Childhood Cancer Survivor Study
Analysis Concept Proposal

Title: Use of an incentive to increase biologic sample (Oragene) participation

Working Group and Investigators: Epidemiology and Biostatistics

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Background and Rationale

It has become increasingly clear in the study of late effects of childhood cancer and its treatment that while many associations between therapeutic exposures and outcomes have been established, their remains variability in the exposure-outcome relationship. Some children who receive high treatment doses do not develop late effects, and other children develop multiple late effects with fewer treatment exposures. These observations suggest that other factors such as genetic susceptibility may play an important role in subsequent neoplasm risk. [1-3].

A necessary first step for studies of genetic susceptibility is to collect sufficient DNA samples from participants. Increasingly, studies have been utilizing saliva collection as a relatively low-cost, non-invasive method that can be performed by the participant themselves, while still yielding high quality DNA [1,2,4]. These benefits help overcome some of the logistical challenges of collecting blood and/or other "on site" or more invasive specimen procurement methods. While the self-administered nature of saliva collection clearly offers benefits, a challenge that remains is to obtain samples from an acceptable number of participants, while minimizing cost and recruitment time. This is highlighted in prior studies that have shown participation rates ranging from 12% to 80% [2, 4-6]. Within the Childhood Cancer Survivor Study (CCSS), which is the context for the present study, the participation rate for saliva samples has been approximately 54% for survivors and 39% for the sibling comparison group, however, noting that this participation rate was achieved over many years at great cost [1].

Along with the range in participation rates in prior studies utilizing DNA samples, there is also concern that participation rates for epidemiologic studies are declining in general over the last 30 years [7-8]. Some of the key issues identified include increased refusal rates coupled with difficulty in locating prospective participants [8], as well as concerns about confidentiality and privacy [9]. Regardless of the reasons, lower response rates are an important issue because of the possible threat to the internal validity of a study resulting from selection bias. This occurs

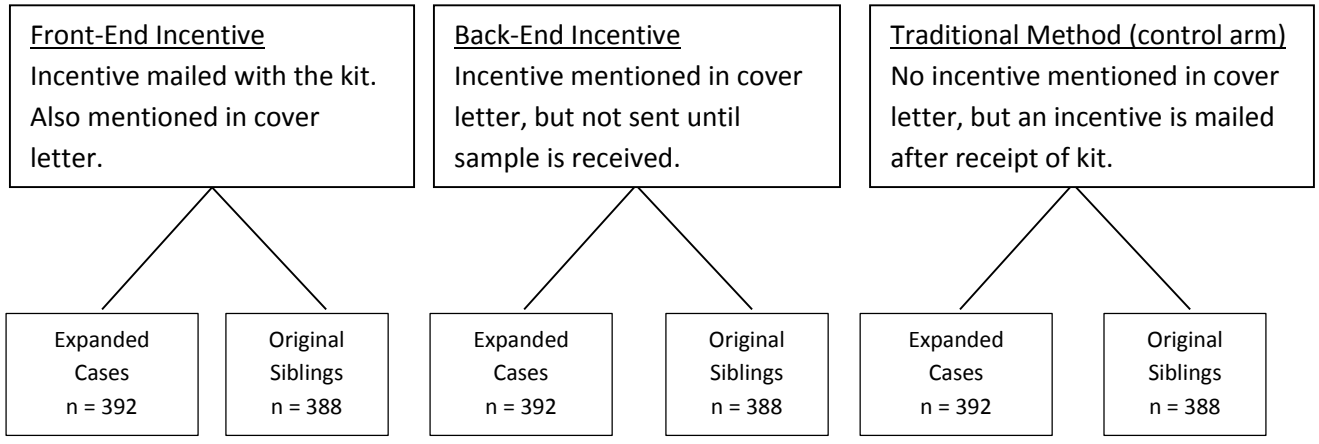
when the people who choose to participate in a study are potentially different from those who do not participate [7].

Given the varying sample accrual rates in DNA collection studies and the overall decline in participation rates in general, one option is to look at the use of incentives to increase response rates. While this may not address all of the noted concerns, the use of incentives has had a generally positive effect on survey return rates and study enrollment [8]. The use of cash incentives, for example, helped improve enrollment in an online health program and then the promise of continued incentives bolstered study retention [10]. The timing of incentives is also important. Sending the incentive with the request (an unconditional incentive) has resulted in significantly higher participation rates than the promise of an incentive for returning a survey in a study of childhood cancer survivors [11]. The use of a pre-paid incentive was also shown to result in a higher response rate when compared to a lottery group (chance to win a large incentive) and a control group [12].

Although the use of incentives has been effective with some prior studies, it is not clear if they would work with DNA based studies. The lack of evidence is highlighted by one researcher who noted, "the utility and impact of financial incentives for biobanking remains unclear" [9]. Thus, the goal of this study is to examine the effect of incentives on the participation rate for DNA collection amongst childhood cancer survivors.

Within CCSS we previously performed an IRB approved pilot study to determine whether use of an incentive ($25 Target gift card), either at the time of the initial mail-out of the Oragene kit, or promised after the receipt of the kit would increase participation at six months from the mail-out, compared to a control population who were not offered the incentive in the mailed materials.

Methodology Summary :



Controls who participated subsequently did receive the incentive. We evaluated this methodology within two populations: 1) Expansion cohort participants who had never previously been recruited for Oragene and 2) Original cohort siblings who had previously been recruited for Oragene but had not provided a specimen.

Sample size was determined based on assessing a difference of 10% in response rate (40% to 50% in Sibling Cohort) with 40% response rate with no incentive (Control) and 50% for either of the two incentive groups (Front-end and Back-end) and both incentive groups were compared to the control group without adjusting for multiple comparison using two sample z-test. Similarly, the sample size for the expansion cohort was based on assessing a 10% difference in response rate (45% to 55%) in the Control group vs. either of the two incentive groups and compared using two-sample z-test.

	p_0	p_1	N_1	N_2	Method
Siblings	0.40	0.50	388	388	Asymptotic Binomial (Normal Approximation)
Cases	0.45	0.55	392	392	Asymptotic Binomial (Normal Approximation)

Results indicated that receiving the incentive on the front end (i.e. with the initial mail-out statistically significantly maximized recruitment rates.

Return Rate Summary at 6 Month Follow-Up

Expanded Cohort Survivors

Method	Number Sent	Mailing Date	Response Rate (6 mos.)	P value
Front-End	392	10/19/2012	204 (52.0%)	<0.001
Back-End	392	11/9/2012	162 (41.3%)	0.047
Traditional (control)	392	11/30/2012	139 (35.5%)	---

Original Cohort Siblings (previous passive non-responders)

Method	Number Sent	Mailing Date	Response Rate (6 mos.)	P value
Front-End	388	10/12/2012	111 (28.6%)	<0.001
Back-End	388	10/25/2012	65 (16.7%)	0.696
Traditional (control)	388	11/6/2012	60 (15.5%)	---

In addition we wanted to determine the six-month cost per study arm, as well as, given certain assumptions below, determine the 24-month cost per arm if recruitment were ongoing beyond the six-month pilot. We hypothesized that while the immediate cost of a front end incentive would be higher, the advantage of rapid recruitment may reduce costs associated with prolonged follow-up including multiple attempts by mail and phone. Based on the assumptions below we found:

	N	**Response Rate**	**6 month cost**	**7-24 month cost**	**Total cost**
Front end	392	204 (52.0%)	$11,489	$18,612	$30,101
Back end	392	162 (41.3%)	$10,439	$22,770	$33,209
Control	392	139 (35.5%)	$9,864	$25,047	$34,911

Assumptions:
-24 months to complete oragene recruitment
-$15 cost/oragene kit
-$2.30/phone call, at 10 minutes of interviewer time per call

Known:
-6 month trial required 1 mailed kit and 1 call per survivor

24 month Aggressive Recruitment Assumptions:
-2 mass resends ($30/non-participating survivor)
-30 calls over remaining 18 months (at $2.30/call)

Our goal with this analysis is to provide additional descriptive and multivariate data regarding participation for publication as a brief report in an epidemiologic journal anticipating that future Oragene ascertainment within CCSS will employ a front-end incentive.

Specific Aims and Hypotheses

1. Determine, in a three-arm trial, whether the addition of a gift card incentive would improve participation compared to the control arm.
2. Determine whether an incentive mailed with a saliva kit (front end incentive) or only after the sample is returned (back end incentive) impacts participation.
3. Examine which arm is most cost effective while also considering return rates.

A Priori Hypotheses:
The arms receiving notification of the incentive will have a higher response rate than the control arm which is unaware of the incentive. Rapid recruitment in six months through use of an incentive may reduce costs associated with prolonged follow-up including multiple attempts at follow-up by mail and phone.

Analysis Framework

1. Outcome of Interest- Participation in Oragene sample study, by returning an Oragene kit within six months from mail-out.
2. Subject Population- A sample, randomly selected, of a) 1,176 survivors from the Expansion Cohort and b) 1,164 siblings from the Original Cohort.
3. Exploratory Variables- To include sex, race/ethnicity, age at Oragene mail-out, educational attainment, marital status, primary cancer diagnosis, age at diagnosis, treatment exposures (yes/no), chronic health condition (CTCAE maximum grade), fully enumerated in Tables 1 and 2.
4. Statistical analysis- In addition to data previously generated (see Background) we will include a descriptive analysis of demographic, cancer, cancer treatment characteristics by treatment arm (Table 1) and a multiple logistic regression analysis will be undertaken to evaluate the effects of recruitment strategy (Front-end, Back-end, Control) and other

covariates with participation rate. Specifically, for the expanded cohort, we will first independently model the relationship between each type of recruitment strategy vs. control group while adjusting for other covariates. We may consider combining the back-end group with the control group. A similar strategy will be adopted for analyzing the sibling cohort. (Table 2). Finally, we will perform multiple logistic regression in a stratified approach by developing models within each of the three recruitment arms to identify covariates associated with participation within each arm. (Tables 3-5).

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Table 1. Demographic and Treatment Characteristics by Recruitment Arm						
	Survivors			Siblings		
	Front-end	Back-End	Control	Front-end	Back-end	Control
Gender						
Male						
Female						
Race						
Non-Hispanic White						
Non-Hispanic Black						
Hispanic						
Other						
Age at request						
20 - 29						
30 - 39						
40 - 49						
50 - 59						
60+						
Educational Attain						
Less than college						
College graduate						
Not reported						
Marital status						
Divorced/sep/wid						
Married/Living as						
Never married						
Not reported						
Primary diagnosis						
Leukemia						
CNS						
Hodgkin lymphoma						
Non-Hodgkin lymphoma						
Kidney						
Neuroblastoma						
Soft Tissue Sarcoma						
Bone						
Age at diagnosis						
0 – 5						
6 – 10						
11 – 15						
16 - 20						
Treatment (yes/no)						
Surgery						
Chemotherapy						
Any chemo						
Alkylator						

Anthracycline						
Bleomycin						
Cisplatin						
Methotrexate						
Radiotherapy						
Any RT						
Brain						
Chest						
Abdomen						
Pelvis						
Chronic health status						
None						
I - II						
III - IV						

Table 2. Multivariable Associations with Participation in Oragene						
	Survivors			Siblings		
	Percent Participation	Odds Ratio	95% Conf. Interval	Percent Participation	Odds Ratio	95% Conf. Interval
Recruitment Arm						
Front End						
Back End						
Control						
Gender						
Male						
Female						
Race						
Non-Hispanic White						
Non-Hispanic Black						
Hispanic						
Other						
Age at request						
20 - 29						
30 - 39						
40 - 49						
50 - 59						
60+						
Educational Attain						
Less than college						
College graduate						
Not reported						
Marital status						
Divorced/sep/wid						
Married/Living as						
Never married						
Not reported						
Primary diagnosis						
Leukemia						
CNS						
Hodgkin Lymphoma						
Non-Hodgkin lymphoma						
Kidney						
Neuroblastoma						
Soft Tissue Sarcoma						
Bone						
Age at diagnosis						
0 – 5						
6 – 10						
11 – 15						
16 - 20						
Treatment (yes/no)						

Surgery						
Chemotherapy						
Any chemo						
Alkylator						
Anthracycline						
Bleomycin						
Cisplatin						
Methotrexate						
Radiotherapy						
Any RT						
Brain						
Chest						
Abdomen						
Pelvis						
Chronic health status						
None						
I - II						
III - IV						

Table 3. Multivariable Associations with Participation in Oragene: Front End Incentive Only						
	Survivors			Siblings		
	Percent Participation	Odds Ratio	95% Conf. Interval	Percent Participation	Odds Ratio	95% Conf. Interval
Gender						
Male						
Female						
Race						
Non-Hispanic White						
Non-Hispanic Black						
Hispanic						
Other						
Age at request						
20 - 29						
30 - 39						
40 - 49						
50 - 59						
60+						
Educational Attain						
Less than college						
College graduate						
Not reported						
Marital status						
Divorced/sep/wid						
Married/Living as						
Never married						
Not reported						
Primary diagnosis						
Leukemia						
CNS						
Hodgkin Lymphoma						
Non-Hodgkin lymphoma						
Kidney						
Neuroblastoma						
Soft Tissue Sarcoma						
Bone						
Age at diagnosis						
0 – 5						
6 – 10						
11 – 15						
16 - 20						
Treatment (yes/no)						
Surgery						
Chemotherapy						
Any chemo						

Alkylator						
Anthracycline						
Bleomycin						
Cisplatin						
Methotrexate						
Radiotherapy						
Any RT						
Brain						
Chest						
Abdomen						
Pelvis						
Chronic health status						
None						
I - II						
III - IV						

Table 4. Multivariable Associations with Participation in Oragene: Back End Incentive Only						
	Survivors			Siblings		
	Percent Participation	Odds Ratio	95% Conf. Interval	Percent Participation	Odds Ratio	95% Conf. Interval
Gender						
Male						
Female						
Race						
Non-Hispanic White						
Non-Hispanic Black						
Hispanic						
Other						
Age at request						
20 - 29						
30 - 39						
40 - 49						
50 - 59						
60+						
Educational Attain						
Less than college						
College graduate						
Not reported						
Marital status						
Divorced/sep/wid						
Married/Living as						
Never married						
Not reported						
Primary diagnosis						
Leukemia						
CNS						
Hodgkin Lymphoma						
Non-Hodgkin lymphoma						
Kidney						
Neuroblastoma						
Soft Tissue Sarcoma						
Bone						
Age at diagnosis						
0 – 5						
6 – 10						
11 – 15						
16 - 20						
Treatment (yes/no)						
Surgery						
Chemotherapy						
Any chemo						

Alkylator						
Anthracycline						
Bleomycin						
Cisplatin						
Methotrexate						
Radiotherapy						
Any RT						
Brain						
Chest						
Abdomen						
Pelvis						
Chronic health status						
None						
I - II						
III - IV						

Table 5. Multivariable Associations with Participation in Oragene: Control Group Only						
	Survivors			Siblings		
	Percent Participation	Odds Ratio	95% Conf. Interval	Percent Participation	Odds Ratio	95% Conf. Interval
Gender						
Male						
Female						
Race						
Non-Hispanic White						
Non-Hispanic Black						
Hispanic						
Other						
Age at request						
20 - 29						
30 - 39						
40 - 49						
50 - 59						
60+						
Educational Attain						
Less than college						
College graduate						
Not reported						
Marital status						
Divorced/sep/wid						
Married/Living as						
Never married						
Not reported						
Primary diagnosis						
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Kidney						
Neuroblastoma						
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Methotrexate						
Radiotherapy						
Any RT						
Brain						
Chest						
Abdomen						
Pelvis						
Chronic health status						
None						
I - II						
III - IV						