment/Ent	0.00			8,487.00	2,478.00	10,965.00
<b>Total Other Personnel</b>							185,204.00
<b>Total Salary, Wages and Fringe Benefits (A+B)</b>							283,923.00

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RESEARCH & RELATED BUDGET - SECTION C, D, & E, BUDGET PERIOD 3

\* ORGANIZATIONAL DUNS: [ ]

\* Budget Type:  Project  Subaward/Consortium

Enter name of Organization: [ ]

Delete Entry \* Start Date: [ ] End Date: [ ] Budget Period 3

C. Equipment Description

List items and dollar amount for each item exceeding \$5,000

	Equipment item	* Funds Requested (\$)
1.	[ ]	[ ]
2.	[ ]	[ ]
3.	[ ]	[ ]
4.	[ ]	[ ]
5.	[ ]	[ ]
6.	[ ]	[ ]
7.	[ ]	[ ]
8.	[ ]	[ ]
9.	[ ]	[ ]
10.	[ ]	[ ]
11.	Total funds requested for all equipment listed in the attached file	[ ]
	Total Equipment	[ ]

Additional Equipment: [ ]

Add Attachment Delete Attachment View Attachment

D. Travel

Funds Requested (\$)

1.	Domestic Travel Costs ( Incl. Canada, Mexico and U.S. Possessions)	4,244.00
2.	Foreign Travel Costs	[ ]
	Total Travel Cost	4,244.00

E. Participant/Trainee Support Costs

Funds Requested (\$)

1.	Tuition/Fees/Health Insurance	[ ]
2.	Stipends	[ ]
3.	Travel	[ ]
4.	Subsistence	[ ]
5.	Other [ ]	[ ]
[ ]	Number of Participants/Trainees	Total Participant/Trainee Support Costs [ ]

RESEARCH & RELATED Budget {C-E} (Funds Requested)

OMB Number: 4040-0001 Expiration Date: 04/30/2008

RESEARCH & RELATED BUDGET - SECTION F-K, BUDGET PERIOD 3

\* ORGANIZATIONAL DUNS: [ ]

\* Budget Type:  Project  Subaward/Consortium

Enter name of Organization: [ ]

Delete Entry Start Date: [ ] \* End Date: [ ] Budget Period 3

F. Other Direct Costs

Funds Requested (\$)

1. Materials and Supplies	4,175.00
2. Publication Costs	
3. Consultant Services	
4. ADP/Computer Services	
5. Subawards/Consortium/Contractual Costs	42,512.00
6. Equipment or Facility Rental/User Fees	
7. Alterations and Renovations	
8. Other Costs	48,853.00
9. Outpatient Costs	36,848.00
10. [ ]	
<b>Total Other Direct Costs</b>	<b>132,388.00</b>

G. Direct Costs

Funds Requested (\$)

Total Direct Costs (A thru F) 420,555.00

H. Indirect Costs

Indirect Cost Type	Indirect Cost Rate (%)	Indirect Cost Base (\$)	* Funds Requested (\$)
1. Research	57.50	341,194.00	196,187.00
2. [ ]			
3. [ ]			
4. [ ]			
<b>Total Indirect Costs</b>			<b>196,187.00</b>

Cognizant Federal Agency DHHS, Dr. [ ]  
(Agency Name, POC Name, and POC Phone Number)

I. Total Direct and Indirect Costs

Funds Requested (\$)

Total Direct and Indirect Institutional Costs (G + H) 616,742.00

J. Fee

Funds Requested (\$)

[ ]

K. \* Budget Justification budget\_justification\_per1.pdf  
(Only attach one file.)

Add Attachment Delete Attachment View Attachment

Previous Period

RESEARCH & RELATED BUDGET - SECTION A & B, BUDGET PERIOD 4

\* ORGANIZATIONAL DUNS: \_\_\_\_\_

\* Budget Type:  Project     Subaward/Consortium

Enter name of Organization: \_\_\_\_\_

Delete Entry    \* Start Date: \_\_\_\_\_    End Date: \_\_\_\_\_    Budget Period 4

A. Senior/Key Person

Prefix	* First Name	Middle Name	* Last Name	Suffix	* Project Role	Base Salary (\$)	Cal. Months	Acad. Months	Sum. Months	* Requested Salary (\$)	* Fringe Benefits (\$)	* Funds Requested (\$)
1.					ED/PI	196,700.00	3.60			59,010.00	17,231.00	76,241.00
2.					Co-Investigator	152,523.00	1.20			15,252.00	4,454.00	19,706.00
3.					Co-Investigator	133,365.00	0.24			2,667.00	779.00	3,446.00
4.												
5.												
6.												
7.												
8.												
<b>Total Senior/Key Person</b>											99,393.00	

9. Total Funds requested for all Senior Key Persons in the attached file

Additional Senior Key Persons: \_\_\_\_\_ [View Attachment](#) [Delete Attachment](#) [Add Attachment](#)

B. Other Personnel

* Number of Personnel	* Project Role	Cal. Months	Acad. Months	Sum. Months	* Requested Salary (\$)	* Fringe Benefits (\$)	* Funds Requested (\$)
	Post Doctoral Associates						
	Graduate Students						
	Undergraduate Students						
	Secretarial/Clerical						
1	Core Lab Director	1.80			18,690.00	5,457.00	24,147.00
1	Project Manager	0.90			9,570.00	2,794.00	12,364.00
1	Research Nurse Coordin	0.00			65,285.00	19,063.00	84,348.00
4	Technician	13.20			45,361.00	13,246.00	58,607.00
1	Data Establishment/Ent	0.00			8,742.00	2,553.00	11,295.00
<b>Total Other Personnel</b>							190,761.00
<b>Total Salary, Wages and Fringe Benefits (A+B)</b>							290,154.00

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RESEARCH & RELATED BUDGET - SECTION C, D, & E, BUDGET PERIOD 4

\* ORGANIZATIONAL DUNS: [ ]

\* Budget Type:  Project  Subaward/Consortium

Enter name of Organization: [ ]

Delete Entry \* Start Date: [ ] \* End Date: [ ] Budget Period 4

C. Equipment Description

List items and dollar amount for each item exceeding \$5,000

	Equipment Item	* Funds Requested (\$)	
1.	[ ]	[ ]	
2.	[ ]	[ ]	
3.	[ ]	[ ]	
4.	[ ]	[ ]	
5.	[ ]	[ ]	
6.	[ ]	[ ]	
7.	[ ]	[ ]	
8.	[ ]	[ ]	
9.	[ ]	[ ]	
10.	[ ]	[ ]	
11.	Total funds requested for all equipment listed in the attached file		[ ]
	Total Equipment		[ ]

Additional Equipment: [ ] [Add Attachment](#) [Delete Attachment](#) [View Attachment](#)

D. Travel

	Funds Requested (\$)
1. Domestic Travel Costs ( Incl. Canada, Mexico and U.S. Possessions)	4,371.00
2. Foreign Travel Costs	[ ]
<b>Total Travel Cost</b>	4,371.00

E. Participant/Trainee Support Costs

	Funds Requested (\$)
1. Tuition/Fees/Health Insurance	[ ]
2. Stipends	[ ]
3. Travel	[ ]
4. Subsistence	[ ]
5. Other [ ]	[ ]
[ ] Number of Participants/Trainees	Total Participant/Trainee Support Costs [ ]

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RESEARCH & RELATED BUDGET - SECTION F-K, BUDGET PERIOD 4

Next Period

\* ORGANIZATIONAL DUNS: [ ]

\* Budget Type:  Project  Subaward/Consortium

Enter name of Organization: [ ]

Delete Entry

Start Date: [ ] \* End Date: [ ] Budget Period 4

F. Other Direct Costs

Funds Requested (\$)

1. Materials and Supplies	4,300.00
2. Publication Costs	
3. Consultant Services	
4. ADP/Computer Services	
5. Subawards/Consortium/Contractual Costs	43,788.00
6. Equipment or Facility Rental/User Fees	
7. Alterations and Renovations	
8. Other Costs	87,821.00
9. Outpatient Costs	37,953.00
10.	

Total Other Direct Costs 173,862.00

G. Direct Costs

Funds Requested (\$)

Total Direct Costs (A thru F) 468,387.00

H. Indirect Costs

Indirect Cost Type	Indirect Cost Rate (%)	Indirect Cost Base (\$)	* Funds Requested (\$)
1. Research	57.50	386,645.00	222,321.00
2.			
3.			
4.			
Total Indirect Costs			222,321.00

Cognizant Federal Agency DHHS, Dr.

(Agency Name, POC Name, and POC Phone Number)

I. Total Direct and Indirect Costs

Funds Requested (\$)

Total Direct and Indirect Institutional Costs (G + H) 690,708.00

J. Fee

Funds Requested (\$)

K. \* Budget Justification budget\_justification\_per1.pdf

Add Attachment

Delete Attachment

View Attachment

(Only attach one file.)

Previous Period

RESEARCH & RELATED BUDGET - SECTION A & B, BUDGET PERIOD 5

\* ORGANIZATIONAL DUNS: \_\_\_\_\_

\* Budget Type:  Project     Subaward/Consortium

Enter name of Organization: \_\_\_\_\_

Delete Entry    \* Start Date: \_\_\_\_\_    \* End Date: \_\_\_\_\_    Budget Period 5

A. Senior/Key Person

Prefix	* First Name	Middle Name	* Last Name	Suffix	* Project Role	Base Salary (\$)	Cal. Months	Acad. Months	Sum. Months	* Requested Salary (\$)	* Fringe Benefits (\$)	* Funds Requested (\$)
1.					PD/PI	196,700.00	3.60			59,010.00	17,231.00	76,241.00
2.					Co-Investigator	157,099.00	1.20			15,710.00	4,587.00	20,297.00
3.					Co-Investigator	137,366.00	0.24			2,747.00	802.00	3,549.00
4.												
5.												
6.												
7.												
8.												
<b>Total Senior/Key Person</b>											100,087.00	

9. Total Funds requested for all Senior Key Persons in the attached file

Additional Senior Key Persons: \_\_\_\_\_

Add Attachment    Delete Attachment    View Attachment

B. Other Personnel

* Number of Personnel	* Project Role	Cal. Months	Acad. Months	Sum. Months	* Requested Salary (\$)	* Fringe Benefits (\$)	* Funds Requested (\$)
	Post Doctoral Associates						
	Graduate Students						
	Undergraduate Students						
	Secretarial/Clerical						
1	Core Lab Director	1.80			19,250.00	5,621.00	24,871.00
1	Project Manager	0.90			9,857.00	2,878.00	12,735.00
1	Research Nurse Coordin	0.00			67,244.00	19,635.00	86,879.00
4	Technician	13.20			46,722.00	13,642.00	60,364.00
1	Data Establishment/Ent	0.00			9,004.00	2,629.00	11,633.00
<b>Total Other Personnel</b>							196,482.00
<b>Total Salary, Wages and Fringe Benefits (A+B)</b>							296,569.00

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Next

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RESEARCH & RELATED BUDGET - SECTION C, D, & E, BUDGET PERIOD 5

\* ORGANIZATIONAL DUNS: [ ]

\* Budget Type:  Project  Subaward/Consortium

Enter name of Organization: [ ]

Delete Entry \* Start Date: [ ] \* End Date: [ ] Budget Period 5

C. Equipment Description

List items and dollar amount for each item exceeding \$5,000

	Equipment Item	* Funds Requested (\$)
1.	[ ]	[ ]
2.	[ ]	[ ]
3.	[ ]	[ ]
4.	[ ]	[ ]
5.	[ ]	[ ]
6.	[ ]	[ ]
7.	[ ]	[ ]
8.	[ ]	[ ]
9.	[ ]	[ ]
10.	[ ]	[ ]
11.	Total funds requested for all equipment listed in the attached file	[ ]
	Total Equipment	[ ]

Additional Equipment: [ ]

Add Attachment

Delete Attachment

View Attachment

D. Travel

Funds Requested (\$)

1.	Domestic Travel Costs ( Incl. Canada, Mexico and U.S. Possessions)	4,502.00
2.	Foreign Travel Costs	[ ]
	Total Travel Cost	4,502.00

E. Participant/Trainee Support Costs

Funds Requested (\$)

1.	Tuition/Fees/Health Insurance	[ ]
2.	Stipends	[ ]
3.	Travel	[ ]
4.	Subsistence	[ ]
5.	Other [ ]	[ ]
[ ]	Number of Participants/Trainees	Total Participant/Trainee Support Costs [ ]

RESEARCH & RELATED Budget {C-E} (Funds Requested)

OMB Number: 4040-0001  
Expiration Date: 04/30/2008

**RESEARCH & RELATED BUDGET - SECTION F-K, BUDGET PERIOD 5**

\* ORGANIZATIONAL DUNS:

\* Budget Type:  Project  Subaward/Consortium

Enter name of Organization:

Start Date:  \* End Date:  Budget Period 5

F. Other Direct Costs	Funds Requested (\$)
1. Materials and Supplies	<input type="text" value="4,429.00"/>
2. Publication Costs	<input type="text"/>
3. Consultant Services	<input type="text"/>
4. ADP/Computer Services	<input type="text"/>
5. Subawards/Consortium/Contractual Costs	<input type="text" value="45,102.00"/>
6. Equipment or Facility Rental/User Fees	<input type="text"/>
7. Alterations and Renovations	<input type="text"/>
8. <input type="text" value="Other Costs"/>	<input type="text" value="97,479.00"/>
9. <input type="text" value="Outpatient Costs"/>	<input type="text" value="39,092.00"/>
10. <input type="text"/>	<input type="text"/>
<b>Total Other Direct Costs</b>	<input type="text" value="186,102.00"/>

G. Direct Costs	Funds Requested (\$)
<b>Total Direct Costs (A thru F)</b>	<input type="text" value="487,173.00"/>

H. Indirect Costs	Indirect Cost Rate (%)	Indirect Cost Base (\$)	* Funds Requested (\$)
Indirect Cost Type			
1. <input type="text" value="Research"/>	<input type="text" value="57.50"/>	<input type="text" value="402,981.00"/>	<input type="text" value="231,714.00"/>
2. <input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>
3. <input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>
4. <input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>
<b>Total Indirect Costs</b>			<input type="text" value="231,714.00"/>

Cognizant Federal Agency   
(Agency Name, POC Name, and POC Phone Number)

I. Total Direct and Indirect Costs	Funds Requested (\$)
<b>Total Direct and Indirect Institutional Costs (G + H)</b>	<input type="text" value="718,887.00"/>

J. Fee	Funds Requested (\$)
	<input type="text"/>

K. \* Budget Justification      
(Only attach one file.)

## BUDGET JUSTIFICATION

This application represents a collaboration of clinical and basic science research using diverse expertise that is all available within few blocks at the University of [redacted]. The cornerstone of this proposal is the large pediatric oncology practice at the Children's Hospital [redacted] and the [redacted] Cancer Center at the University [redacted]. This large clinical population is complemented by a well-established, experienced clinical research unit in reproduction (WHCRC) and an outstanding endocrine laboratory facility at the Clinical and Translational Research Center (CTRC). The multi-disciplinary research team and outstanding facilities will allow a comprehensive evaluation of the acute and chronic reproductive potential effects of cancer therapy. This collaboration has already demonstrated success as evidenced by our preliminary results.

## PERSONNEL

### Principal Investigator, 3.6 calendar

Dr. [redacted] is Assistant Professor of Obstetrics and Gynecology and a member of the Reproductive Endocrinology and Infertility (REI) Division at the University [redacted]. Dr. [redacted] will conduct the study and assure adherence to regulatory guidelines and budgetary requirements. She will oversee recruitment of all subjects in collaboration with the co-investigators, conduct and oversee all research study visits, and analyze the data, working in liaison with the faculty and staff from the Center [redacted].

### [redacted], Co-Investigator / Subcontract PI, [redacted], 0.6 calendar

Dr. [redacted] is Assistant Professor of Pediatrics in the Division of Oncology at The Children's Hospital of [redacted]. Dr. [redacted] and the clinical coordinator at [redacted] will oversee recruitment of newly diagnosed cancer patients and cancer survivors through the Division of Oncology and Cancer [redacted]. Dr. [redacted] shall abstract medical records for data collection, monitor inclusion and exclusion criteria of study subjects, and assure adherence to regulatory guidelines at [redacted]. A Consortium agreement with [redacted] is included.

### [redacted], Co-Investigator, 0.24 calendar

Dr. [redacted] is board certified as an oncology and primary care nurse practitioner and has an appointment as a Clinical Associate Professor at the School of Nursing [redacted] where she was the program director and in 1995 developed one of the first oncology nurse practitioner programs in the country. Dr. [redacted] is well known to the oncology community and is the Director of the multidisciplinary [redacted] at the [redacted] of the University [redacted]. Dr. [redacted] will assist in recruitment of newly diagnosed and survivors of cancer at the [redacted].

### [redacted], 1.2 calendar

Dr. [redacted] is Associate Professor of Biostatistics in the Department of Biostatistics and Epidemiology at University of [redacted] School of Medicine and Senior Scholar in the Center for Clinical Epidemiology and Biostatistics of the University [redacted]. Dr. [redacted] statistical research interests are in the area of multivariate and longitudinal data. Since joining the faculty of the University [redacted] in the Fall of [redacted], she has continued her methodological research and has collaborates extensively with epidemiologists and physicians in the design and analysis of clinical research studies in women's health and reproduction. Dr. [redacted] directs a biostatistical core (funded beginning in 1998) to mentor junior faculty in OB/GYN involved in basic science, translational and clinical research, and is Co-Investigator on several projects including The [redacted] (PI: [redacted]). [redacted] will be working closely with the PI and the data analysts to ensure appropriate statistical analysis.

..., 1.8 calendar, the Director of the Core Lab, will be performing the serum and urinary assays for this study. The urinary E1c and PdG assays are labor intensive and will require validation with the outside laboratory of .

**Research Assistant ( ), 3 calendar** A laboratory assistant will be required to assist Dr. in completing all serum and urinary hormone analyses.

**Clinical Coordinator at the Reproductive Endocrinology and Infertility Division (REI), 12 calendar** Most effort is assigned to this clinical coordinator since the majority of the actual study procedures shall be administered in the Care Clinic, requiring the greatest effort. The REI clinical coordinator will be responsible for initial study enrollment and follow up visits for exposed and unexposed study subjects at the University proper collection and storage of informed consents, organizing the study visit and procedures for both cancer survivors and controls, administering the structured interview based questionnaires, and overseeing quality assurance of collection and storage of the clinical data and specimens.

**TBD, Clinical Research Assistant at the Reproductive Endocrinology and Infertility Division (REI), 7.2 calendar** An additional research assistant will be needed to assist in coordinating and collecting specimens for the specific aims of this investigation. The urinary studies will require particular coordination of freezer and specimen transportation. In addition, assistance will be required for initial study enrollment and follow up visits for exposed and unexposed study subjects, proper collection and storage of informed consents, organizing the study visit and procedures for both cancer patients and unexposed, administering the structured interview based questionnaires, and overseeing quality assurance of collection and storage of the clinical data and specimens.

**Clinical Coordinator at the Children's Hospital of Philadelphia, Consortium, 1.8 calendar** The clinical coordinator will be responsible for identifying and recruiting newly diagnosed female cancer patients and cancer survivors for the study, collecting data from medical records, obtaining and storing informed consent for and coordinating with the REI clinical coordinator the study visit for the subjects and transfer of appropriate data.

**TBD, Clinical Coordinator at the Cancer Center, 1.8 calendar** The clinical coordinator will be responsible for identifying and recruiting newly diagnosed female cancer patients and cancer survivors for this study, collecting data from medical records, and coordinating with the REI clinical coordinator the study visit for the subjects and transfer of appropriate data.

**TBD, Data Entry Assistant, 2.4 calendar** Data assistants will be responsible for data quality control and entry of all data from charts into the database

**Project Manager, 0.9 calendar** Ms. is the Director of Operations for the Women's Health Clinical Research Center (WHCRC). Ms. is an experienced Women's Health Nurse Practitioner and project manager. She has successfully managed more than 45 clinical trials in Women's Health. She has worked on multiple trials for the and Her experience encompasses work on small single-center pilot studies to large multi-center pivotal trials. As project manager Ms. will assist with logistics of the study, ensure case report forms are completed accurately, adverse events are recorded and reported a timely fashion and; identify resources to facilitate study needs; and supervise research staff.

**Lab Technician, 1.2 calendar** is an experienced laboratory technician as well as data manager. She currently oversees a large Tissue Bank within the Division of Reproductive Endocrinology. will be responsible for the collection, processing, labeling and storing of all specimens obtained in this trial.

## EQUIPMENT

**-80C Freezer:** Since a large number of serum and urinary hormone samples will be frozen and batched for analysis for all of the specific aims of this study, a large amount of freezer space will be required. Purchase of an additional -80C freezer will be necessary for storage of all samples. \$7,000 in year 1 only.

## SUPPLIES

**Blood and urine collection supplies:** It will be necessary to purchase supplies for blood draws and urine collection for this study. These will include serum separator tubes, phlebotomy supplies, urine cups with glycerol, and polypropylene tubes for specimen freezer storage. \$5,500 total project.

**Portable freezers:** Subjects will be required to collect and store daily urine specimens at home in a -20 freezer for Specific Aim 3. Subjects may either use their own freezer for storage, or use a portable freezer provided by the study for this purpose. Urine will be collected from subject's homes on a weekly basis. Therefore, 5 portable -20 C freezers will be purchased for this study. The freezers will be transported to subject's homes and retrieved after subjects have completed the urine collection study. These will be reused throughout the study duration. The cost of each portable freezer is approximately \$500.00 at current market values. Total cost \$2,500 in year 1 only.

### **Transportation of freezers and urine specimens:**

Portable freezers will be dropped at the homes of subjects who do not wish to store urine in their home freezers. In addition, weekly collections of urine will be required over the course of this 5 year study. It is estimated that it will cost approximately \$40.00/pick up to cover parking, gas and mileage. Given that each participant will collect urine for approximately 8 weeks and there are 45 subjects, 360 weekly collections of urine will be required over the course of this 5 year study. \$15,000 total project

**Centrifuge:** serum and urine processing will require centrifugation prior to storage. Given the large number of specimens to be collected for this project, we will purchase a dedicated centrifuge for this study. \$1,800 in year 1 only.

**Computer:** A laptop computer and software will be purchased for this project and is anticipated to last the duration of the study. This computer will facilitate data entry into the web based database that has been created by the NIH for this purpose. \$2000 in year 1 only.

## TRAVEL

The estimated cost will offset expenses for study related travel. It is anticipated that the PI will attend one national meeting per year to present results derived from this work. In addition, the PI will meet with other investigators in the area of Oncofertility at least once yearly to discuss research activities and new ideas.

**PATIENT CARE COSTS**

**Specific Aim 1:**

Study costs for subjects are based on recruitment of 115 subjects who will undergo 7 visits for the assessment of reproductive function over time.

Ultrasound costs are estimated at \$80/patient x 7 assessments and shall be performed by and staff at the Reproductive Research Unit, or at the Children’s Hospital Both facilities have ultrasounds available for use (\$80.00/visit x 7 visits x 115 subjects = \$64,400.00)

**Specific Aim 2:**

Study costs for subjects are based on a recruitment of 100 young cancer survivors and 200 unexposed subjects who will undergo up to 5 study visits.

Ultrasound costs are estimated at \$80/patient and shall be performed by and staff at the Reproductive Research Unit within the Division of Reproductive Endocrinology at the (\$80.00/visit x 5 assessments x 300 subjects = \$ 120,000)

**OTHER COSTS**

**Data Management & Statistical Support**

The C3D database currently developed for this project by the NCI as part of the Consortium will be expanded to accommodate data for the urinary hormone study (Specific Aim 3). In addition, data entry will be performed by full time staff in the

**Biostatistics Analysis Core**

Statistical support will be required for data analysis from the biostatistical core at the Center for Clinical Epidemiology and Biostatistics. will be working closely with the PI and the data analysts to ensure appropriate statistical analysis. Given the size of this project and the complexity of longitudinal data analysis, support from the BAC will be required during years 4 and 5 to ensure appropriate analyses. Analysts will perform extensive data checks to assure high quality data. They will perform all necessary data analyses to meet the objectives of each aim, and assist with presentation of results. The cost for this support has been estimated to be \$40,562 for year 4 of the project and \$48,711 for year 5 of this proposal.

		<i>year 1</i>	<i>year 2</i>	<i>year 3</i>	<i>year 4</i>	<i>year 5</i>	<i>Total</i>
BAC							
Biostatistician	Percent				10.00%	30.00%	
	Amount				\$14,774	\$45,651	\$60,424.31
BAC							
Programmer	Percent				20.00%		
	Amount				\$22,729		\$22,728.72
<b>Information Systems Support</b>							
	Amount				\$3,060	\$3,060	\$6,120.00
							<b>\$89,273.03</b>

## OTHER COSTS (continued)

### Clinical and Translational Research Core

#### **Specific Aim 1:**

Study costs for subjects are based on recruitment of 115 subjects who will undergo 7 visits for the assessment of reproductive function over time.

Hormone Assays costs are estimated at \$33.70/patient x 7 assessment x 115 subjects = \$27,128.50

#### **Specific Aim 2:**

Study costs for subjects are based on a recruitment of 100 young cancer survivors and 200 unexposed subjects who will undergo up to 5 study visits.

Assays costs are estimated at \$33.70 /visit x 5 assessments x 291 subjects = \$49,033.50

#### **Specific Aim 3:**

Study costs for the subjects are based on recruitment of 45 cancer survivors and unexposed subjects who will collect daily urine x 2 menstrual cycles (60days on average), for hormone analyses.

Assays costs are estimated at \$20.00/specimen x 60 specimens x 45 subjects = \$54,000.00

### Patient Incentives

Specific Aim 1: are estimated at \$30/assessment/patient x 7 assessments x 115 subjects = \$24,150.00

Specific Aim 2: \$40/visit x 5 assessments x 300 subjects = \$60,000.00

Specific Aim 3: are estimated at \$200.00 per subject x 45 subjects = \$9,000.00

### Advertising

Advertising will be necessary in order to recruit sufficient study participants for this proposal. While exposed subjects will be primarily identified in the oncology practices at \_\_\_\_\_ and at the \_\_\_\_\_, advertising through local cancer support groups will help ensure adequate enrollment. In addition, in order to enroll sufficient unexposed controls, it will be necessary to advertise via local newspapers and media such as radio. We have conducted many successful clinical trials and have experience using various methods of advertising. For approximately every ten inquires received 3 to 5 potential subjects may be eligible and of that 1-2 may be successfully enrolled. \$7,000 total project

## SUBCONTRACT/CONSORTIUM COSTS – <sup>1</sup>

See full description under PERSONNEL

See full description under PERSONNEL

### ***Patient care costs***

Lab draws estimated at \$4.00 per venipuncture. Each patient will undergo 7 lab draws, and for 40 patients that will be 280 venipunctures or approximately \$1,200.

**RESEARCH & RELATED BUDGET - Cumulative Budget**

		Totals (\$)
<b>Section A, Senior/Key Person</b>		491,373.00
<b>Section B, Other Personnel</b>		926,831.00
Total Number Other Personnel	40	
<b>Total Salary, Wages and Fringe Benefits (A+B)</b>		1,418,204.00
<b>Section C, Equipment</b>		7,000.00
<b>Section D, Travel</b>		21,237.00
1. Domestic	21,237.00	
2. Foreign		
<b>Section E, Participant/Trainee Support Costs</b>		
1. Tuition/Fees/Health Insurance		
2. Stipends		
3. Travel		
4. Subsistence		
5. Other		
6. Number of Participants/Trainees		
<b>Section F, Other Direct Costs</b>		753,959.00
1. Materials and Supplies	27,192.00	
2. Publication Costs		
3. Consultant Services		
4. ADP/Computer Services		
5. Subawards/Consortium/Contractual Costs	214,736.00	
6. Equipment or Facility Rental/User Fees		
7. Alterations and Renovations		
8. Other 1	327,630.00	
9. Other 2	184,401.00	
10. Other 3		
<b>Section G, Direct Costs (A thru F)</b>		2,200,400.00
<b>Section H, Indirect Costs</b>		1,046,076.00
<b>Section I, Total Direct and Indirect Costs (G + H)</b>		3,246,476.00
<b>Section J, Fee</b>		

OMB Number:  
 Expiration Date: 04/30/2008

**RESEARCH & RELATED BUDGET - SECTION A & B, BUDGET PERIOD 1**

\* ORGANIZATIONAL DUNS: 00000000000000

\* Budget Type:  Project  Subaward/Consortium

Enter name of Organization:

\* Start Date:                      \* End Date:                      Budget Period: 1

A. Senior/Key Person												
Prefix	* First Name	Middle Name	* Last Name	Suffix	* Project Role	Base Salary (\$)	Cal. Months	Acad. Months	Sum. Months	* Requested Salary (\$)	* Fringe Benefits (\$)	* Funds Requested (\$)
1.					Co-Inv./Subcontract	147,680.00	0.6			7,384.00	1,654.00	9,038.00
Total Funds Requested for all Senior Key Persons in the attached file										Total Senior/Key Person		9,038.00
Additional Senior Key Persons:										Mime Type:		

B. Other Personnel										
* Number of Personnel				* Project Role	Cal. Months	Acad. Months	Sum. Months	* Requested Salary (\$)	* Fringe Benefits (\$)	* Funds Requested (\$)
	Post Doctoral Associates									
	Graduate Students									
	Undergraduate Students									
	Secretarial/Clerical									
1	Clinical Coordinator				1.8			11,608.00	3,714.00	15,322.00
1	Total Number Other Personnel							Total Other Personnel		15,322.00
Total Salary, Wages and Fringe Benefits (A+B)										24,360.00

**RESEARCH & RELATED Budget (A-B) (Funds Requested)**

Principal Investigator/Program Director (Last, first, middle):

**RESEARCH & RELATED BUDGET - SECTION C, D, & E, BUDGET PERIOD 1**

\* ORGANIZATIONAL DUNS: 0000000000000

\* Budget Type:  Project  Subaward/Consortium

Enter name of Organization:

\* Start Date:

\* End Date:

Budget Period: 1

<b>C. Equipment Description</b>		
List items and dollar amount for each item exceeding \$5,000		
Equipment Item		* Funds Requested (\$)
Total funds requested for all equipment listed in the attached file		
	Total Equipment	
Additional Equipment:	File Name:	Mime Type:

<b>D. Travel</b>	<b>Funds Requested (\$)</b>
1. Domestic Travel Costs ( Incl. Canada, Mexico, and U.S. Possessions)	
2. Foreign Travel Costs	
	Total Travel Cost

<b>E. Participant/Trainee Support Costs</b>	<b>Funds Requested (\$)</b>
1. Tuition/Fees/Health Insurance	
2. Stipends	
3. Travel	
4. Subsistence	
5. Other:	
Number of Participants/Trainees	Total Participant/Trainee Support Costs

RESEARCH & RELATED Budget {C-E} (Funds Requested)

Principal Investigator/Program Director (Last, first, middle):

**RESEARCH & RELATED BUDGET - SECTIONS F-K, BUDGET PERIOD 1**

\* ORGANIZATIONAL DUNS: 0000000000000

\* Budget Type:  Project  Subaward/Consortium

Enter name of Organization:

\* Start Date:

\* End Date:

Budget Period: 1

F. Other Direct Costs		Funds Requested (\$)
1. Materials and Supplies		
2. Publication Costs		
3. Consultant Services		
4. ADP/Computer Services		
5. Subawards/Consortium/Contractual Costs		
6. Equipment or Facility Rental/User Fees		
7. Alterations and Renovations		
8. Other Costs		595.00
<b>Total Other Direct Costs</b>		<b>595.00</b>

G. Direct Costs	Funds Requested (\$)
<b>Total Direct Costs (A thru F)</b>	<b>24,955.00</b>

H. Indirect Costs			
Indirect Cost Type	Indirect Cost Rate (%)	Indirect Cost Base (\$)	* Funds Requested (\$)
1. MTDC		24,955.00	16,096.00
<b>Total Indirect Costs</b>			<b>16,096.00</b>
<b>Cognizant Federal Agency</b>			
(Agency Name, POC Name, and POC Phone Number)			

I. Total Direct and Indirect Costs	Funds Requested (\$)
<b>Total Direct and Indirect Institutional Costs (G + H)</b>	<b>41,051.00</b>

J. Fee	Funds Requested (\$)

K. * Budget Justification	File Name:	Mime Type:
	(Only attach one file.)	

RESEARCH & RELATED Budget {F-K} (Funds Requested)



Principal Investigator/Program Director (Last, first, middle):

**RESEARCH & RELATED BUDGET - SECTION C, D, & E, BUDGET PERIOD 2**

\* ORGANIZATIONAL DUNS: 0000000000000

\* Budget Type:  Project  Subaward/Consortium

Enter name of Organization:

\* Start Date:

\* End Date:

Budget Period: 2

**C. Equipment Description**

List items and dollar amount for each item exceeding \$5,000

Equipment Item	* Funds Requested (\$)
Total funds requested for all equipment listed in the attached file	
<b>Total Equipment</b>	
Additional Equipment:	File Name:
	Mime Type:

**D. Travel**

Funds Requested (\$)

1. Domestic Travel Costs ( Incl. Canada, Mexico, and U.S. Possessions)
2. Foreign Travel Costs

Total Travel Cost

**E. Participant/Trainee Support Costs**

Funds Requested (\$)

1. Tuition/Fees/Health Insurance
2. Stipends
3. Travel
4. Subsistence
5. Other:

Number of Participants/Trainees

Total Participant/Trainee Support Costs

RESEARCH & RELATED Budget {C-E} (Funds Requested)

Principal Investigator/Program Director (Last, first, middle):

### RESEARCH & RELATED BUDGET - SECTIONS F-K, BUDGET PERIOD 2

\* ORGANIZATIONAL DUNS: 0000000000000

\* Budget Type:  Project  Subaward/Consortium

Enter name of Organization: \_\_\_\_\_

\* Start Date: \_\_\_\_\_

\* End Date: \_\_\_\_\_

Budget Period: 2

F. Other Direct Costs		Funds Requested (\$)
1. Materials and Supplies		
2. Publication Costs		
3. Consultant Services		
4. ADP/Computer Services		
5. Subawards/Consortium/Contractual Costs		
6. Equipment or Facility Rental/User Fees		
7. Alterations and Renovations		
8. Other Costs		614.00
<b>Total Other Direct Costs</b>		<b>614.00</b>

G. Direct Costs	Funds Requested (\$)
<b>Total Direct Costs (A thru F)</b>	<b>25,705.00</b>

H. Indirect Costs			
	Indirect Cost Type	Indirect Cost Rate (%)	Indirect Cost Base (\$) * Funds Requested (\$)
1. MTDC			25,704.00 16,579.00
<b>Total Indirect Costs</b>			<b>16,579.00</b>
<b>Cognizant Federal Agency</b>			
(Agency Name, POC Name, and POC Phone Number)			

I. Total Direct and Indirect Costs	Funds Requested (\$)
<b>Total Direct and Indirect Institutional Costs (G + H)</b>	<b>42,284.00</b>

J. Fee	Funds Requested (\$)

K. * Budget Justification	File Name:	Mime Type:
	(Only attach one file.)	

RESEARCH & RELATED Budget {F-K} (Funds Requested)

**RESEARCH & RELATED BUDGET - SECTION A & B, BUDGET PERIOD 3**

\* ORGANIZATIONAL DUNS: 00000000000000  
 \* Budget Type:  Project  Subaward/Consortium  
 Enter name of Organization:

\* Start Date: Budget Period: 3 \* End Date:

A. Senior/Key Person		Prefix	* First Name	Middle Name	* Last Name	Suffix	* Project Role	Base Salary (\$)	Cal. Months	Acad. Months	Sum. Months	* Requested Salary (\$)	* Fringe Benefits (\$)	* Funds Requested (\$)
1.							Co-Inv./Subcontract	156,674.00	0.6			7,834.00	1,755.00	9,589.00
Total Funds Requested for all Senior Key Persons in the attached file														
Additional Senior Key Persons:													Total Senior/Key Person	9,589.00

File Name: Mime Type:

B. Other Personnel		* Number of Personnel	Post Doctoral Associates	Graduate Students	Undergraduate Students	Secretarial/Clerical	Clinical Coordinator	* Project Role	Cal. Months	Acad. Months	Sum. Months	* Requested Salary (\$)	* Fringe Benefits (\$)	* Funds Requested (\$)
1		1							1.8			12,315.00	3,940.00	16,255.00
Total Number Other Personnel													Total Other Personnel	16,255.00
Total Salary, Wages and Fringe Benefits (A+B)													Total Salary, Wages and Fringe Benefits (A+B)	25,844.00

**RESEARCH & RELATED Budget (A-B) (Funds Requested)**

Principal Investigator/Program Director (Last, first, middle):

**RESEARCH & RELATED BUDGET - SECTION C, D, & E, BUDGET PERIOD 3**

\* ORGANIZATIONAL DUNS: 0000000000000

\* Budget Type:  Project  Subaward/Consortium

Enter name of Organization:

\* Start Date:

\* End Date:

Budget Period: 3

**C. Equipment Description**

List items and dollar amount for each item exceeding \$5,000

Equipment Item

\* Funds Requested (\$)

Total funds requested for all equipment listed in the attached file

Total Equipment

Additional Equipment:

File Name:

Mime Type:

**D. Travel**

Funds Requested (\$)

1. Domestic Travel Costs ( Incl. Canada, Mexico, and U.S. Possessions)
2. Foreign Travel Costs

Total Travel Cost

**E. Participant/Trainee Support Costs**

Funds Requested (\$)

1. Tuition/Fees/Health Insurance
2. Stipends
3. Travel
4. Subsistence
5. Other:

Number of Participants/Trainees

Total Participant/Trainee Support Costs

RESEARCH & RELATED Budget {C-E} (Funds Requested)

Principal Investigator/Program Director (Last, first, middle):

**RESEARCH & RELATED BUDGET - SECTIONS F-K, BUDGET PERIOD 3**

\* ORGANIZATIONAL DUNS: 0000000000000

\* Budget Type:  Project  Subaward/Consortium

Enter name of Organization:

\* Start Date:

\* End Date:

Budget Period: 3

<b>F. Other Direct Costs</b>		<b>Funds Requested (\$)</b>
1. Materials and Supplies		
2. Publication Costs		
3. Consultant Services		
4. ADP/Computer Services		
5. Subawards/Consortium/Contractual Costs		
6. Equipment or Facility Rental/User Fees		
7. Alterations and Renovations		
8. Other Costs		0.00
<b>Total Other Direct Costs</b>		<b>0.00</b>

<b>G. Direct Costs</b>		<b>Funds Requested (\$)</b>
<b>Total Direct Costs (A thru F)</b>		<b>25,844.00</b>

<b>H. Indirect Costs</b>				<b>* Funds Requested (\$)</b>
	<b>Indirect Cost Type</b>	<b>Indirect Cost Rate (%)</b>	<b>Indirect Cost Base (\$)</b>	
1.	MTDC		25,843.00	16,669.00
			<b>Total Indirect Costs</b>	<b>16,669.00</b>
<b>Cognizant Federal Agency</b>				
(Agency Name, POC Name, and POC Phone Number)				

<b>I. Total Direct and Indirect Costs</b>		<b>Funds Requested (\$)</b>
<b>Total Direct and Indirect Institutional Costs (G + H)</b>		<b>42,513.00</b>

<b>J. Fee</b>		<b>Funds Requested (\$)</b>
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<b>K. * Budget Justification</b>		File Name:	Mime Type:
		(Only attach one file.)	

RESEARCH & RELATED Budget {F-K} (Funds Requested)

**RESEARCH & RELATED BUDGET - SECTION A & B, BUDGET PERIOD 4**

\* ORGANIZATIONAL DUNS: 00000000000000

\* Budget Type:  Project  Subaward/Consortium

Enter name of Organization:

\* Start Date: \* End Date: Budget Period: 4

A. Senior/Key Person												
Prefix	* First Name	Middle Name	* Last Name	Suffix	* Project Role	Base Salary (\$)	Cal. Months	Acad. Months	Sum. Months	* Requested Salary (\$)	* Fringe Benefits (\$)	* Funds Requested (\$)
1.					Co-Inv./Subcontract	161,374.00	0.6			8,069.00	1,807.00	9,876.00
Total Funds Requested for all Senior Key Persons in the attached file												
Additional Senior Key Persons:											Total Senior/Key Person	9,876.00

Mime Type:

File Name:

B. Other Personnel									
* Number of Personnel		* Project Role	Cal. Months	Acad. Months	Sum. Months	* Requested Salary (\$)	* Fringe Benefits (\$)	* Funds Requested (\$)	
	Post Doctoral Associates								
	Graduate Students								
	Undergraduate Students								
	Secretarial/Clerical								
1	Clinical Coordinator		1.8			12,684.00	4,058.00	16,742.00	
1	Total Number Other Personnel					Total Other Personnel		16,742.00	
Total Salary, Wages and Fringe Benefits (A+B)								26,618.00	

RESEARCH & RELATED Budget (A-B) (Funds Requested)

Principal Investigator/Program Director (Last, first, middle):

**RESEARCH & RELATED BUDGET - SECTION C, D, & E, BUDGET PERIOD 4**

\* ORGANIZATIONAL DUNS: 0000000000000

\* Budget Type:  Project  Subaward/Consortium

Enter name of Organization:

\* Start Date:

\* End Date:

Budget Period: 4

**C. Equipment Description**

List items and dollar amount for each item exceeding \$5,000

Equipment Item

\* Funds Requested (\$)

Total funds requested for all equipment listed in the attached file

Total Equipment

Additional Equipment:

File Name:

Mime Type:

**D. Travel**

Funds Requested (\$)

1. Domestic Travel Costs ( Incl. Canada, Mexico, and U.S. Possessions)
2. Foreign Travel Costs

Total Travel Cost

**E. Participant/Trainee Support Costs**

Funds Requested (\$)

1. Tuition/Fees/Health Insurance
2. Stipends
3. Travel
4. Subsistence
5. Other:

Number of Participants/Trainees

Total Participant/Trainee Support Costs

RESEARCH & RELATED Budget {C-E} (Funds Requested)

Principal Investigator/Program Director (Last, first, middle):

**RESEARCH & RELATED BUDGET - SECTIONS F-K, BUDGET PERIOD 4**

\* ORGANIZATIONAL DUNS: 0000000000000

\* Budget Type:  Project  Subaward/Consortium

Enter name of Organization:

\* Start Date:

\* End Date:

Budget Period: 4

F. Other Direct Costs		Funds Requested (\$)
1. Materials and Supplies		
2. Publication Costs		
3. Consultant Services		
4. ADP/Computer Services		
5. Subawards/Consortium/Contractual Costs		
6. Equipment or Facility Rental/User Fees		
7. Alterations and Renovations		
8. Other Costs		0.00
<b>Total Other Direct Costs</b>		<b>0.00</b>

G. Direct Costs	Funds Requested (\$)
<b>Total Direct Costs (A thru F)</b>	<b>26,618.00</b>

H. Indirect Costs			
Indirect Cost Type	Indirect Cost Rate (%)	Indirect Cost Base (\$)	* Funds Requested (\$)
1. MTDC		26,618.00	17,170.00
<b>Total Indirect Costs</b>			<b>17,170.00</b>
<b>Cognizant Federal Agency</b>			
(Agency Name, POC Name, and POC Phone Number)			

I. Total Direct and Indirect Costs	Funds Requested (\$)
<b>Total Direct and Indirect Institutional Costs (G + H)</b>	<b>43,788.00</b>

J. Fee	Funds Requested (\$)
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K. * Budget Justification	File Name:	Mime Type:
	(Only attach one file.)	

RESEARCH & RELATED Budget {F-K} (Funds Requested)

**RESEARCH & RELATED BUDGET - SECTION A & B, BUDGET PERIOD 5**

\* ORGANIZATIONAL DUNS: 0000000000000

\* Budget Type:  Project  Subaward/Consortium

Enter name of Organization:

\* Start Date: 12-01-2013 \* End Date: 11-30-2014 Budget Period: 5

A. Senior/Key Person												
Prefix	* First Name	Middle Name	* Last Name	Suffix	* Project Role	Base Salary (\$)	Cal. Months	Acad. Months	Sum. Months	* Requested Salary (\$)	* Fringe Benefits (\$)	* Funds Requested (\$)
1.					Co-Inv./Subcontract PI	166,215.00	0.6			8,311.00	1,862.00	10,173.00
Total Funds Requested for all Senior Key Persons in the attached file												
Additional Senior Key Persons:										Total Senior/Key Person		10,173.00

File Name:

Mime Type:

B. Other Personnel										
* Number of Personnel				* Project Role	Cal. Months	Acad. Months	Sum. Months	* Requested Salary (\$)	* Fringe Benefits (\$)	* Funds Requested (\$)
1							1.8	13,065.00	4,180.00	17,245.00
1								Total Other Personnel		17,245.00
Total Salary, Wages and Fringe Benefits (A+B)										27,418.00

**RESEARCH & RELATED Budget (A-B) (Funds Requested)**

Principal Investigator/Program Director (Last, first, middle):

**RESEARCH & RELATED BUDGET - SECTION C, D, & E, BUDGET PERIOD 5**

\* ORGANIZATIONAL DUNS: 0000000000000

\* Budget Type:  Project  Subaward/Consortium

Enter name of Organization:

\* Start Date:

\* End Date:

Budget Period: 5

**C. Equipment Description**

List items and dollar amount for each item exceeding \$5,000

Equipment Item

\* Funds Requested (\$)

Total funds requested for all equipment listed in the attached file

Total Equipment

Additional Equipment:

File Name:

Mime Type:

**D. Travel**

Funds Requested (\$)

1. Domestic Travel Costs (Incl. Canada, Mexico, and U.S. Possessions)

2. Foreign Travel Costs

Total Travel Cost

**E. Participant/Trainee Support Costs**

Funds Requested (\$)

1. Tuition/Fees/Health Insurance

2. Stipends

3. Travel

4. Subsistence

5. Other:

Number of Participants/Trainees

Total Participant/Trainee Support Costs

RESEARCH & RELATED Budget {C-E} (Funds Requested)

Principal Investigator/Program Director (Last, first, middle):

### RESEARCH & RELATED BUDGET - SECTIONS F-K, BUDGET PERIOD 5

\* ORGANIZATIONAL DUNS: 0000000000000

\* Budget Type:  Project  Subaward/Consortium

Enter name of Organization:

\* Start Date:

\* End Date:

Budget Period: 5

F. Other Direct Costs		Funds Requested (\$)
1. Materials and Supplies		
2. Publication Costs		
3. Consultant Services		
4. ADP/Computer Services		
5. Subawards/Consortium/Contractual Costs		
6. Equipment or Facility Rental/User Fees		
7. Alterations and Renovations		
8. Other Costs		0.00
<b>Total Other Direct Costs</b>		<b>0.00</b>

G. Direct Costs	Funds Requested (\$)
<b>Total Direct Costs (A thru F)</b>	<b>27,418.00</b>

H. Indirect Costs			
Indirect Cost Type	Indirect Cost Rate (%)	Indirect Cost Base (\$)	* Funds Requested (\$)
1. MTDC		27,417.00	17,685.00
<b>Total Indirect Costs</b>			<b>17,685.00</b>
<b>Cognizant Federal Agency</b>			
(Agency Name, POC Name, and POC Phone Number)			

I. Total Direct and Indirect Costs	Funds Requested (\$)
<b>Total Direct and Indirect Institutional Costs (G + H)</b>	<b>45,103.00</b>

J. Fee	Funds Requested (\$)
--------	----------------------

K. * Budget Justification	File Name:	Mime Type:
	(Only attach one file.)	

RESEARCH & RELATED Budget {F-K} (Funds Requested)

**RESEARCH & RELATED BUDGET - Cumulative Budget**

	<b>Totals (\$)</b>	
<b>Section A, Senior/Key Person</b>	<b>47,986.00</b>	
<b>Section B, Other Personnel</b>	<b>81,345.00</b>	
Total Number Other Personnel	5	
<b>Total Salary, Wages and Fringe Benefits (A+B)</b>	<b>129,331.00</b>	
<b>Section C, Equipment</b>		
<b>Section D, Travel</b>		
1. Domestic		
2. Foreign		
<b>Section E, Participant/Trainee Support Costs</b>		
1. Tuition/Fees/Health Insurance		
2. Stipends		
3. Travel		
4. Subsistence		
5. Other		
6. Number of Participants/Trainees		
<b>Section F, Other Direct Costs</b>	<b>1,209.00</b>	
1. Materials and Supplies		
2. Publication Costs		
3. Consultant Services		
4. ADP/Computer Services		
5. Subawards/Consortium/Contractual Costs		
6. Equipment or Facility Rental/User Fees		
7. Alterations and Renovations		
8. Other 1	1,209.00	
9. Other 2		
10. Other 3		
<b>Section G, Direct Costs (A thru F)</b>	<b>130,540.00</b>	
<b>Section H, Indirect Costs</b>	<b>84,199.00</b>	
<b>Section I, Total Direct and Indirect Costs (G + H)</b>	<b>214,739.00</b>	
<b>Section J, Fee</b>		

# PHS 398 Cover Page Supplement

OMB Number: 0925-0001

## 1. Project Director / Principal Investigator (PD/PI)

Prefix:  \* First Name:   
Middle Name:   
\* Last Name:   
Suffix:

\* New Investigator?  No  Yes

Degrees:  MSCE

## 2. Human Subjects

Clinical Trial?  No  Yes

\* Agency-Defined Phase III Clinical Trial?  No  Yes

## 3. Applicant Organization Contact

Person to be contacted on matters involving this application

Prefix:  \* First Name:   
Middle Name:   
\* Last Name:   
Suffix:

\* Phone Number:  Fax Number:   
Email:

\* Title:   
\* Street1:   
Street2:   
\* City:   
County:   
\* State:   
Province:   
\* Country:  \* Zip / Postal Code:



[Close Form](#)[Print Page](#)[About](#)

OMB Number: 0925-0001

## PHS 398 Research Plan

### 1. Application Type:

From SF 424 (R&R) Cover Page and PHS398 Checklist. The responses provided on these pages, regarding the type of application being submitted, are repeated for your reference, as you attach the appropriate sections of the research plan.

\*Type of Application:

 New
  Resubmission
  Renewal
  Continuation
  Revision

### 2. Research Plan Attachments:

Please attach applicable sections of the research plan, below.

1. Introduction to Application	<input type="text"/>	<a href="#">Add Attachment</a>	<a href="#">Delete Attachment</a>	<a href="#">View Attachment</a>
(for RESUBMISSION or REVISION only)				
2. Specific Aims	<input type="text" value="rplan_nar.pdf"/>	<a href="#">Add Attachment</a>	<a href="#">Delete Attachment</a>	<a href="#">View Attachment</a>
3. Background and Significance	<input type="text" value="rplan_bas.pdf"/>	<a href="#">Add Attachment</a>	<a href="#">Delete Attachment</a>	<a href="#">View Attachment</a>
4. Preliminary Studies / Progress Report	<input type="text" value="rplan_prs.pdf"/>	<a href="#">Add Attachment</a>	<a href="#">Delete Attachment</a>	<a href="#">View Attachment</a>
5. Research Design and Methods	<input type="text" value="rplan_rdm.pdf"/>	<a href="#">Add Attachment</a>	<a href="#">Delete Attachment</a>	<a href="#">View Attachment</a>
6. Inclusion Enrollment Report	<input type="text"/>	<a href="#">Add Attachment</a>	<a href="#">Delete Attachment</a>	<a href="#">View Attachment</a>
7. Progress Report Publication List	<input type="text"/>	<a href="#">Add Attachment</a>	<a href="#">Delete Attachment</a>	<a href="#">View Attachment</a>

#### Human Subjects Sections

Attachments 8-11 apply only when you have answered "yes" to the question "are human subjects involved" on the R&R Other Project Information Form. In this case, attachments 8-11 may be required, and you are encouraged to consult the Application guide instructions and/or the specific Funding Opportunity Announcement to determine which sections must be submitted with this application.

8. Protection of Human Subjects	<input type="text" value="rplan_hs.pdf"/>	<a href="#">Add Attachment</a>	<a href="#">Delete Attachment</a>	<a href="#">View Attachment</a>
9. Inclusion of Women and Minorities	<input type="text" value="Inclusion_Women_Upload.pdf"/>	<a href="#">Add Attachment</a>	<a href="#">Delete Attachment</a>	<a href="#">View Attachment</a>
10. Targeted/Planned Enrollment	<input type="text" value="Targetted_Enroll_Upload.pdf"/>	<a href="#">Add Attachment</a>	<a href="#">Delete Attachment</a>	<a href="#">View Attachment</a>
11. Inclusion of Children	<input type="text" value="Inclusion_Children_Upload.p"/>	<a href="#">Add Attachment</a>	<a href="#">Delete Attachment</a>	<a href="#">View Attachment</a>

#### Other Research Plan Sections

12. Vertebrate Animals	<input type="text"/>	<a href="#">Add Attachment</a>	<a href="#">Delete Attachment</a>	<a href="#">View Attachment</a>
13. Select Agent Research	<input type="text"/>	<a href="#">Add Attachment</a>	<a href="#">Delete Attachment</a>	<a href="#">View Attachment</a>
14. Multiple PI Leadership Plan	<input type="text"/>	<a href="#">Add Attachment</a>	<a href="#">Delete Attachment</a>	<a href="#">View Attachment</a>
15. Consortium/Contractual Arrangements	<input type="text" value="rplan_cca.pdf"/>	<a href="#">Add Attachment</a>	<a href="#">Delete Attachment</a>	<a href="#">View Attachment</a>
16. Letters of Support	<input type="text" value="rplan_con.pdf"/>	<a href="#">Add Attachment</a>	<a href="#">Delete Attachment</a>	<a href="#">View Attachment</a>
17. Resource Sharing Plan(s)	<input type="text" value="rplan_res.pdf"/>	<a href="#">Add Attachment</a>	<a href="#">Delete Attachment</a>	<a href="#">View Attachment</a>

18. Appendix	<a href="#">Add Attachments</a>	<a href="#">Remove Attachments</a>	<a href="#">View Attachments</a>
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Title: ( )

### **A. Specific Aims**

Recent diagnostic and therapeutic advances in oncology have led to greater survival rates in children and young adults with malignancies. However, while cancer therapies, especially alkylating agents, improve long-term survival, such treatments often lead to reproductive dysfunction and accelerated ovarian aging. Even young women who maintain cyclic menses after therapy are at high risk of infertility, early menopause, and long-term health problems related to early ovarian failure. Surprisingly, there is essentially no data on precise endocrine endpoints measured at time intervals before, during and after cancer treatments predictive of the severity and duration of post-treatment ovarian endocrine dysfunction and reproductive failure in this population.

The current proposal represents a comprehensive clinical investigation of the acute and long-term reproductive effects of cancer therapies. This investigation is based on our own preliminary data, which include the intriguing observation that childhood and young adult cancer survivors exposed to high risk cancer therapies in their mid 20's have hormone and ultrasound measures of ovarian aging similar to naturally aging women in their mid 40's.

**General Hypothesis:** Chemotherapy and radiation therapy destroy ovarian follicles resulting in acute amenorrhea as reflected by hormone measures indicative of depleted ovarian reserve. It is further hypothesized that in women with incomplete follicular destruction, small follicles emerge from the follicular pool several months post therapy, resulting in partial normalization of endocrine and reproductive function. Finally, measures of ovarian function reflect the accelerated ovarian aging seen in cancer survivors and these measures (1) can be used to estimate the "reproductive age" of these patients and (2) can be helpful in predicting a survivor's "fertile window". To test these hypotheses, the following specific aims are proposed:

#### **Specific Aim 1: Assess acute changes in reproductive function during and after chemotherapy in cancer patients.**

*Specific Hypothesis to be tested: Chemotherapy causes acute follicular depletion, resulting in significant changes in functional markers of the Hypothalamic Pituitary Ovarian (H-P-O axis and such changes are dependent on pre-treatment level of ovarian function, treatment parameters and subject characteristics.*

Study design: Longitudinal cohort study of newly diagnosed post-menarchal females up to 35 years of age receiving chemotherapy compared to unexposed similarly aged controls.

#### **Specific Aim 2: Assess the long-term reproductive function of women exposed to cancer therapies.**

*Specific Hypothesis to be tested: Chemotherapy results in long-term endocrine changes that are distinct from comparably aged matched controls, but similar to women in their late reproductive years. These changes will be more dramatic in women who receive high dose therapy compared to women who receive low dose therapy.*

Study design: Prospective cohort study comparing mean levels and changes in measures of ovarian reserve over 3 years between post-menarchal females up to 35 years of age previously exposed to alkylating agent chemotherapy and two unexposed populations: comparably aged healthy unexposed subjects and naturally aging women in the late reproductive years. In addition, the strength of association between several risk factors and measures of ovarian functioning among females exposed to alkylating agents will be determined.

#### **Specific Aim 3: Assess for the presence of follicular and luteal dysfunction in cancer survivors.**

*Specific Hypothesis to be tested: Cancer survivors have luteal phase dysfunction despite normal menstrual cycles reflected by a difference in integrated levels of urinary pregnanediol glucuronide FSH, LH and Estrone conjugate from comparably aged matched controls, but similar to women in their late reproductive years.*

Study design: Prospective cohort study comparing daily urinary hormones over 2 menstrual cycles in females of mid-reproductive age exposed to high dose alkylating agent therapy compared to 2 unexposed populations: comparably aged healthy unexposed subjects and naturally aging women in the late reproductive years.

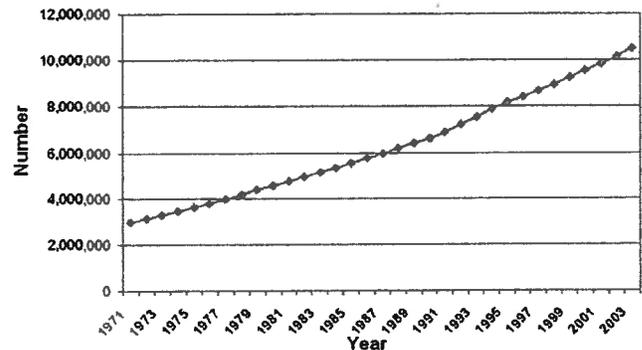
## B. Background and Significance

### Background:

#### Scope of the problem

Over 100,000 females less than 45 years of age are diagnosed with cancer annually. Of these, approximately 12,400 are children < 20 years of age [1, 2]. The types of cancer affecting children are diverse, while breast cancer accounts for a large proportion of cases affecting young adult women [3]. Treatment is usually multi-modal including a combination of surgical resection, multi-agent chemotherapy, often with alkylating agents, radiotherapy and, in cases of hematologic malignancies, bone marrow transplantation [4-8]. Over the past 4 decades, advancements in cancer therapies, particularly chemotherapeutics, have led to dramatic improvements in survival. The number of cancer survivors in the U.S. has grown considerably: currently there are estimated to be over 10 million adult cancer survivors and over 250,000 survivors of childhood cancer in the U.S (Figure 1). Of note, one in 1000 adults in their thirties is a survivor of childhood cancer [9, 10]. Given this prolonged survival, care has now focused also on improving the long term health and quality of life. Specifically, in female survivors of cancer future reproductive capacity and symptoms and health risks related to premature ovarian failure are of paramount concern [11, 12].

Figure 1. Number of cancer survivors in the U.S.



### Gonadotoxicity of Cancer Treatments

The ovary is particularly sensitive to the adverse effects of cancer treatments because of the finite number of germ cells present in the post-natal ovary [13, 14]. Reproductive lifespan is determined by the size of the follicular pool and therefore, cancer treatments that cause follicular depletion are thought to accelerate the onset of menopause [15]. Large retrospective cohort studies assessing menstrual function post chemotherapy have clearly demonstrated that cancer survivors are at risk of both acute and long-term ovarian failure [4, 8]. The irreversible gonadotoxic effects of some of the chemotherapeutic agents are well documented and particularly for alkylating agents, such as cyclophosphamide, busulfan, and ifosfamide, common components of polychemotherapy for sarcomas, leukemia, lymphomas, and breast cancer [16, 17]. Pelvic radiation therapy is also known to cause follicular destruction followed by reproductive dysfunction [4, 8, 18, 19]. Ovarian failure from these agents appears to be dose-related and the effect is dependent on age at the time of treatment [16, 20]. In women 30-39 years of age, a dose of 9 gm/m<sup>2</sup> of cyclophosphamide results in ovarian failure, while in women who are a decade younger, 20 gm/m<sup>2</sup> causes a similar effect. In contrast, the prepubescent female has been shown to tolerate as much as 25-30 gm/m<sup>2</sup> of cyclophosphamide and still retain ovarian function. However, such patients remain at high risk for eventual development of infertility and premature ovarian failure [17, 21]. This reduced frequency does not mean that young girls are unaffected by the chemotherapy, but the observation likely reflects the larger follicular pool at the time of treatment. Eventual early ovarian failure in children does occur, but it is not immediate [22, 23]. It is clear that the reproductive effects of cancer therapies cannot be predicted with accuracy from age and treatment parameters alone. We believe that the severity of the reproductive effects depends largely on the size of the follicular pool prior to treatment. Those with the largest reserve, will be more resistant to the effects of cancer therapy, and therefore will be less likely to experience acute and chronic premature ovarian failure and infertility. One of the overarching goals of the proposed study is to determine if measures of ovarian function can be used to predict the ultimate prevalence or severity of subsequent reproductive dysfunction in this population.

### Clinical Signs of Ovarian Dysfunction Occur Late Following Treatment

In women already treated for cancer, it is difficult to predict whether, and the extent to which, they will experience reproductive dysfunction. Once clinical symptoms of ovarian dysfunction occur such as irregular menses and vasomotor symptoms, the hormonal changes have already occurred and pregnancy is usually not possible even with aggressive fertility treatments. Even women who maintain cyclic menses after therapy are at risk for early menopause, infertility, and long-term health problems related to early ovarian failure. [8, 16, 17, 24-28] Childhood and young adult cancer patients are the MOST likely to suffer from the long term reproductive effects since they have many years to live and the majority have not had children. Therefore

understanding the effect of these cancer therapies on the H-P-O axis and possible recovery is important because early detection of compromised ovarian function is necessary to offer cancer survivors viable fertility options and improvement in their quality of life. For instance, being able to predict when ovarian failure is expected to occur would be helpful in determining the need for sex steroid replacement in achieving normal puberty, the window of fertility for family planning, and the onset of menopause for bone and cardiovascular health.

### **The Importance of Fertility to Cancer Patients**

The ability to lead full reproductive lives is very important to young cancer survivors [11, 12]. Indeed, there is substantial evidence that this is a major issue of concern. According to a recent study, three-fourths of cancer patients surveyed raised the issue of fertility with their physician and one third of young women with breast cancer reported that fertility concerns influenced their treatment decisions [29]. Moreover, reproductive problems often lead to substantial anxiety which negatively affects quality of life in cancer survivors [30]. Given the importance of this area, fertility concerns will be assessed as part of this investigation.

While fertility is not the focus of this proposal, the findings will nonetheless have a significant impact on counseling cancer patients about fertility preservation. Currently, limited options are available for girls and young women suffering from cancer to ensure future reproductive capacity. The most successful option for fertility preservation in women facing cancer is emergency IVF and embryo cryopreservation prior to chemotherapy. However, this method is not appropriate for young women without a partner or who do not have time to delay lifesaving treatment. Other yet unproven options for fertility preservation in cancer patients include oocyte and ovarian tissue cryopreservation (being studied by us as part of the .t) [23, 31-33]. These methods are considered experimental, costly, and have no guarantee of success. Better methods to predict the degree of post treatment reproductive dysfunction would allow those at highest risk to pursue these procedures before treatment. In addition, assessment of reproductive potential post treatment would also provide an opportunity for women to seek aggressive fertility therapy before menopause occurs.

### **Similarities to Natural Reproductive Aging**

Like reproductive aging caused by cancer treatments, natural reproductive aging is a result of a decline in ovarian follicle numbers [34] and is accompanied by classic changes in reproductive function. It has been well documented that fertility declines and the risk of miscarriage increases after the age of 35 and even more dramatically after age 40 [35]. Later, menstrual cycles become irregular primarily due to anovulation. Previous work from our group has shown that classic symptoms of natural reproductive aging and the menopausal transition described in longitudinal studies include vasomotor symptoms, sleep disturbances, changes in sexual function, and mood symptoms [36].

As seen in the cancer survivor, ovarian follicle number and quality are impaired well before any clinical signs (menstrual irregularity or symptoms) of the menopausal transition occur. Even in still regularly menstruating women, studies have documented progressive decreases in hormones secreted by follicles such as Inhibin B (INH) and anti-mullerian hormone (AMH), while Follicle Stimulating Hormone (FSH) levels rise as a result of the removal of inhibin restraint on the pituitary [37-43]. Morphometric assessments of the ovaries using ultrasonography reveal decreased antral follicle counts (AFC) and a reduced ovarian volume (OV) [44, 45]. AMH and AFC are highly correlated and decreases in these measures are thought to reflect the size of the primordial follicle pool. Data also suggests that the rate of change of measures of ovarian reserve (FSH, INH, AMH, AFC) over time is greater during the late reproductive years compared to the mid-reproductive years [43] and that a AMH levels may be an accurate predictor of age at menopause [46]. Daily urinary hormone studies in menstruating women during the late reproductive years compared to mid-reproductive aged women have demonstrated elevations in follicular gonadotropin levels, elevations in estradiol metabolites, and evidence of luteal dysfunction [47-49]. These findings from urinary measures further support that ovarian follicle quality and quantity are impaired even in ovulatory women in the late reproductive years. We hypothesize that if premature ovarian failure secondary to gonadotoxic treatment is preceded by reproductive changes analogous to those seen with age-related changes, similar changes in reproductive hormones, and ultrasound measures will be observed. We hypothesize further, that such measures should reflect fertility potential and time to menopause in cancer survivors.

**What measures have been used to assess reproductive capacity?** Several of the above mentioned hormones and ultrasound measures have been utilized to evaluate a woman's fertility potential and response to fertility treatments in the infertility clinic setting. Specifically, these include early follicular phase measures of serum FSH, Inhibin B, and AMH, and ultrasound measures of OV and AFC.

**Basal Follicle Stimulating Hormone (FSH)** is an indirect measure of ovarian function and has been the most commonly utilized biochemical surrogate marker for decreased ovarian reserve. It should be noted that interpretation of FSH results requires determination of basal estradiol (E2) levels. Studies indicate that FSH is highly sensitive for poor response to ovarian stimulation and is highly predictive of pregnancy rates primarily in older patients (over 35) undergoing IVF. Even in younger patients with elevated FSH there is evidence for poor quality oocytes, lower pregnancy rates, and higher aneuploidy rates [41, 50-56].

**Inhibin B (INH)**, secreted mainly by granulosa cells of the pre-antral ovarian follicles, is thought to be a more sensitive measure of the ovarian follicular pool than FSH and may be of value in predicting pregnancy with assisted reproduction [57-60].

**Anti-Mullerian Hormone (AMH)**, a member of the transforming growth factor  $\beta$  super family, is produced by granulosa cells from small pre-antral and antral follicles and is hypothesized to inhibit the recruitment of primordial follicles into the pool of growing follicles [61]. AMH levels show a progressive decrease with age [62, 63], supporting the notion that AMH levels correlate directly with the size of the available follicle pool in the ovary. Levels fluctuate minimally during the menstrual cycle [63, 64], which makes AMH a convenient measure of fertility potential. AMH levels appear to correlate with ovarian response in IVF, but use of serum AMH levels to predict pregnancy needs validation [65-68].

**Ovarian Volume (OV)** is determined by ultrasound based measurement of ovarian size, has been shown to decrease in women aged 40 years and older and predict pregnancy with assisted reproduction [45, 69, 70].

**Antral Follicle Count (AFC)**, defined as the number of follicles < 10mm in diameter detected by ultrasound in the early follicular phase of the menstrual cycle, is another parameter found to correlate with age [44]. In particular, there is evidence that small antral follicles (2-5mm) correlate well with AMH levels [71]. A recent meta-analysis comparing basal FSH levels and AFC revealed that AFC is more predictive of ovarian response to ovarian stimulation as part of infertility treatment [72]. AFC, however, has more inter-cycle variability, reflecting the biological variation of ovarian function from cycle to cycle and may be more difficult to assess accurately in the pediatric patient unwilling to undergo transvaginal sonography.

**Other measures** in banked serum and urine may be assessed if novel markers are identified during this study.

### **Effect of cancer therapy on measures of ovarian function**

Limited data, only in late reproductive aged breast cancer patients, exists documenting the acute effects of chemotherapeutic agents on endocrine function prior to, during and immediately following treatment. A large prospective study of menstrual diaries reported that acute amenorrhea during chemotherapy affected approximately 60% of breast cancer patients, and that return of menstrual function 6 months post treatment was dependent on a patient's age and chemotherapy regimen [73]. Two small studies have reported that AMH and INH levels fall while FSH levels rise during the first 3-6 months of chemotherapy [74] and there is further evidence to suggest that the occurrence of chemotherapy related amenorrhea may correlate with pretreatment measures of AMH [75]. Years after treatment for cancer, basal FSH, INH, AMH, OV and AFC are impaired in survivors compared to controls (See Preliminary Data) [76-80]. Of these, it appears that AMH and AFC are the most sensitive measures of ovarian reserve since they have been found to be lower even in subjects with normal basal FSH levels and regular menstrual cycles (See Preliminary Data) [81]. It is important to recognize that studies conducted to date on this topic are severely limited by several factors that may have substantially biased the results: cross sectional assessment of ovarian measures or short follow up time, small sample sizes, age disparities between cases and controls, diverse gonadotoxic treatments, and inclusion of subjects taking exogenous hormones. No longitudinal studies have been conducted assessing similar measures of ovarian function in adolescent and young adult cancer survivors (perhaps the most clinically relevant population). Moreover, no study has compared the day to day characteristics of reproductive hormones in menstruating cancer survivors to better assess follicle competency. Such data would help to elucidate which test(s) may best predict the otherwise "invisible transition" toward decreased ovarian reserve and/or premature ovarian failure and help define a cancer survivor's time to menopause, or "reproductive window".

### **Significance:**

The proposed study will be the first to our knowledge to comprehensively investigate the acute and chronic reproductive effects of chemotherapy and radiation treatment in adolescent and young reproductive age women. This is relevant to addressing one of the most important quality of life issues in cancer survivors, namely, reproductive potential. The information gained will broaden our scientific understanding of the effects of cancer therapy on the H-P-O axis. Moreover, this has direct clinical implications as it will help to establish a method to predict the impact of such treatments on subsequent reproductive function prior to therapy and enable rapid assessment of the fertility risk of newly developed therapeutics. Ultimately this study will help to determine if these measures are useful in predicting fertility and premature ovarian failure in this population. Specifically these data will be critical for targeting fertility preservation efforts in newly diagnosed cancer patients and will be instrumental in the establishment of an effective surveillance protocol for the early detection of compromised ovarian function after cancer treatment so that young cancer survivors may rationally decide to pursue aggressive treatment with assisted reproductive technologies while there is still a reasonable chance of success. As the technology for effectively preserving fertility with oocyte and ovarian tissue banking rapidly progresses, it will be critical to effectively counsel patients about the gonadotoxic risk of specific treatments. We believe that the findings from this study will have a major impact on the quality of life of cancer survivors.

It should be stressed that we are well positioned to successfully complete these investigations. As outlined below, we have the collective expertise, a supportive environment, and we have already demonstrated the ability to recruit cancer patients for such studies. Most importantly, we have established critical research collaborations within the [redacted], the [redacted] and the [redacted] and have established a web based database that will make this important research possible.

### **The Research Team**

[redacted] is an Assistant Professor in the Department of Obstetrics and Gynecology at the University of [redacted]. Following training in Obstetrics and Gynecology at [redacted] Dr. [redacted] completed a fellowship in Reproductive Endocrinology and a Master of Science Degree in Clinical Epidemiology and Biostatistics (MSCE) at the University of [redacted]. During her training, she was supported by an NICHD Reproductive Epidemiology Training Grant (T32- [redacted]) and it should be highlighted that during her subspecialty and research training the focus was placed in preparing her for a career conducting independent clinical research. Dr. [redacted] is one of the few specialists specifically trained in both reproductive endocrinology and epidemiology with a track record in the important area of reproductive aging and Oncofertility. This is the niche she has developed since joining the faculty at the University of [redacted] as an Institutional [redacted]. Her NIH-funded academic development has progressed to an individual [redacted] award [redacted] as part of the [redacted] consortium roadmap grant ( [redacted] ) (as of June [redacted], and an R03 ( [redacted] ). In addition and complementing the studies in cancer patients, Dr. [redacted] has been involved in studies assessing ovarian function in otherwise healthy women approaching the menopausal transition. Dr. [redacted] is a co-investigator in the [redacted] [redacted] has been ongoing for 12 years assessing symptomatic and hormonal changes during the menopausal transition. She has spearheaded and published several investigations assessing reproductive function in late reproductive age women, similar to those proposed in this application [82-86]. With her involvement in the [redacted] she has established herself as a regional expert in [redacted] and has given multiple presentations nationally and regionally on this topic. She has clinical hours dedicated to this activity and sees newly diagnosed cancer patients and cancer survivors for counseling regarding fertility preservation and for the treatment of the long term reproductive and endocrine complications associated with cancer treatments. Importantly, Dr. [redacted] is the principal investigator on 2 experimental protocols at [redacted] for oocyte and ovarian tissue cryopreservation, in addition to conducting the 2 ongoing prospective cohort studies studying the acute and long-term reproductive effects of cancer therapies described below. In summary, Dr. [redacted] has been supported on K [redacted] awards for 4 years, has developed a research niche and has generated compelling preliminary data. Her contributions and productivity to date make her an ideal candidate to now progress to a comprehensive investigator-initiated RO1-funded research program as proposed in this application.

is Assistant Professor of Pediatrics in the Division of Oncology at The [redacted] with a particular interest in cancer survivorship. She completed her medical degree at [redacted] her residency in pediatrics at [redacted] and subspecialty training in Oncology at The [redacted]. She has been collaborating successfully with Dr. [redacted] assessing the reproductive effects of cancer therapies in survivors ([redacted]) and has recently received IRB approval to conduct the longitudinal study of reproductive function in newly diagnosed subjects. Dr. [redacted] has also been working in collaboration with Dr. [redacted] on establishing a fertility preservation program for children at [redacted]. Dr. [redacted] and the clinical coordinator at [redacted] will identify and enroll newly diagnosed cancer patients and cancer survivors through the Division of [redacted] in close collaboration with the investigative team at the University [redacted].

[redacted] is board certified as an oncology and primary care nurse practitioner and has an appointment as a Clinical Associate Professor at the School of Nursing at [redacted] where she was the program director and in 1995 developed [redacted] in the country. Dr. [redacted] is well known to the oncology community and is the Director of the multidisciplinary [redacted] at the [redacted] of the University [redacted]. [redacted] supported in part by the [redacted] in collaboration with [redacted] she developed the [redacted] at [redacted] into a national model for the care of adult cancer survivors, and established the [redacted], a joint effort between the [redacted] and the [redacted] Center, to provide care to adult survivors of childhood cancer. Dr. [redacted] consults with institutions across the country and has an extensive list of publications, many that focus on cancer survivorship issues. Dr. [redacted] will assist in recruitment of newly diagnosed and survivors of cancer at the [redacted].

[redacted] is Associate Professor of Biostatistics in the Department of Biostatistics and Epidemiology at the University [redacted] and Senior Scholar in the [redacted]. Dr. [redacted]'s statistical research interests are in the area of multivariate and longitudinal data analyses. Since joining the faculty in the Fall of 1997, she has continued her methodological research and has collaborated extensively with epidemiologists and physicians in the design and analysis of clinical research studies in women's health and reproduction. Dr. [redacted] directs a biostatistical core (funded beginning in 1998) to mentor junior faculty in OB/GYN involved in basic science, translational and clinical research, and is Co-Investigator on several projects including The [redacted] aging study (PI: Dr. [redacted]). Dr. [redacted] is actively involved in training future medical researchers through her teaching and mentoring in the Master of Science in Clinical Epidemiology program. She has also served as the Associate Director of residency research to the Department of Ob/Gyn since 2005. She and Dr. [redacted] have worked closely in the past and have co-authored multiple publications. [redacted] will be working closely with Dr. [redacted] and the data analysis team to ensure appropriate statistical analysis.

[redacted] is a Professor and Director of the Division of Reproductive Endocrinology and Infertility in the Department of Obstetrics, Gynecology and Women's Health at the [redacted]. Dr. [redacted]'s major research interests include the reproductive endocrinology of the menopausal transition; infertility; and the [redacted]. She has been involved with numerous industry- and government-supported clinical trials, including the [redacted] and the [redacted]; has authored or co-authored more than 100 peer-reviewed articles, books, book chapters and abstracts. She brings a wealth of experience to this investigation as an expert in urinary hormone studies. She and Dr. [redacted] have a collaborative relationship and have worked together in the past successfully [36] (postgraduate course ACOG 2009). She will be a consultant for optimizing performance and validating the urinary hormone assays performed as part of Specific Aim 3 (Refer to letter of support).

## **Resources**

[redacted]. This consortium, which is funded by an NIH Roadmap grant ([redacted] PI) represents a unique multi-disciplinary research collaboration aimed at bringing novel reproductive technologies, specifically ovarian tissue cryopreservation, to preserve fertility in cancer patients from bench to bedside. Collaboration between diverse disciplines including basic reproductive research, clinical research and the social sciences makes this program exciting and unique. As one of the core investigators of the

(K01 recipient), has collaborated closely with well known investigators in this area across the country meeting with the investigators monthly at laboratory and national meetings. intends to continue close collaboration with the investigators who have supported her development into an independent clinical investigator and use these individuals as consultants. Some of these key individuals include: , and (Refer to letters of support)

The will be one of the primary sites for recruitment of subjects for this investigation. treats approximately 80 percent of all children with cancer in the Greater region. Approximately 400 new patients with cancer or related diseases are admitted annually to the t at and more than 2,000 children and young adults are evaluated for the possibility of recurrent cancer and for the development of treatment-related disease. has the second largest pediatric research program in the United States and was the first children's hospital to initiate a pediatric research department. , a member of this division, has been and will continue to collaborate closely with the PI,

is an NIH funded unit (via the CTSA) located in the dedicated to facilitating clinical and translational research at Penn. The supports a wide range of clinical research, supporting 152 clinical research protocols under the direction of a total of 74 investigators. The grant that supports the is the largest NIH grant at the School of Medicine, and one of its missions is to support junior faculty in the transition towards independence. In 1991 was recruited by the to develop the original GCRC Core Lab. has set up more than 150 different assays & has published (author or co-author) in more than 70 publications. will be performing the serum and urinary assays for this study.

The staff will be responsible for facilitating the clinical portions of the proposal and obtaining, cataloging and distributing all clinical specimens for analysis. The staff are highly experienced in conducting high quality clinical research in women's health, and have been involved in over 35 multi-center trials. Currently, the is participating in two NICHD clinical trial networks, (Reproductive Medicine Network and the Contraception Clinical Trials Network) as well 5 NIH sponsored multi-center trials. is a member of this Center and the staff are committed to supporting the proposed project (see letter of support from , Center Director).

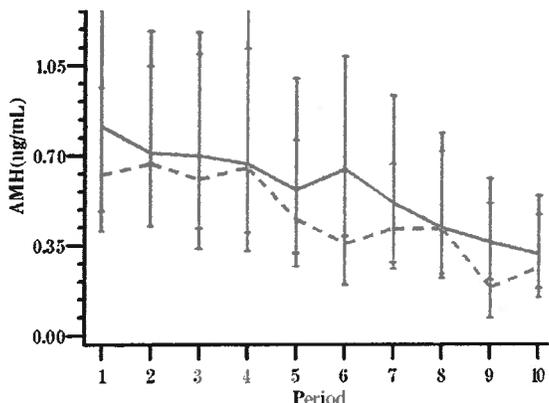
### C. Preliminary Studies

This application represents a collaboration of clinical and basic science research using diverse expertise that is all available within a few blocks on the campus. The cornerstone of this proposal is the large oncology practices at the and the at the

This large clinical population is complemented by a well-established, experienced clinical research unit in reproduction ) and an outstanding endocrine laboratory facility at the CTCRC.

The multi-disciplinary research team and outstanding facilities will allow a comprehensive evaluation of the acute and chronic reproductive potential effects of cancer therapy. This collaboration has already demonstrated success as evidenced by our preliminary results.

**Figure 2. AMH levels over 10 years**



### Evidence of Productivity in the Area of Reproductive Aging

has been studying reproductive aging for several years as a co-investigator on the This is a large-scale longitudinal study of over 400 women examining the natural progression of ovarian function during the transition to menopause. This cohort is unique in that it is composed of women enrolled prior to the earliest stages of the transition (women between the ages of 35 – 45 were enrolled). To date, subjects have been followed for a total of 12 years with extensive questionnaires, anthropometric measures and hormone assessments. and colleagues have

published 19 manuscripts (of which she is first author on 4) studying hormone changes and menopausal symptoms during the transition [37, 82-85, 87-90]. interests have focused on the association between bleeding patterns and reproductive hormones; in particular she has focused on the study of INH and AMH levels during the late reproductive years [82-86]. The study of AMH was one of the first to clearly document the steady decline in levels over time in late reproductive aged women (Figure 2). This work directly relates to the proposed investigation which aims to compare the change in measures, including AMH, over time between women exposed to gonadotoxic therapy and unexposed controls [87].

### Acute Changes in Measures of Reproductive Function During Cancer Treatment

Over the past year, has recruited 19 newly diagnosed adult cancer patients for the longitudinal assessment of measures of ovarian reserve prior to, during and after cancer therapy. Table 1 presents preliminary data from 13 subjects. All subjects in this preliminary study underwent a baseline assessment of ovarian reserve and at least 1 assessment during cancer therapy, with a median time between visits of 5.8 months. Table 1 presents median pretreatment and during treatment hormone and ultrasound measures of ovarian reserve.

Preliminary observations suggest that direct measures of ovarian reserve (AMH, INH, AFC) decline while indirect measures (FSH) rise. These findings support the hypothesis that developing follicles are destroyed acutely by treatment resulting in expected derangements in the H-P-O axis. It is anticipated that measures should partially normalize as a new cohort of follicles emerges from the primordial follicular pool. To date, this hypothesis has not been tested in a longitudinal study of pediatric and young adult cancer patients. More intriguing is the question: can we predict future measures of ovarian reserve (and reproductive lifespan) based on baseline measures and specific treatment parameters? (We plan to evaluate this in Specific Aim 1).

	Pretreatment Median (Range) N=13	During Treatment Median (Range) N=10	P – value*
FSH (mIU/ml)	8.4 (2.6-17.6)	12.5 (7.3-155.4)	0.07
E2 (pg/ml)	45.7 (2.7-271.9)	16.3 (5.4-132.5)	0.114
<b>Inhibin B (pg/ml)</b>	<b>41.4 (14.1-113.5)</b>	<b>8.9 (2.7-78.1)</b>	<b>0.007</b>
<b>AMH (pg/ml)</b>	<b>3880 (79-10760)</b>	<b>116.5 (62-3820)</b>	<b>0.005</b>
Uterine Volume (mm <sup>3</sup> )	42,291	37,924	0.33
OV (mm <sup>3</sup> )	7,015	5,704	0.58
<b>AFC</b>	<b>20.5</b>	<b>5</b>	<b>0.02</b>

\*Wilcoxon signed rank test

**Late Effects of Cancer Therapy on Measures of Reproductive Function:**

Over the past 2 years, [redacted] has enrolled 52 adolescent and young reproductive age women between the ages of 15-35 years exposed to chemotherapy, and 63 similarly aged unexposed subjects for the longitudinal study of reproductive function ([redacted]). To date, she has conducted a cross-sectional analysis comparing reproductive hormones and ultrasound measures between 45 females exposed to chemotherapy and 57 unexposed females of similar age. The majority of the cancer survivors were exposed to alkylating agent chemotherapy (90%), specifically cyclophosphamide (80%), and 27% had undergone pelvic radiotherapy.

A comparison of baseline characteristics reveals a similar demographic makeup of the two populations (mean age 25.1 vs. 26.8 years, BMI 23.8 vs. 25.1 kg/m<sup>2</sup>, and largely Caucasian). Analyses using linear regression models of log transformed hormones, adjusted for age, race and BMI demonstrate that FSH, E2, AMH and AFC's are significantly different between exposed and unexposed subjects (Table 2). When the analysis was restricted to only those subjects experiencing regular menstrual cycles (35 exposed, 57 unexposed), levels of AMH and AFC's were significantly lower than unexposed subjects (AMH 396.1

	Exposed (N=45)	Unexposed (N=57)	P value
<b>FSH (mIU/ml)</b>	<b>11.5 (5.1, 25.8)</b>	<b>7.2 (3.0, 17.2)</b>	<b>0.002</b>
<b>E2 (pg/ml)</b>	<b>6.8 (3.1, 14.9)</b>	<b>9.7 (4.1, 22.5)</b>	<b>0.015</b>
INH (pg/ml)	15.5 (5.1, 47.1)	19.2 (5.8, 64.1)	0.282
<b>AMH (pg/ml)</b>	<b>533.7 (86.1, 3309.7)</b>	<b>3360.1 (467.1, 24170.2)</b>	<b>&lt;0.001</b>
OV (mm <sup>3</sup> )	2521 (0, 4997.0)	3105 (0, 10528.8)	0.65
<b>AFC</b>	<b>27.7 (21.2, 34.2)</b>	<b>42.9 (23.0, 62.7)</b>	<b>&lt;0.001</b>
Geometric Means (95% CI) of hormone values, adjusted for age, BMI, race			

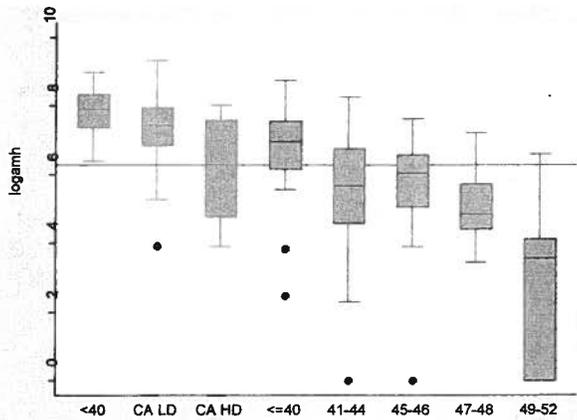
vs. 1903.6pg/ml, p<0.001; AFC 28.2 vs. 41.8, p<0.001). We also noted a dose relationship: FSH and AMH levels were significantly lower in subjects exposed to high dose therapy (cyclophosphamide ≥ 15g/m<sup>2</sup>, ifosfamide >40g/m<sup>2</sup>, or bone marrow transplant) compared to those exposed to low dose therapy (Table 3).

This supported the aims of the R03. Our next step was to determine whether these measures predict the time remaining before the occurrence of menopause (reproductive window). As a first step towards this goal, it was important to correlate these measures to naturally aging women at various times in their reproductive life. This was accomplished by comparing the measures collected from regularly menstruating women post chemotherapy to the measures of regularly menstruating subjects in the late reproductive years followed in

	Low Dose (N=20)	High dose (N=25)	P value
<b>FSH (mIU/ml)</b>	<b>9.8 (2.1, 46.6)</b>	<b>18.3 (4.1, 80.7)</b>	<b>0.028</b>
E2 (pg/ml)	5.1 (1.3, 19.7)	4.3 (1.2, 15.6)	0.460
INH (pg/ml)	12.1 (1.7, 88.2)	9.0 (1.4, 60.1)	0.405
<b>AMH (pg/ml)</b>	<b>295.3 (23.7, 3680.8)</b>	<b>77.4 (7.0, 861.1)</b>	<b>0.004</b>
OV (mm <sup>3</sup> )	4044.2 (0, 12776.8)	3116.4 (0, 2136.2)	0.544
AFC	10.8 (0, 32.6)	5.2 (0, 12.8)	0.146
Geometric Means (95% CI) of hormone values, adjusted for age, BMI, race			

[redacted] Table 4 presents early follicular phase reproductive measures in regularly menstruating subjects by group: 1) unexposed, 2) low dose exposure, 3) high dose exposure, and 3) late reproductive aged women. Subjects exposed to high dose therapy have levels of AMH more similar to those of the late reproductive aged women than healthy similarly aged unexposed subjects.

	Unexposed (N=57)	Low Dose (N=19)	High dose (N=16)	Late Reproductive (N=57)	P value
Age	27.1	25.2	24.9	43.0	0.002
FSH (mIU/ml)	7.08 (4.2, 11.8)	7.33 (4.2, 12.7)*	9.07(5.4, 15.3)*	8.35 (4.9, 14.3)	0.318
E2 (pg/ml)	27.2 (15.5, 47.7)	21.1 (11.5,38.7)*	22.4 (12.6, 39.6)	33.4 (18.5, 60.1)	0.261
INH (pg/ml)	45.8 (20.0, 104.8)*	47.3 (19.4, 115.6)	45.2 (19.5, 104.9)	82.5 (34.7, 196.2)	0.013
AMH (pg/ml)	4803.9 (1369.2, 16854.4)**	2068.7 (533.9, 8016.8)**	367.0 (102.3, 1316.3)	206.9 (55.2, 776.1)	<0.001
**< 0.01 difference compared to late reproductive group; * <0.05 difference compared to late reproductive group					



**Figure 3. Log AMH by exposure group.** Unexposed (1<sup>st</sup> bar), low dose (CALD), high dose (CAHD), late reproductive age women stratified by age (last 5 bars)

In order to further compare measures in cancer survivors to those of naturally aging women, we plotted hormone levels by group and further stratified the late reproductive women by age. Figure 3 represents log AMH levels in each group: unexposed, low dose exposure, high dose exposure, and in the late reproductive age women stratified by age. It appears from this plot of untransformed raw data that measures of log AMH in the high dose exposure group approximate levels in late reproductive age women during the early 40's. These data are compelling since it suggests that these measures may help to predict time to menopause. However, the wide confidence intervals indicate that a larger, more appropriately powered study is needed to confirm these findings. In addition, the predictive value of these measures for fertility should be further evaluated because over the past 2 years, 7 cancer survivors have conceived spontaneously (Table 5). Interestingly, not all subjects who conceived had

“normal” ovarian reserve measures. In fact, 2 subjects had what one would define as extremely compromised ovarian reserve. This data demonstrates that a number of subjects recruited for this study are attempting conception. Analysis of time to pregnancy data in this population will yield important information about the predictive value of these measures for pregnancy. No study to date has reported the utility of these measures for predicting pregnancy in this population. These data will be critical for designing definitive studies to validate these measures with time to pregnancy and menopause. The remaining batched specimens are being analyzed for this study and the manuscript is being prepared for publication.

Spontaneous pregnancies = 7	Median	Range
Age	29	24-35
FSH (mIU/ml)	7.96	4.9 - 20.8
E2 (pg/ml)	31.45	16.6 – 81.0
Inhibin (pg/ml)	38.77	<5 - 133.7
AMH (pg/ml)	624	<50 – 8,650
AFC	3	2 - 45

**Evidence of Collaboration with**

has also collaborated with investigators within the at the to determine the relationship between post-chemotherapy menstrual patterns and reproductive hormones. To date, 127 breast cancer patients with Stages I-III disease, premenopausal at diagnosis, have been enrolled post-chemotherapy and have been followed prospectively. The primary endpoint is chemotherapy-related amenorrhea (CRA, >12 months of amenorrhea after chemotherapy). Associations between hormones and CRA have been assessed. Analyses compared cancer to healthy, age-matched control subjects. Median age at

chemotherapy was 43.2 years (range 26.7-57.8). At Assessment 1, median follow up since chemotherapy was 2.1 years. 55% of subjects had CRA. AMH and INH were inversely associated with CRA risk (RR=0.87, p=0.01; RR 0.84, p<0.001). FSH increases were associated with CRA (RR1.94, p<0.001). Undetectable AMH, undetectable INH and FSH levels > 40 mIU/mL were 81%, 81%, and 94% specific for CRA, respectively. Compared to controls, breast cancer subjects had higher FSH, lower AMH and INH levels and more advanced menopausal stages. This study suggests that AMH, INH and FSH are promising surrogate measures of post-chemotherapy ovarian function. This work highlights the importance of evaluating the utility of these measures in a younger, menstruating population of survivors (the focus of Aim 2) and demonstrates Dr. Gracia's successful collaboration with the investigators at the . This manuscript has been submitted for publication [91].

**Ability to recruit subjects and conduct study procedures:**

The cornerstone of this proposal is the large pediatric and adult oncology practices at and the at the . This large clinical population is complemented by a well-established experienced clinical research center in reproduction, the Center. This Center will facilitate the clinical portions of the proposal and obtaining, cataloging and distributing all clinical specimens for analysis. This collaboration has already demonstrated success as evidenced by our preliminary results. We are uniquely situated to perform these investigations as is a large pediatric and

adult tertiary care medical center for the greater tri-state area. In addition, as the only core site for the roadmap grant on the \_\_\_\_\_ is a major referral center for for both newly diagnosed cancer patients and cancer survivors. Moreover, collaboration with \_\_\_\_\_ Director of the multidisciplinary, multi-center \_\_\_\_\_ of Excellence at the \_\_\_\_\_, will also promote referrals of cancer survivors for this proposal.

As described above, the principal investigator has been involved in similar studies assessing ovarian function not only in cancer patients, but also in otherwise healthy women approaching the menopause \_\_\_\_\_ has established both a clinical and research niche in the area of \_\_\_\_\_ and has demonstrated fruitful collaborations with investigators at the \_\_\_\_\_ and \_\_\_\_\_. In addition, as a core investigator in the \_\_\_\_\_ has established important collaborations with several institutions across the country. \_\_\_\_\_ has obtained multiple referrals from outside institutions through this network and this number is growing steadily. \_\_\_\_\_ previous research experience, \_\_\_\_\_ clinical expertise, and \_\_\_\_\_ ability to establish a cohort of cancer patients and survivors in order to obtain preliminary data demonstrates the principal investigator's ability to conduct such research procedures in an efficient manner.

#### **How this proposal differs from previous studies**

This investigation is a comprehensive evaluation of the acute and chronic reproductive effects of cancer treatments. We will assess the acute and chronic (long-term) effects simultaneously in this proposal by conducting studies in both newly diagnosed cancer patients until at least 6 months post treatment (Specific Aim 1), and in cancer survivors at least 1 year from therapy (Specific Aim 2 and 3). Both groups will be followed prospectively to allow for an assessment of change in parameters over time compared to similarly aged and late reproductive aged controls. This is the first investigation to make direct comparisons to unexposed women across the reproductive lifespan. These data will provide an important framework for predicting fertility and time to menopause in the cancer population. Our prospective approach will minimize confounding and bias and will comprehensively assess reproductive function in cancer patients. Our goal is to study the effects of alkylating agent therapy, but we will include other treatments in order to make the results generalizable. While data on time to pregnancy will be captured, fertility is not the main goal of this proposal since it is not a feasible outcome in a study of this scope. In addition, a novel component of this project is the urinary assessment of hormone metabolites in regularly menstruating high risk cancer survivors to further establish that reproductive dysfunction in cancer survivors is analogous to that of late reproductive aged women.

It should be noted that the ideal study would have involved the prospective evaluation of cancer patients prior to treatment, during treatment and for 20+ years following completion of therapy. For pediatric cancer patients, the follow-up period would have to have been even longer. Obviously, such an ideally designed study would go beyond funding timetables and would take many years for any interpretable results to be obtained. Thus, the present study was designed to obtain the acute change data (Specific aim 1) within a year from completion of cancer therapy and the long-term effects will be evaluated by recruitment of another cohort of patients who had received their therapies in the past (Specific aims 2 and 3). Analysis of the aggregate data will thus provide information about the long-term, chronic effects within the constraints of a five-year funding award.

## D. Experimental Design and Methods

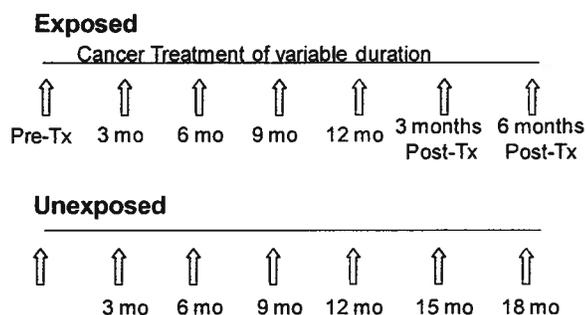
### Specific Aim 1: Assess acute changes in reproductive function during and after chemotherapy in cancer patients.

*Specific Hypothesis to be tested: Chemotherapy causes acute follicular depletion, resulting in significant changes in functional markers of the H-P-O axis and such changes are dependent on pre-treatment level of ovarian function, treatment parameters and subject characteristics.*

#### Rationale

The objective of this study is to assess changes in surrogate measures of reproductive function during and after chemotherapy compared to similarly aged unexposed controls. This aim will help to document the acute endocrine changes that occur during and immediately after cancer therapy. Specifically, it will help establish the time course of ovarian dysfunction that occurs with chemotherapy, and enable the assessment of whether baseline variables and specific treatment parameters predict changes in measures of ovarian function.

**Figure 4. Study Design**



#### Study Design

This is designed as a prospective cohort study assessing measures of reproductive function every 3 months for 1 year in newly diagnosed cancer patients up to 35 years of age receiving chemotherapy and then every 3 months post treatment for 6 months, compared to unexposed similarly aged controls (Figure. 3).

#### Study Population

Subjects with cancer will be identified through the Oncology practices at [redacted]

[redacted] and at the [redacted] of the [redacted], and through community referrals. Unexposed subjects will be recruited from the same centers through local advertising at physicians' practices and in the community. Recruitment of an unexposed population, is critical to definitively demonstrate that changes in measures in the exposed population are greater than unexposed subjects. Targeted recruitment of the unexposed population will be conducted so that the unexposed population is balanced with respect to age and oral contraceptive use to the exposed population.

#### Inclusion and Exclusion Criteria

Inclusion Criteria for exposed population: Postmenarchal females to be treated with chemotherapy between the ages of 11-35 years, with a uterus and at least one ovary. Unexposed females will be healthy, postmenarchal, with no prior exposure to chemotherapy, between the ages of 11-35, with a uterus and at least one ovary. Exclusion criteria for all subjects includes current pregnancy and lactation within the previous 3 months, previous diagnosis of an illness associated with premature ovarian failure (Turner's syndrome, Fragile X permutation carrier) or endocrine disorder associated with irregular menstrual cycles (Cushing's disease, Thyroid disease, hyper-prolactinemia, polycystic ovary syndrome, congenital adrenal hyperplasia). Additional exclusions for the unexposed population include a history of infertility, defined as at least 12 months of unprotected intercourse without conception

#### Study Procedures

A pretreatment visit and visits every 3 months x 4 and 2 post-treatment visits will be completed. These visits will include:

**Demographics:** A self report form will be completed by the patient for this purpose.

**Structured interview:** All study participants will be questioned regarding medical history, menstrual data, fertility concerns, fertility preservation/treatments, pregnancy risk, pregnancy history, medication use, and social history. Specifically, questions regarding cancer diagnosis and treatment plan will be collected. Use of hormonal contraception, gonadotropin releasing hormone agonist therapy, or use of hormone replacement therapy will be recorded. Of note, the oncologists at [redacted] do not routinely administer gonadotropin releasing

hormone agonist therapy for ovarian protection to cancer patients since there is insufficient data to support its use. In addition, the Menopausal Symptom List (MSL), a validated instrument for assessing menopausal symptoms, will be used to assess the presence or absence of menopausal symptoms during the past month, the frequency and severity of each symptom. Symptoms captured include: hot flashes, vaginal dryness, concentration/memory problems, irritability, mood swings, feeling sad, feeling anxious, trouble sleeping, aches, joint pain, headaches [92].

**Physical Examination Data:** Height and weight will be determined for the calculation of body mass index. In addition, a brief physical examination will be conducted to document Tanner Staging.

**Menstrual Diaries** will be given to participants and they will be instructed to keep track of any bleeding.

**Serum Testing:** Blood samples will be obtained for determining levels of FSH, E2, INH, and AMH. In regularly menstruating girls and young women every attempt will be made to collect hormone measures during the early follicular phase of the menstrual cycle (days 1-4).

**Pelvic Ultrasonography** OV and AFC by size (2-5 mm, 6-9 mm, and >10 mm) will be determined. Uterine size and endometrial thickness will also be performed.

**Review and Documentation of Cancer Therapy** Cancer treatments will be abstracted from the clinical chart by the oncology offices caring for the patient (See Appendix).

### **Exposure Data**

Exposure data will be obtained from a structured interview during the study visits and by reviewing medical records of all treatments from the subject's primary oncology office. Treatment will be summarized in terms of chemotherapeutic type, duration and cumulative dose; total radiation dose and location; history and type of bone marrow transplantation; and any surgery. Any attempts at fertility preservation or use of gonadotropin releasing hormone agonist treatment during cancer therapy will be captured as well. (See Appendix)

### **Primary Outcome**

The primary outcomes for this study will include hormone measures: FSH, INH, and AMH. E2 will be assessed primarily for interpreting FSH levels. Every effort will be made to obtain hormone measures during a subject's usual clinical examinations. Approximately 20 ml of blood will be collected and serum will be frozen in aliquots (-80C). Hormones will be measured in batches at the Clinical and Translational Research Center at the Hospital of the University of California, San Francisco using FSH, E2 Coat-A-Count kits (Siemens, Los Angeles, CA) and INH and AMH ELISA kits (Diagnostic Systems Laboratories, Webster TX). The FSH IRMA assay has a range of 1.0 – 100 mIU/ml, sensitivity of 0.25 mIU/ml, inter-assay and intra-assay coefficients of variation of less than 8% and 4 % respectively. The E2 RIA assay has a range of 10 – 1800 pg/ml, sensitivity of 10 pg/ml, inter-assay and intra-assay coefficients of variation of less than 8% and 6 % respectively. The INH ELISA assay has a dynamic range of 10-531pg/ml with sensitivity of 7 pg/ml; inter-assay and intra-assay coefficients of variation are less than 5% and less than 8% respectively. The AMH ELISA assay has a dynamic range of 25-15,000 pg/ml, sensitivity of 50 pg/ml, inter-assay and intra-assay coefficients of variation less than 7% and 3%.

### **Secondary Outcomes**

Additional outcomes of interest include ultrasound measures of the ovary including OV and AFC. At the Hospital of the University of California, San Francisco, in the division of Gynecology and Obstetrics, pelvic ultrasonography will be performed by one of 3 ultrasonographers to assess AFC and OV during the early follicular phase of the menstrual cycle. Transvaginal ultrasonography is the preferred method of measurement, though transabdominal ultrasound will be performed in participants who feel uncomfortable with the transvaginal approach. A standard protocol will be followed: the uterus and both ovaries will be measured in the transverse, AP and longitudinal dimensions. Endometrial thickness will be measured. OV will be calculated using the following equation: (Volume = Transverse x AP x Longitudinal x 0.52) [93]. In addition, all ovarian follicles and cysts will be measured. Follicles will be measured in millimeters and grouped according to size: 2-5 mm, 6-9 mm, and >9 mm in diameter. The AFC will be defined as the number of ovarian follicles less than 10mm in average of 2 diameters. The number of follicles of different sizes will be also be compared between groups since smaller follicles are likely to be most different between the groups [71]. Inter-observer reproducibility of transvaginal measurement of ovarian OV and AFC is excellent with intra-class coefficients of 0.96 for OV and 0.98 for AFC [94-96].

### **Additional Outcomes of Interest**

Menstrual diaries will be collected and data will be used to determine the timing of amenorrhea and resumption of menses. This information will only be valuable in subjects who are not taking exogenous hormones during the study duration. Exclusion of subjects using hormone therapy is not realistic since reproductive aged cancer patients are often encouraged to use hormonal contraception to prevent pregnancy and regulate bleeding during treatments. In addition, adjuvant therapy with medications such as tamoxifen and GnRH agonists may be prescribed for the treatment of breast cancer in young women. Menopausal symptoms will be assessed using a validated checklist. The presence and severity of symptoms will be compared between exposure groups and correlations made with measures of ovarian reserve.

**Database:** A web based database (C3D) has been constructed to our specifications by the NIH National Cancer Institute as part of the initiative. This database will be used for this study and all data will be entered in duplicate by staff at the

**Monitoring for completeness.** The study coordinator will promptly review the collected data for missing information and outlying values. Questions will be referred back to the interviewer, who will re-contact the participant if needed to supply the missing information.

**Data entry, back-up and storage.** All data will be entered promptly in computer files on an ongoing basis. Data entry will be backed up daily. Cleaning and validation procedures will be conducted on an ongoing basis. A full back-up of the data files on a zip disk will be made weekly. Additional zip disk copies of both data bases will be stored in a fire-proof locked safe. Confidentiality procedures for the data will be reviewed and approved by the IRB.

**Data archiving for investigators.** In compliance with the A110 amendment, we will prepare the study data for access by qualified and approved investigators. The currently establishing guidelines for web-based research networks. We plan to actively participate in this project and will prepare our data in accordance with these guidelines.

### **Statistical Plan**

#### **Sample Size Determination**

A total of 115 subjects will be enrolled: 90 exposed and 25 unexposed.

**Exposed:** Target enrollment will be a total of 90 exposed subjects.

The sample size calculations which were used to derive this number utilized the following information. The outcome of interest will be the anticipated change in log transformed AMH levels from baseline to post treatment. We used the power calculation for a one sample paired t-test. According to preliminary data, we noted the standard deviation for within woman change in log AMH was 1.74. Other assumptions included power 0.8, and type I error, alpha, 0.05. Complete data on 72 subjects would allow detection of a 1/3 change in standard deviation of log AMH. To account for a 25% rate of loss to follow up, we have estimated the sample size to be 90 subjects over 2 years. While this study requires a substantial commitment on the part of study subjects, we anticipate that pediatric and young adult cancer patients will be enthusiastic to participate given the paramount fertility concerns in this population. With substantial increase in effort, we anticipate no difficulty in recruiting up to 40 subjects per year.

**Unexposed:** Total enrollment will be a total of 25 unexposed subjects. The outcome of interest will be the difference in change of log transformed AMH levels from baseline to post treatment between exposed and unexposed populations. We used the power calculation for a two sample t-test for these computations. According to preliminary data, we assumed the standard deviation for within women change in log AMH is 1.74 for exposed and 0.63 for unexposed. Other assumptions included power 0.8, alpha 0.05. Complete data on 20 subjects would allow detection of a 1 standard deviation difference in change of log AMH between groups. To account for a 25% rate of loss, we have estimated the sample size to be 25 subjects over 2 years. Targeted recruitment of the unexposed population will be conducted so that the unexposed population is balanced with respect to age and oral contraceptive use to the exposed population.

Our preliminary investigation strongly suggests the likelihood of recruiting and enrolling sufficient subjects to complete this proposed investigation. We have found that the majority of reproductive age cancer patients welcome the opportunity to participate in this study since there is widespread concern regarding future fertility and there may be an opportunity for additional counseling and early intervention if monitored. Unexposed

subjects have been successfully recruited by the health studies requiring multiple visits similar to this proposal [97-100]. for many women's

### **Statistical Methods**

Since the statistical methodology is similar for Specific Aim 1 and 2, the Statistical Methods for both aims are described in Specific Aim 2.

### **Study Duration**

This aim is projected to be completed over 60 months (5 years). It is estimated that 115 subjects will be enrolled over a 2-year period (approximately 4 subjects per month). The length of a subject's participation will be up to 30 months, depending on the duration of cancer therapy. One visit will occur prior to treatment, 4 visits during the first year of treatment, and 2 visits after treatment has been completed. Therefore, 7 visits will occur over a 30 month period to obtain all study measures.

**Expected Results:** This study will be the first to investigate longitudinal measures of ovarian function in pediatric and young adult cancer survivors who receive gonadotoxic agents. It will, for the first time, describe changes in the H-P-O axis during and immediately after cancer therapy. We expect that most women about to enter cancer treatment will exhibit evidence of normal H-P-O function and normal imaging of the ovaries and uterus. With the initiation of cancer therapy from baseline to 6 months, measures of ovarian functioning will become markedly impaired with acute decrements in INH, AMH, OV, and AFC and a rise in FSH. Amenorrhea will occur and menopausal symptoms such as vasomotor symptoms, sleep disturbances, and mood instability will increase in frequency and severity. We predict that the maximum insult to the ovary will occur after 6 months of chemotherapy. It is anticipated that measures will begin to normalize 6 months after completing cancer therapy as small follicles develop into larger, recruitable follicles. Some subjects will likely show partial recovery of ovarian function whereas others will fail to regain any ovarian function. The hypothesis to be tested is that pretreatment measures of ovarian function and treatment parameters will be predictive of 6 month post treatment measures. In particular, we anticipate that AMH and AFC will be the most informative measures to assess underlying ovarian reserve in this population.

**Potential Problems and Alternative Approaches:** Several challenges have been identified conducting the preliminary study of this aim. We recognize some women will decline transvaginal ultrasound, the preferred technology for measurement of OV and AFC. We anticipate that this will not be a large issue since our preliminary experience suggests that the majority of teenagers are willing to undergo transvaginal ultrasonography even if they have not been sexually active. In addition, OV measurements have been found to be comparable via the transabdominal or transvaginal approach [101-103]. However, AFC has not been validated by transabdominal approach. In the worst case scenario we will not have valid measurement of antral follicles in a minority of women, and will rely on serum measurements of reproductive function. Another challenge is that the timing of visits during the early follicular phase prior to cancer therapy has been difficult due to the urgency of cancer care. However we have noted that while cycle independent samples may affect interpretation of FSH values, it does not affect AMH levels. Thus we will be able to examine our hypotheses in all women independent of the date of first sampling. In addition, we recognize that the use of leuprolide acetate, tamoxifen, and hormonal contraception may confound hormone and ultrasound measures. We are confident that the increase in sample size presented in this proposal is sufficient to account for this potential confounder. Importantly, the measurement of AMH will be most informative when hormonal contraception is used since these measures do not appear to be affected by hormone therapy [104]. In addition, recruitment of subjects at ( ) where the use of hormone therapy is much less common, will minimize confounding. We have also boosted potential recruitment by enhancing collaboration with the ( ) at the ( ). Given the high volume of cancer patients seen at the participating centers and the high level of concern regarding fertility potential among cancer survivors, we believe that it will not be difficult to enroll an adequate number of subjects in this longitudinal study. In addition, since these patients are followed closely with frequent office visits and survival is high, it is anticipated that loss to follow up will be minimal. In order to maximize subject retention and minimize missed visits, we will maintain close contact with subjects by email and telephone. Follow up study visits will be schedule at the preceding visit, and subjects will be contacted 1-2 weeks before the visit to confirm availability. In addition, subjects will be compensated \$30.00 per visit plus parking. In the

event that a subject has missed a study visit, every attempt will be made to reschedule that visit within the week. Nurses may also travel to subjects homes to perform the study visit and phlebotomy (with the exception of the ultrasound) in the case that subjects are unable to travel. We have found excellent retention using these methods for both exposed and unexposed study subjects for this investigation and others.

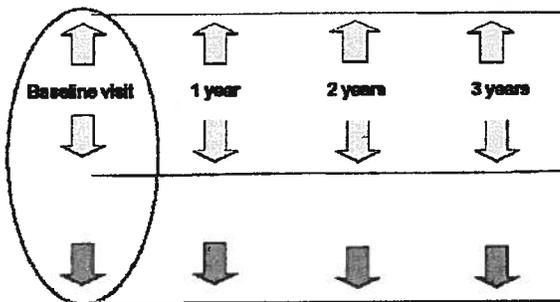
**Specific Aim 2: Assess the long-term reproductive function of women exposed to cancer therapies.**

Specific Hypothesis to be tested: Chemotherapy results in long-term endocrine changes that are distinct from similarly aged controls, but similar to women in their late reproductive years. These changes will be more dramatic in women who receive high dose therapy compared to women who receive low dose therapy.

**Rationale**

It has been demonstrated that measures of ovarian reserve are impaired in late reproductive aged women, and that these changes in measures occur more rapidly than in women during the mid-reproductive years [43]. Similarly, measures will be most impaired, and will change most rapidly, in women who received high dose alkylating agent therapy and exposure to pelvic irradiation. Comparing change in measures of reproductive function over time will be important in estimating the time to menopause and reproductive lifespan of cancer survivors. Importantly, measures of ovarian reserve are currently used routinely in cancer survivors and these data would help establish the value of these measures in this population to detect hypogonadism and development of impaired fertility. Ultimately, these tests would be used to improve counseling and to offer fertility preserving techniques. The knowledge gained through this research has widespread implications for female cancer survivors and may eventually help revolutionize their long-term care.

**Prospective Cohort Study**



**Study Design**

Study design: A prospective cohort study will be performed comparing mean levels and changes in measures of ovarian reserve over 3 years between post-menarchal females up to 35 years of age exposed to alkylating agent chemotherapy and two unexposed control populations: comparably aged healthy subjects and naturally aging women in the late reproductive years (between the ages of 40-50 years).

**Study Population**

Subjects with a history of cancer will be identified through the \_\_\_\_\_ at The \_\_\_\_\_ through the \_\_\_\_\_ at the \_\_\_\_\_ and through community referrals. In addition, newly diagnosed subjects (currently N=19) who have received alkylating agent therapy will be eligible to participate. Healthy unexposed subjects will be identified primarily through the local advertising and recruitment efforts in the same centers where the population is of a similar demographic makeup. Two groups of regularly menstruating unexposed subjects will be recruited: a group of similar age subjects and another group of subjects in the late reproductive years. Because age is highly associated with the outcomes of interest, the study design will involve frequency matching exposed and unexposed controls with respect to age (within 2 years given that all subjects will not be older than 35 years) at enrollment. In addition, because measures may be associated with race/ethnicity, subjects will be balanced with respect to self reported race/ethnicity. On a monthly basis, a study coordinator will determine the number of cancer patients in each age group enrolled in the study and will target enrollment to recruit the same number of unexposed controls in each age category. Unexposed late reproductive aged controls will only be balanced with respect to race/ethnicity. Enrollment is purposefully targeted and stratified for this study and will reflect the population in the pediatric and adult oncology practices.

**Inclusion and Exclusion criteria**

Inclusion criteria for exposed population: Otherwise healthy postmenarchal females between the ages of 11-35 years with a history of alkylating agent exposure, at least 1 year from cancer therapy, presence of a uterus and at least one ovary. Inclusion criteria for unexposed: Otherwise healthy postmenarchal females between the ages of 11-35 years (age matched within 2 years), or 40-50 years (late reproductive aged), with a no prior

chemotherapy or radiation exposure, regular menstrual cycles (every 21 – 35 days), and the presence of a uterus and at least one ovary.

**Exclusion criteria:** Current pregnancy, use of hormone therapy hormone within the previous 4 weeks, lactation within the previous 3 months, any chronic illness that would limit ability of participants to comply with study protocol, any medical condition other than cancer, which in the judgment of the investigator is known to be associated with premature ovarian failure (such as Turner's Syndrome or Fragile X) or ovulatory dysfunction (such as thyroid disease, congenital adrenal hyperplasia, Cushing's syndrome, hyperprolactinemia, and polycystic ovary syndrome). Additional exclusion criteria for unexposed: history of infertility, defined as 1 year of unprotected intercourse without achieving pregnancy.

### Study Procedures

All potential participants identified will be asked to participate in the study at their routine office visit at the survivorship clinics or they will receive a letter inviting them to participate in the study. If interested, a visit will be arranged during the first 4 days of their menstrual period at the . Participants on hormonal therapy such as oral contraception may be included if they are willing to discontinue the medications and return with their second menstrual bleed subsequent to discontinuation (at least 4 weeks from discontinuation). If cancer survivors have irregular cycles, and have not had spontaneous menses for more than three months, routine evaluation with Thyroid Stimulating Hormone and Prolactin will be scheduled without regard to the menstrual timing. Subjects will be eligible as long as these values are within normal limits. Visits will occur annually for at least 3 years, and as long as 5 years, depending on the date of enrollment. Follow-up visits will take place even if subjects are pregnant, lactating or using hormones in order to collect questionnaire data (hormone and ultrasound measures will be censored for such visits). At each annual study visit, during the first four days of the menstrual period, the following will be collected:

**Demographics:** A self report form will be completed by the participant for this purpose.

**Structured interview:** All study participants will be questioned regarding medical history, menstrual data, fertility concerns, fertility preservation/treatment, pregnancy risk, pregnancy history, medication use, and social history. Specifically questions regarding cancer diagnosis and treatment plan will be collected. Previous use of hormonal contraception, gonadotropin releasing hormone agonist therapy, or use of hormone replacement therapy will be recorded. In addition, the Menopausal Symptom List (MSL), a validated instrument for assessing menopausal symptoms, will be used to assess the presence or absence of menopausal symptoms during the past month, the frequency and severity of each symptom. Symptoms captured include: hot flashes, vaginal dryness, concentration/memory problems, irritability, mood swings, feeling sad, feeling anxious, trouble sleeping, aches, joint pain, headaches [92].

**Physical Examination Data:** Height and weight will be determined for the calculation of body mass index. In addition, a brief physical examination will be conducted to document Tanner Staging.

**Menstrual Diaries:** will be given to participants and they will be instructed to keep track of any bleeding during the study. Subjects will be called every 3 months to document bleeding and encourage compliance with menstrual calendars.

**Serum Testing:** Blood samples will be obtained for determining levels of FSH, E2, INH, and AMH.

**Pelvic Ultrasonography** OV and AFC by size (2-5 mm, 6-9 mm, and >10 mm), uterine volume and endometrial thickness will be determined.

**Review and Documentation of Cancer Therapy:** Cancer treatments will be abstracted for the clinical chart by the oncology offices caring for the patient. (See Appendix for data collection forms)

### Exposure Data

Exposure data will be obtained from a structured interview during the study visits and by reviewing medical records of all treatments from the subject's primary oncology office. Treatment will be summarized in terms of chemotherapeutic type, duration and cumulative dose; total radiation dose and location; history and type of bone marrow transplantation; and any surgery. The dose group definition applied in the preliminary investigation will be used to assess a dose dependent relationship between measures (High dose cyclophosphamide  $\geq 15\text{g/m}^2$ , ifosfamide  $>40\text{g/m}^2$ , or history of bone marrow transplant). In addition, in subjects who receive multi-agent chemotherapy with cyclophosphamide or ifosfamide, dose groups also be defined as follows: Low dose: cyclophosphamide cumulative dose 1-4 grams/m<sup>2</sup>; Medium dose: cyclophosphamide cumulative dose  $>4\text{-}15\text{ grams/m}^2$ ; High dose: cyclophosphamide  $>15\text{-}30\text{ grams/m}^2$  or high

dose ifosfamide 40-80 grams/m<sup>2</sup>. Any attempts at fertility preservation or use of GNRH agonist treatment during cancer therapy will be captured as well. (See Appendix)

### **Study Outcomes**

**Primary Outcomes** for this study will include mean and changes in the following hormone measures obtained during the early follicular phase of the menstrual cycle (days 1-4) over 3 years (FSH, INH, and AMH) E2 will be assessed primarily for interpreting FSH levels. Assay specifics are described above for Specific Aim 1.

**Secondary Outcomes** include mean and changes in OV and AFC over at least 3 years. These measures are described for Specific Aim 1. In addition, menstrual data will be informative in subjects who do not use exogenous hormones during the 5 year study period. In this population, data from menstrual diaries will be used to determine menopausal status according to the Stages of Reproductive Aging Workshop (STRAW) classification system as we have previously demonstrated that reproductive hormone levels differ by menopausal stage using that classification system [83]. Menopausal symptoms will be assessed using a validated checklist. The presence and severity of symptoms will be compared between exposure groups and correlations made with measures of ovarian reserve. Finally, time to pregnancy and infertility is an outcome of interest, though power may be limited to assess this outcome.

**Other data to be collected:** Because H-P-O function can be influenced by a number of medical, physical, and psychological factors, we shall exclude anyone with other medical causes of underlying ovarian dysfunction and probe for the possible presence of various factors that may confound the analysis. For instance, we shall document current age, body mass index, race, age at menarche, typical menstrual cycle lengths and duration, tanner staging, history of smoking, alcohol use, medical and surgical history, medications used, exercise, and eating disorders [105].

**Database:** The C3D database described for Specific Aim 1 will be used as described above.

### **Sample Size**

Target enrollment during a 2 year period will be a total of 291 participants, or 97 participants per group. We already have recruited a cohort of 52 exposed and 63 similarly aged unexposed subjects. Of the existing cohort, 45 subjects are eligible for participation. We believe that the existing cohort is a unique strength of this application. An additional 52 exposed, 34 similarly aged unexposed subjects, and 97 late reproductive aged subjects will be recruited over 2 years. The sample size calculation was performed estimating the anticipated change in log transformed AMH levels over 1 year from preliminary data from the [43] and published data [43]. We used the calculation for a two sample t-test. According to longitudinal data from the [43] we noted the standard deviation for within women change in log AMH was 0.12. Other assumptions included power 0.8, alpha 0.05. Complete data on 77 subjects per group would allow detection of a change of 1/2 a standard deviation in AMH per year, which corresponds to a 15% decrease in mean AMH per year. To account for a 25% rate of loss to follow up, we have estimated the sample size to be 97 subjects per group.

### **Statistical Methods for Aims 1 and 2**

**Descriptive Statistics:** Standard descriptive statistics will be used to describe subject characteristics, patient self-reported symptoms and menstrual function, and outcome variables both overall and within exposure groups. Summary statistics such as means, medians, and ranges will be produced for all measured variables. Graphical methods such as stem-and-leaf diagrams and boxplots will be used to examine distributions and guide in the choice of transformations if warranted. Frequencies will be computed for all categorical and ordinal variables. Quantitative measures will be initially compared between the exposure groups using appropriate tests (Student's t-tests, exact Wilcoxon rank-sum tests, or analysis of variance methods). Pearson and Spearman rank correlations among serum and urinary measures will be computed. Non-Gaussian-distributed variables will be transformed prior to analysis. Within subject changes in continuous variables (hormones, OV, AFC) will be compared using paired t-tests (nonparametric tests as appropriate) by exposure group.

**Specific Aim 1:** The goal of this analysis is to establish the time course of ovarian dysfunction that occurs with cancer therapy, and determine the extent to which changes during treatment are dependent on treatment parameters, baseline ovarian function markers and subject characteristics. In general, changes from baseline to every 3 month assessment will be compared individually as well as changes from baseline to post treatment.

Change in measures will also be compared between exposed and unexposed subjects. In addition, regression models for repeated measures will be used to describe the pattern of change in these outcomes over time. Predictive models will be constructed to determine whether baseline measures, age, cancer type, dose and duration of treatment predict post-treatment measures. Secondary analyses will include assessing the association between treatment parameters and menstrual function. The association between measures of ovarian reserve and menopausal symptoms will also be assessed.

For Specific Aim 2 the goal of analysis is to determine the degree and rate of ovarian depletion (change over time) in order to estimate the reproductive lifespan of cancer survivors. One set of comparisons will focus on levels and rate of change over time between cancer survivors and similarly aged controls. A second set of comparisons will be between cancer survivors and healthy late reproductive aged women. We will also model the age at menopause by calculating the slope in change of AMH and published hormone cutoffs for defining menopause [46]. While these models will be informative to estimate the remaining time to menopause, or reproductive window, in cancer survivors, we realize that such models will require future validation with prospectively collected data on time to menopause. We will also assess the strength of association between several risk factors and measures of ovarian functioning among females exposed to cancer therapies. Specifically we shall assess the association between measures of ovarian function and treatment parameters such as the dose of alkylating agent (see definitions above) and radiation exposure to the ovaries.

Longitudinal modeling for Specific Aims 1 and 2: To describe average levels and longitudinal trends in ovarian function markers (AMH, FSH, AFC, etc.) we will utilize two approaches to the analysis to elucidate the structure of the data. Analyses will first consider exposed and unexposed women separately. We will utilize all available outcome data for each participant (Aim 1: up to 7 repeated measures taken over an 18 month period, Aim 2: up to 5 repeated measures over 5 years). These markers will be transformed using the natural logarithm or other appropriate transformation to more closely approximate a normal distribution. The first type of model will examine levels over time with robust assumptions about the structure of the correlation among the repeated measurements [106], so that any unequal spacing in time will have little impact on statistical inferences regarding covariate effects on average ovarian function levels. Secondly, we will utilize a random coefficients (effects) model [107-109], in which each woman is allowed to have her own intercept and slope for the outcome trajectory over time. Of interest is the change of the marker over time. Statistical tests of the interaction between the slope terms (change over time) and important cancer treatment factors such as dose and duration of chemotherapy and radiation exposure to the ovaries. Other covariates, for example age at diagnosis, race, body mass index, cycle day of blood draw, use of hormones will also be considered in this fashion. A confounder will be defined as any variable that changes the estimate of association by at least 15% [110]. Additionally, joint models for cancer patients and control data will be developed if there is sufficient homogeneity within each group to assume valid estimation of within group trends.

Additionally, while fertility is not a primary outcome in this study, it will be informative to summarize hormone measures among those subjects who conceive during the study and to explore whether measures of ovarian reserve correlate with time to pregnancy compared to the unexposed group. These evaluations will have limited statistical power, but will be used for the purpose of hypothesis generation. We realize that the number of statistical tests conducted may lead to alpha error, and therefore we will not over interpret our findings and adjust the level of significance appropriately.

### **Study Duration**

This aim is projected be completed over 60 months (5 years). It is estimated that a total of 291 subjects will be enrolled in this study. Since 45 eligible exposed subjects and 63 unexposed subjects have already been enrolled in the investigation, an additional 183 subjects will be enrolled over the first two years. Each participant will complete yearly study visits for up to 60 months, depending on the date of enrollment.

### **Anticipated Results, Problems, and Alternative Approaches**

**Expected Results:** It is hypothesized that overall measures of FSH will be higher (with a suppressed E2), INH lower, AMH lower, and AFC lower in women exposed to chemotherapy compared to unexposed similarly aged women. Moreover, it is expected that the rate of change in reproductive hormones will depend on the baseline measurement. In women's whose measures are impaired (FSH > 10mIU/ml, with an E2 < 50pg/ml, INH < 100

pg/ml, AMH < 2,500pg/ml, AFC  $\leq$  4), the rate of change of AMH will be greater than in women with "normal" measures of ovarian reserve. Mean measures and the rate of change in mid-reproductive aged subjects exposed to high dose alkylating agent therapy will be similar to late reproductive aged women in their 40's. Moreover we anticipate that models correlating the rate of change in hormones with published threshold levels for menopause will indicate that menopause will occur within 10 years in such high risk subjects (during the mid-30's). Correlates to natural reproductive aging will be extremely valuable to estimate a woman's reproductive window.

**Difference from Past Studies:** Our proposed study differs from prior studies investigating measures of fertility potential in cancer survivors in several notable ways. Unlike prior studies that were limited by small sample sizes, cross sectional designs, and potential confounding by many factors including age, cancer treatments, and hormonal medications, our proposal has been designed to avoid these problems. In particular, the study has been structured to avoid confounding from the primary factors influencing hormone values and ultrasound measures by restricting the study to healthy females who have no other medical causes of ovarian dysfunction, and who are not pregnant, lactating or using hormones for at least 4 weeks. In addition, we will restrict the focus by including only subjects treated with alkylating agents, drugs known to be gonadotoxic. Most importantly the design allows assessment of change over time and is the first to make correlates to women in the late reproductive years. Since age is the single most important predictor of ovarian reserve, the design involves frequency matching cases and controls on age (within 2 years) for similarly aged subjects. The groups will also be balanced with respect to race, and BMI and we plan to adjust for these potential confounders in our analysis as well. The clinical sites chosen from which to select controls are demographically similar to the cancer population precisely to minimize other differences between cases and controls, which could lead to selection bias. After half of the subjects have been recruited, the age distributions within each dose group will be assessed. If the ages are not similar, the sample size may be expanded in order to adequately account for age in the statistical analysis. \_\_\_\_\_ will serve as a statistical co-investigator for this proposal.

**Achieving Projected Enrollment:** Given the high volume of cancer survivors followed at the survivorship programs at \_\_\_\_\_ and \_\_\_\_\_ and the high level of concern regarding fertility potential among cancer survivors, we believe that it will not be difficult to enroll an adequate number of subjects previously exposed to alkylating agents. Furthermore, while unexposed subjects may be less motivated to participate, we are confident in our ability to enroll women eligible for this proposal, as we have been highly successful at recruiting and retaining women for a variety of other studies including the \_\_\_\_\_ Study. Moreover, our preliminary data is proof that we are well poised to enroll sufficient subjects. In addition, recruitment and enrollment will be assessed every 6 months and if recruitment is insufficient we will reach out to regional centers, the \_\_\_\_\_ and \_\_\_\_\_ for referrals.

**Retention:** Because cancer survivors are followed with at least yearly office visits and survival is high, it is anticipated that loss to follow up will be minimal. In order to maximize subject retention and minimize missed visits, we will maintain close contact with subjects by email and telephone. Follow up study visits will be scheduled 1-2 months before scheduled return to tentatively schedule a visit during the anticipated early follicular phase of the cycle. Then subjects will be contacted 1-2 weeks before the visit and the day before the visit to confirm appropriate scheduling according to menstrual cycles. In addition, subjects will be compensated modestly (\$40.00) for completing each visit and for parking. In the event that a subject has missed a study visit, every attempt will be made to reschedule that visit during the week, or following the subsequent menstrual cycle. Nurses may also travel to subjects' homes to perform the study visit and phlebotomy (with the exception of the ultrasound) in the case that subjects are unable to travel. We have found excellent retention using these methods for both exposed and unexposed study subjects for this investigation and others.

**Heterogeneous Population:** Depending on the number of different treatment regimens, stratified analyses to assess the association between treatment parameters and measures of reproductive function may have limited power to detect significant differences between selected treatments. Posthoc power calculations will be conducted to determine whether sufficient power exists for such analyses. These investigations will provide important clues and preliminary data for designing future investigations further assessing such differences. We do not want to limit this study to a narrow group of cancer diagnoses since we may not capture important, new information that would be valuable for further study.

### **The rationale for selecting unexposed women with regular menstrual cycles**

We have selected unexposed controls with regular menstrual cycles (21-35 days) to obtain true measures of ovarian reserve – which should be obtained during the early follicular phase of the menstrual cycle. Measures of ovarian reserve have not been tested and validated during random days in anovulatory women and therefore every attempt will be made to obtain these measures during the early follicular phase in both cases and controls. However, because irregular menstrual cycles may be a clinically important endpoint indicating ovarian dysfunction, cancer survivors with irregular menstrual cycles will be included. In such cases, visits will be scheduled irrespective of menstrual cycle. Only those with a significant elevation in FSH and amenorrhea will be classified as having premature ovarian failure. It must be acknowledged that if a substantial proportion of cancer survivors have irregular menstrual cycles, the study results may be biased. As we have demonstrated in our preliminary results, we will conduct stratified analyses to assess the association between menstrual function and measures of ovarian reserve. It may be necessary to recruit additional cancer survivors with regular menstrual cycles to minimize this bias. The size of the cancer survivorship program and the willingness of cases to participate will allow for a larger sample size to be collected if needed.

**Why allow hormone use during the study?** Given the frequency of hormonal contraception use in young reproductive age women and the risk of unintended pregnancy, it is not reasonable to require that subjects not take hormonal contraception during the entire 5 year study period. Therefore, it is required that subjects stop hormonal contraception for at least 4 weeks prior to participation and schedule a visit during the early follicular phase of a natural menstrual cycle. We recognize that menstrual data will not be informative during study periods in which subjects are taking hormonal contraception. Data on hormone and ultrasound measures will be censored for analyses at visits where subjects are pregnant or lactating. In subjects using hormonal contraception, AMH values will be informative.

### **Specific Aim 3: Assess for the presence of follicular and luteal dysfunction in cancer survivors.**

*Specific Hypothesis to be tested: Cancer survivors have luteal phase dysfunction despite normal menstrual cycles reflected by a difference in integrated levels of urinary pregnanediol glucuronide (Pdg) FSH, LH and Estrone conjugate (E1c) from age matched controls, but similar to women in their late reproductive years.*

### **Rationale**

As described above, women with a reduced follicular pool either from natural aging or previous chemotherapy, may have no clinical signs or symptoms and traditional measures of ovarian reserve, such as basal FSH may be within the normal range. However, there may be alterations in the luteal or follicular phases (shortened follicular phase and luteal insufficiency) due to compromised follicle competency and alternations in the H-P-O axis. Therefore this important aim uses novel methodology to identify subtle changes in the reproductive endocrine axis which may have important implications for reproduction and may signal reproductive senescence. Compared to yearly follicular measures of reproductive hormones, daily urine hormone analysis provides a more integrative assessment of this axis. The findings will help to corroborate the findings of Specific Aim 2. The ultimate goal of this work is to better estimate the reproductive window, or time to menopause, of patients exposed to cancer therapy so that treatment can be tailored to improve fertility and long term health and quality of life.

### **Study Design**

Prospective cohort study comparing daily urinary hormones over 2 menstrual cycles in females of mid-reproductive age exposed to high dose alkylating agent therapy compared to 2 unexposed populations: comparably aged healthy unexposed subjects and naturally aging women in the late reproductive years.

### **Study Population**

A subset of subjects enrolled in Specific Aim 2 will be recruited to participate in this aim of the project. Regularly menstruating postmenarchal mid-reproductive aged female cancer patients treated with high dose alkylating agent chemotherapy will be identified through the divisions of pediatric oncology at The [redacted] and through the oncology practices at the [redacted].

For the purpose of this investigation high dose therapy will be defined as having received cumulative doses of cyclophosphamide  $\geq 15\text{g/m}^2$ , ifosfamide  $>40\text{g/m}^2$ , or having had alkylating chemotherapy prior to a bone marrow transplant. In our preliminary data, measures of ovarian reserve were found to be significantly different

when women exposed to cancer therapies were categorized into 2 groups using this definition. Indeed, those who received high dose therapy were found to have hormone levels more similar to those of late reproductive age women compared to those who received low dose therapy. 2 unexposed study subjects will also be recruited for this study from Specific Aim 2: unexposed regularly menstruating mid-reproductive aged women, and unexposed regularly menstruating late reproductive aged women. Of note, the age ranges specified for this aim are narrower compared to aims 1 and 2 since the sample size is smaller, and since urinary hormones have found to be valid in women of these ages [49]. We have not included any subjects from Specific Aim 1 in this aim because most of the subjects will be amenorrheic or have irregular menses during treatment for the 6 months of chemotherapy follow-up.

### **Inclusion and Exclusion criteria**

Three groups of subjects will be recruited. Group 1: Otherwise healthy mid-reproductive aged women between the ages of 20 and 35 years previously exposed to high dose alkylating agent therapy as defined above, and at least 1 year from cancer treatment. Group 2: healthy mid-reproductive aged women between the ages of 20 to 35 who have not been exposed to cancer therapy. Group 3: healthy late reproductive aged women between the ages of 43-50 who have not been exposed to cancer therapy, nor have a history of infertility. Subjects in all groups must have regular menstrual cycles every 21-35 days, and have a uterus and both ovaries. Exclusion criteria include pregnancy or lactation within the previous 3 months, use of hormonal contraception or replacement within the previous 3 months, Body Mass Index > 30 kg/m<sup>2</sup>, excessive exercise greater than 1 hour per day, any medical condition other than cancer, which in the judgment of the investigator is known to be associated with premature ovarian failure (such as Turner's Syndrome or Fragile X) or ovulatory dysfunction (such as thyroid disease, congenital adrenal hyperplasia, Cushing's syndrome, hyperprolactinemia, and polycystic ovary syndrome). In addition, since race is associated with urinary hormones, recruitment will be targeted so that the groups are balanced with respect to race.

### **Primary Outcomes**

Integrated urinary follicular phase FSH and LH, Integrated PdG, Integrated E1c, Luteal and follicular phase lengths

### **Study Procedures**

**Collection and processing of first morning urine** Participants will receive specimen collection kits delivered to their homes containing: a supply of labeled polypropylene tubes (prefilled with glycerol to a final concentration of 7%), an indelible marker, disposable plastic cups. In addition, a miniature non-frost free freezer will be delivered (if the participant wishes) to store the collected specimens. Each woman will be asked to contribute 2 menstrual cycles of urine. For each cycle collected, women will be instructed to begin specimen collection on the first day of the menstrual bleed and stop the first day of the subsequent bleed, or for a total of 50 days if no menses occurs. They will be instructed to collect the first morning voided urine into a cup, fill two tubes to the indicated line (5ml), and place each tube into a box in the freezer at -20C within 2 hours of collection. A specimen collection log will be provided to allow participants to record any irregularities in collection. Weekly telephone calls will be made to the participant's preferred telephone number to encourage adherence. At the end of collection, all specimens will be transported on ice to the laboratory at for storage. Specimens will then be analyzed in the

### **Laboratory Analysis**

Glycerol preserved specimens will be used since this allows measurement of LH and FSH over long storage intervals and does not interfere with E1c or PdG assays. Laboratory analyses will be conducted in the University. FSH will be measured using an ELISA kit (Leinco Technologies, Inc. MO), which has a sensitivity of 1.0 mIU/ml, a range of 10-100 mIU/ML, an intra-assay coefficient of variation of 5.6% and an inter-assay coefficient of variation of 7.3%. LH will also be measured using an ELISA kit (DRG International, NJ), which has a sensitivity of 5.0 mIU/ml, a range of 5-200 mIU/ml, an intra-assay coefficient of variation of 6.9% and an inter-assay coefficient of variation of 7.2%. The E1c assay uses a polyclonal capture antibody R522-2 from Coralie Munroe at UC Davis. The competitor for this assay is E1c conjugated to horseradish peroxidase (E1c-HRP). An endpoint substrate color reaction is developed with azino-bis-ethylbenzthiazoline sulfonic acid and peroxidase. E1c standards from Sigma are used for the standard curve, and high and low internal controls are in-house samples. The inter-assay coefficients of variation for high and

low internal controls for the E1G assay are 14.7% and 13.1% respectively. The PdG assay uses the polyclonal capture antibody R13904 developed at the UC Davis and the competitor PdG-HRP. PdG standards from Sigma are used for the standard curve, and high and low internal controls are in-house samples. Both E1G and PdG assays are identical. The inter-assay coefficients of variation for high and low internal controls for the PdG assay are 15.6% and 12.9% respectively. Urinary creatinine will be assayed using a direct colorimetric reaction. All urinary hormones will be normalized for Cr and corrected for glycerol and are expressed per mg Cr for sex steroids and as international units per mg Cr for gonadotropins. [redacted] will serve as a laboratory consultant for this project. A subset of E1c and PdG assays conducted in the [redacted] at [redacted] will be validated by [redacted] to ensure quality control since she is one of the experts in this area.

**Determination of Menstrual Disturbances:** Participants will be provided with calendars on which to record detailed menstrual cycle information during the study. The total menstrual cycle length will be defined as the number of days from day 1 of menses to the day before the next menses. The Kassam method will be used to determine evidence of luteal activity, presumably ovulation. This method appears to have the highest sensitivity and specificity for luteal function. Briefly this method defines a cycle specific baseline as the minimum follicular phase PdG five day nadir, and the threshold for evidence of luteal activity requires at least three times this baseline for 3 consecutive days [111]. The probably day of luteal transition (DLT) will be determined in cycles with ELA using the modified method by Waller [112]. This method defines the DLT as the first date that the E1c/Pcg ratio decreases by at 75% [47]. Follicular and luteal phase lengths will be calculated excluding the DLT. Follicular phase will be defined as the number of days from day 1 of menses up to the DLT and the luteal phase length will be defined as the number of days beginning from the day after the DLT to the day before the next menses. Hormones (FSH, LH, E1c and PdG) will be integrated, or summed, over the total cycle, follicular, and luteal phases using the AUC method (trapezoidal rule) and compared between groups. In addition peak PdG levels will be compared between groups. The primary variables used to determine whether ovulation has occurred and whether a luteal phase defect has occurred will be the luteal phase length, and the luteal phase PdG. Luteal phase deficiency (LPD) will include cycles with short luteal phases i.e., less than 12 days and or cycles displaying luteal phase inadequacy i.e., urinary excretion of PdG less than 3 µg/ml for 3 or more mid-luteal phase days [113]. Luteal phase will be considered long if greater than 16 days. Oligomenorrheic cycles will be considered cycles that are greater than 36 days. For isolated missing days the hormone concentrations will be interpolated. Cycles missing hormones for more than 2 consecutive days will be omitted from analyses of integrated hormones. In large prospective studies using similar methodology, 7% of subjects missed 2 or more consecutive days of collection [48].

### Sample Size

The calculation for a two sample t-test was used to calculate the sample size for this aim. Estimates for PdG levels and standard deviations (mean peak PdG 55.6, SD=2.188) were obtained from published data comparing urinary hormones in late reproductive aged women with regular menstrual cycles compared to mid-reproductive aged women using the methodology proposed for the current study. [49]. Other assumptions include power of 0.8, and type I, alpha, error of 0.05. In order to detect an 8% relative difference in means, or a 2 SD effect size, 9 subjects per group are required. To account for a 25% rate of loss to follow up, and a conservative estimate of 25% likelihood of noncompliance (missing 2 consecutive days of collection), 15 subjects will be enrolled per group. For 3 groups, a total 45 subjects will be enrolled. Since each subject will contribute 2 menstrual cycles, this will represent data on 90 menstrual cycles.

### Statistical Analysis

After cleaning, data will be summarized using means and standard deviations for continuous variables and frequency distributions for categorical variables. Patterns of daily hormone excretion (FSH, LH, E1c and PdG) in cycles with ELA will be examined by plotting the mean (+/- SE) of daily concentration, standardized to the DLT. Menstrual cycle summaries of ovarian function measures, (total-cycle integrated E1c and PdG, integrated follicular FSH and LH, and peak PdG) will be compared between cancer survivors and unexposed subjects using repeated measures analyses (as described above), adjust for total cycle length (to account for the obvious dependence of total hormones on number of collection days), as well as age, ethnicity, BMI, and smoking status. Model fit will be assessed using the Chi-square goodness of fit statistics for categorical outcomes and residual analyses for integrated hormones. Integrated hormones will be log-transformed for

analyses. The correlation between serum and urinary metabolite measures will be assessed using Pearson and Spearman correlation coefficients. Intra-class correlation estimates within group (cancer survivor, control) will be evaluated to establish the extent of consistency between markers within groups.

### **Study Duration**

This aim is projected to be completed over 60 months (5 years). During the first 6 months, we will write protocols, obtain IRB approval and set up the urinary assays in the CTSC laboratory. It is estimated that a total of 45 subjects will be enrolled in this study over four years. Each participant will complete daily urinary collections for 2 menstrual cycles. Urinary assays will be conducted in the laboratory in batches and data entered into the database during the 4 years. After data collection is complete, we shall analyze our data statistically over a 6 month period and report our findings at professional society meetings and journals.

### **Anticipated Results, Problems, and Alternative Approaches**

**Anticipated Results:** This will be the first time that the reproductive endocrine axis of cancer survivors will be investigated using the most sensitive methods. It is anticipated that elevated follicular FSH and LH, elevated E1c, decreased PdG urinary excretion, and a shortened luteal phase will be observed in mid reproductive age women exposed to high dose alkylating agent therapy and in women during the late reproductive years, but not in mid-reproductive unexposed subjects. This will (i) complement the findings from Specific Aim 2, showing similarities between the effects of high dose alkylating agent therapy and ovarian aging, (ii) will help support the hypothesis that cancer therapies accelerate ovarian aging, and (iii) will determine that measures of ovarian reserve and other endocrine parameters can help to estimate the fertile window in such patients.

**Recruitment and compliance:** It is possible that subjects will be unwilling to participate, or will be noncompliant with collection in the daily urine study since participation requires substantial commitment from subjects. We do not believe that this will be the case since experience in field studies has demonstrated over 90% compliance and over 80% complete collection of urinary specimens [48]. In addition, subjects will be called weekly to encourage compliance with study procedures and specimens will be picked up on a weekly basis from subject's homes. Compensation for study participation will be \$200.00.

**Laboratory Methodology:** we are confident that we will be able to optimize the urinary hormone assays for this study given the expertise and resources within the . To ensure optimal assay conditions, , who is well published in this area, will serve as a consultant for these procedures and has agreed to validate a subset of assays run in our lab. In the event that the assay results are inadequate, we will send the urine specimens to her lab for analysis.

### **Summary of Proposal**

**Strengths:** There are compelling reasons to assess the reproductive effects of cancer therapies since this is an area that significantly affects the quality of life of thousands of cancer survivors in the U.S. and has been identified as an area of special interest of the National Institutes of Child Health and Human Development (NICHD) [114]. Our progress to date has been substantial, including the establishment of close collaborations within the adult and pediatric oncology divisions at and the ongoing successful recruitment of both newly diagnosed cancer patients and childhood cancer survivors to a study of reproductive function. Hypotheses to be tested are supported by our own preliminary data and the project is a natural progression from these findings. We have assembled a unique multidisciplinary team of investigators with a proven productive collaboration, and outstanding institutional support, enhancing successful completion of our aims. We are also confident that the findings from this proposal will significantly impact the counseling of cancer patients before and after therapy, and will help to appropriately target rapidly emerging fertility preserving technologies such as oocyte and ovarian tissue cryopreservation.

### **General Limitations**

**Selection Bias:** We recognize that one of the challenges of this study will be to avoid selection bias. We anticipate that unexposed subjects with reproductive concerns may be more likely to volunteer for this study in order to gain information about their reproductive health. This would minimize the difference between exposed and unexposed subjects and bias the results towards the null. In order to minimize such bias, unexposed women with a history of infertility and those with menstrual irregularities will be excluded from participation.

**Confounding** by factors that affect hormone parameters is another potential source of bias. The recruitment for the aims in this study are designed to minimize confounding by balancing exposed and unexposed subjects with respect to confounding factors. In addition, data on other potential confounders will be collected so that the relationship between these factors and outcome measures can be examined, and appropriate stratified or adjusted models will be constructed to account for confounders.

**Heterogeneous population:** There is no single cancer diagnosis that affects many young patients. The reality of clinical practice is that there are multiple types of cancers with different treatments. To make our results more generalizable and to detect important difference in the reproductive effects of treatments, we firmly believe that we must be inclusive rather than restrictive. Because there is substantial data to suggest that alkylating agents and pelvic radiotherapy are the most gonadotoxic, Specific Aims 2 and 3 have focused on subjects with alkylating agent exposure. The goal is not to determine the risk of every possible treatment, but to evaluate if the measures of ovarian reserve pretreatment and post-treatment are helpful in predicting an individual's long term reproductive function in order to help target fertility preservation options. We recognize that there are limitations to a longitudinal study such as selection bias and confounding, however this is the best design to study the reproductive effects of chemotherapy since it is not possible to randomize, and we have ample experience to minimize these with careful planning and in our analysis plan.

**Is This Project Overambitious?** This proposal is not overly ambitious. It is focused and is designed to maximize collection of complete, interpretable data within a relatively short period of time (five years). In addition, this investigator has had extensive mentored research support over the past 4 years ( ), has developed a research and clinical niche in the area of Oncofertility, has obtained important preliminary data that demonstrates her ability to recruit cancer patients, and has developed critical collaborations locally and nationally which will enable her to successfully complete the proposed investigations. This project represents a natural progression in the PI's transition to independence and will provide the needed funds to complete these projects. Without substantial additional funding, these projects cannot be completed with the support provided by the

**Future Studies:** the goal of this proposal is to identify surrogate measures of reproductive function to estimate a cancer survivor's reproductive window, or time remaining before menopause. These findings must next be validated in long term longitudinal studies assessing "gold standard" outcomes such as time to menopause. This proposal represents a critical step towards this goal since it is essential to establish a cohort of subjects committed to participation in long term studies of this type.

**Innovation:** The innovation of this proposal is not in the topic, but rather in the comprehensive approach and study population. This will be the first investigation conducted in a rigorous fashion to assess several of the most novel markers of ovarian reserve in pediatric and young female cancer survivors. The proposal involves a comparison of these measures to unexposed, and also involves the assessment of measures over time before, during and after cancer treatment. Importantly, no study has tested several measures simultaneously, perhaps elucidating which test(s) may best predict the otherwise "invisible" transition toward decreased ovarian reserve and/or premature ovarian failure in this population. We have anticipated the pitfalls and have developed a strategy to address them so that the results will be meaningful. The design is intended to address paramount gaps in our current knowledge about this important subject, and to collect high quality data to pursue this line of research in the future. This is an opportunity to prove feasibility and adequately design a large scale prospective study assessing ovarian function and determinants of reproductive lifespan, fecundity, sexual dysfunction and long term health in female cancer survivors.

**Timeline:** We plan to collect data continuously for the duration of the grant. In year one: we will write protocols, obtain IRB approval and start recruiting. It is planned to recruit subjects for all 3 aims of this proposal simultaneously during the first 24 months of the grant. By the end of year 2, we plan to have enrolled 115 subjects for Aim 1, 297 subjects for Aim 2, and 23 subjects (1/2 of our goal) for Aim 3. Data will be entered in the existing web-based database constructed for this purpose by NCI in collaboration with the Oncofertility consortium. A separate database will be constructed to enter data for Aim 3. For Aims 1 and 2, our first analysis will be after 24 months of data collection in order to compare measures cross sectionally in exposed and unexposed subjects. Longitudinal analyses for Aims 1 and 2 will be performed at 54 months, so that all subjects have completed study visits for Aim 1, and after all subjects have had at least 3 years of follow up for

Principal Investigator/Program Director (Last, first, middle):

Aim 2. Data for Aim 3 will be analyzed after data collection is complete. After data collection is complete for all aims, we shall analyze our data statistically over a 6 month period and report our findings at professional society meetings and journals.

## E. Human Subjects

This Human Subjects Research meets the definition of "Clinical Research."

### 1. Risks to the Subjects

#### a. Human Subjects Involvement and Characteristics

The study population will consist of otherwise healthy newly diagnosed female cancer survivors who have received care at the \_\_\_\_\_ of the \_\_\_\_\_ or through local referrals.

Healthy females will be recruited from the \_\_\_\_\_, at the Hospital of the \_\_\_\_\_, or through local referrals for comparison. The \_\_\_\_\_ and the Hospital of the \_\_\_\_\_

serves as a referral center to \_\_\_\_\_. Because this is a study of reproductive potential in females, 100% of the study population will be female. The age range for all specific aims will be between 11-50 years of age. The ethnic distribution of the study population will reflect the prevalence within the population of cancer patients and survivors at the \_\_\_\_\_.

However, targeted, stratified enrollment of healthy similarly aged and late reproductive aged unexposed subjects will be performed as part of the study design to reduce bias. Adolescents will be included in this study since the study is designed to identify early signs of decreased fertility potential, which may occur during the early adolescent years. Thus, by definition, this study includes women and children. As part of Specific Aim 1, 90 newly diagnosed cancer patients and 25 unexposed subjects between the ages of 11-35 will be enrolled. For Specific Aim 2, 97 cancer survivors and 97 unexposed females between the ages of 11-35 will be enrolled, as well as 97 late reproductive aged women between the ages of 40-50 years. For Specific Aim 3, 15 cancer survivors and 15 unexposed females between the ages of 20-35 will be enrolled, as well as 15 late reproductive aged women 43-50 years of age.

#### b. Sources of Materials

For Specific Aim 1, data will be collected from: a structured interview with participants, physical examination, blood tests, and pelvic ultrasonography as part of this study. A pretreatment visit and visits every 3 months x 4 and at least 2 post-treatment visits will be completed. These visits will include:

- **Demographics:** Self report form is completed by the patient for this purpose.
- **Structured interview:** All study participants will be questioned regarding medical history, menstrual data, fertility treatment, pregnancy risk, pregnancy history, medication use, and social history. Specifically questions regarding cancer diagnosis and treatment plan will be collected. Use of hormonal contraception, gonadotropin releasing hormone agonist therapy, or use of hormone replacement therapy will be recorded. In addition, the Menopausal Symptom List (MSL), a validated instrument for assessing menopausal symptoms, will be used to assess the presence or absence of menopausal symptoms during the past month, the frequency and severity of each symptom. Symptoms captured include: hot flashes, vaginal dryness, concentration/memory problems, irritability, mood swings, feeling sad, feeling anxious, trouble sleeping, aches, joint pain, headaches.
- **Physical Examination Data:** Height and weight will be determined for the calculation of body mass index. In addition, a brief physical examination will be conducted to document Tanner Staging.
- Menstrual Diaries will be given to participants and they will be instructed to keep track of any bleeding during the study.
- **Serum Testing:** Blood samples will be obtained for determining levels of FSH, E2, INH, and AMH. In regularly menstruating girls and young women every attempt will be made to

collect hormone measures during the early follicular phase of the menstrual cycle (days 1-4).

- **Pelvic Ultrasonography** OV and AFC by size (2-5 mm, 6-9 mm, and >10 mm) will be determined. Uterine size and endometrial thickness will also be performed. The transvaginal approach is preferred, but transabdominal ultrasound will be performed in girls who do not feel comfortable with the transvaginal procedure.
- **Review and Documentation of Cancer Therapy** Cancer treatments will be abstracted for the clinical chart by the oncology offices caring for the patient (See Appendix).

For Specific Aim 2, data will be collected from: a structured interview with participants, physical examination, blood tests, and pelvic ultrasonography. Up to five annual visits will be completed. Data collection will include:

**Demographics:** Self report form is completed by the patient for this purpose.

- **Structured interview:** All study participants will be questioned regarding medical history, menstrual data, fertility treatment, pregnancy risk, pregnancy history, medication use, and social history. Specifically questions regarding cancer diagnosis and treatment plan will be collected. Use of hormonal contraception, gonadotropin releasing hormone agonist therapy, or use of hormone replacement therapy will be recorded. In addition, the Menopausal Symptom List (MSL), a validated instrument for assessing menopausal symptoms, will be used to assess the presence or absence of menopausal symptoms during the past month, the frequency and severity of each symptom. Symptoms captured include: hot flashes, vaginal dryness, concentration/memory problems, irritability, mood swings, feeling sad, feeling anxious, trouble sleeping, aches, joint pain, headaches.
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- Menstrual Diaries will be given to participants and they will be instructed to keep track of any bleeding during the study.
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- **Review and Documentation of Cancer Therapy** Cancer treatments will be abstracted for the clinical chart by the oncology offices caring for the patient (See Appendix).

All information will be kept confidential and will not be shared except as may be required by law. Data collected as part of this study will only be accessed by the principal investigator and other members of the investigative team. An identifying code will be assigned to each female who participates in this study. All data and laboratory results will have all patient identifiers removed and replaced with this code. A master list will link the study identification number to the subject's name. This master list will be kept on the password protected hard drive of the principal investigator. Hard copies of all testing results (without patient identifiers) will be kept in a locked drawer inside the secured office of the principal investigator.

### c. Potential Risks

There is a minimal risk to the patient from the venipuncture, which is necessary for the hormonal evaluation. The collection of blood in this manner may cause pain, swelling,

bruising or infection at the site of the needle puncture. In addition, pelvic ultrasonography has minimal risk. Depending on the route of ultrasonography, transvaginal vs. abdominal, patients may experience skin or vaginal irritation and mild discomfort during the procedure. Participants will not be forced to undergo transvaginal ultrasonography if they do not feel comfortable with this procedure. In that case, transabdominal ultrasonography will be performed. Finally, thinking about fertility issues or having to face the possibility that one is infertile may also cause some emotional distress. At any point during the study, subjects may refuse to participate in any portion and withdraw from the study.

## **2. Adequacy of Protection against Risks**

### **a. Recruitment and Informed Consent**

Participation in this project is entirely voluntary. Choosing to not participate will not impact the care received at this institution. The informed consent process will be fully documented by the research staff in the research notes. The informed consent discussion will include the purpose of the research, procedures, risks, benefits and subject's rights. The subject will be granted time to read the informed consent document, and all questions will be answered to her satisfaction. Informed consent will be obtained from the child's parent or guardian, or the patient herself if age 18 or older, prior to entrance to the study. Written assent will be also be obtained and documented in the space provided on the consent form.

### **b. Protection Against Risk**

Data collected as part of this study will only be accessed by the principal investigator and other members of the investigative team. All information will be kept confidential and will not be shared except as may be required by law. An identifying code will be assigned to each female who participates in this study. All data and laboratory results will have all patient identifiers removed and replaced with this code. A master list will link the study identification number to the subject's name. This master list will be kept on the password protected hard drive of the principal investigator. Hard copies of all testing results (without patient identifiers) will be kept in a locked drawer inside the secured office of the principal investigator. We have had extensive experience with clinical studies and are confident that this plan will keep subjects personal data confidential.

## **3. Potential Benefits of the Proposed Research to the Subjects and Others**

There may be no benefits to the subjects and controls participating in the study. However, if any of the tests indicate the high likelihood of decreased fertility potential, as the study investigators include reproductive endocrinologists, we will be able to counsel and assist in referring for appropriate care regarding reproductive health. The findings from this proposal may eventually allow pediatric cancer survivors to be diagnosed with decreased fertility potential at an early stage when fertility treatments are still an option. As there is minimal risk to the subjects and significant potential for benefit, the risk/benefit ratio is extremely favorable.

## **4. Importance of the Knowledge to be Gained**

The knowledge gained through this research may serve to revolutionize the care of pediatric cancer survivors. The findings from this proposal may eventually allow pediatric cancer survivors to be diagnosed with decreased fertility potential at an early stage when fertility treatments are still an option. We believe that the minimal risk to the subject is justified in this study since there is significant potential that this investigation will lead to substantial benefit for many cancer survivors in the future.

### Inclusion of Women and Minorities

- a. \_\_\_\_\_ serves as a referral center to \_\_\_\_\_ A review of charts from the pediatric oncology practice demonstrates that the cancer population to be studied will be composed of 80-90% Caucasians, 10-20 % African Americans, and 3-5% other. In addition, it is anticipated that approximately 5% of the population will be Hispanic. Therefore, we anticipate a largely Caucasian study population.
- b. Males will be excluded from this research, as the condition being studied, ovarian reserve, is only relevant to females. Therefore 100% of the study population will be female.
- c. The majority of the study population will consist of newly diagnosed cancer patients and survivors followed at the \_\_\_\_\_

Based on the numbers of patients seen per year at these institutions, we do not anticipate that we will need to actively recruit cancer patients from outside of these institutions into the study. However, unexposed subjects will be recruited and enrollment will be targeted to recruits subjects with a similar demographic makeup. Given this design there will be no outreach program to recruit members of any particular racial/ethnic group.

## Targeted/Planned Enrollment Table

This report format should NOT be used for data collection from study participants.

Study Title:

Total Planned Enrollment: 451

<b>TARGETED/PLANNED ENROLLMENT: Number of Subjects</b>			
<b>Ethnic Category</b>	<b>Sex/Gender</b>		
	<b>Females</b>	<b>Males</b>	<b>Total</b>
Hispanic or Latino	23	0	23
Not Hispanic or Latino	428	0	428
<b>Ethnic Category: Total of All Subjects *</b>	451	0	451
<b>Racial Categories</b>			
American Indian/Alaska Native	4	0	4
Asian	10	0	10
Native Hawaiian or Other Pacific Islander	3	0	3
Black or African American	73	0	73
White	361	0	361
<b>Racial Categories: Total of All Subjects *</b>	451	0	451

\* The "Ethnic Category: Total of All Subjects" must be equal to the "Racial Categories: Total of All Subjects."

### **Inclusion of Children**

a. Human Subjects Involvement and Characteristics

The age range for all specific aims will be between 11-50 years of age. Adolescents will be included in this study since the study is designed to identify early signs of decreased fertility potential, which may occur during the early adolescent years. Thus, by definition, this study includes women and children. . Informed consent will be obtained from the child's parent or guardian, or the patient herself if age 18 or older, prior to entrance to the study. Written assent will be also be obtained and documented in the space provided on the consent form.

Principal Investigator/Program Director (Last, first, middle):

## G. Literature Cited

Principal Investigator/Program Director (Last, first, middle):

### **Consortium / Contractual arrangements**

For this proposal, an experienced investigator in pediatric and adolescent oncology, is an absolute necessity. [redacted] an established pediatric oncologist with a special interest in cancer survivorship issues; her expertise and ability to recruit pediatric patients is essential to this proposal. The efficient and accurate completion of these proposed aims have high clinical significance but require an interdisciplinary and collaborative approach. Therefore, [redacted] where [redacted] is an Assistant Professor, will serve as a sub-contract for this proposal. The addition of this site provides the needed expertise to perform and complete these studies. The inclusion of [redacted] and [redacted] team adds significant and invaluable strength to our proposal.

Formal cost-reimbursement subaward arrangements will be employed between [redacted] and [redacted] with appropriate subrecipient monitoring activities and flow-down of prime award terms and conditions as appropriate.

January 22, 2009

Dear Dr.

We write this letter to express our enthusiastic support for your proposal "Ovarian Reserve After Cancer: Longitudinal Effects" and confirm our interest in collaborating on the project with you. As investigators at The we will insure that all the required resources of the pediatric oncology program are available for this work.

This type of research fits exceedingly well with our Survivorship Program and our Fertility Preservation Research. We believe the data from this investigation will be critical for targeting fertility preservation efforts in newly diagnosed cancer patients and will be instrumental in the establishment of an effective surveillance protocol for the early detection of compromised ovarian function after cancer treatment. We look forward to collaborating on this important project.

Thank you very much.

Sincerely,

January 25, 2009

Re: " " "

Dear

It is with great pleasure and honor that I offer my most enthusiastic support of your grant proposal, entitled "

As an experienced clinician and the director of the

Center, I will insure successful patient recruitment to your clinical investigation working with the oncologists and nurse practitioners in clinical practices who follow appropriate subjects for your study. Our mutual interests in fertility preservation for cancer survivors will create many opportunities for future collaborations.

I have enjoyed working with you over the past few years recruiting patients through our transition program for adult survivors of childhood cancer for your earlier study, and you will have our complete support with this project. The research coordinator for the survivorship program will screen and recruit patients from all of the oncology practices for this study. She has an excellent recruitment record and is very excited about her involvement in this project.

I am pleased to offer my expertise in survivorship clinical care and research, as well as my most enthusiastic support for your project. I look forward to working with you on this endeavor.

Sincerely yours,

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February 2, 2009

Dear Dr.

I am very excited to serve as a Co-Investigator collaboration and support for your research proposal entitled "

We have met and discussed the proposal and I have given input into the study design and analysis plan which will assess serum and urinary hormone levels along with ultrasound measures to detect compromised ovarian function in adolescents and young women with cancer.

This is an extremely important area of investigation which may lead to early detection and fertility options for these women at risk for premature ovarian failure. I look forward to working with you and contributing to this important area of research.

Sincerely,

January 23, 2009

Dear

I am delighted to support your grant application to examine potential reproductive dysfunction in young women with cancer. Your proposed use of urinary monitoring is a powerful clinical research method for such a patient sample. I will provide you with any collaboration you need, and as we have discussed you are welcome to visit my laboratory as needed to help you assimilate these techniques. We have been measuring urinary gonadotropins and sex steroids for 20 years now. It is particularly valuable for you to collect two cycles in your proposal, as we have found in the Study that the prior cycle's hormones appear to have a strong relationship to the subsequent cycle. You will be able to discern the nature of these relationships in your sample after the reproductive challenge of cancer therapy.

My laboratory will assist you by running validation samples as necessary until you are certain that you have mastered the quality control necessary to produce reliable and reproducible results. I will also help you trouble-shoot these assays should you run into any problems as some of them can be a bit tricky. In the event that you need our help to measure all of your samples, this can certainly be arranged, but I doubt that will be necessary. My laboratory has been involved in training several junior investigators in adapting these methods to their laboratories and none have had difficulty doing so.

Moreover I am happy to help you in any way you may need in data analysis and interpretation, as we have been running algorithms on menstrual cycles of both midreproductive aged and older reproductive aged women for many years and are well acquainted with the issues involved in objective algorithm analysis and pattern recognition.

I wish you the best of luck with your excellent application and hope to be working with you in the near future.

Sincerely yours,

January 22, 2009

Dear Dr.

As the Core Laboratory Director of the Clinical and Translational Research Center at the \_\_\_\_\_, I am writing to provide enthusiastic support for your NIH R01 grant proposal in which you will investigate the effect of cancer therapy on the reproductive function of adolescents and young women. The Core Laboratory provides extensive services for specimen collection and processing, as well as the performance of non-routine laboratory assays.

You have proposed a novel study assessing serum measures of FSH, Estradiol, Inhibin B, and AMH prospectively in young females exposed to cancer therapy compared to unexposed females. In addition, you will be assessing daily urinary FSH, LH, Estrone conjugate, pregnanediol glucouronide in a subset of cancer survivors and unexposed females.

As we have discussed, the primary role of the Core Laboratory in your project will be the performance of the biochemical assays involved in this project. We have already collaborated successfully on projects requiring a variety of serum assays, including these. I am committed to continuing these services for you. In addition, I intend to perform the urinary hormone assays (FSH, LH, Estrone conjugate, pregnanediol glucouronide) in consultation with one of the experts in this area, \_\_\_\_\_. I am dedicated to this project and look forward to working on it with you in the future.

Sincerely,

January 28, 2009

Re:

Dear Study Section:

It is with enthusiasm that I pledge my support and that of the Women's Health  
for [redacted] R01 grant application,  
Longitudinal Effects. I have worked with [redacted] for a number of years and she is a  
promising investigator with particular interests in the field of oncofertility. She has exceeded  
expectations in the recruitment and data obtained from the R03 and is poised to conduct a very  
valuable larger scale investigation into reproductive function after treatment of cancer.

As Director of the Women's Health [redacted] I pledge full access and support of  
the infrastructure available to conduct clinical research. The Women's Health [redacted]  
[redacted] has dedicated specialists to assist in subject recruitment, retention, scheduling research  
visits, collection of biomaterials, processing of all regulatory documentation and oversight. The  
goal of the Women's Health [redacted] is to have a pool of clinical research  
specialists to fill in the gaps necessary for the highs and lows of clinical research. Over the past  
ten years, this research has participated in many multicenter NIH-funded trials and has the  
experience and expertise to help [redacted] facilitate the excellent conduct of this trial. We have  
a strong track record in recruiting healthy volunteers as well as those with specific diseases and  
should have no trouble in identifying and taking very good care of women as described in Dr.  
[redacted] grant.

The main advantage of the Women's Health [redacted] is the cultivation of the  
culture of research within the department and its collaboration among other divisions,  
departments, and centers in the School of Medicine. I look forward to working with  
and will take an active role in insuring the success of this grant.

Sincerely yours,

January 30, 2009

Dear Dr.

This letter is written in strong support of your grant titled, \_\_\_\_\_). Your aim is to examine the specific fertility threats that chemotherapeutic agents present to young women with a cancer diagnosis. You are an ideal PI of this grant given your prior work in this field and the extensive preliminary data you have collected to this point. Your goals are ambitious but appropriate. You are currently funded by a K01 award through the \_\_\_\_\_. I have tracked your work on this mentored K grant and have been impressed by your scope of knowledge, your ability to communicate your work to large audiences ( \_\_\_\_\_) and your clinical skills in recruitment and analysis of patient data. You are clearly ready to begin work on an R01 and enter the rank of independent clinical investigator.

I am delighted to serve as a consultant to this grant and to specifically provide you with access to the \_\_\_\_\_ under the auspices of the \_\_\_\_\_.

This network of 50 physician practices has developed unified strategies in order to provide fertility sparing options to young women with cancer. These practice sites provide a collaborative and highly engaged group of clinical investigators who are poised to assist in the aims of your grant. The \_\_\_\_\_ does not have the funds to assist in the capture of patient data, thus, the funds you are requesting on the R01 do not duplicate work already ongoing in the \_\_\_\_\_ grant. Importantly, however, the R01 takes full advantage of the infrastructure and partnership relationships that have been created by the consortium. This is precisely what we wanted to foster when we initiated this consortium program.

Your work is important and timely and will contribute a great deal to how we define fertility risks to cancer patient cohorts in the future. I am enthusiastic about you, the project and the potential of your work.

Good luck with this important application.

Sincerely,

January 22, 2009

As one of the core investigators of the ( ) and the

I am writing this letter to provide my enthusiastic support for your R01 grant proposal entitled

Because of the growing survival rates among women treated for cancer, issues of quality of life have assumed significant roles for those with successful outcomes. It has been well recognized that the reproductive effects of chemotherapy and radiation may be devastating for the thousands of young women and children affected by cancer annually in the United States. However, some individuals are less affected and retain a limited amount of short-lived ovarian function. Unfortunately, it is difficult to predict the extent to which reproductive capacity may be compromised due to lack of investigation into this area. While new technologies such as ovarian tissue and oocyte cryopreservation have been promoted and performed in young women to preserve fertility, these treatments remain highly experimental and expensive. There is a clear need to establish the safety and effectiveness of these technologies. In an effort to improve options for fertility preservation, it is incumbent that we understand the acute and chronic reproductive effects of cancer therapies. This information will pave the way for predicting reproductive capacity following cancer treatment and devising therapeutic strategies to best preserve fertility in newly diagnosed cancer patients.

Your research proposal is vitally important and unique. A careful and detailed examination of the reproductive consequences of cancer treatment in women has not been performed and is warranted given the increased number of cancer survivors. Your preliminary data are very encouraging and demonstrate your ability to conduct the proposed studies. I enthusiastically support your research proposal and will help to move this project forward in any way possible.

Sincerely,



## Resource Sharing

1. Resource Tools will be made available, in accordance with the Principles and Guidelines for Recipients of NIH Research Grants and Contracts on Obtaining and Disseminating Biomedical Research Resources, to all researchers in both the private and public sector free or for a nominal charge and with minimal restriction. We will comply with free exchange of information and complete data sharing, with careful attention to the protection of participant confidentiality and HIPPA regulation. After primary analyses and acceptance for publication of the main findings, the final analytic dataset will be made available in accordance with NIH and University of Pennsylvania guidelines.
2. The institution will transfer data and materials to outside researchers under a Material Transfer Agreement issued and managed by \_\_\_\_\_ for Technology Transfer.
3. We will strive to publish findings in a timely manner and acknowledge that the research was supported by the NIH.

# PHS 398 Checklist

OMB Number: 0925-0001  
Expiration Date: 9/30/2007

## 1. Application Type:

From SF 424 (R&R) Cover Page. The responses provided on the R&R cover page are repeated here for your reference, as you answer the questions that are specific to the PHS398.

\* Type of Application:

New    Resubmission    Renewal    Continuation    Revision

Federal Identifier:

## 2. Change of Investigator / Change of Institution Questions

Change of principal investigator / program director

Name of former principal investigator / program director:

Prefix:

\* First Name:

Middle Name:

\* Last Name:

Suffix:

Change of Grantee Institution

\* Name of former institution:

## 3. Inventions and Patents (For renewal applications only)

\* Inventions and Patents:   Yes    No

If the answer is "Yes" then please answer the following:

\* Previously Reported:   Yes    No

**4. \* Program Income**

Is program income anticipated during the periods for which the grant support is requested?

Yes       No

If you checked "yes" above (indicating that program income is anticipated), then use the format below to reflect the amount and source(s). Otherwise, leave this section blank.

*Budget Period	*Anticipated Amount (\$)	*Source(s)
<input type="text"/>	<input type="text"/>	<input type="text"/>
<input type="text"/>	<input type="text"/>	<input type="text"/>
<input type="text"/>	<input type="text"/>	<input type="text"/>
<input type="text"/>	<input type="text"/>	<input type="text"/>
<input type="text"/>	<input type="text"/>	<input type="text"/>

**5. Assurances/Certifications (see instructions)**

In agreeing to the assurances/certification section 18 on the SF424 (R&R) form, the authorized organizational representative agrees to comply with the policies, assurances and/or certifications listed in the agency's application guide, when applicable. Descriptions of individual assurances/certifications are provided at: <http://grants.nih.gov/grants/funding/424>

*If unable to certify compliance* , where applicable, provide an explanation and attach below.

Explanation: