Childhood Cancer Survivor Study
Concept Proposal and Analytic Plan

1. **Study Title**
   Psychological distress, functional dependence and neurologic morbidity among adult survivors of childhood cancer treated with CNS-directed therapies

2. **Primary Working Group:** Psychology
   Secondary Working Group: Chronic Disease

3. **Investigators:**
   Stefanie Vuotto
   Kevin Krull
   Kevin Oeffinger
   Nicole Ullrich
   Daniel Bowers
   Elizabeth Wells
   Fatih Okcu
   Wendy Leisenring
   Rebecca Howell
   Leslie Robison
   Gregory Armstrong
   Tara Brinkman

4. **Background and Rationale**

   Past reports from the Childhood Cancer Survivor Study (CCSS) indicate that adult survivors of childhood cancer are at-risk of developing chronic health conditions and experiencing symptoms of psychological distress compared with siblings.[1-6] Importantly, survivors of pediatric brain tumors (i.e. those who receive the most intensive CNS-directed therapies) are at heightened risk of psychological distress[6-8] and suicide ideation[9] compared to siblings and other cancer diagnostic groups. Survivors' perception of worsening physical health has been associated with increasing psychological distress symptoms over time[10] and poor physical health status with increased risk of suicide ideation.[11-13] We have recently shown that the development of treatment-related chronic health conditions (i.e. cardiac, pulmonary, endocrine) is associated with elevated symptoms of anxiety, depression and posttraumatic stress among adult survivors.

   Potential functional consequences associated with CNS-directed therapies include reduced educational attainment,[14,15] use of special education services,[16,17] unemployment[18,19] non-independent living,[14,20] and a greater likelihood of never marrying.[21] However, past CCSS studies have examined markers of adult independence as discrete indicators of functional independence, without considering the fact that they often co-occur. Therefore, we will examine specific profiles of independence using multiple concurrent indicators of adult functioning.

   Adult survivors of childhood cancer who received CNS-directed therapies also are at-risk for late neurologic sequelae. Compared with siblings, survivors of childhood brain tumors,[22] acute lymphoblastic leukemia,[23] and rhabdomyosarcoma[24] are at increased risk of developing seizures. In addition, survivors of childhood CNS tumors and leukemia are at risk of late-occurring first stroke,[25] with higher doses of cranial radiation therapy (CRT) exposure associated with elevated risk of stroke.[26] Neurologic sequelae of CNS-directed therapies may

impact psychological functioning and functional independence in adult survivors of childhood cancer. For example, in non-cancer populations, stroke has been associated with depression, functional impairment, disability, diminished quality of life and anxiety,[27-30] and seizures have been implicated in psychiatric symptoms[31-33] and suicide attempts[34] among individuals with epilepsy. Additionally, adverse effects of anticonvulsant medication use have been associated with severity of anxiety and depression.[35] We previously reported that seizures were associated with 2- to 3-fold increased odds of suicide ideation;[11,13] however, associations between neurologic morbidity and psychological distress have not been comprehensively evaluated.

As temporal changes in cancer therapies have resulted in the elimination of CRT for most children diagnosed with leukemia and significant dose reductions for patients with central nervous system tumors, we hypothesize that we will observe a corresponding reduction in psychological distress and functional limitations in adult survivors treated with CNS-directed therapies. Nevertheless, we expect that neurological morbidity will have an adverse impact on survivor psychological health and functional independence.

5. Specific Aims

Aim 1: To estimate the prevalence of psychological distress and suicide ideation in long-term survivors of childhood cancer treated with CNS-directed therapies, and compare the frequency of distress and suicide ideation across decades of diagnosis (1970's v 1980's v 1990's) and then evaluate contributions of therapy to risks of distress and their associated temporal changes.

Aim 2: To identify classes of functional dependence in long-term survivors of childhood cancer treated with CNS-directed therapies and compare the frequency of dependence across decades of diagnosis (1970's v 1980's v 1990's) and evaluate how treatment associated risks change across time.

Aim 3: To examine associations between neurologic morbidity (memory problems, stroke, seizures, auditory-vestibular-visual-sensory deficits, focal neurologic dysfunction, severe headaches) and psychological distress and suicide ideation among adult survivors of childhood cancer treated with CNS-directed therapies.

Aim 4: To examine associations between neurologic morbidity (memory problems, stroke, seizures, auditory-vestibular-visual-sensory deficits, focal neurologic dysfunction, severe headaches) and functional dependence among adult survivors of childhood cancer treated with CNS-directed therapies.

6. Analysis Framework

6.1 **Study Population:** Survivors enrolled in CCSS original and expansion cohorts with CNS disease and/or exposed to CNS-directed therapies (defined below).

6.2 **Inclusion criteria:**

- CCSS survivors ≥18 years of age at study baseline (original and expansion) who self-completed study questionnaires and with treatment data available.
- Diagnosed with CNS disease and/or received CNS-directed therapy:
    - Cranial irradiation
        - None

        - >0-20Gy
        - >20-30Gy
        - >30-50Gy
        - >50Gy
    - Intravenous methotrexate (mg/m^2)
        - Dose range 1 (yes/no)
        - Dose range 2 (yes/no)
        - Dose range 3 (yes/no)
    - Intrathecal cytarabine or methotrexate (number of IT injections)"
        - 1 injection (yes/no)
        - 2 injections (yes/no)
        - 3 or more injections (yes/no)

6.3 **Outcomes:**

- **Psychological Distress** will be assessed by the Brief Symptom Inventory (BSI-18), a widely used measure of psychological distress including subscales of anxiety, depression and somatization. Distress will be defined as T-scores ≥ 63 for each subscale.

- **Suicide Ideation** will be assessed using a single item of the BSI-18 ("thoughts of ending your life") where participants respond on a 5-point Likert scale ("not at all", "a little bit", "moderately", "quite a bit", "extremely"). Consistent with previous CCSS methods, suicide ideation will be defined dichotomously as a response of $\geq$1 on this suicide ideation item.

- **Functional independence** will be assessed using the following CCSS baseline survey items. Individual classes of functional independence will be identified using latent class analysis.
    - Marital status [original baseline survey L1-L2; expansion baseline survey M2, M3]
    - Independent living [original baseline survey A8-A9; expansion baseline survey M1]*
    - Employment [original baseline survey O5, O6; expansion baseline survey S1, S2]
    - Assistance with personal care needs [original baseline survey N10; expansion baseline survey O16]
    - Assistance with routine needs [original baseline survey N11; expansion baseline survey O17]

*The items used to define independent living differ for the original and expansion cohorts. Original survey items pertain to current residence description (house, condo, apartment, dorm) and ownership status (own, rent, live with parents), while expansion survey item pertains to living arrangement (e.g. with whom they reside).

6.4 **Exposures [Aims 3 & 4]:** Stroke and neurologic chronic health conditions will be based on grading for chronic conditions per the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. We will examine the distribution of grades for each condition (i.e. 1-4).

- **Memory problems** will be defined as Grade 1 (mild problems with learning or memory), Grade 2 (moderate problems with learning or memory), Grade 3 (severe problems with learning or memory), or Grade 4 (mental retardation, disabling problems with learning or memory) [variable 28].

- **Stroke** will be defined as Grade 1 (mild), Grade 2 (moderate), Grade 3 (severe, medically significant, disabling) or Grade 4 (life-threatening) stroke (variable 18a).

- **Epilepsy** will be defined as Grade 1 (mild epilepsy/seizures not requiring medication) or Grade 2 (moderate epilepsy/seizures requiting medication) [variable 29].

- **Balance** will be defined as Grade 1 (problems with balance or ability to manipulate objects, mild), Grade 2 (problems with balance or ability to manipulate objects, moderate), Grade 3 (problems with balance or ability to manipulate objects, severe) or Grade 4 (problems with balance or ability to manipulate objects, disabling) balance [variable 30].

- **Tremors** will be defined as Grade 1 (tremors or problem with movement) [variable 31].

- **Weakness in leg** will be defined as Grade 1 (weakness in leg(s), mild limitation) or Grade 2 (weakness in leg, moderate limitation) weakness in leg [variable 32].

- **Weakness in arm** will be defined as Grade 1 weakness in arm [variable 33].

- **Sensory neuropathy** will be defined as Grade 1 sensory neuropathy [variable 34].

- **Paralysis** will be defined as Grade 1 (mild), Grade 2 (moderate), Grade 3 (severe, medically significant, disabling) or Grade 4 (paralysis) [variable 32a].

- **Other neurologic conditions** will be defined as Grade 1 (mild), Grade 2 (moderate), Grade 3 (severe, medically significant, disabling) or Grade 4 (life-threatening) other neurologic conditions [variable On].

6.5 **Covariates [Aims 3 & 4]:**

- Age (years, continuous)
- Sex
- Race/ethnicity (White/non-Hispanic vs. other)
- Age at diagnosis (years, continuous)
- Cancer-related pain (none, small amount vs. medium, a lot, very bad)
- Physical health status (poor, fair vs. good, very good, excellent)
- Radiation (none, >0-20Gy, >20-30Gy, >30-50Gy, >50Gy)*
    - Maximum dose to 4 regions: frontal, temporal, posterior fossa, parieto-occipital regions
- Chemotherapy
    - Number of IT injections
    - IV MTX (mg/m^2)

- Cyclophosphamide Equivalent Dose (CED)
- Disease relapse/second malignant neoplasms

*We will review distribution of radiation doses to determine appropriate dosage cut-off and number of levels of this variable

7. **Analytic Approach**

Aim 1: To estimate the prevalence of psychological distress in long-term survivors of childhood cancer treated with CNS-directed therapies, and compare the frequency of distress across decades of diagnosis (1970's v 1980's v 1990's) and then evaluate contributions of therapy to risks of distress and their associated temporal changes.

For aim 1, we will assess the proportion of survivors treated with CNS directed therapies with elevated psychological distress (depression, anxiety, somatization, suicide ideation). First we will compare the frequency of psychological distress symptoms across treatment era (1970's v 1980's v 1990's). Then we will calculate a treatment-based "risk score" to estimate treatment associated propensity for psychological distress based on methods described by Ness et al. We will select a set of treatment variables considered to potentially contribute to psychological distress for the primary cancer types included in the current study (i.e. leukemia [cranial irradiation; IV/IT methotrexate; corticosteroids], CNS tumor [cranial irradiation]). The treatment scores will be modeled using multivariable piecewise exponential models with psychological distress as the outcome, but not including calendar year in the models. Treatment risk scores will be plotted as a function of calendar time to illustrate the degree to which treatment related risks have changed over time. As described by Ness et al., internal validation will be performed by splitting the CCSS treatment institutions into two groups by stratified random sampling, using one group for developing the treatment score and the second for validating it.

Aim 2: To identify classes of functional independence in long-term survivors of childhood cancer treated with CNS-directed therapies and compare the frequency of functional dependence across decades of diagnosis (1970's v 1980's v 1990's) and evaluate how treatment associated risks change across time.

For aim 2, we will use latent class analysis (LCA) to identify classes of functional independence. Five observed variables from the original and expansion baseline surveys will be used to identify unobserved latent classes of functional independence. We will not pre-specify the number of expected classes. LCA fit indices will include the Bayesian Information Criterion (BIC) and a likelihood difference test (VLMR) with *P* values reported to indicate which model provides the best fit, with the greatest emphasis placed on the BIC values and substantive meaning when selecting the number of classes.

Consistent with aim 1, we will assess the proportion of survivors treated with CNS directed therapies who are functionally dependent, based on identified latent classes from Aim 2. We will compare the frequency of functional dependence by treatment era (1970's v 1980's v 1990's). Then we will calculate a treatment-based "risk score" to estimate treatment associated propensity for functional dependence based on methods described by Ness et al. We will select a set of treatment variables considered to potentially contribute to functional dependence for the primary cancer types included in the current study (i.e. leukemia [cranial irradiation; IV/IT methotrexate; corticosteroids], CNS tumor [cranial irradiation]). The treatment scores will be modeled using multivariable piecewise exponential models with psychological distress as the outcome and treatment variables as risk factors. For each diagnosis group, we

will fit the model with logarithm of person years as an offset. Treatment risk scores will be plotted as a function of calendar time. As described by Ness et al., internal validation will be performed by splitting the CCSS treatment institutions into two groups by stratified random sampling, using one group for developing the treatment score and the second for validating it.

Aim 3: To examine associations between neurologic late effects and psychological distress among adult survivors of childhood cancer treated with CNS-directed therapies.

For aim 3, we will assess the proportion of survivors with psychological distress (depression, anxiety, somatization, suicide ideation) among those with and without neurologic late effects (stroke, epilepsy, balance, tremors, weakness in arm or leg, sensory neuropathy, paralysis, other). We will then examine associations between specific neurologic late effects (exposure) and psychological distress (outcome). Because prior CCSS studies indicate prevalence estimates for depression and somatization exceed 10%, we will use multivariate log-binomial regression modeling to estimate risk ratios (RRs) and corresponding 95% confidence intervals (CIs) for these outcomes. For anxiety and suicide ideation, which are more rare outcomes (i.e. <10% in past CCSS reports), we will use logistic regression modeling to estimate odds ratios (ORs) and corresponding 95% CIs. We will adjust for age at evaluation, age at diagnosis, time since neurologic late effect (or age at condition), sex, race/ethnicity, cranial radiation, CNS-directed chemotherapies, neurosurgery, CED, cancer relapse, and secondary malignant neoplasms.

Aim 4: To examine associations between late neurologic morbidity and functional dependence among adult survivors of childhood cancer treated with CNS-directed therapies.

For aim 4, we will first assess the proportion of survivors with neurological morbidity in each class of functional dependence identified in Aim 2. We will then examine associations between neurologic morbidity (stroke, epilepsy, balance, tremors, weakness in arm or leg, sensory neuropathy, paralysis, other) and classes of functional dependence identified in Aim 2. Multinomial regression will be used to estimate risk ratios (RRs) and corresponding 95% confidence intervals, adjusting for age at evaluation, age at diagnosis, time since neurologic late effect (or age at condition), sex, race/ethnicity, cranial radiation, CNS-directed chemotherapies, neurosurgery, CED, cancer relapse, and secondary malignant neoplasms.

Table 1. Characteristics of study population

	M	SD
Age at evaluation		
Age at diagnosis		
Time since diagnosis		
	n	**%**
Sex		
Female		
Male		
Race/Ethnicity		
White/non-Hispanic		
Other		
Neurologic Morbidity		
Seizure		
Stroke		
Marital Status		
Single, never married		
Married, living as married		
Widowed, divorced, separated		
Independent Living		
Live alone / with spouse, partner		
Live with parents, roommates, sibling, other relative		
Employed in past year		
Yes (full time, part time, caring for home, student)		
No (unemployed, looking for work, disability, retired)		
Assistance with personal care needs		
Yes		
No		
Assistance with routine needs		
Yes		
No		
Cancer-related pain		
None, small amount		
Medium amount, a lot, very bad		
Physical health status		
Poor, fair		
Good, very good, excellent		
Radiation		
None		
Non-cranial		
Cranial (2-3 levels to be identified)		
Chemotherapy		
IV MTX		
Number of IT injections		

Table 2. Psychological distress outcomes by decade of diagnosis

	1970s		1980s		1990s	
	n	**%**	**n**	**%**	**n**	**%**
Depression						
Anxiety						
Somatization						
Suicide Ideation						

Table 3. Classes of functional dependence by decade of diagnosis

	1970s		1980s		1990s	
	n	**%**	**n**	**%**	**n**	**%**
Class 1						
Class 2						
Class 3						

Table 4. Prevalence of neurologic morbidity by psychological distress outcome

		Depression		Anxiety		Somatization		Suicide Ideation	
	Total N	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Memory problems									
None									
Grade 1-2									
Grade 3-4									
Stroke									
None									
Grade 1-2									
Grade 3-4									
Epilepsy									
None									
Grade 1-2									
Balance									
None									
Grade 1-2									
Grade 3-4									
Tremors									
None									
Grade 1									
Weakness in leg									
None									
Grade 1-2									
Weakness in arm									
None									
Grade 1									
Sensory neuropathy									
None									
Grade 1									
Paralysis									
None									
Grade 1-2									
Grade 3-4									
Other									
None									
Grade 1-2									
Grade 3-4									

Table 5. Association between Grade 3-4 neurologic events and psychological outcomes

	Depression		Anxiety		Somatization		Suicide Ideation	
	RR	**CI**	**RR**	**CI**	**RR**	**CI**	**RR**	**CI**
Memory problems								
Stroke								
Balance								
Paralysis								
Other								

Models adjusted for age, sex, race/ethnicity, age at diagnosis, CNS-directed chemotherapies, cranial radiation, CED, cancer relapse, secondary malignant neoplasms. Abbreviations: RR=risk ratio, CI=confidence interval

Table 6. Prevalence of neurologic morbidity by classes of functional dependence

		Functional dependence Class 1		Functional dependence Class 2		Functional dependence Class 3	
	Total N	**n**	**%**	**n**	**%**	**n**	**%**
Memory problems							
None							
Grade 1-2							
Grade 3-4							
Stroke							
None							
Grade 1-2							
Grade 3-4							
Epilepsy							
None							
Grade 1-2							
Balance							
None							
Grade 1-2							
Grade 3-4							
Tremors							
None							
Grade 1							
Weakness in leg							
None							
Grade 1-2							
Weakness in arm							
None							
Grade 1							
Sensory neuropathy							
None							
Grade 1							
Paralysis							
None							
Grade 1-2							
Grade 3-4							
Other							
None							
Grade 1-2							
Grade 3-4							

Table 7. Associations between Grade 3-4 neurologic morbidity and functional dependence

	Functional dependence Class 1		Functional dependence Class 2		Functional dependence Class 3	
	RR	**95% CI**	**RR**	**95% CI**	**RR**	**95% CI**
Memory Problems						
Stroke						
Balance						
Paralysis						
Other						

Models adjusted for age, sex, race/ethnicity, age at diagnosis, CNS-directed chemotherapies, cranial radiation, CED, cancer relapse, secondary malignant neoplasms. Abbreviations: RR-risk ratio.

Supplemental Table 1.Model fit indices for classes of functional dependence

	BIC	**Adjusted BIC**	**VLMR*p***	**Adjusted VLMR*p***	**Entropy**	**Minimum Posterior Probability**	**Smallest Class %**
Functional dependence Class 1							
Functional dependence Class 2							
Functional dependence Class 3							

References

1. Hudson MM, Mertens AC, Yasui Y, et al. Health status of adult long-term survivors of childhood cancer: A report from the childhood cancer survivor study. *JAMA.* 2003;290(12):1583-1592.
2. Nathan PC, Ness KK, Greenberg ML, et al. Health-related quality of life in adult survivors of childhood Wilms tumor or neuroblastoma: A report from the childhood cancer survivor study. *Pediatr Blood Cancer.* 2007;49(5):704-715.
3. Ness KK, Gurney JG, Zeltzer LK, et al. The impact of limitations in physical, executive, and emotional function on health-related quality of life among adult survivors of childhood cancer: a report from the Childhood Cancer Survivor Study. *Arch Phys Med Rehabil.* 2008;89(1):128-136.
4. Schultz KA, Ness KK, Whitton J, et al. Behavioral and social outcomes in adolescent survivors of childhood cancer: a report from the childhood cancer survivor study. *J Clin Oncol.* 2007;25(24):3649-3656.
5. Zeltzer LK, Lu Q, Leisenring W, et al. Psychosocial outcomes and health-related quality of life in adult childhood cancer survivors: a report from the childhood cancer survivor study. *Cancer Epidemiol Biomarkers Prev.* 2008;17(2):435-446.
6. Zeltzer LK, Recklitis C, Buchbinder D, et al. Psychological status in childhood cancer survivors: a report from the Childhood Cancer Survivor Study. *J Clin Oncol.* 2009;27(14):2396-2404.
7. Bruce M, Gumley D, Isham L, Fearon P, Phipps K. Post-traumatic stress symptoms in childhood brain tumour survivors and their parents. *Child Care Health Dev.* 2011;37(2):244-251.
8. Poggi G, Liscio M, Galbiati S, et al. Brain tumors in children and adolescents: cognitive and psychological disorders at different ages. *Psychooncology.* 2005;14(5):386-395.
9. Brinkman TM, Liptak CC, Delaney BL, Chordas CA, Muriel AC, Manley PE. Suicide ideation in pediatric and adult survivors of childhood brain tumors. *J Neurooncol.* 2013;113(3):425-432.
10. Brinkman TM, Zhu L, Zeltzer LK, et al. Longitudinal patterns of psychological distress in adult survivors of childhood cancer. *Br J Cancer.* 2013;109(5):1373-1381.
11. Brinkman TM, Zhang N, Recklitis CJ, et al. Suicide ideation and associated mortality in adult survivors of childhood cancer. *Cancer.* 2014;120(2):271-277.
12. Recklitis CJ, Diller LR, Li X, Najita J, Robison LL, Zeltzer L. Suicide ideation in adult survivors of childhood cancer: a report from the Childhood Cancer Survivor Study. *J Clin Oncol.* 2010;28(4):655-661.
13. Brinkman TM, Liptak CC, Delaney BL, Chordas CA, Muriel AC, Manley PE. Suicide ideation in pediatric and adult survivors of childhood brain tumors. *J Neurooncol.* 2013;113(3):425-432.
14. Mody R, Li S, Dover DC, et al. Twenty-five-year follow-up among survivors of childhood acute lymphoblastic leukemia: a report from the Childhood Cancer Survivor Study. *Blood.* 2008;111(12):5515-5523.
15. Mulrooney DA, Dover DC, Li S, et al. Twenty years of follow-up among survivors of childhood and young adult acute myeloid leukemia: a report from the Childhood Cancer Survivor Study. *Cancer.* 2008;112(9):2071-2079.
16. Haupt R, Fears TR, Robison LL, et al. Educational attainment in long-term survivors of childhood acute lymphoblastic leukemia. *JAMA.* 1994;272(18):1427-1432.
17. Mitby PA, Robison LL, Whitton JA, et al. Utilization of special education services and educational attainment among long-term survivors of childhood cancer: a report from the Childhood Cancer Survivor Study. *Cancer.* 2003;97(4):1115-1126.

18. de Boer AG, Verbeek JH, van Dijk FJ. Adult survivors of childhood cancer and unemployment: A metaanalysis. *Cancer.* 2006;107(1):1-11.
19. Pang JW, Friedman DL, Whitton JA, et al. Employment status among adult survivors in the Childhood Cancer Survivor Study. *Pediatr Blood Cancer.* 2008;50(1):104-110.
20. Rauck AM, Green DM, Yasui Y, Mertens A, Robison LL. Marriage in the survivors of childhood cancer: a preliminary description from the Childhood Cancer Survivor Study. *Med Pediatr Oncol.* 1999;33(1):60-63.
21. Janson C, Leisenring W, Cox C, et al. Predictors of marriage and divorce in adult survivors of childhood cancers: a report from the Childhood Cancer Survivor Study. *Cancer Epidemiol Biomarkers Prev.* 2009;18(10):2626-2635.
22. Packer RJ, Gurney JG, Punyko JA, et al. Long-term neurologic and neurosensory sequelae in adult survivors of a childhood brain tumor: childhood cancer survivor study. *J Clin Oncol.* 2003;21(17):3255-3261.
23. Goldsby RE, Liu Q, Nathan PC, et al. Late-occurring neurologic sequelae in adult survivors of childhood acute lymphoblastic leukemia: a report from the Childhood Cancer Survivor Study. *J Clin Oncol.* 2010;28(2):324-331.
24. Punyko JA, Mertens AC, Gurney JG, et al. Long-term medical effects of childhood and adolescent rhabdomyosarcoma: a report from the childhood cancer survivor study. *Pediatr Blood Cancer.* 2005;44(7):643-653.
25. Mueller S, Fullerton HJ, Stratton K, et al. Radiation, atherosclerotic risk factors, and stroke risk in survivors of pediatric cancer: a report from the Childhood Cancer Survivor Study. *Int J Radiat Oncol Biol Phys.* 2013;86(4):649-655.
26. Bowers DC, Liu Y, Leisenring W, et al. Late-occurring stroke among long-term survivors of childhood leukemia and brain tumors: a report from the Childhood Cancer Survivor Study. *J Clin Oncol.* 2006;24(33):5277-5282.
27. Amaricai E, Poenaru DV. The post-stroke depression and its impact on functioning in young and adult stroke patients of a rehabilitation unit. *Journal of mental health (Abingdon, England).* 2015:1-5.
28. Shi YZ, Xiang YT, Yang Y, et al. Depression after minor stroke: the association with disability and quality of life - a 1-year follow-up study. *Int J Geriatr Psychiatry.* 2015.
29. Schottke H, Giabbiconi CM. Post-stroke depression and post-stroke anxiety: prevalence and predictors. *Int Psychogeriatr.* 2015:1-8.
30. Galligan NG, Hevey D, Coen RF, Harbison JA. Clarifying the associations between anxiety, depression and fatigue following stroke. *J Health Psychol.* 2015.
31. Dumbray S, Naik S. Anxiety and depression levels in clients with epilepsy in selected hospital of Pune City. *Nurs J India.* 2014;105(4):160-163.
32. Kwong KL, Lam D, Tsui S, et al. Anxiety and Depression in Adolescents With Epilepsy. *J Child Neurol.* 2015.
33. Tegegne MT, Mossie TB, Awoke AA, Assaye AM, Gebrie BT, Eshetu DA. Depression and anxiety disorder among epileptic people at Amanuel Specialized Mental Hospital, Addis Ababa, Ethiopia. *BMC Psychiatry.* 2015;15(1):210.
34. Buljan R, Santic AM. Suicide attempts in hospital-treated epilepsy patients. *Acta Clin Croat.* 2011;50(4):485-490.
35. Gomez-Arias B, Crail-Melendez D, Lopez-Zapata R, Martinez-Juarez IE. Severity of anxiety and depression are related to a higher perception of adverse effects of antiepileptic drugs. *Seizure.* 2012;21(8):588-594.