revised version
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# CHILDHOOD CANCER SURVIVOR STUDY

## Analysis Concept Proposal

1. **Title:** Long Term Outcomes in Pediatric Cancer Survivors who Received an Hematopoietic Stem Cell Transplant with Total Body Irradiation

2. **Working Group and Investigators:** This analysis and publication would be completed within the Chronic Disease Working Group. Investigators will include:

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3. **Background and Rationale**

Background: The first successful allogeneic stem cell transplant (SCT) was performed in 1968[1], and now over 30 years later SCT has become a standard of therapy for many malignant and non-malignant conditions. There currently are over 12,000 allogeneic SCT procedures and 18,000 autologous SCT performed worldwide yearly. In addition to increasing numbers of transplants being performed, survival after SCT has also been increasing and therefore the population of long-term survivors is rapidly expanding. While the initial goal of SCT was focused only on cure of the underlying disease, further efforts now must also be focused on what the long-term impact this treatment has on the overall health and well being of the individual. Research focused on late effects of SCT is necessary so that we may more specifically identify what the long-term risks of SCT are, what pre-and post-transplant factors are most significant, and what can be done to modify the risks of the procedure. Thus, the need for well designed investigations into the long term complications that these individuals are at risk for is becoming increasingly more important. The limitations of previous studies have included overall small numbers of patients with few, if any, long-term pediatric survivors. Most studies are retrospective and none have included an adequate analysis of the pre-transplant therapy which has been received. These studies have been limited to short follow-up times, and have not provided any focused analysis of specific subgroups that have been identified as having a higher incidence of late effects.

The etiology of post-SCT late effects is multifactorial and includes therapy received prior to SCT, the SCT preparative regimen, as well as transplant-related complications. Several

studies have focused on the impact of total body irradiation (TBI, single dose vs. fractionated dose) and some have compared this to the effects of busulfan in chemotherapy only preparative regimens. One such study evaluated the effects on growth, thyroid function, puberty, cardiac function and incidence of cataracts in children who underwent a SCT for AML and received TBI (single dose or fractionated, n=19) to children who received busulfan instead of TBI (n=26). The authors report that the risk of posttransplant growth impairment, thyroid dysfunction, Leydig cell damage and the incidence of cataracts were all reduced in the group of children receiving busulfan and no TBI.[2] An extensive review by Boulad, Sklar and others[3] details the current status of what is known regarding late complications after bone marrow transplantation in children and adolescents. The effects on various endocrine late effects are the best studied to date. Growth impairment is related to several variables such as young age at time of SCT, use of TBI in the preparative regimen, history of prior cranial radiation therapy, and the development of chronic GVHD.[4] Treatment with high dose cyclophosphamide alone, as frequently done for severe aplastic anemia, or the utilization busulfan based chemotherapy only preparative regimens has not lead to significant growth disturbances, although follow-up remains short.[5,6] Several studies have documented a significant decline in growth and reduced final adult heights in children receiving either single dose or fractionated TBI, although the effect was somewhat greater in children exposed to single dose TBI[7-9]
In at least one study, prior cranial radiation therapy is an important determinant of poor growth after SCT regardless of the transplant preparative regimen[10], although the impact of other treatments received prior to SCT has never been adequately analyzed. Therapy induced primary hypothyroidism, autoimmune thyroiditis, and thyroid carcinoma have all been reported as late effects after SCT with patients receiving TBI at greatest risk.[3,11,12] At least two studies have evaluated the impact of SCT with TBI as compared to standard chemotherapy without SCT for patients wit leukemia. In a small number of subjects (n=7), when treatment included TBI there was a higher likelihood of growth failure, gonadal and thyroid damage.[13] Another study which included 26 patients who were treated with chemotherapy only and 26 who received a SCT (n=9 with TBI) found that growth, renal and cardiac function were similar in the two groups but more ovarian failure was identified in females exposed to TBI. These studies were both limited by small numbers of patients who had received TBI, and indicates that a larger study is required to more adequately address this question.

A significant concern after TBI exposure is the potential adverse late-effects on gonadal and reproductive function. With the utilization of TBI, males have generally retained their ability to produce testosterone and enter puberty,[14,15] but germ cell dysfunction will develop in the vast majority.[16] Ovarian function after TBI is determined to a large extent upon the age of the patient at the time of SCT. Only fifty-percent of pre-pubertal girls who undergo fractionated TBI will enter puberty spontaneously.[15] Ovarian failure is seen in essentially all patients who are greater than 12 years of age at the time of treatment with TBI.[17,18] Only a limited data are available regarding pregnancy outcome. In at least one small study, spontaneous abortions occurred in 5 pregnancies of women who had TBI at a pre-pubertal age, and for women undergoing TBI at a later age, pregnancies were associated with an increased number off pre-term deliveries and low birth weight, but otherwise normal

infants.[19] These data are very preliminary and much larger numbers of women need to be observed over longer periods of time.

In addition to endocrine dysfunction, a significant problem experienced by transplant survivors are the effects of therapy on the CNS. Neuropsychological sequelae after SCT, particularly in children, are related to two main prognostic variables 1) young age at the time of radiation exposure, 2) cumulative dose of radiation received including pre-transplant cranial plus TBI with the SCT.[20] Patients who have undergone TBI with a history of having received prior cranial radiation therapy have a greater decline in full scale IQ as well as a declining fund of vocabulary, expressive language skills, and verbal memory ability compared to patients who underwent TBI with no prior history of cranial radiation.[21] There have also been reported pronounced motor delays and moderate developmental delays in children who had TBI when they were less than 3 years of age.[22] This effect seems to be less severe in children 3-11 years at the time of SCT although they were noted to develop gradual declines in cognitive functioning over time.[23] Other studies have not found convincing evidence of significant declines in overall intelligence or adaptive behavior functioning in children who have received TBI or non-TBI containing regimens.[24] It is possible however the length of follow-up may be a critical factor as many neuropsychological abnormalities may not be evident within the first 3 years post-transplant, and continued longitudinal follow-up for many years after treatment will be necessary.

Another area of significant concern in SCT survivors is in relation to the development of new post-transplant malignancies. As survival after SCT increases, and the length of follow-up becomes greater, the incidence of second malignant neoplasms (SMN) increases. The majority of SMN have been Epstein-Barr virus (EBV) associated post-transplant lymphoproliferative disorders (PTLD), leukemias or myelodysplastic syndromes, or solid tumors such as sarcomas or carcinomas[25]. The estimated incidence of any SMN was 9.9% at 13 years post-SCT and the cumulative probability of developing a second solid tumor malignancy was 5.6% at 13 years[26]. The dose of TBI was associated with an increased risk of a second tumor. A dose of >1000 cGy for single dose TBI doubled the risk and a dose of >1300 cGy for fractionated TBI quadrupled the risk of secondary solid cancers.

Finally, there remain several issues in long-term SCT survivors that have not been examined to a significant degree such as the effects on the cardiac, pulmonary, and skeletal systems, where transplant related morbidity is experienced, but little is known regarding the incidence, risk factors or natural history of the process. Additionally, as patients survive into adulthood, problems with attaining higher educational degrees, stable employment, and emotional well being could also be significantly problematic in this patient population given the intensity of the therapy they have received.

Significance: This study will be the first with survivors having the amount and length of detailed follow-up data available, in addition to pre-transplant treatment exposure data. The data generated from this study will be useful for the ongoing long-term follow-up of SCT survivors, as their follow-up monitoring may need to be more detailed than cancer survivors who have not undergone SCT. This study will also provide useful information for the design of future SCT trials that could focus on decreasing late effects.

## 4. Specific Aims/Objectives/Research Hypotheses

Objectives: This study will consist of an analysis of late effects seen among the subset of survivors within the CCSS who received TBI. This will allow us to characterize a large group of cancer survivors who had a SCT during childhood and compare them to a similar group of children who have undergone treatment for a malignancy which did not include SCT. While one might assume that the late effects seen in survivors of SCT will be greater than what is seen in patients with a similar diagnosis that did not have as SCT, this has never been directly compared before in a large cohort. It will not only be important to test that hypothesis, but also to describe the frequency, severity, and potential modifying factors (age, sex, diagnosis, etc) for specific health-related outcomes. This will be particularly important in regards to cardiopulmonary, endocrine (growth), fertility, and second cancer late effects.

Specific Aim: To perform an analysis of the cohort of subjects within the CCSS who have undergone SCT and received TBI to evaluate risks associated with late mortality, endocrine and cardiopulmonary outcomes, second malignant neoplasms, fertility and offspring, and health-related behaviors.

Hypothesis 1: Compared to children treated without SCT/TBI, children undergoing SCT/TBI will be at substantially higher risks for treatment related sequelae than children with the same underlying diagnosis who have not received SCT as part of their therapy.

Hypothesis 2: Cranial radiation therapy received prior to SCT/TBI will have an additional negative impact on endocrine and potentially other major adverse outcomes and this impact will be greater in children who were less than 5 years of age at the time of transplant.

Hypothesis 3: In leukemia survivors, psychosocial outcomes will not be different in patients whose treatment included SCT/TBI as compared to those who were treated with chemotherapy only.

**Analysis Framework:** All patients to be included in this analysis will have a baseline questionnaire completed and all treatment data abstracted. Stratification will be made within the cohort to adjust for diagnosis, age at diagnosis, age at time of SCT, and sex between patients who have had a SCT and those who have not. The first step in this analysis would be to examine all outcomes of interest (as outlined below) to determine the frequency of occurrence of each, and then to subsequently focus the comparative analyses only on those outcomes which are found to occur at or above a pre-determined frequency (likely $\geq$ 5%) or those in which there would be a specific interest in a SCT/TBI population. For demonstration purposes, the initial step in this process was completed with the data set maintained by Pauline Mitby here at the University of Minnesota. We reviewed the frequencies of yes/no responses to each requested variable (n=195) and set a cutoff at $\geq$ 5% of yes responses required in order for a variable to be considered potentially significant for evaluation in the final analysis. From this the variable list was cut to n=75 and this example is listed in Appendix 1. We would propose that this same

process be undertaken with the final data set of TBI recipients that is generated. There would also be some variables that would be excluded from this final list or potentially combined (for example, several questions are very non-specific regarding "other _____, please describe"), as they would be very difficult to analyze for this proposal.

Psychosocial and Health Status outcomes would be analyzed in a similar manner to that which has recently been completed on the entire cohort in the manuscript submitted by Melissa Hudson et al. This will include an analysis of six health status domains that includes an assessment of general health (N15), mental health (Brief Symptom Inventory, J16-35), functional status (N10, N11, N12), limitations of activity (N14b, N14c, N14e), pain as a result of the cancer or its treatment (J36), and anxiety/fears as a result of the cancer or its treatment (J37), and these domains will be compared between subjects and controls.

Comparisons of all parameters surveyed with the LTFS questionnaire will be made between the SCT/TBI, non-SCT, and sibling control groups. This will be performed for the group as a whole as well as among subsets of particular diagnoses in which there are enough subjects to make meaningful comparisons. For the cohort analyses, rates of occurrence for specific outcomes will be calculated using person-years of observation and when appropriate will be standardized using age-, sex-, race-specific national rates (e.g., cancer, mortality). Actuarial methods, including life-table analyses and proportional hazards models (i.e., Cox), will be utilized to assess endpoints that may be associated with factors such as the original diagnosis, treatment-specific exposures, age, etc. Use of multivariate techniques will allow investigation of the simultaneous effect(s) of covariates and thus assessment of interactions and adjustment for potential confounding covariates. Conditional or unconditional (as appropriate) logistic models will be used to investigate the simultaneous effects of several factors. Finally, analyses using a cross-sectional design may be encountered in the assessment of specific parameters in the respective study populations. For the analysis of new cancers, cumulative incidence, standardized incidence ratios, and excess risk calculations will be performed. Data analysis will be performed at the CCSS biostatistical center at the Fred Hutchinson Cancer Center, Seattle WA.

a. Outcomes of interest: (baseline questionnaire number; examples of expected adverse outcomes)

   i. Hearing/vision/speech (C1-19; hearing loss, cataracts, dry eyes)
   ii. Urinary system (D1-5; kidney/bladder infections, dialysis)
   iii. Hormonal (E1-18; hypo-, hyper-thyroid, diabetes, growth hormone deficiency, infertility issues)
   iv. Heart/Circulatory (F1-20; arteriosclerosis, cardiomyopathy, hypertension, stroke)
   v. Respiratory (G1-13; shortness of breath, need for oxygen, fibrosis)
   vi. Digestive (H1-18; cirrhosis, hepatitis, ulcer)
   vii. Surgical Procedures (I1-31; joint replacement, spine surgery, coronary bypass, biopsies, heart or lung transplant, cataracts)

viii. Brain/CNS (J1-15;seizures, headaches, pain)
ix. New Cancers (K1-18)
x. Off-spring/pregnancy (M1-11)
xi. Psychosocial Health Status (to include the domains of general health (N15), mental health (Brief Symptom Inventory, J16-35), functional status (N10, N11, N12), limitations of activity (N14b, N14c, N14e), pain as a result of the cancer or its treatment (J36), and anxiety/fears as a result of the cancer or its treatment (J37).

b. Subject population to be included: Any subject within the CCSS with a diagnosis of acute lymphoblastic or acute myeloid leukemia who has undergone SCT with TBI as part of the therapy for their first malignancy. The cohort will be compiled in the following manner. All leukemia subjects who responded with a "yes" or "not sure" to question I. 26 (Indicate whether you have ever had a bone marrow transplant) will be considered as potentially eligible for this study (n= approximately 370). From radiation therapy records at MD Anderson, we currently know that 226 of these had received TBI.

In order to acquire additional cases and to obtain additional necessary information for this analysis including stem cell source, occurrence of acute or chronic graft vs. host disease (GVHD) and center where transplant was performed, subjects will contacted for individual interviews. These interviews will be conducted as part of the Follow-up 2 Survey either after completion/return of the questionnaire for those that return them in a timely fashion, or as part of the standard interviewer follow-up process for subjects that do not return their Follow-up 2 Questionnaire. A standardized set of questions will be developed that will determine stem cell source (autologous vs. allogeneic), whether they received TBI or not (in case medical records abstraction has missed cases that received a TBI at an institution other than the CCSS primary institution), and will include a series of questions that will be developed in order to determine whether they had received treatment for acute and/or chronic GVHD and when this treatment had been discontinued. Subjects will also be asked to identify where the transplant was performed so that medical records can be obtained if necessary. Funding will be sought to provide the additional personnel necessary to perform these interviews and they will be conducted on the entire BMT cohort, although analysis for this concept will be limited to transplants for acute leukemia that included TBI.

c. Explanatory variables: age at diagnosis, age at time of SCT, sex, diagnosis, date of diagnosis, date of SCT (defined as date of TBI), other radiation therapy/site/dose, life status, acute GVHD, chronic GVHD, ongoing GVHD treatment at time of baseline, stem cell source, death cause.

d. Examples of Tables/Figures

1) Patient Characteristics

| **Patient Characteristics** | TBI Cohort | No TBI Cohort | Sibling Cohort |
|---|---|---|---|
| Sex | | | |
| Age at Baseline | | | |
| Age at Diagosis | | | |
| Age at Transplant | | - | - |
| Vital Status (alive/dead) | | | |
| Year of Diagnosis | | | - |
| Diagnosis | | | - |
| Time from Diagnosis to SCT | | - | - |
| Time from SCT to Baseline Questionnaire | | - | - |
| Stem cell Source<br>Autologous<br>Allogeneic | | - | - |
| Graft vs. Host Disease<br>Acute<br>Chronic<br>GVHD treatment at baseline | | - | - |

2) Radiation Therapy

| **Radiation Therapy** | TBI Cohort (total) | Fraction-ated TBI | Single Fraction TBI | Control (leukemia) |
|---|---|---|---|---|
| TBI Dose<br>≤750 cGy<br>751-1000 cGy<br>1001-1200 cGy<br>>1200 cGy | | | | - |
| CNS directed XRT prior to or concurrent with SCT<br><1200<br>1200-1800 cGy<br>>1800 cGy | | - | - | |

3) Outcome of Interest/Frequencies (Hormonal Systems for example)

| **Hormonal Systems** | TBI Cohort N (%) | No TBI Cohort N (%) | Sibling Cohort N (%) |
|---|---|---|---|
| Hyperthyroid | | | |
| Hypothyroid | | | |
| Thyroid nodules | | | |
| Diabetes | | | |
| Growth Hormone Deficiency | | | |
| Osteoporosis | | | |

| | | | |
|---|---|---|---|
| Delayed Puberty | | | |
| Infertility | | | |
| Low sperm count | | | |
| Menstrual periods | | | |

4) Outcome of Interest/Relative Risks (Hormonal Systems for example)

| **Hormonal Systems** | TBI Cohort RR (95% CI) | No TBI Cohort RR (95% CI) | Sibling Cohort RR (95% CI) |
|---|---|---|---|
| Hyperthyroid | | | |
| Hypothyroid | | | |
| Thyroid nodules | | | |
| Diabetes | | | |
| Growth Hormone Deficiency | | | |
| Osteoporosis | | | |
| Delayed Puberty | | | |
| Infertility | | | |
| Low sperm count | | | |
| Menstrual periods | | | |

5) Impact of Radiation Therapy Dose on Major Adverse outcomes (focus on outcomes with highest frequencies, need to confirm dose categories with Dr. Donaldson)

| **Organ System** | TBI ≤1000 cGy RR (95% CI) | TBI 1001-1200 cGy RR (95% CI) | TBI >1200 cGy RR (95% CI) |
|---|---|---|---|
| Hormonal | | | |
| Heart | | | |
| Respiratory | | | |
| Brain/CNS | | | |

6) Additional Impact of Pre-BMT Cranial Radiation Therapy Dose Major Adverse outcomes in Patients with Leukemia (focus on outcomes with highest frequencies)

| **Organ System** | TBI + Cranial XRT RR (95% CI) | TBI without Cranial XRT RR (95% CI) | Cranial XRT without TBI RR (95% CI) |
|---|---|---|---|
| Hormonal | | | |
| Heart | | | |
| Respiratory | | | |
| Brain/CNS | | | |

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**Appendix 1** (Light gray shading = yes response ≥ 5%, dark gray shade = yes response ≥ 10%)

| GROUP# | QUESTION | FREQ YES | FREQ NO | YES % | NO % | MISSING |
|---|---|---|---|---|---|---|
| C8 | C8 Legally blind in one or both eyes | 14 | 250 | 5.30 | 94.70 | 5 |
| C4 | C4 Tinnitus | 14 | 249 | 5.32 | 94.68 | 6 |
| C6 | C6 Problems hearing sounds/words | 16 | 247 | 6.08 | 93.92 | 6 |
| C13 | C13 Other trouble seeing | 24 | 242 | 9.02 | 90.98 | 3 |
| C19 | C19 Loss of taste or smell | 26 | 242 | 9.70 | 90.30 | 1 |
| C18 | C18 Abnormal sense of taste | 34 | 234 | 12.69 | 87.31 | 1 |
| C14 | C14 Very dry eyes | 49 | 217 | 18.42 | 81.58 | 3 |
| C15 | C15 problems Other eye | 55 | 208 | 20.91 | 79.09 | 6 |
| C9 | C9 Cataracts | 100 | 167 | 37.45 | 62.55 | 2 |
| E11 | E11 Medication to go into puberty | 23 | 242 | 8.68 | 91.32 | 4 |
| E10 | E10 Osteoporosis | 25 | 242 | 9.36 | 90.64 | 2 |
| E9 | E9 Growth hormone injections | 28 | 239 | 10.49 | 89.51 | 2 |
| E2 | E2 Underactive thyroid | 34 | 231 | 12.83 | 87.17 | 4 |
| E14 | E14 Fertility tests | 36 | 232 | 13.43 | 86.57 | 1 |
| E15 | E15 Low sperm count | 21 | 128 | 14.09 | 85.91 | 120 |
| E12 | E12 Other hormonal problems | 38 | 223 | 14.56 | 85.44 | 8 |
| E8 | E8 Growth hormone deficiency | 40 | 210 | 16.00 | 84.00 | 19 |
| E18 | E18 Female hormones to have period | 44 | 46 | 48.89 | 51.11 | 179 |
| E17 | E17 Currently having periods | 56 | 16 | 77.78 | 22.22 | 197 |
| E16 | E16 Ever had menstrual period | 94 | 21 | 81.74 | 18.26 | 154 |
| E13 | E13 Fertility problem | 227 | 41 | 84.70 | 15.30 | 1 |
| F4 | F3 Arrhythmia | 14 | 252 | 5.26 | 94.74 | 3 |
| F9 | F9 Stroke | 17 | 250 | 6.37 | 93.63 | 2 |
| F8 | F8 Hypertension - medication | 17 | 249 | 6.39 | 93.61 | 3 |
| F19 | F19 Heart attack in immediate family | 17 | 249 | 6.39 | 93.61 | 3 |
| F3 | F20 Other heart/circulatory problem | 30 | 236 | 11.28 | 88.72 | 3 |
| F17 | F17 Chest pain with exercise | 34 | 217 | 13.55 | 86.45 | 18 |
| F18 | F18 Seen cardiologist | 66 | 201 | 24.72 | 75.28 | 2 |
| G10 | G10 Pneumonia 3+ times last 3 years | 16 | 236 | 6.35 | 93.65 | 17 |
| G13 | G12 Lung fibrosis | 16 | 236 | 6.35 | 93.65 | 17 |
| G6 | G6 Asthma | 32 | 234 | 12.03 | 87.97 | 3 |
| G8 | G8 Chronic cough | 33 | 233 | 12.41 | 87.59 | 3 |
| G14 | G13 Other respiratory problem | 39 | 225 | 14.77 | 85.23 | 5 |
| G4 | G4 Tonsillitis | 47 | 218 | 17.74 | 82.26 | 4 |
| G9 | G9 Ever needed extra oxygen | 55 | 211 | 20.68 | 79.32 | 3 |
| G2 | G2 Hay fever | 57 | 207 | 21.59 | 78.41 | 5 |
| G3 | G3 Recurrent sinus infections | 75 | 191 | 28.20 | 71.80 | 3 |
| G1 | G1 Bronchitis | 85 | 163 | 34.27 | 65.73 | 21 |
| H8 | H8 Esophagus disease | 13 | 238 | 5.18 | 94.82 | 18 |
| H7 | H7 Ulcer | 17 | 235 | 6.75 | 93.25 | 17 |
| H4 | H4 Hepatitis | 18 | 235 | 7.11 | 92.89 | 16 |
| H15 | H15 Frequent constipation | 23 | 229 | 9.13 | 90.87 | 17 |
| H6 | H6 Other liver problem | 32 | 219 | 12.75 | 87.25 | 18 |
| H5 | H5 Jaundice | 33 | 218 | 13.15 | 86.85 | 18 |
| **GROUP#** | **QUESTION** | **FREQ YES** | **FREQ NO** | **YES %** | **NO %** | **MISSING** |
| H16 | H16 Chronic diarrhea | 34 | 219 | 13.44 | 86.56 | 16 |
| H10 | H10 Frequent heartburn | 36 | 215 | 14.34 | 85.66 | 18 |

| | | | | | | |
|---|---|---|---|---|---|---|
| H11 | H11 Other stomach problem | 37 | 213 | 14.80 | 85.20 | 19 |
| H9 | H9 Frequent indigestion | 39 | 214 | 15.42 | 84.58 | 16 |
| H10 | H10 Heartburn medication | 18 | 15 | 54.55 | 45.45 | 236 |
| I16 | I16 Spleen removal | 13 | 239 | 5.16 | 94.84 | 17 |
| I29 | I29 Sinus surgery | 16 | 234 | 6.40 | 93.60 | 19 |
| I20 | I20 Other lung surgery | 24 | 230 | 9.45 | 90.55 | 15 |
| I6 | I6 Other bone surgery | 29 | 224 | 11.46 | 88.54 | 16 |
| I28 | I28 Cataract surgery | 30 | 222 | 11.90 | 88.10 | 17 |
| I31 | I31 Other surgery (y/n | 143 | 112 | 56.08 | 43.92 | 14 |
| I26 | I26 Bone marrow transplant | 219 | 34 | 86.56 | 13.44 | 16 |
| J2 | J2 Paralysis | 16 | 235 | 6.37 | 93.63 | 18 |
| J5 | J5 Seizures/convulsions/blackouts | 18 | 234 | 7.14 | 92.86 | 17 |
| J12 | J12 Decreased touch or feeling | 20 | 244 | 7.58 | 92.42 | 5 |
| J38 | J38 Migraine last 12 months | 15 | 172 | 8.02 | 91.98 | 82 |
| J6 | J6 Migraine | 22 | 230 | 8.73 | 91.27 | 17 |
| J10 | J10 Weakness/unable to move arm | 27 | 240 | 10.11 | 89.89 | 2 |
| J8 | J8 Problems with balance | 28 | 237 | 10.57 | 89.43 | 4 |
| J38 | J38 Bronchitis last 12 months | 21 | 166 | 11.23 | 88.77 | 82 |
| J38 | J38 Freq indigestion last 12 months | 24 | 162 | 12.90 | 87.10 | 83 |
| J14 | J14 Problems chewing or swallowing | 35 | 232 | 13.11 | 86.89 | 2 |
| J15 | J15 Other BNS problems | 35 | 231 | 13.16 | 86.84 | 3 |
| J11 | J11 Weakness/unable to move leg | 39 | 225 | 14.77 | 85.23 | 5 |
| J13 | J13 Pain or abnormal sensation | 46 | 219 | 17.36 | 82.64 | 4 |
| J38 | J38 Hay fever last 12 months | 36 | 151 | 19.25 | 80.75 | 82 |
| J38 | J38 Freq headaches last 12 months | 37 | 150 | 19.79 | 80.21 | 82 |
| J7 | J7 Other frequent headaches | 51 | 199 | 20.40 | 79.60 | 19 |
| O3 | O3 Learning disabled/special ed | 61 | 184 | 24.90 | 75.10 | 24 |
| R6 | R6 concern re. other issues | 50 | 63 | 44.25 | 55.75 | 156 |
| R5 | R5 Concern re. life insurance | 76 | 95 | 44.44 | 55.56 | 98 |
| R4 | R4 Concern re. health insurance | 101 | 87 | 53.72 | 46.28 | 81 |
| R1 | R1 Concern re. future health | 122 | 65 | 65.24 | 34.76 | 82 |
| R2 | R2 Concern re. ability to have children | 129 | 56 | 69.73 | 30.27 | 84 |
| R3 | R3 Concern re. developing a cancer | 132 | 54 | 70.97 | 29.03 | 83 |