Childhood Cancer Survivor Study
Analysis Concept Proposal

Date: 3/9/18
Title: Temporal trends in late-onset morbidity and mortality in rhabdomyosarcoma survivors

Working Groups

Primary- Chronic Disease
Secondary- Cancer Control; Biostatistics/ Epidemiology

Investigators

Pooja Hingorani	phingorani@phoenixchildrens.com
Kevin Oeffinger	kevin.oeffinger@duke.edu
Paul Nathan	paul.nathan@sickkids.ca
Yutaka Yasui	Yutaka.Yasui@stjude.org
Wendy Leisenring	wleisenr@fhcrc.org
Greg Armstrong	Greg.Armstrong@stjude.org
Rebecca Howell	rhowell@mdanderson.org
Carola Arndt	carndt@mayo.edu
Emily Mueller	elmuelle@iupui.edu
Todd Gibson	Todd.Gibson@STJUDE.ORG
Suzanne Wolden	woldens@MSKCC.ORG
Daniel Green	Daniel.green@stjude.org
Kari Bjornard	kari.bjornard@stjude.org
Kirsten Ness	Kiri.Ness@stjude.org
William H. Meyer	William-Meyer@ouhsc.edu
Leslie Robison	les.robison@stjude.org

Background and Rationale

Over the past several decades, survival outcomes for children with rhabdomyosarcoma (RMS) have improved significantly. This achievement is attributable to a series of trials done from 1972-1997 by the Intergroup Rhabdomyosarcoma Study Group (IRSG) (IRS-I to IRS-IV).[1] These studies progressively risk-stratified patients based on their clinical and pathological features, used previous results to determine the best multi-agent chemotherapy, and employed new and advanced surgical and radiation therapy techniques for local tumor control.[2,3] As a result of improved survival (from 55% on IRS-1 to 71% on IRS-IV), a large cohort of childhood RMS survivors now exist.

Despite improved survival, studies in long-term survivors, treated for soft tissue sarcoma during childhood, document an increased risk for both prevalent and incident endocrine,

visual, auditory, cardiac, pulmonary, musculoskeletal and neurological impairment when compared to siblings.[4] A recent analysis, using data from the CCSS cohort diagnosed from 1970-1986, indicates that survivors report an increased burden of chronic medical conditions when compared to siblings (42% of survivors and 10% of siblings reported >/= 1 severe, disabling or life-threatening chronic medical condition). Survivors exposed to radiation are at particularly high risk of developing multiple chronic medical conditions. Survivors also have increased incidence of developing second malignancies compared to the general population (SIR of 5.6).[5] These late effects have an impact on survivors' daily life, as soft-tissue sarcoma survivors are less likely than siblings to complete high school, be employed or get married.[6]

Because the series of IRSG studies included treatment modifications over time (outlined below in Table 1), and because previous data suggest that specific treatment exposures and doses are associated with adverse outcomes, there may be differences in health outcomes for survivors treated during different treatment eras. The premise of this analysis will be to evaluate differences in late mortality, chronic health conditions and health status between RMS survivors treated from 1970-1990 (IRS-I to III trials were open from 1972-1991) to those treated from 1991-1999 (IRS-IV was open 1991-1997). In addition, if we find outcome differences by era of treatment, we will evaluate whether or not accounting for treatment intensity[7,8] attenuates or accentuates the effects of era on adverse health outcomes. Finally, we will evaluate the associations between specific treatment exposures and doses across the entire cohort to identify the most important treatment related risk-factors for adverse outcomes in the RMS survivor cohort. We will also attempt to evaluate how many patients were actually treated on study on protocol IRS I-IV and if numbers are sufficient, will perform a subset analysis of these patients (IRS I-III vs. IRS IV) with the same aims of determining differences in chronic health conditions and mortality. These data may provide additional information for risk-based screening for late effects or for decision making among oncologists designing new trials to treat RMS.

Table 1 lists some of the key differences in approaches to treat RMS patients across different IRS studies as dictated by the IRS protocols (but there was also considerable overlap in actual treatments across these time periods). Table 2 details the chemotherapy dose exposures recommended on the four IRS studies in this time period along with actual treatment exposures that survivors received as abstracted from CCSS dataset.

Table 1: Treatment differences

	IRS I-III[9-11]	IRS IV[12]
Risk-stratification to tailor therapy	a) Initially based on extent of surgical resection; Clinical Groups I- IV. (See Appendix 1a) b) Progression of treatment stratification over the three studies to include tumor site and histology.	a) Based on both surgical grouping (Clinical Groups I-IV) AND IRS pre-surgical staging (See Appendix 1b) similar to contemporary RMS studies
Surgery	a) Amputation and extensive GU resections used more commonly	a) Surgical mutilation avoided if possible
Radiation	a) Whole cranium RT for parameningeal tumors with intracranial extension	a) Whole cranium RT was omitted for any parameningeal tumors. b) Half of the patients on IRS-IV were randomized to hyperfractionated RT (59.4Gy) arm and the other half to standard RT (50.4 Gy).
Chemotherapy	a) Three-drug therapy with vincristine, dactinomycin and cyclophosphamide (VAC) was the main backbone across IRS studies although dosing and schedules changed with each study. b) Doxorubicin was given in each of the three IRS studies at least to a subset of patients c) Intrathecal chemotherapy was given for patients with para meningeal tumors and	a) VAC therapy was randomized to vincristine, dactinomycin and ifosfamide or vincristine ifosfamide and etoposide for majority of non-metastatic patients except low risk patients. b) Doxorubicin was not part of planned therapy on IRS IV. c) Intrathecal chemotherapy was omitted.

	intracranial extension in IRS I and II d) Platinums such as cisplatin were part of IRS III	d) Platinums were not part of planned therapy on IRS IV

Table 2: Proposed and actual treatment exposures across the four IRS study time period

IRS studies/ Time Periods	Range of Proposed Exposures by treatment protocols	Mean Actual Exposures in CCSS (min-max)
1) IRS-1 (1972-78) N= 308	**Vincristine** 24-72mg/m2 **Dactinomycin** 0.375- 0.45mg/kg **Cyclophosphamide** (oral+IV) 0-51gm/m2 **Doxorubicin** 0-300mg/m2	**Vincristine** NA **Dactinomycin** 2.24mg/kg (0.002-199) **Cyclophosphamide** (oral+IV) 36.42 gm/m2 (0-130) **Doxorubicin** 337 mg/m2 (29-842)
2) IRS-2 (1978-84) N= 274	**Vincristine** 24-72mg/m2 **Dactinomycin** 0.375- 1.8mg/kg **Cyclophosphamide** (oral+ IV) 0-51gm/m2 **Doxorubicin** 0-480mg/m2	**Vincristine** NA **Dactinomycin** 0.97mg/kg (0.0006-18.3) **Cyclophosphamide** (oral+ IV) 26gm/m2 (0-98.5) **Doxorubicin** 347 mg/m2 (0-882) **Cisplatin** 338mg/m2 (0-985) **Etoposide** 1639 mg/m2 (0-7590) **Ifosfamide** 38 gm/m2 (0-127)
3) IRS-3 (1984-91) N= 302	**Vincristine** 72-80mg/m2 **Dactinomycin** 0.45- 1.8mg/kg **Cyclophosphamide** IV 0-24gm/m2 **Doxorubicin** 0-420mg/m2 **DTIC** 0-2000mg/m2 **Etoposide** 0-900mg/m2 **Cisplatin** 0-360mg/m2	**Vincristine** 47mg/m2 (1-109) **Dactinomycin** 0.59mg/kg (0.0004- 3) **Cyclophosphamide** IV 12.6gm/m2 (29-49) **Doxorubicin** 340mg/m2 (0-811) **DTIC** 893.75 mg/m2 (0-1787) **only 2 survivors recorded to get DTIC* **Etoposide** 2645 mg/m2 (285-13046) **Cisplatin** 330mg/m2 (3-933) **Ifosfamide** 56gm/m2 (0-155)
4) IRS-4 (1991-97) N=207	**Vincristine** 36-50mg/m2 **Dactinomycin** 0.3- 0.75mg/kg **Cyclophosphamide** 0-26.4gm/m2 **Doxorubicin** 0 mg/m2 **Ifosfamide** 0-72mg/m2 **Etoposide** 0-3000mg/m2	**Vincristine** 31mg/ m2 (1-102) **Dactinomycin** NA **Cyclophosphamide** 12gm/ m2 (0- 37) **Doxorubicin** 246mg/m2(0.35- 487) **Ifosfamide** 50gm/m2 (0-86.5) **Etoposide** 2547 mg/m2 (3.45-4929)
5) 1997-1999 N=72		**Vincristine** 38mg/ m2 (0.72- 86) **Dactinomycin** NA **Cyclophosphamide** 21.26 gm/ m2 (0.014- 36.5) **Doxorubicin** 359 mg/m2 (121-679) **Ifosfamide** 41 gm/m2 (11.8-72) **Etoposide** 2400 mg/m2 (519-4039)

NA- not available

As highlighted in Table 2, there were considerable overlaps in actual chemotherapy exposures in CCSS cohorts across IRS studies making clean comparisons harder. However, there were some key differences elicited between the IRS I-III time periods and IRS IV and up to 1999 time period.

1) Overall cumulative mean cyclophosphamide equivalent dose (calculated using cyclophosphamide (CPM) and Ifosfamide doses mainly) was higher in IRS-I-III as compared to IRS-IV onwards (97,936mg/m^2 vs 55,464mg/m^2 respectively). The percentage of survivors who received any CPM was similar in the 2 eras (70% vs. 77%).
2) Although doxorubicin was not part of treatment protocol on IRS-IV for non-metastatic patients, there were survivors in both these eras that did receive doxorubicin. But importantly, fewer survivors received doxorubicin in IRS-IV time period as compared to IRS I-III (28% vs. 42% respectively).
3) Similarly, 11% of patients received cisplatin in IRS I-III time period versus 1.7% in IRS IV and beyond.
4) Additionally, in IRS IV intrathecal chemotherapy was omitted for patients with parameningeal (PM) primaries and intracranial extension.

Based on the above information, we propose the following aims for our study:

Specific Aims and Hypotheses

Specific Aim 1: Determine the cumulative incidence of chronic health conditions (any condition, grade 3-5 conditions, multiple grade 3-5 conditions, and selected conditions [e.g., second malignant neoplasms, hearing and visual loss, cardiac conditions, genitourinary problems and endocrine conditions]) and compare by era of therapy (1970-1990 to 1991-1999)*.
*Subset analysis of patients actually enrolled and treated on study will be performed if adequate numbers exist in the 2 groups (IRS I-III vs. IRS IV)

Hypotheses: The cumulative incidence of any condition and grade 3-5 conditions (including the selected conditions listed above in Specific Aim 1) will be lower for RMS survivors diagnosed 1991-1999 compared with those diagnosed 1970-1990.

Specific Aim 2: Estimate all-cause and cause-specific mortality for 5+ year survivors of childhood RMS diagnosed from 1970 through 1999 and compare by era of therapy (1970-1990, 1991-1999)*.
*Subset analysis of patients actually enrolled and treated on study will be performed if adequate numbers exist in the 2 groups (IRS I-III vs. IRS IV)

Hypotheses:

1) In rhabdomyosarcoma survivors who survived more than 5 years after diagnosis, all- cause mortality at 10 and 15 years post-diagnosis will be lower in those treated during 1991-1999 as compared to those treated during 1970-1990.

2) Cause-specific mortality (recurrent disease, SMN or chronic health conditions such as cardiac and pulmonary) will also be lower in the cohort treated more recently.

Specific Aim 3: To determine if accounting for treatment intensity (RMS specific) attenuates or accentuates the effects of era on chronic health outcomes and mortality among RMS survivors.

Hypothesis: The effects of era on incidence of chronic health conditions and on mortality will be attenuated when treatment intensity (determined using a RMS specific treatment intensity score) is accounted for.

Specific Aim 4: To evaluate specific treatment related risk for chronic health conditions and mortality across the two eras.
For this aim we will select certain therapies/ combination of therapies across the two eras to determine their specific impact on CHCs and mortality. See below for more detail.

Specific Aim 5: To describe the prevalence of adverse health status outcomes in childhood survivors of RMS treated during 1970-1990 and those treated during 1991-1999
Hypotheses:

1) Differences in treatment over different time periods may impact health status of survivors as measured by general health, mental health, functional status, activity limitations and cancer related pain and anxiety.

Analysis Framework

1) Study Population

Study participants will include individuals enrolled in the original as well as the expansion CCSS cohorts during 1970-1999 with a diagnosis of rhabdomyosarcoma. For time to event analyses survivors should have to have responded to Baseline questionnaire and will include data to their most recent follow-up available.

2) Outcome Measures

a. Chronic Health Conditions: These will be scored as
   - No chronic condition
   - Any grade 1-5 condition
   - At least one grade 3-5 condition
   - Multiple ($\geq$ 2)grade 3-5 conditions

   In addition, incidence of specific sub-types of chronic conditions such as SMN, vision and hearing problems, cardiovascular disease, genitourinary problems, pulmonary, CNS and endocrine problems will be assessed individually.

b. Mortality: Vital status (alive/ dead) will be determined from the national death index using the most recently available data. Vital status will be used to calculate cumulative incidence of mortality and standardized mortality ratios (SMR). SMR will be generated using the US mortality rates from the Centers for Disease Control. Cause of death will be determined from death certificates and classified as due to recurrence/ progression of rhabdomyosarcoma, external cause (accidents, injuries, etc.) and other health-related causes (including second malignant neoplasm or chronic health conditions).

c. Health Status: This will be determined in the following categories using the results from the latest questionnaire that was filled by an individual participant-

    a. Poor general health: answers fair or poor vs. good, very good or excellent
    b. Poor mental health: score of 63 or higher on the Brief Symptom Inventory (BSI) on any of the three subscales vs. no score of 63 or higher on any of the subscales of the BSI
    c. Activity limitations- answers limited to more than three months for the past two years to any of the three questions
    d. Functional impairment- answers yes to any of the three questions vs. answers no to all three questions
    e. Cancer related pain- answers a lot, very bad excruciating pain, medium amount of pain vs. small or no amount of pain
    f. Cancer related anxiety- answers a lot, very many/ extreme, medium amount of anxiety/ fears vs. small or no amount of anxiety/ fears

3) Explanatory Variables

    g. Treatment Era: 1970-1990 and 1991-1999. Individuals will be assigned to treatment era based on their date of diagnosis.
    h. Treatment Exposures within 5 years from diagnosis: Treatment exposures previously abstracted from the medical records of RMS survivors will be used. A **treatment intensity score** will be calculated for each survivor based on the following treatment variables included in the score (for specific Aim 3)-
        i. Any Head and Neck Radiation (yes, no)
        ii. Whole Cranial Radiation (yes, no)
        iii. Chest Radiation (yes, no)
        iv. Abdominal/ Pelvic Radiation (yes, no)
        v. Extremity Radiation (yes, no)
        vi. Extremity surgery (amputation, limb sparing, no)
        vii. Genitourinary surgery (bladder, other pelvic organs)
        viii. Alkylating agents (≥6000mg/m2, <6000mg/m2)
        ix. Anthracyclines (≥250mg/m2, <250mg/m2)

x. Platinums (yes, no)

i. Specific treatment risks across the two treatment eras that may have had an impact on outcomes (for specific aim 4)-
   i. Cumulative dose of anthracycline exposure
   ii. Cumulative alkylator exposure (cyclophosphamide equivalent dose)
   iii. Head and neck RT (Y/N)
   iv. GU or extremity surgery for primary local control

4) Covariates

- attained age
- age at diagnosis
- gender
- race, ethnicity
- recurrence prior to 5-yr time point

Statistical Analysis

A. Mortality
Canadian residents will be excluded from the mortality analysis. Follow-up for mortality analysis will start at cohort entry (5 years post-diagnosis) and end on the date of death or censoring (December 31, 2013), whichever is earlier. Kaplan-Meier estimates of overall survival and cumulative incidence of cause-specific mortality will be estimated by and compared between treatment eras. SMRs will be calculated using the age-, calendar year-, and sex- matched rates in the general population obtained from the Centers for Disease Control. Piecewise exponential models will be used to assess the effect of treatment era on all-cause and cause-specific mortality rates (or SMRs) using the logarithm of person-years (or expected counts of death for the SMR analysis) as the offset.

B. Chronic Health Conditions
Cumulative incidence of chronic conditions will be estimated, treating death, SMNs, and late recurrence as competing risks for non-cancer chronic conditions and death and late recurrence as competing risks for overall chronic conditions; conditions diagnosed before study entry but after cancer diagnosis will be included as prevalent at study entry (5 years post diagnosis). Among participants free of any chronic health condition at study entry, piecewise exponential models will be used to compare rates of chronic conditions by treatment eras.

C. Health Status

Health status outcomes were measured in 4 questionnaires in the original cohort and 2 questionnaires for the expansion cohort. We will use data from the latest questionnaire that the participants filled out in each cohort. For each of the 6 domains, prevalence of adverse health status will be compared between treatment eras, using generalized linear models with a log-link function to estimate the prevalence ratios (PR) of treatment era, with random effects or generalized estimating equation to account for with-person correlation.

For each of the outcomes above, we will first assess the effect of treatment era in a base model that adjusts for age at diagnosis, attained age (modeled by natural cubic splines), and sex. Treatment exposures will then be added to the base model to examine the change in treat era effect to assess whether treatment exposures partially explain the association between treatment era and the outcomes. Given the sample size and the large number of treatment exposures considered, if the models encounter converge issue, the propensity score technique may be used. If the adjustment of treatment exposures does change the effect of treatment era, we will examine which treatment or combination of treatments contribute to the change.

D. Treatment intensity score

Similar to previously published papers [7,8], to illustrate treatment changes over time, we will calculate treatment score. This will be done by using multivariable piecewise exponential model to estimate the rate for any grade 3 or higher chronic conditions, with the treatment exposure listed in 3.h as the covariates, as well as age at diagnosis, sex, and attained age as cubic splines. This value will be standardized so survivors from 1970 to 1990 have a mean of 0.0 and SD of 1 and then plotted using boxplots.

References

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Table 1: Patient Demographics

	1970-1990	**1991-1999**

Age at questionnaire Mean Median		
Age at diagnosis Mean Median		
Time since diagnosis Mean Median		
Total number of survivors	N (%)	N (%)
Sex Male Female		
Race White (Non-Hispanic) Black (Non-Hispanic) Hispanic/ Latino Asian Other		

Table 2: Treatment Characteristics

	1970-1990	**1991-1999**
Overall Treatment	N (%)	N (%)

Chemotherapy and surgery Chemotherapy and radiation Chemotherapy, surgery and radiation		
Chemotherapy Alkylator exposure (CED) 0 gm/m2 <6 gm/m2 6-20gm/m2 ≥20 gm/m2		
Anthracycline Exposure 0 <250 mg/m2 ≥250mg/ m2		
Platinums		
Surgery Abdomen/ Pelvis/ GU Extremity		
Radiation sites Whole cranium Other head and neck Chest Abdomen Pelvis Extremity Other		
Major combination treatment arms VA±RT VAC±RT VAC+Doxo±RT VAC+Doxo+ "other chemo" ±RT Other		

VA= Vincristine+Dactinomycin
VAC= Vincristine+Dactinomycin+ Cyclophosphamide equivalent dose (CED)
Other chemo= either one or more of these agents: etoposide, cisplatin, DTIC, melphalan
Other= Any other combination of chemo treatments that do not fall under previous 4 arms described

Table 3: Chronic Health Conditions by Treatment Era

	1970-1990 N (%)	**1991-1999** N (%)
All CHCs • Any grade • Grade 3-5 • 1 grade 3-5 • >1 grade 3-5		
Cardiovascular • Any grade • Grade 3-5		
Pulmonary • Any grade • Grade 3-5		
Endocrine • Any grade • Grade 3-5		
CNS • Any grade • Grade 3-5		
Hearing/ Vision/ Speech • Any grade • Grade 3-5 *Genitourinary* • Any grade • Grade 3-5		

Table 4a: Rate ratio of having a grade 3-5 CHC with individual treatment factors

		Univariate		**Multivariate**
Variables		RR (95% CI)		RR (95% CI)

All survivors				
Treatment Era				
1970-1990		ref		ref
1991-1999				
Surgery				
GU/ pelvic	Yes			
	No	ref		ref
Extremity Amputation	Yes			
	No	ref		ref
Radiation	Yes			
	No	ref		ref
Head and Neck	Yes			
	No	ref		ref
Chest	Yes			
	No	ref		ref
Abd/ Pelvis	Yes			
	No	ref		ref
Extremity	Yes			
	No	ref		ref
Chemotherapy				
Alkylator (CED gm/m2)	≥20			
	> 6- <20			
	≤ 6			
	None	ref		ref
Anthracycline (mg/m2)	≥250			
	≤250			
	none	ref		ref

Table 4b. Rate ratio of having a grade 3-5 CHC with combination treatments

		Univariate		**Multivariate**

Variables		RR (95% CI)		RR (95% CI)
Treatment Era				
1970-1990		ref		ref
1991-1999				
Other specific treatment or combination exposures				
VAC±RT		ref		ref
VA±RT				
VAC+Doxo±RT				
VAC+Doxo+other chemo±RT				
Other				

VA= Vincristine+ Dactinomycin
VAC= Vincristine+Dactinomycin+CED

In both tables 4a and 4b, analysis will be adjusted for other variables such as attained age, age at diagnosis, gender and ethnicity.

Table 5: Survival after diagnosis

Survival after diagnosis	1970-1990 (N%)	1991-1999 (N%)	Total Alive	Total Dead
5-9 years				
10-14 years				
15-19 years				
20-29 years				
30-34 years				

Table 6a: All cause and Cause Specific Mortality by Treatment Era, Demographics and Treatment Exposures

	All Causes			Recurrence/ Progression			Nonrecurrence/ Non external Causes			Second Malignancy			Cardiac			Pulmonary		
	No. of deaths	SMR	95% CI	No. of deaths	SMR	95% CI	No. of deaths	SMR	95% CI	No. of deaths	SMR	95% CI	No. of deaths	SMR	95% CI	No. of deaths	SMR	95% CI
All Survivors																		
Treatment Era																		
1970-1990																		
1991-1999																		
Sex																		
M																		
F																		
Ethnicity																		
White																		
Black																		
Asian																		
Hispanic																		
Other																		
Individual Treatment Exposure																		
Any site RT																		
Head and neck RT																		
Chest RT																		
Abd/ pelvis RT																		
Alkylator- >20gm/m2 <20gm/m2																		
Anthracycline- >250mg/m2 <250mg/m2 none																		
Combination therapy																		
VA+RT																		
VAC+RT																		
VAC+Doxo+ RT																		
VAC+Doxo+ other agents +RT																		

Table 6b: Rate ratio of all-cause mortality by treatment era and treatment exposures

	All Causes		
Variables		RR	95% CI
All survivors			
Treatment Era			
1970-1990			
1991-1999			
Tumor Surgery			
	Yes		
	No		
Radiation	Yes		
	No		
Head and Neck	Yes		
	No		
Chest	Yes		
	No		
Abd/ Pelvis	Yes		
	No		
Extremity	Yes		
	No		
Chemotherapy			
Alkylator (CED gm/m2)	≥20		
	> 6- <20		
	≤ 6		
	None		
Anthracycline (mg/m2)	≥250		
	≤250		
	none		
Other specific treatment or combination exposures			
VAC±RT			
VA±RT			
VAC+Doxo±RT			

VAC+Doxo+other chemo±RT			
Other			

Rate ratio for cause specific mortality will be assessed for causes that have adequate numbers of events in each category.
Both univariate and multivariate analysis will be performed taking into account other variables such as attained age, gender, and ethnicity.

Table 7
Percentage of patients with adverse health status by therapeutic modality and treatment era

	N	Poor General Health	Poor Mental Health	Functional Impairment	Activity Limitation	Cancer Related Pain	Cancer Related Anxiety

Treatment Exposure and Era		N(%)	N(%)	N(%)	N(%)	N(%)	N(%)
Anthracyclines							
1970-1990							
1991-1999							
Alkylators							
1970-1990							
1991-1999							
Platinums							
1970-1990							
1991-1999							
Cranial Radiation							
1970-1990							
1991-1999							
Chest Radiation							
1970-1990							
1991-1999							
Abdominal/ Pelvic Radiation							
1970-1990							
1991-1999							
Extremity Radiation							
1970-1990							
1991-1999							
Amputation							
1970-1990							
1991-1999							
GU surgery							
1970-1990							
1991-1999							

Appendix 1a

Clinical (Surgical Grouping)

Group	Classification
I	Localized disease, completely resected, regional nodes not involved
II	Grossly resected localized tumor with microscopic residual OR

	Regional disease (regional lymph nodes and/or extension into adjacent organ), completely resected, no microscopic residual OR Regional Disease with lymph node involvement, gorssly resected with microscopic residual
III	Incomplete resection or biopsy with gross residual disease
IV	Distant metastatic disease

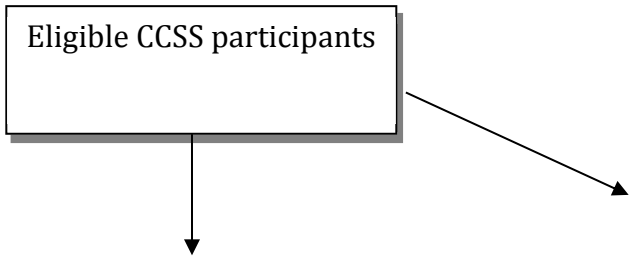
Appendix 1b

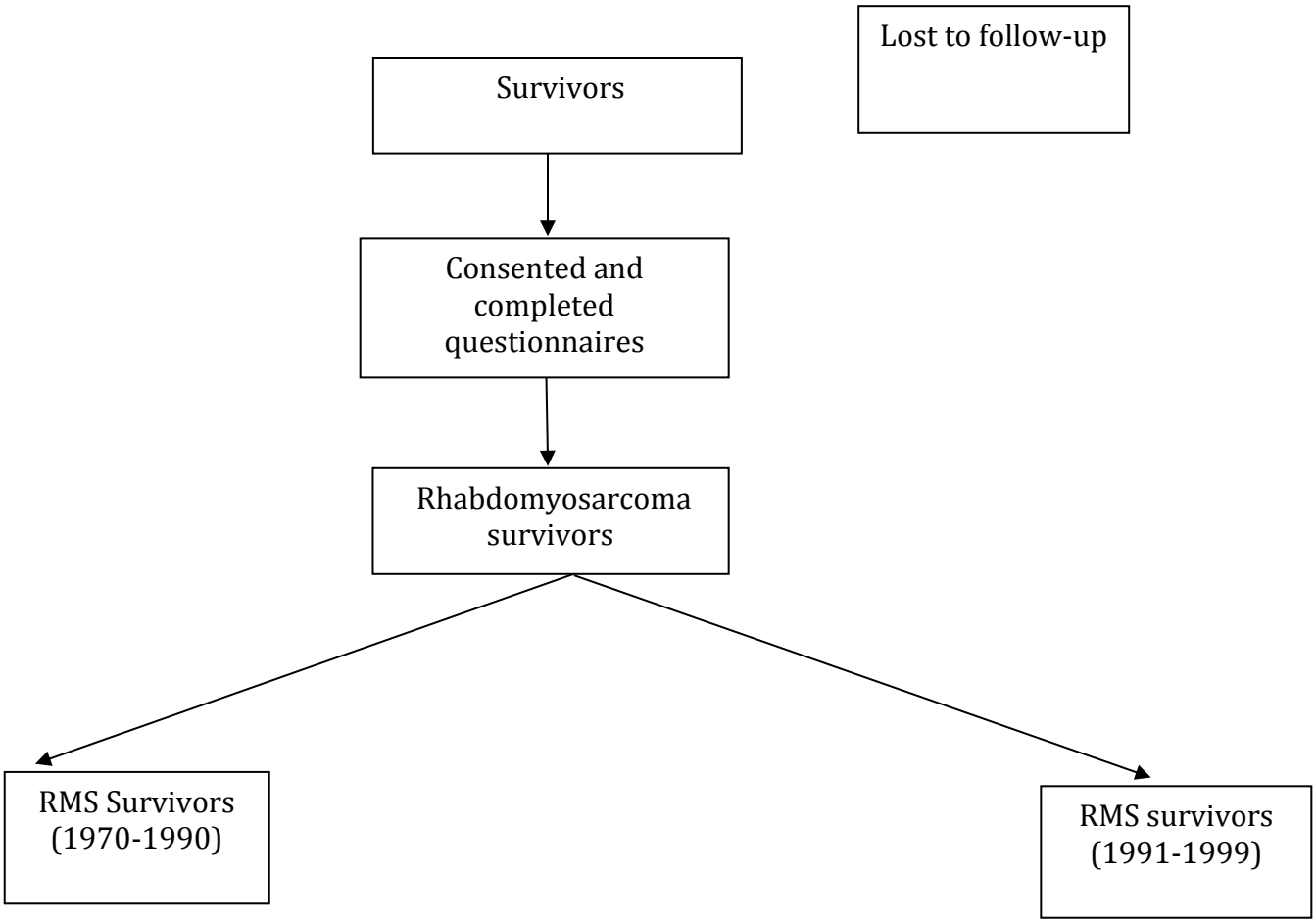
IRS pre-surgical staging

Stage	Sites	Tumor (T)	Size	Node (N)	Metastases (M)
I	Orbit, head and neck (excluding parameningeal) GU: nonbladder/nonprostate	T_1 or T_2	a or b	N_0, N_1, or N_x	M_0
II	Bladder/prostate, extremity, cranial, parameningeal, other (includes trunk, retroperitoneum, and so on)	T_1 or T_2	a	N_0 or N_x	M_0
III	Bladder/prostate, extremity, cranial parameningeal, other (includes trunk, retroperitoneum, and so on)	T_1 or T_2	a	N_1	M_0
			b	N_0, N_1, or N_x	
IV	All	T_1 or T_2	a or b	N_0 or N_1	M_1

NOTE. Tumor: T_1, confined to anatomic site of origin, (a) $\leq$ 5 cm in diameter in size, (b) $>$ 5 cm in diameter in size; T_2, extension and/or fixative to surrounding tissue, (a) $\leq$ 5 cm in diameter in size, (b) $>$ 5 cm in diameter in size; regional nodes: N_0, regional nodes not clinically involved; N_1, regional nodes clinically involved by neoplasm; N_x, clinical status of regional nodes unknown; metastasis: M_0, no distant metastasis; M_1, metastasis present.
Abbreviation: GU, genitourinary.

Figure 1: Flow diagram for Rhabdomyosarcoma Survivors




Lost to follow-up
Survivors
Consented and completed questionnaires
Rhabdomyosarcoma survivors
RMS Survivors (1970-1990)
RMS survivors (1991-1999)