CCSS Analysis Concept Proposal:

1. Study Title: Infertility, assisted reproductive technology utilization and pregnancy outcomes in childhood cancer survivor population: A CCSS and SART CORS data linkage study
2. Working group and investigators:
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3. Background and rationale:

    Over 80% of childhood cancer patients survive long term; therefore, understanding the impact of cancer treatments on future fertility is a priority (Zebrack B 2012, Phillips SM 2015). Prior studies of female cancer survivors have shown that chemotherapy and/or radiation can lead to premature ovarian insufficiency or diminished ovarian reserve even when regular menses return post-treatment (Sklar CA 2006, Reh A 2008, Partridge AH 2010). There appears to be a dose dependent relationship between chemotherapy and/or radiation and ovarian reserve (Gracia CR 2012, Gao W 2015). Additionally, spontaneous pregnancy rates for both female and partners of male childhood cancer survivors are affected by type and dose of chemotherapy administered or total dose of radiation exposure (Green DM 2010, Chow EJ 2016.) Limited data suggest that female cancer survivors have a higher risk of infertility and have poorer IVF outcomes if they seek infertility treatment (Ginsburg 2001, Dolmans 2005, Barton SE 2012, Barton SE 2013). Though one study has touched on ART utilization in female childhood cancer survivors through self-reporting questionnaires (Barton 2013), none has examined post-treatment ART outcomes of female childhood cancer survivors.

    Regardless of whether assisted reproductive technologies are used, both childhood and adult female cancer survivors are more likely to have preterm deliveries if pregnancies are achieved (Signello LB 2006, Mueller BA 2009, Lie Fong S 2010, Madanat-Harjuoja L 2010, Metallo 2016). If female cancer survivors received pelvic radiation, their offspring are also at risk for low birth weight even after adjustment for preterm delivery (Green DM 2002, Reulen 2009). In male childhood cancer survivors and their partners, there was no significant increase in adverse outcomes in spontaneous pregnancies compared to controls (Green DM 2003, Reulen 2009). No

study has examined pregnancy outcomes specifically in female childhood cancer survivors who have undergone ART.

Barton SE et al (2013) examined infertility, infertility treatment and pregnancy outcomes in the Childhood Cancer Survivor Study (CCSS) population. Based on self-reported survey data, 3531 CCSS females were compared to 1366 sibling female controls. Survivors had increased risk of clinical infertility at earlier reproductive ages when compared to controls. Smaller subgroups answered questions based on infertility treatment. Both survivors and controls were equally likely to seek infertility treatment (315/455, 69.2% vs. 100/137, 73.0%), but survivors were less likely to be prescribed infertility medication (87/208, 41.8% vs. 56/75, 74.7%), which suggests a lower utilization of ART. This study was limited by its utilization of self-reported data, it did not include IVF specific information, and it included only the original CCSS cohort of women diagnosed between 1970 and 1986. The first birth from IVF in the US was in 1981 and thus, in the earlier reproductive years of the original CCSS cohort, ART was less widely available and less likely to be commonly utilized. Thus, ART utilization may be higher among the expanded CCSS cohort due to increased availability of the technology in the more recent era.

The Society for Assisted Reproductive Technology Clinic Outcome Reporting System (SART CORS) database includes comprehensive data from more than 90% of all assisted reproductive technology (ART) clinics in the United States of America. Historically, data for IVF cycles were collected and verified by SART and then reported to the CDC in accordance with the Fertility Clinic Success Rate and Certification Act of 1992 (Public Law 102-493). In 2004 SART changed its contract with the CDC and gained access to the SART CORS data for research purposes. Thus, data starting in 2004 are available for research purposes to persons or entities who agree to comply with SART research guidelines. Patients undergoing ART at SART-associated clinics sign consent forms that include permission to use their data for research. The data are submitted by individual clinics and vouched for by the director of each clinic. Approximately 10% of clinics are audited each year by the CDC and SART to validate the accuracy of the reported data. Accuracy is high.

Prior studies have utilized Redshift Technologies to reliably link the SART CORS database to other databases. In Luke B et al (2012), SART CORS was linked to birth registries to elucidate cumulative birth rates with ART. An algorithm that utilized a woman's date of birth, last name, first name and social security number were used to match repeat cycles within a single clinic and between clinics. In a second linkage study, Luke B et al (2016) linked SART CORS with state cancer registries to determine ART usage in adult cancer populations. Women with their first ART treatment in 2004-2009, as identified in the SART database, were linked to state registries in NY, TX and IL. 441 women were diagnosed with cancer (breast, endocrine, melanoma, female genital) within 5 years before the first ART cycle start. Mean age at cancer diagnosis was 33.4 yr. Women who had cancer started ART at a younger age and were less likely to achieve a live birth with autologous oocytes. Live birth rates among women using donor oocytes did not significantly differ by cancer status. We will utilize a similar process to link the CCSS cohort to SART CORS.

Our aim is to determine the utilization and success of IVF, as well as pregnancy outcomes, in childhood cancer survivors. We will compare childhood cancer survivors who underwent IVF to childhood cancer survivor siblings, as well as general and specific IVF populations for IVF cycle characteristics, implantation rates, clinical pregnancy rates, live birth rates, and pregnancy outcomes. We will accomplish this by linking the Childhood Survivor Cancer Study data to the SART CORS database. It is important to note that we will not address the utilization of non-ART infertility treatments, potentially comprising a large proportion of infertility treatments in the US, because we cannot quantify this usage with the databases available.

4. Specific aims/objectives/research hypotheses:
    a. Determine utilization rate of ART in childhood cancer survivors as defined by utilizing ART in a SART member clinic at least once in any given year.
        i. Hypothesis 1: The ART utilization rate in childhood cancer survivors overall is higher than CCSS sibling controls and as compared to the general population in the US as reported by the CDC in the 2017 MMWR Surveillance Summary, "Assisted Reproductive Technology Surveillance-United States, 2014."
        ii. Hypothesis 2: The ART utilization rate will be lower in childhood cancer survivors who have diagnoses and treatment that affect the brain or pelvic organ radiation as compared to other lower risk diagnoses in childhood cancer survivors and as compared to sibling controls.
    b. Compare cumulative and cycle-specific implantation, clinical pregnancy, and live birth rates in childhood cancer survivors who pursue ART to general and specific (male factor infertility) IVF populations.
        Hypothesis: Implantation, clinical pregnancy and live birth rates per stimulation, per embryo transfer, and therefore cumulatively, are lower in cancer survivors as compared to general and specific IVF populations.
    c. Compare pregnancy outcomes for childhood cancer survivors pursuing ART (gestational age at delivery, birth weight, route of delivery, and multiple gestation) to outcomes in siblings and general and specific (male factor infertility) IVF populations.
        i. Hypothesis: Childhood cancer survivors have more premature deliveries, lower birth weights, and lower risk of multiple gestations as compared to siblings, general and specific IVF controls.
    d. Determine donor gamete utilization and pregnancy outcomes in childhood cancer survivors as compared to siblings and general IVF population.
        i. Hypothesis: Childhood cancer survivors who undergo pelvic radiation or gonadotoxic chemotherapies are more likely to use donor gametes and have increased risk of premature delivery and lower birth weights than their siblings or as compared to a general IVF infertile cohort.

5. Subject population + Eligibility criteria:
        i. CCSS Survivor and Sibling (Control) Eligibility Criteria:
            a. Female Survivors and siblings enrolled in CCSS database and could potentially be found in SART CORS database

b. Between the years of 2004-2015, must have at least one year in which they were aged 18-55

ii. Available Survivor population: Tables 1 and 2 below summarize the number of CCSS participants who have years of reproductive adult age that fall within the study time frame:

Table 1: Number of females who were ages 20-55 after CCSS cohort entry and prior to last follow-up in calendar years 2004-2014

age	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	Total in Each Age Group
20	318	316	275	241	228	226	227	200	198	163	169	2392
21	358	316	315	274	239	227	224	227	200	198	163	2578
22	425	356	316	313	272	239	227	223	227	200	198	2798
23	415	424	355	314	313	272	238	226	223	227	200	3007
24	437	414	421	353	314	310	270	238	226	223	227	3206
25	466	434	414	421	352	312	308	268	238	226	223	3439
26	419	462	434	413	420	352	312	307	268	238	226	3625
27	406	416	462	433	411	418	350	311	306	268	238	3781
28	350	406	412	460	432	408	416	350	310	306	268	3850
29	325	350	405	411	459	431	407	414	348	310	306	3860
30	377	323	348	405	410	459	426	407	413	347	310	3915
31	293	373	322	346	404	408	454	425	407	413	347	3845
32	315	291	371	319	346	403	406	452	424	406	413	3733
33	316	314	291	367	318	345	402	406	450	424	406	3633
34	335	316	314	291	365	318	343	401	405	450	424	3538
35	265	335	314	311	287	361	316	343	398	404	450	3334
36	220	265	335	311	309	284	361	315	342	398	404	3140
37	233	220	264	335	310	307	282	359	315	342	398	2967
38	179	229	217	262	334	307	305	282	358	314	342	2787
39	182	178	228	217	261	327	307	303	281	358	314	2642
40	181	180	177	223	215	261	324	304	302	281	358	2448
41	164	179	179	177	220	213	261	322	304	302	281	2321
42	146	163	177	173	174	219	211	258	321	302	302	2144
43	122	144	161	174	169	172	217	210	255	319	302	1943

44	113	121	143	159	172	165	171	215	210	254	319	1723
45	104	111	119	143	157	169	165	167	214	209	254	1558
46	87	102	110	119	142	156	169	162	163	213	209	1423
47	67	87	100	109	117	142	155	167	160	161	213	1265
48	33	66	87	98	108	114	141	151	166	160	161	1124
49	45	33	63	87	97	108	112	138	148	164	160	995
50	36	45	33	63	83	94	108	109	137	148	164	856
51	16	36	44	31	62	83	94	106	106	136	148	714
52	11	15	34	42	30	61	81	92	100	105	136	571
53	11	10	15	34	39	28	58	75	92	99	105	461
54	6	11	10	15	33	35	28	55	73	91	99	357
55	.	6	11	10	14	33	35	28	55	72	91	264

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Notes: Each woman only appears once in each row, but may appear in multiple rows. For example, there are a total of 2392 women who were age 20 sometime between 2004-2014. As a woman ages, she shifts diagonally down the table (e.g. she's 20 in 2015, 21 in 2016, etc). Follow-up is considered available from 5 years post cancer diagnosis to death (regardless of last date of CCSS survey).

Table 2: Number of females in the CCSS cohort (ages 20-55, years 2004-2014)

Years in Cohort (2004-2014)	N
>= 1	10019
>= 2	9798
>= 3	9585
>= 4	9325
>= 5	9058
>= 6	8756
>= 7	8456
>= 8	8139
>= 9	7831
>= 10	7488
>= 11	7110

iii. Additional comparison populations for Aims b-d:

2. Women with only Male factor diagnosis: Women whose diagnosis of infertility is based solely on the infertility of her male partner (severe oligospermia, azoospermia, etc). These women are presumed to be

otherwise fertile, and do not have decreased ovarian reserve or uterine factor infertility which negatively impact IVF pregnancy rates.

3. General IVF Population (All IVF diagnoses): All women who undergo IVF with the full range of infertility diagnoses as defined by SART (male factor, endometriosis, ovulation disorders, diminished ovarian reserve, tubal factors, uterine factors, other factors, unexplained, multiple diagnoses)

6. Analysis framework:
    a. Outcome(s) of interest:
        i. ART utilization: dichotomous variable per person-year
        ii. Implantation rate: dichotomous variable per person per embryo transfer
            1. Defined as number of gestational sacs/number of embryos transferred.
        iii. Clinical pregnancy: dichotomous variable per person
            1. Defined presence of fetal heart rate.
        iv. Live Birth: dichotomous variable per person
            1. Defined as infant born alive after 22 weeks gestation.
        v. Pregnancy outcomes:
            1. Multiple pregnancy: dichotomous variable
            2. Gestational age at birth: continuous variable by number of weeks
            3. Birth weight: categorical variable

    b. Exploratory variables: (confounders and effect modifiers)
        i. Cancer specific:
            1. Primary cancer diagnosis: categorical variable
            2. Age at diagnosis: continuous variable
            3. Treatment exposure
                a. Chemotherapy
                    i. Cyclophosphamide exposure (dichotomous) + Age at exposure (continuous)
                    ii. Procarbazine exposure (dichotomous) + Age at exposure (continuous)
                    iii. Number of alkylating agents in total (categorical)
                    iv. Dosage of each alkylating agent administered (if available, total dosage and dosage normalized to standard body surface area)
                    v. Cyclophosphamide Equivalent Dose (CED)
                b. Radiation
                    i. Maximum prescribed tumor dose to the abdomen body region (continuous) + Age at exposure (continuous)

ii. Average dose to right and left ovaries (continuous) + age at exposure (continuous)
iii. Maximum prescribed tumor dose to the pelvic body region (continuous) + age at exposure (continuous)
iv. Average dose to pituitary gland (continuous) + age at exposure (continuous)
v. Maximum prescribed total body irradiation dose (continuous) + age at exposure (continuous)

c. Stem Cell Transplantation (dichotomous)

4. Surgery: dichotomous variable
    a. Type of surgery: categorical variable by body part affected

ii. ART specific:

1. Oocyte age: continuous variable Recipient age: continuous variable Parity: categorical variable
2. BMI: continuous variable
3. Smoking: dichotomous variable
4. Infertility diagnoses: categorical variable
5. Number of fertility diagnoses: continuous variable
6. AMH: continuous variable
7. Day 3 FSH: continuous variable
8. Number of fresh ART cycles: continuous variable
9. Number of frozen ART cycles: continuous variable
10. Number of cancelled ART cycles: continuous variable
11. Year of ART treatment: continuous variable
12. Cumulative FSH dosage: continuous variable
13. Cumulative HMG dosage: continuous variable
14. Trigger injection type: categorical variable
15. Number of oocytes: continuous variable
16. Number of mature oocytes: continuous variable
17. ICSI used: dichotomous variable
18. Assisted hatching used: dichotomous variable
19. Number of 2pn: continuous variable
20. Cleavage stage embryo transferred: dichotomous variable
21. Cleavage stage embryo quality: categorical variable
22. Blastocyst transferred: dichotomous variable
23. Blastocyst embryo quality: categorical variable
24. Number of embryos transferred: continuous variable
25. Donor sperm used: dichotomous variable
26. Donor egg cycle: dichotomous variable
27. Gestational carrier cycle: dichotomous variable
28. Insurance coverage state of residence: categorical variable (no coverage, Insurance coverage suggestion, Insurance coverage mandate)

c. Statistical Methods:

i. For Aim "a," all subjects who were eligible to contribute at least one person-year of data to SART (as defined above) will be included in the analysis. We will treat ART as a dichotomous variable (yes/no) evaluated for each person-year of inclusion in the eligible time frame and determine a rate of usage per 100 person-years using a Poisson regression framework. Since each subject may have different potential years of age and calendar year available for contribution to the analysis, we will examine these rates stratified by age and/or prior pregnancies (determined by CCSS surveys) to try to identify and understand potential "survivor bias" wherein subjects who did not enter the SART database time frame until later reproductive ages may have had ART prior to entry. ART utilization rates for survivors will be compared to those of CCSS siblings using Poisson regression models adjusted for current age. Descriptively, rates will be compared with general population reported by CDC (Sunderam S et al, 2017). Among survivors, we will compare those who have diagnoses and treatment that affect the brain or pelvic organs as compared to other lower risk diagnoses in childhood cancer survivors. To evaluate socioeconomic influence on ART utilization, will examine ART utilization by state with the assumption that in an insurance-mandated state, socioeconomic status will play a lesser role in ART utilization. Ideally, we will be able to categorize states by insurance mandated status by year and utilize survivors' most recent residence to classify and evaluate rates by type of state (No coverage, Insurance coverage suggestion, Insurance coverage mandated).

ii. For Aims "b," "c," and "d" we will limit analyses to those survivors, siblings and other controls that utilized ART and will examine their reproductive outcomes. ART cycle characteristics of the subjects and comparison groups (in the "Explanatory variable" list above) will be compared. Outcomes described in section 6a will be examined using several methodologies. For binary outcomes, such as clinical pregnancies, live birth and multiple pregnancy, we will examine the proportion of women who attempted ART and achieved the outcome of interest and will examine the impact of covariates and comparisons between groups using logistic regression models. For multiple pregnancies, whether or not multiple embryos were transferred will be examined as a covariate or stratification factor. For all of the above analyses, comparisons will be made between survivors and siblings and male factor infertility patients utilizing comparison groups in models adjusted will be made for age at ART. Among survivors, we will examine the impact of diagnosis and cancer treatments on IVF outcomes.

d. Tables/figures:

Table 1a: Patient demographics for Childhood Cancer Survivors and Siblings

Factor	Categories	CCSS Population	CCSS Siblings
Woman's age *(mean years, SD)*	Age (at cancer diagnosis)		
Parity *n (%)*	0 1 ≥2		
Race/ethnicity *n (%)*	-White -Asian or Pacific Islander -Black or African American - American Indian or Alaskan Native -Hispanic or Latino -Not Asked -Refused -Unknown		
BMI *n (%)*	<18.5 18.5-24.9 25-29.9 30-34.9 35-39.9 ≥40		
Cancer type *n (%)*	-Acute lymphoblastic leukemia -Acute myeloid leukemia -Other leukemia -Hodgkin Lymphoma -Non-Hodgkin lymphoma - Astrocytoma -Medulloblastoma, PNET -Other CNS tumors -Ewing sarcoma -Osteosarcoma -Kidney tumor -Soft-tissue sarcoma -Neuroblastoma - Other neoplasm		
Any chemotherapy	Yes No Unsure		
Age at Exposure	<13 13-20 Unknown		
Cyclophophamide Exposure	Yes No		

	Unsure		
Procarbazine Exposure	Yes No Unsure		
CED (mg/m^2)	0 0-3999 4000-5999 6000-7999 8000+		
Any radiation	Yes No Unsure		
Pelvis RT Dose	<5 Gy 5-10 Gy 11-20 Gy >20 Gy		
Abdomen RT Dose	<5 Gy 5-10 Gy 11-20 Gy >20 Gy		
RT to HPO Axis Dose	<5 Gy 5-10 Gy 11-20 Gy >20 Gy		
Spinal RT Dose			
Total Body Irradiation Dose	<12 Gy 12 Gy >12 Gy		
Stem Cell Transplant	Yes No Unsure		
Removal of one ovary	Yes No Unsure		
Removal of both ovaries	Yes No Unsure		
Removal of uterus	Yes No Unsure		
Other pelvic organ surgery	Yes No Unsure		

Table 1b: Patient demographics for those pursuing fertility treatment

Factor	Categories	CCSS Population	CCSS Siblings	Male Factor Infertility	General SART IVF Population
Woman's Age *(mean years, SD)*	Age (at start of IVF)				
Parity *n (%)*	0 1 ≥2				
Race/ethnicity *n (%)*	-White -Asian or Pacific Islander -Black or African American - American Indian or Alaskan Native -Hispanic or Latino -Not Asked -Refused -Unknown				
BMI *n (%)*	<18.5 18.5-24.9 25-29.9 30-34.9 35-39.9 ≥40				
Infertility diagnosis	-Male factor -Endometriosis -Ovulation disorders -Diminished ovarian reserve -Tubal factors -Uterine factors -Other factors -Unexplained				
Number of infertility diagnoses	1 2 3 4 ≥5				

Table 2: Patient cycle characteristics

Characteristics		Childhood cancer survivors	CCSS Siblings	SART IVF population	Male factor IVF population
Oocyte age (years)					
Recipient age (years)					
Day 3 FSH (mean, SD)					
AMH (mean, SD)					
Number of fresh autologous oocyte IVF Cycles *n (%)*	1 2 3 4 ≥5				
Number of frozen autologous oocyte IVF cycles *n (%)*	1 2 3 4 ≥5				
Number of fresh donor oocyte IVF cycles *n (%)*	0 1 2 3 4 >5				
Number of frozen donor oocyte IVF cycles *n (%)*	0 1 2 3 4 >5				
Number of cancelled cycles *n(%)*					
Donor sperm used *n (%)*					
Stimulation protocol	-GnRH agonist flare -GnRH agonist suppression -GnRH antagonist suppression -Clomiphene - Letrozole -Unstimulated				

Cumulative FSH Dosage	None <2000IU 2000-3999IU 4000-6999IU ≥7000IU				
Cumulative HMG Dosage					
Trigger type	HCG Lupron Combination				
Number of mature oocytes retrieved *Mean (SD)*					
ICSI *n (%)*					
Assisted hatching used *n (%)*					
No. 2 pn *Mean (SD)*					
Cleavage-stage embryo transfer n *(%)*	-Total transfers -No. embryos transferred 1 2 3 ≥4 - Mean cell number of cohort				
Blastocyst transfer *n (%)*	-Total transfers -No. embryos transferred 1 2 >2				

Table 3. ART utilization in person-years by presence of state insurance mandate as compared to sibling controls

Diagnosis	N (person-years)	All CCSS	CCSS Siblings	US Population
Insurance mandated states				
Insurance suggested states				

States with no insurance coverage				

Table 4: Probability of Conception and Live Birth Rate for women after ART by Oocyte Source and Gestational Carrier Status

		All cancers	Siblings	Male factor infertility	SART IVF population
Autologous oocytes (n, %)	Implantation rate				
	Clinical pregnancy rate				
	Live birth rate				
Donor oocytes (n, %)	Implantation rate				
	Clinical pregnancy rate				
	Live birth rate				
Autologous oocytes in gestational carrier (n, %)	Implantation rate				
	Clinical pregnancy rate				
	Live birth rate				
Donor oocytes in gestational carrier (n, %)	Implantation rate				
	Clinical pregnancy rate				
	Live birth rate				

Table 5: Probability of Other IVF Cycle Outcomes for Women after ART by Oocyte Source and Gestational Carrier Status

		All cancers	Siblings	Male factor infertility	SART IVF population
Autologous oocytes (n, %)	Chemical				
	Ectopic				
	Spontaneous abortion				
	Stillbirth				
Donor oocytes (n, %)	Chemical				
	Ectopic				
	Spontaneous abortion				
	Stillbirth				
Autologous oocytes in gestational carrier (n, %)	Chemical				
	Ectopic				
	Spontaneous abortion				
	Stillbirth				
Donor oocytes in gestational carrier (n, %)	Chemical				
	Ectopic				
	Spontaneous abortion				
	Stillbirth				

Table 6: Likelihood of conception and live birth for women after ART by cancer diagnosis, limited to women who only used autologous oocytes

Treatment	N, women	Implantation rate	Clinical pregnancy rate	Live Birth rate
None (Siblings)				
None (SART IVF)				
None (Male Factor)				
Hodgkin's lymphoma				
Non-Hodgkin lymphoma				
Leukemia				
CNS tumor				
Kidney tumor				
Neuroblastoma				
Soft-tissue sarcoma				

Bone tumor				

Table 7: Pregnancy outcomes in the live-born children of childhood cancer survivor population undergoing ART and controls from both male factor and general ART population

Outcome		Survivors	Survivor Siblings	Male factor Infertility patients	SART IVF population	OR (95% CI)
Duration of gestation	Preterm Full term Unknown					
Gestation	Singleton Twins Triplets or more					
Birth weight, g	<1500 1500-1999 2000-2499 2500-2999 3000-3499 3500-3999 ≥4000					
Low Birth Weight (<2.5kg)	Yes No Unknown					
Non-LBW (2.5kg or higher)						
Small for gestational age	Yes No Unknown					

7. Special considerations:
    a. Additional calculations include: cumulative live birth rate, live birth rate per embryo transferred, live birth rate per cycle start, live birth rate per egg retrieval, cancellation rate(including reason for cancellation)

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