Study of Obesity in Survivors of Childhood Acute Lymphoblastic Leukemia (All)

Nikhil U. Bhat

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STUDY OF OBESITY IN SURVIVORS OF CHILDHOOD ACUTE LYMPHOBLASTIC LEUKEMIA (ALL)

INTERNSHIP PRACTICUM REPORT

Presented to the Graduate Council of the Graduate School of Biomedical Sciences

University of North Texas Health Science Center at Fort Worth

In Partial Fulfillment of the Requirements

For the Degree of

MASTER OF SCIENCE IN CLINICAL RESEARCH MANAGEMENT

By

Nikhil Bhat, M.B.B.S

Fort Worth, Texas

February 2013
ACKNOWLEDGEMENTS

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allowed times in their busy schedule to see me. They always gave me to the point guidance and suggested appropriate changes whenever they were needed.

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Finally, I cannot forget to thank all the new friends I made here at UNTHSC. Completing my Masters’ education would have been impossible without all the study groups and kindness from all my friends. They are a constant source of inspiration for me because of their creativity and hard-working attitudes while pursuing their own goals and dreams.
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CHAPTER 1:

Introduction

The number of childhood cancer survivors has dramatically increased over the last two decades (1, 2). Survivorship programs focus on the health problems childhood cancer survivors face because of their cancer treatments. These programs provide surveillance for health problems, and educate survivors about their risk for health problems, to encourage them to engage in activities to minimize the development of severe health related problems.

Clinicians perceive there to be a problem of increasing obesity among leukemia survivors. Obesity should not be considered simply a consequence of an unhealthy lifestyle: it is a condition in which weight gain has reached the point where it poses significant risks to health (3). The use of chemotherapy agents such as anthracyclines and radiation (to the thorax) are associated with cardiovascular disease (4, 5, 6).

Obesity in cancer survivors is not yet well understood but may further increase cardiovascular risks. Cancer treatments, lifestyles, and medications other than chemotherapy may contribute to obesity among cancer survivors. Survivors of acute lymphoblastic leukemia (ALL) may be more likely to develop obesity or cardiovascular diseases due to their cancer treatments, which include chemotherapy, steroids, and sometimes radiotherapy (7). Strategies to reduce obesity in ALL survivors include a multifaceted approach, drug therapy and interventions to address psychological problems, as well as lifestyle modifications (7, 8).

This practicum project examined obesity as an adverse health condition among survivors of childhood ALL. Considering the fact that the there are various factors which may lead to obesity among cancer survivors and all are not proven yet, this practicum project examined whether the type of treatment and the medications given to the patients contributed to the changes in BMI in
the patients. The project also evaluated trends in Body Mass Index (BMI) among patients at each
time points and the changes in BMI with respect to variables like ethnicity. The objective of this
study was to evaluate these trends was to use a database to determine the frequency of obesity
among ALL survivors and thereby get some concrete information as to how the type of treatment
affected the BMI in the group of patients who were considered for the study and whether there
was a trend related to changes in BMI seen in a specific ethnic group which was part of the
study. Since obesity is a major risk factor among ALL survivors, steps need to be taken to reduce
its threat not only among survivors but also among other people in the community. This project
was a step taken in that direction to combat the threat of obesity among ALL survivors.
CHAPTER 2:

Background and Literature Review

ALL is the most common cancer diagnosed in children and nearly 23% of children younger than 15 years of age who are diagnosed with cancer have ALL (9). The annual incidence of ALL is approximately 30 to 40 cases per million children less than 15 years of age in the United States (9). The occurrence of ALL has increased gradually over the past 25 years (9). Children between the ages of 2 to 3 years are at a higher risk of developing ALL compared to infants and adolescents (9). According to a study published in 2012, the five-year survival rates among children with ALL enrolled into Children’s Oncology Group clinical trials between 1990 and 2005, increased from 83.7% in 1990-1994 to 90.4% in 2000-2005 (10).

Obesity and overweight are considered a ‘global epidemic’ by the World Health Organization (3). Obesity can be interpreted as a disease and a potential risk factor for various other diseases (3). Obesity is a pandemic problem not only in the US but worldwide. Obesity in childhood most often persists into adulthood (11). In spite of documented obesity in ALL survivors off treatment, we do not have adequate information as to when and why some children gain weight. The effect of long term obesity on the outcome of childhood cancer survivors is still unknown (12) and this study is a first step in our research trajectory to address this problem.

The CCMC and the H/O Program also have investigative and clinical programs to monitor survivors of childhood cancer such as Childhood Cancer Survivor Study (CCSS) and Life after Cancer Program (LACP). The LACP addresses the late health and emotional consequences in children, adolescents, and young adults treated for cancer in the institution, while the CCSS is a multicenter collaborative research project, funded by the National Cancer Institute (NCI). The goal is to determine the magnitude of the problem, as a foundation upon which to develop further
studies, focusing on factors which may influence risk of obesity and which may be subject to intervention (13). According to a study conducted in August 2012, genetics has a role in the development of obesity in ALL survivors (14). It is reported that a combination of genetic variations and insulin resistance can also lead of obesity in cancer survivors (15). According to a study conducted on a population of North American survivors of childhood ALL with a mean age of 32 years at follow-up, it was observed that there was not only an increased susceptibility to obesity but also a greater alteration in BMI over time (16).

The following table presents several of the mechanisms for Obesity in ALL survivors (17):

**Table 1: Identify mechanism for obesity in ALL survivors (17).**

<table>
<thead>
<tr>
<th>Identify mechanism for obesity in ALL survivors</th>
<th>Other Mechanisms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cranial Radiation (12 - 24 Gy)</td>
<td>Genetic Alterations</td>
</tr>
<tr>
<td>Leptin Gene Alterations</td>
<td>Familial Background</td>
</tr>
<tr>
<td>Premature Adipose Rebound</td>
<td>Dietary Choices</td>
</tr>
<tr>
<td>Growth Hormone Deficiency due to Cranial Radiation</td>
<td>Reduced Physical Activity</td>
</tr>
<tr>
<td>Chemotherapy Agents (&lt;common&gt;)</td>
<td></td>
</tr>
</tbody>
</table>

According to another study, the chances of pediatric ALL survivors becoming obese vary from 11% to 57% (19). A research on the type of diet can help us know about the dietary risks leading to obesity and opportunities for intervention (19). Childhood acute lymphoblastic leukemia

---

(ALL) is a type of cancer in which the number of immature white blood cells (lymphocytes) increases abnormally (20).

The Signs and Symptoms of Childhood ALL include the following (20):

- Loss of appetite
- Bone or joint pain
- Petechiae (flat, pinpoint, dark-red spots under the skin caused by bleeding)
- Fever
- Painless lumps in the neck, underarm, stomach, or groin
- Pain or feeling of fullness below the ribs
- Weakness, feeling tired, or looking pale
- Easy bruising or bleeding

There are several tests used to diagnose childhood ALL (20). These include:

- Physical exam and history
- Complete blood count (CBC) with differential
- Immunophenotyping
- Cytogenetic Analysis
- Blood chemistry studies
- Chest x-ray

Obesity in relation to ALL can be explained in terms of Body mass index (BMI), expressed as weight in kilograms divided by height in meters squared (kg/m2), is used to observe obesity among adults and is recommended for use with children (21). Cutoff criteria depend on the Centers for Disease Control and Prevention’s 2000 BMI-for-age growth charts for the United States (21).
In this practicum project, a retrospective observational study was designed to measure the frequency of obesity in a subset of 90 ALL patients treated at CCMC on the Total Therapy XV Protocol and the risk factors that may have influenced the development of obesity in these ALL survivors were evaluated. The trends in occurrence of obesity along with demographic and treatment factors that may lead to the development of obesity in this population were examined.
Specific Aims

The protocol represents a resumption and continuation of a previously approved study (Ken Heym MD, P.I.; Amber Ledbetter Research Intern). The results of those preliminary studies were reported in 2010 (22). The main objective of the current practicum was to determine the frequency and evolution of obesity among a group of 90 ALL patients enrolled on the St. Jude Total Therapy XV, who received their treatment at Cook Children’s Medical Center and who were diagnosed between February 2004 and July 2007.

The specific aims to achieve this objective were to:

- Establish a data base for evaluating the problem of obesity in ALL survivors.
- Measure the frequency of obesity in a population of patients treated at CCMC on Total XV.
- Evaluate changes in BMI according to key time points during patient’s ALL therapy and follow up and observe if there is a trend seen in any variable like ethnicity or gender.
- Identify risk factors that may be associated with increased risk of obesity and analyze if the treatment given to the patients contributed to changes in BMI.
Significance

As survival rates for ALL patients have increased, it is important to obtain a better understanding of the severity of late effects such as obesity which may have a negative influence on longevity as well as quality of life. Today, the number of cancer survivors has risen to approximately 12 million in the United States. Out of these, approximately 270,000 survivors were diagnosed with cancer before the age of 21 (1, 2). Due to the scientific advances in the treatment of childhood cancer, approximately 80% of children currently treated for cancer are expected to be long term survivors (23). Long-term survivors are defined as patients who have survived for 5 years or more after their initial childhood cancer diagnosis (24). However, survivors have an increased risk of facing a multitude of chronic and late effects due to treatment which can affect the quality of their life. Obesity is one of the major long-term health problems that occur in a subgroup of survivors (2). In this project, we focused on a group of 90 patients with ALL. These patients were categorized into subgroups and then changes in BMI and other variables in each subset were evaluated. We also examined the frequency of obesity in this population. These results identified subsets of the population that are more susceptible to obesity over a period of time and could potentially benefit from systematic intervention to improve the health of these patients. Furthermore, these results helped us to identify potential risk factors associated with development of obesity and thereby could be used to minimize the severity of late effects such as obesity in ALL patients.
Material and Methods

Ninety ALL patients were identified that were diagnosed and treated on the St. Jude Total Therapy XV at Cook Children’s Medical Center (CCMC) between the years 2004-2007 and later followed up through August 2012. The data described in the table below were obtained from medical records of each patient. A database was created to record the measurements of each patient. The database included the patient’s demographic information, the values related to the BMI of the patient (height and weight) during each time point of the study.

Table 2: The complete list of variables, in addition to height and weight, collected from the patient charts are listed below.

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Category/Unit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at Diagnosis</td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td>Male (1) Female (2)</td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
</tr>
<tr>
<td>Height</td>
<td>_____ cm</td>
</tr>
<tr>
<td>Weight</td>
<td>_____ kg</td>
</tr>
<tr>
<td>Body Mass Index (BMI)</td>
<td>_____ m²</td>
</tr>
<tr>
<td>Osteonecrosis (Yes/No)Sites</td>
<td></td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>Total cumulative Anthracyclines _____ / m²</td>
</tr>
<tr>
<td></td>
<td>Each Phase: Total cumulative Pred. dose _____ / m²</td>
</tr>
<tr>
<td></td>
<td>Each Phase: Total cumulative Decadron dose _____ / m²</td>
</tr>
</tbody>
</table>

In this practicum project, changes were analyzed in the sequential measurements taken during treatment for ALL on Total XV and during follow up evaluations.
The values were tracked during specific time points (see below) in the course of leukemia treatment and follow-up to determine any relationships among these variables to the development of obesity in this patient population.

The time points were:

- At Diagnosis/ Prior to Therapy
- Prior to Consolidation/Remission
- Prior to Each subsequent Phase or Cycle
- After Treatment (Beginning of Follow Up)
- Every 1 year, Then
- Every 2 years

The database (spreadsheet) developed for this study will be used as a tool to monitor trends in obesity in this group of ALL survivors, including treatment and laboratory variables influencing the development of obesity, in order to recognize opportunities for early intervention. The database could also be used to monitor other late health conditions such as osteonecrosis and selected treatment variables known to be associated with its development.

The database developed is attached in appendix B.

In this practicum project, a retrospective observational study to measure the frequency of obesity in a subset of 90 ALL patients treated at CCMC on the Total Therapy XV Protocol was conducted and the risk factors that may have influenced the development of obesity in these ALL survivors were evaluated. Eleven patients were lost during follow up and hence the database consists of 79 patients.
**IRB approval:**

The practicum project was approved by Cook Children’s Health Care System Institutional Review Board and the IRB at the University of North Texas Health Science Center. The approval letters are shown in appendix B.

**Statistical analysis:** The study data collected for this study included demographic, treatment information, height, weight, and BMI of the 79 subjects who underwent treatment for ALL on the Total XV protocol (chemotherapy, steroids). The influence of different variables such as age, race/ethnicity, risk assignment and chemotherapy regimen on weight and BMI was evaluated. Each subject's weight and height was measured before treatment, prior to each chemotherapy cycle, and at multiple levels of follow-up. The BMI was calculated at each level. Each patient's pre-treatment weight served as a baseline. The data was adjusted for pre-treatment variation of BMI. To monitor the change in BMI over time, the mixed regression model was used to analyze the data. The outcome variable was BMI at each time point and the predictor variable was time. The time trend model was studied to see how BMI changed over time. To begin with, a simple random intercept model was used and then the model was analyzed to see if the time trend was linear or quadratic. The mixed regression allowed us to model both the population trend as well as the trend in individuals over time. It also tracked the correlation between multiple observations from the same subject over time. In order to examine the occurrence of obesity in this population, a retrospective statistical analysis was done. The changes in BMI in these patients were analyzed using the standard T test. These changes were plotted graphically based upon the statistical data.
Results

A linear mixed regression model was used in order to account for the longitudinal follow-up, repeated measurements of the Body Mass Index (BMI) in each subject and to accommodate the correlation between BMI scores. A total of 79 patients were seen at baseline out of which 75 completed the study, giving a follow up rate of 94%.

**Table 3: The mean BMI for all the patients who were followed up from diagnosis to 2 years after end of therapy.**

<table>
<thead>
<tr>
<th></th>
<th>Week 0</th>
<th>Week 7</th>
<th>Week 20</th>
<th>Week 48</th>
<th>Week 72</th>
<th>Week 96</th>
<th>Week 120</th>
<th>Week 146</th>
<th>Week 198</th>
<th>Week 250</th>
</tr>
</thead>
<tbody>
<tr>
<td>No of Patients</td>
<td>79</td>
<td>78</td>
<td>78</td>
<td>78</td>
<td>76</td>
<td>77</td>
<td>77</td>
<td>77</td>
<td>77</td>
<td>75</td>
</tr>
<tr>
<td>Std. Deviation</td>
<td>9.59</td>
<td>4.85</td>
<td>5.03</td>
<td>5.80</td>
<td>7.83</td>
<td>6.02</td>
<td>5.72</td>
<td>6.03</td>
<td>6.61</td>
<td>7.33</td>
</tr>
</tbody>
</table>

The data shown in Table 3 indicates that there is a gradual increase in the Mean BMI of the total population of patients at each time point from diagnosis to 2 years after end of therapy. The Mean BMI for the total population of patients at diagnosis (Week 0) is 19.03. This Mean BMI has increased for the total population of patients to 22.09 at 2 years post therapy (Week 250).
Table 4: The sample size at the stated follow up times below.

<table>
<thead>
<tr>
<th></th>
<th>Baseline Number of patients</th>
<th>End of Therapy* Number of patients</th>
<th>End of Therapy** Number of patients</th>
<th>2 Year Post Therapy Number of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>79</td>
<td>32</td>
<td>47</td>
<td>75</td>
</tr>
<tr>
<td>Underweight</td>
<td>7(8.86)</td>
<td>3(9.37)</td>
<td>1(2.12)</td>
<td>3(4.0)</td>
</tr>
<tr>
<td>Normal</td>
<td>66(83.54)</td>
<td>24(75)</td>
<td>38(80.85)</td>
<td>54(72.0)</td>
</tr>
<tr>
<td>Overweight</td>
<td>5(6.33)</td>
<td>3(9.37)</td>
<td>6(12.76)</td>
<td>11(14.7)</td>
</tr>
<tr>
<td>Obese</td>
<td>1(1.27)</td>
<td>2(6.25)</td>
<td>2(4.25)</td>
<td>7(9.3)</td>
</tr>
<tr>
<td>Mean BMI</td>
<td>19.03</td>
<td>20.46</td>
<td>20.58</td>
<td>22.09</td>
</tr>
<tr>
<td>Std. Deviation</td>
<td>9.60</td>
<td>5.72</td>
<td>6.04</td>
<td>7.33</td>
</tr>
</tbody>
</table>

* End of therapy for females
** End of therapy for males

Values in parentheses = % of patients
Std = Standard

Table 4 presents the sample size for four different categories of patients at 3 specific time points. The patients are categorized as underweight, normal, overweight and obese based on their BMI. After categorizing the patients into 4 categories, the number and percentage of patients in each category are recorded at 3 specific time points. The time points are Baseline (at diagnosis), End of therapy for females and males and 2 year post therapy. It is observed that the number and percentage of obese patients has increased from 1 and 1.27% to 7 and 9.3% respectively from Baseline to 2 year post therapy. Similarly the number and percentage of overweight patients has increased from 5 and 6.33% to 11 and 14.7% respectively from Baseline to 2 year post therapy.
Figure 1 shows the relationship between mean BMI and time from baseline (at diagnosis) to follow up for 2 years post therapy. The BMI shows a biphasic response; that is the BMI increases initially from Week 0 to Week 90, and then begins to decreases at about 90 weeks from baseline until about the 150 weeks from the start of the study before it begins to increase again.
An analysis of several predictors of BMI was conducted using a Mixed Regression Model in order to evaluate changes in BMI at specific time points during each patients ALL therapy and follow up and to identify whether treatment variables like chemotherapy or steroids, demographic variables like gender or ethnicity or any other variable like time had any effect on BMI.

Table 5: Predictors of BMI across time.

<table>
<thead>
<tr>
<th>Predictors of BMI across time</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time</td>
<td>0.0008</td>
</tr>
<tr>
<td>Time 2 (quadratic)</td>
<td>0.0082</td>
</tr>
<tr>
<td>Time 3 (cubic)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Race</td>
<td>0.2921</td>
</tr>
<tr>
<td>Gender</td>
<td>0.4881</td>
</tr>
<tr>
<td>Osteonecrosis</td>
<td>0.0033</td>
</tr>
<tr>
<td>Anthracycline</td>
<td>0.6651</td>
</tr>
<tr>
<td>Steroids</td>
<td>0.1285</td>
</tr>
<tr>
<td>Race/Time</td>
<td>0.4889</td>
</tr>
<tr>
<td>Gender/time</td>
<td>0.6667</td>
</tr>
<tr>
<td>Osteonecrosis/time</td>
<td>0.4500</td>
</tr>
</tbody>
</table>

Table 5 shows the adjusted parameter estimates of some important variables analyzed for the repeated measurements of the BMI. This table reveals a significant relationship with time of the tendency of BMI to increase, decrease before a second increase (cubic change) (p=0.01). Anthracycline(p=0.67), Prednisolone(p=0.12) did not show any significant association with BMI across time. The table also shows that males and females did not differ in the tendency for BMI to change across time (p=0.67) and in their BMI measurements at the start of the study (p=0.49). Similarly, the table also shows that no specific ethnic group is affected less compared to other ethnic groups across time (p=0.29) or in changes in BMI across time (p=0.49). Patients with osteonecrosis differed significantly from those without osteonecrosis at the baseline (p=0.003).
however, there was no significant difference in the tendency for change in BMI across time between the two groups.


Discussion

Based on the results and the statistical interpretation, it is observed that this group of childhood ALL survivors show an increase in BMI with time. It is observed that the number of obese and overweight patients has increased from diagnosis to 2 years post therapy in this group. Hence, preventive measures need to be taken to minimize the risk of obesity in childhood ALL survivors. Preventive measures need to be taken at the primary level, secondary level and tertiary level. We need to reduce the number of new cases of obesity in ALL survivors, decrease the number of existing cases of obesity in ALL survivors and prevent the complications related to obesity in ALL survivors who are already obese. It is essential to involve the entire family of a child to take preventive measures related to obesity in ALL survivors (25). Physicians and the hospitals need to educate the family about the importance of a balanced diet and a healthy lifestyle and how it can have a positive effect on the weight of a child (25). It is necessary to educate the family about the benefits of giving low calorie foodstuffs, fruits and nutritious foodstuffs to children (25). It is important to encourage the family to motivate a child to play a physical sport for sometime in a day or do some physical activity daily. It is essential to monitor the time that each child spends on laptops or video games daily. It is important to provide authentic information to parents of childhood ALL survivors about how to monitor the weight of their children when they are being treated for ALL. It is essential to educate the parents of a childhood ALL survivor as to how they can calculate the BMI of their child every week and keep a record of it. It is necessary to inform the parents of a childhood survivor that communicating with their child is extremely important (25). The parents need to see that their child is psychologically strong and not depressed since depression can lead to over eating resulting in increase in weight. It is important to communicate with the family of a childhood ALL survivor.
patient about the advantages of encouraging the child to drink lot of water since it can help with the metabolism of the body. It is necessary to keep a record of the sleep cycle of a child since lack of sleep may have a negative effect on the weight of childhood ALL survivors. These are a few preventive measures which can be taken to prevent obesity in ALL survivors (25). Based on the results, it is observed that there is an increased susceptibility to obesity in ALL survivors and this project is a small step in the direction of prevention obesity in ALL survivors.
Summary and Conclusion

Based on the specific aims of the project, the following results were observed:

- Table 3 indicates that the mean BMI for all the patients who were followed from diagnosis to 2 years after end of therapy increased from 19.03 to 22.09.

- Table 4 indicates the sample size at diagnosis, at the end of therapy and 2 year post therapy. The patients were classified into underweight, normal, obese and overweight based on their BMI. For the obese category, it was observed that the percentage and number of obese patients increased from 1 (1.27%) at baseline to 7 (9.3%) at 2 year post therapy.

- It was observed that the number of obese patients increased during the course of the therapy and follow up. In addition to this, graphs were plotted for BMI with Time and BMI with Log of Time. Both the graphs showed an increase in BMI over time.

- Table 5 shows the results of a mixed regression model which reveals that there is significant individual variation with respect to BMI changes across time (p=0.0008). The other variables that we specifically looked at did not show any significant increase in BMI. Hence, time is a major factor which influenced the increase in BMI.

- Table 5 shows the results of a mixed regression model which reveals that there is no significant individual variation with respect to BMI changes because of steroids and anthracyclines treatment. Considering the side effects of steroids and anthracyclines, which include weight gain and osteonecrosis, further research is needed to look at the effect of these predictors on BMI.
• Since there is an increase in BMI in the population with time, it is essential to monitor the changes in BMI every week with continuous follow up by the hospital and with the help and support from the family of each child.

• These data suggest that the susceptibility to obesity increased with the passage of time from diagnosis to 2 year post therapy.

• At the same time, the effect of other variables like steroids and anthracyclines were not significant but considering the side effects of these drugs and their correlation with osteonecrosis, it is important that the effects of these drugs on the changes in BMI are analyzed retrospectively in other groups of ALL survivors.

• Based on the data and results, it is observed that obesity is a major risk factor in ALL survivors and preventive measures need to be taken to minimize the risk of obesity in ALL survivors.
CHAPTER 3:

Internship Site and Experience

The internship took place at Cook Children’s Medical Center, Fort Worth. Student, Nikhil Bhat worked with Dr. Paul Bowman who is a Pediatric Oncologist at Cook Children’s Medical Center and Chair of Pediatrics at University of North Texas Health Science Center. The main focus of internship was to do a retrospective analysis on a group of 90 childhood ALL survivors to determine the susceptibility of this group to obesity, and take correct measures to observe the prevalence of obesity by undertaking a minimal-risk clinical protocol. The internship practicum project started with the development of this protocol. This was followed by assembling and sorting all the necessary documents for IRB submission. After IRB approval, the study was undertaken by collecting the data from Cook Children’s Total XV database and supplementing by abstracting medical records. These data were analyzed for the practicum project.

Responsibilities given to me included maintenance of essential documents, recruitment of potential subjects, screening and enrollment of subjects, participation in the informed consent and child assenting process, communicating with the IRB, assisting in writing protocols and other study documents, data collection, and data monitoring and verification. Apart from these activities, I was able to gain valuable experience by getting a chance to shadow under Clinical research Associates in the Clinical Research department in Cook Children’s. The experience gained during shadowing included getting to know about the process of tracking medical records, HIPAA policy information, communicating with patients about clinical trials on the phone and setting up a database to monitor all the records related to ongoing clinical trials.

Other activities included attending clinical, educational, research, and administrative meetings of Cook Children’s Hematology-Oncology program, and meeting with the principal investigator.
and/or advisor weekly to discuss progress and issues. The day-to-day activities were recorded in a daily journal and submitted at the end of the practicum. The main aim of the practicum was to for the student to obtain experience in the field of clinical research and to be well equipped to contribute to clinical trial projects as a clinical research associate.


22. Ledbetter, AB, Siddiqui, M, Heym, K. Age at Diagnosis and Changes in Body Mass Index in Pediatric Acute Lymphoblastic Patients on Total Therapy XV Protocol treated at Cook Children’s Medical Center, 2004-2010 Abstract. (Personal Communication)


Appendix A

*Internship Daily Report*

20\textsuperscript{th} Aug 2012:

Attended a seminar with Dr. Bowman. A seminar by Dr. Cohen on her past, present and future research in the field of Breast cancer and IVF. Assisted Dr. Bowman with his patients who he was observing. These patients were Life After Cancer patients who had survived serious disorders like Leukemia, Lymphomas, Brain Tumors etc.

21\textsuperscript{st} Aug 2012:

Attended Grand Rounds with Dr. Bowman at Cook. There was a presentation on focal lesions and the diagnostic methods and surgical procedures related to focal lesions in infants during the Grand Rounds. The presentation was by an eminent Physician from Philadelphia. Later met the Medical Library staff of Cook and checked the resources in the library. Then attended a conference on Brain Tumors (Neuro-Oncology) in Cook which was conducted by Dr. Jeff Murray.

22\textsuperscript{nd} Aug 2012:

Met Lisa Bashore at Cook who works with Dr. Bowman. Saw the hospital and the staff that works with her. She showed me the clinic and the other hospital areas. Later attended a meeting with Dr. Bowman. In that meeting, we discussed about the Cook Children’s CCSS recruitment update. Attended the AYA conference in Cook on the types of cancer, the demographics etc..

23\textsuperscript{rd} Aug 2012:

Attended a conference in Cook with Dr. Bowman on Lymphoma and Leukemia. Many Lymphoma and Leukemia patients and their progress was discussed in this conference. Had a
tour of the Cook Children’s hospital after the conference. Saw the different departments of the hospital.

24th Aug 2012:

Attended the Clinic in Cook with Dr. Bowman. Looked at his patients in the hospital and observed them. The patients were life after cancer patients who were treated for cancer. Later met Clinical Research Coordinators in Cook and got some information about the Informed Consent procedure from them. Then attended Grand Rounds with Dr. Bowman where there was a presentation by Dr. Bowman on Leukemia and Lymphoma and the treatment modules and diagnostic factors related to them.

27th Aug 2012:

Discussed various clinical trial projects with Dr. Bowman. Spoke about what can be a good option to choose for my internship project. Discussed about the outline of a clinical trial, talked about intervention research trials etc etc. We also spoke about the tools that can used to conduct a clinical trial.

28th Aug 2012:

Attended Grand Rounds with Dr. Bowman at Cook. There was a presentation on Retinoblastoma and the diagnostic methods and surgical procedures related to Retinoblastoma in infants during the Grand Rounds. The presentation was by an eminent Physician from Philadelphia. Later met the Medical Library staff of Cook and checked the resources related to risk factors in cancer survivors in the library. Then attended a conference on Brain Tumors (Neuro-Oncology) in Cook by Dr. Jeff Murray.

29th Aug 2012:
Met Lisa Bashore at Cook who works with Dr. Bowman. Later attended a meeting with Dr. Bowman. In that meeting, we discussed about the Cook Children’s CCSS recruitment update. Later discussed with Lisa Bashore and Dr. Bowman about my project. Got some literature from Lisa Bashore related to my project to go through about obesity, risk factors in cancer survivors etc. Later attended Grand Rounds with Dr. Bowman at UNT. There was a presentation on improving the development of children (public health perspective) during the Grand Rounds.

30th Aug 2012:
Attended a conference in Cook on Lymphoma and Leukemia. Later had my 1st Committee meeting with my Committee members in Cook. We discussed about my project and other stuff which I can learn during internship which included an overview of conducting clinical trials, shadowing clinical research associates, getting IRB approval for my project, the timeline for my project and the next committee meeting agenda.

31st Aug 2012:
Attended Grand Rounds with Dr. Bowman where there was a presentation on a few cases from Cook related to Leukemia and Lymphoma.

4th Sept 2012:
Studied and read few articles related to my project on Risk factors in Life after Cancer Patients. Read a few templates of the research proposals of previous students to get a rough idea of how to write a research proposal for my project.

5th Sept 2012:
Attended a meeting with Dr. Bowman in Cook. In that meeting, we discussed about the Cook Children’s CCSS recruitment update. Later read some literature related to the risk factors in life after cancer patients.
6th Sept 2012:

Read some articles to get some information about the risk factors that life after cancer patients come across. Then met Lisa Bashore and worked on getting my computer access in Cook. Later had an appointment with Karen Keller in Cook. She gave some information about how to look for some sources related to literature review.

7th Sept 2012:

Attended a conference at Cook with Dr. Bowman. The conference was headed by Dr. Wilson. In the conference, there were various topics discussed related to Pediatric Obesity Management. The theme of discussion was how effectively we can look at various tools to gather information which will help us look at obesity as a risk factor in life after cancer patients.

10th Sept 2012:

Met Dr. Bowman and Lisa Bashore. We discussed about what literature we can look at to help me prepare my research proposal. We spoke of different options and tools from which we can gather information related to risk factors in life after cancer patients.

11th Sept 2012:

Met Karen Keller in Cook. She gave some information about how to look for some sources related to literature review. We discussed about what options we can look at and search for related to my project.

12th Sept 2012:

Met Dr. Bowman at Cook. We discussed about how to frame the research proposal. We spoke about how to compare different type of cancers based on the literature and what inputs can be given based on the literature.

13th Sept 2012:
Studied and read few articles related to my project on Risk factors in Life after Cancer Patients. Read some more articles to get some information about the risk factors that life after cancer patients come across. Searched for some literature related to Obesity as a complication in cancer survivors. Made some notes based on the literature.

14th Sept 2012:

Searched for more articles related to my project on Risk factors in Life after Cancer Patients. Got some information about the risk factors that life after cancer patients come across. Summarized the data related to Obesity as a complication in a tabular form.

17th Sept 2012:

Met Dr. Bowman in UNT. Discussed about the Research proposal based on the data that I had summarized last week. Chalked out a plan to construct the Research proposal.

18th Sept 2012:

Did some more literature review based on the rough draft of my Research proposal. Searched for a few specific articles related to obesity and made notes as told by Dr. Bowman. Chalked out a few points related to my project from that.

19th Sept 2012:

Met Dr. Bowman at Cook. We discussed about the plan of action for my Research proposal. I told him about the notes which I made based on a few specific articles. He introduced me to a couple of Clinical Research Associates from Cook. They gave their inputs related to the proposal and how we can handle the project and get some more information about it.

20th Sept 2012:
Studied and read few articles related to my project on Risk factors in Life after Cancer Patients. Read a few templates of the research proposals of previous students to get a rough idea of how to write a research proposal for my project.

21\textsuperscript{st} Sept 2012:
Met Dr. Bowman in Cook today. Later met Clinical Research Coordinators in Cook and got some information about the Clinical Trials conducted in Cook. Then attended a Case Conference (Grand Rounds) with Dr. Bowman where there was a presentation on the dosage of Chemotherapy in Cancer patients related to Obesity.

24\textsuperscript{th} Sept 2012:
Met Dr. Bowman in UNT. Discussed about the Research proposal based on the data that I had summarized last week. We spoke how getting the right information and how to get the final draft done.

25\textsuperscript{th} Sept 2012:
Studied and read few articles related to my project on Risk factors in Life after Cancer Patients. Read a few templates of the Research proposals of previous students.

26\textsuperscript{th} Sept 2012:
Met Dr. Bowman at Cook. We discussed about the plan of action for my Research proposal. I told him about the notes which I made based on a few specific articles. We discussed about the database tool which we can use related to our project.

27\textsuperscript{th} Sept 2012:
Worked on the Research proposal format. Took some inputs from Lisa Bashore. Modified a few things which were written in the proposal. Tried to get some information about the database tool which we would be using for the project.
28th Sept 2012:
Took help from the UNT library staff and resources to update the information in my proposal with respect to the required template and format. Got some more information related to the background of the project.

1st Oct 2012:
Took help from the UNT library staff and resources to update the information in my proposal with respect to the required template and format. Got some more information related to the significance of the project, the aim and the background of the project. Then prepared a soft copy of the proposal based on the inputs from Lisa Bashore.

2nd Oct 2012:
Prepared the rough draft of the Research proposal which is to be sent to the committee members to get their views on it.

3rd Oct 2012:
Worked on the Research proposal draft to modify it before submitting it to the IRB. Met Dr. Simecka to discuss his views and suggestions on the draft. Sent the Research proposal draft to all the committee members.

4th Oct 2012:
Worked on the proposal based on the views and suggestions given by Dr. Simecka. Added and modified a few things from the proposal. Took some help from the UNT library resources for the same.

5th Oct 2012:
Worked on the references section and sorted out a few things of the proposal with respect to the required template for the proposal. Worked with the UNT library resources to modify the proposal based on the suggestions.

8th Oct 2012:
Met Dr. Bowman and discussed about my project with him. Spoke with him about the modifications suggested by Dr. Simecka for the Research proposal. We spoke about other ways to modify the proposal before submitting it to the IRB.

9th Oct:
Met Lisa Bashore in Cook. We discussed about the modifications necessary for the Research proposal. She gave her inputs on the proposal and suggested a few things. I went through a few papers on obesity to get some more information.

10th Oct:
Worked on the Research proposal. The UNT library staff helped me with the references and modifications. Modified the proposal based on inputs from my committee members.

11th Oct:
Worked on the Research proposal based on the feedback given by Lisa Bashore. Read a few articles related to the proposal.

12th Oct:
Finished writing the modified draft of the Research proposal. Sent the soft copy to Dr. Gwirtz and Dr. Simecka.

15th Oct:
Worked on the Research proposal. The UNT library staff helped me with the references and modifications. Modified the proposal based on inputs from my committee members.
16\textsuperscript{th} Oct:
Met Dr. Bowman in UNT. Discussed about the Research proposal based on the data that I had summarized last week.

17\textsuperscript{th} Oct:
Worked on the final feedback given by Lisa Bashore for the Research proposal.

18\textsuperscript{th} Oct:
Sent the final proposal draft to my committee members. Got their approval. Studied the process of submitting the draft to IRB.

19\textsuperscript{th} Oct:
Worked on the Research proposal based on feedback from Dr. Bowman. Got approval from Dr. Gwirtz for IRB submission.

22\textsuperscript{nd} Oct:
Met Dr. Bowman. Discussed a few minor points about the proposal before IRB submission. Gave a few forms to Dr. Bowman to be filled out for IRB submission.

23\textsuperscript{rd} Oct:
Worked on the IRB submission form filling. Sent the completed forms to Dr. Bowman. Filled out the HIPAA, Waiver and conflict of interest forms and worked on the minor changes in the proposal as suggested by Dr. Bowman.

24\textsuperscript{th} Oct:
Met Dr. Bowman in Cook. We discussed about the Cook Children’s CCSS recruitment update. Then took signatures from Dr. Bowman on the IRB forms which would have to be submitted to
UNTHSC IRB. Spoke with Melinda Meacham about my Research proposal and the process that we would have to carry out to submit the proposal to the IRB in Cook.

25th Oct:
Worked on the IRB forms as per the changes suggested with respect to the IRB forms. Discussed about the IRB forms and the changes required with Dr. Bowman. Enquired with Melinda Meacham regarding shadowing with Clinical Research professionals in Cook.

26th Oct:
Attended Grand Rounds with in Cook where there was a presentation on Neuroblastoma and the treatment modules and diagnostic factors related to them.

29th Oct:
Worked on the IRB forms as per few more changes suggested with respect to the IRB forms on 28th Oct. Went through the proposal to check the changes with respect to IRB requirements.

30th Oct:
Looked at the statistical data of the Research proposal. Modified the proposal based on the suggestions by IRB. Went through the IRB forms after modifications.

31st Oct:
Met Dr. Bowman. We discussed about the modifications suggested by IRB in the Retrospective Chart Review form and the HIPAA Waiver form. Later met Itzel Perez in the IRB office in UNT and told her about my meeting with Dr. Bowman. Later on met Dr. Simecka and we discussed about the statistical data which we would want to have in the proposal.

1st Nov:
Attended a conference in Cook with Dr. Bowman on Lymphoma and Leukemia. Many Lymphoma and Leukemia patients and their progress was discussed in this conference.
2\textsuperscript{nd} Nov:

Added a few statistical facts related to the proposal in the proposal. This was based on the discussion which I had with Dr. Aryal from UNT. I met him and he told me the exact statistical analysis which would be required for my project and I added it in my proposal accordingly.

5\textsuperscript{th} Nov:

Started shadowing in with Steve (Clinical Research Associate) in Cook. He explained to me the procedures he undertakes in Clinical trials and I stayed with him to gain experience and see how it performs his task. He explained to me about the medical record documents and other stuff related to clinical trials. Met Dr. Bowman in UNT and updated him about it and also spoke with him about my Research proposal.

6\textsuperscript{th} Nov:

Had my second Committee meeting with my committee members in UNT. We discussed about my Research proposal and my progress on it. I also told the committee members that I met Dr. Aryal and got the statistical part updated in my proposal after talking with him. I also updated them about the updates from UNTHSC IRB on my proposal.

7\textsuperscript{th} Nov:

Attended a meeting with Dr. Bowman. In that meeting, we discussed about the Cook Children’s CCSS recruitment update. We then discussed about my research proposal and how we need to modify it before submitting it to Cook IRB. Then I shadowed with Steve. He guided me with the data entry stuff information. He also told me about how to get informed consent from patients for clinical trials.

8\textsuperscript{th} Nov:
Met Dr. Bowman in Cook. He gave his inputs on my proposal and suggested changes before submitting the proposal to Cook IRB. Later I shadowed with Steve. He was working on contacting and getting in touch with a few patients to check with them if they would want to be part of the clinical trials in Cook.

9th Nov:
Worked on the suggestions given by Dr. Bowman on my proposal. Edited it as required and then submitted it to Dr. Bowman to get his feedback on it.

12th Nov:
Got updates from Dr. Bowman on the edited proposal. Asked him if he wants me to edit anything more. Spoke with Steve about shadowing and his experiences.

13th Nov:
Met Dr. Bowman in Cook. He gave some inputs on some minor things which would be required to be edited. Then we discussed about the IRB approval process for my proposal from Cook IRB. Later shadowed with Steve. He told me about data entry and recruiting volunteers.

14th Nov:
Met Dr. Bowman in Cook. In this meeting, we discussed about the Cook Children’s CCSS recruitment update. We then discussed about my research proposal and how we need to modify it before submitting it to Cook IRB. Later edited my proposal and met Dr. Bowman in UNT and submitted the hard copy to him.

15th Nov:
Met Dr. Bowman in UNT. Worked on the last few things of my proposal. Edited the proposal based on inputs from my committee members ie Dr. Gwirtz, Dr. Simecka and Dr. Bowman.

16th Nov:
Sent the edited version of the proposal to Dr. Gwirtz and Dr. Simecka. Discussed about the proposal with Dr. Bowman. Later shadowed with Steve. He told me about data entry and recruiting volunteers.

19th Nov:
Worked on the changes suggested by Dr. Bowman. Shadowed with Steve in Cook. He told me about Inform Consent and the procedure related to it.

20th Nov:
Met Dr. Bowman in UNT. We discussed about the data base that we would be using for our project and how we can insert the values. We also discussed about the Plan of Action for the project.

21st Nov:
Went to the GSBS office in UNT to get the information about the forms to be submitted with the Research proposal. Emailed Dr. gwirtz and updated her about the proposal.

22nd Nov:
Worked on reading some literature related to the project. Went through the data base given by Dr. Bowman.

23rd Nov:
Sent the edited proposal to Dr. Simecka, Dr. Gwirtz and Dr. Bowman. Read a few articles related to obesity.

26th Nov:
Met Dr. Gwirtz and Dr. Simecka today to discuss about my edited Research proposal. Spoke with Dr. Bowman about my proposal. Got some signatures on the Research proposal form for my proposal submission to the GSBD office.
27th Nov:
Attended Grand Rounds with Dr. Bowman at Cook. There was a presentation on the experiences that parents undergo after the death of a child during the Grand Rounds. The presentation was by an eminent Physician from Arizona. Later attended a Poster presentation in Cook. It was by the UNTHSC TCOM students. Then shadowed with Steve in Cook. He told me about how to track lost patients which can be enrolled in clinical trials.

28th Nov:
Met Dr. Bowman in UNT. A student who had worked on a similar project like me was also there for the meeting. She told us her experience about her project. She helped us set up a plan for my project.

29th Nov:
Worked on the formalities for the proposal submission process to the IRB in Cook. Read a few papers on Obesity and clinical research.

30th Nov:
Shadowed with Steve and other clinical research associates in Cook. Steve explained to me about the minor aspects that we have to be careful about when we interact with patients who we want to enroll in clinical trials.

3rd Dec:
Worked on the formalities and the paper work required for getting iRIS program access in Cook. Sent the proposal to the concerned department in Cook and told them to update me about it.
Later met Dr. Gwirtz in UNT and updated her about my internship work.

4th Dec:
Updated Dr. Bowman about the iRIS program access procedure in Cook. Later shadowed with Steve. He told me about the process of enrolling patients in the database before and during clinical trials.

5th Dec:
Shadowed with Steve. He explained to me about the documents that we need to monitor during clinical trials.

6th Dec:
Updated Dr. Bowman about the status of the documents that I have submitted to Cook IRB.

7th Dec:
Went through a few articles on Obesity to get some more information related to my project.
Worked on a few minor aspects related to the database for my project.

10th Dec:
Went through a few articles on Obesity to get some more information related to my project.
Shadowed with Steve to get some experience related to clinical trials submission process.

11th Dec:
Met Melinda Meacham in Cook. Submitted the complete iRIS application to the Cook IRB with her help. Updated Dr. Bowman about it. Later shadowed with Steve. He told me about the process of tracking records in clinical trials.

12th Dec:
Met Dr. Bowman in Cook. In that meeting, we discussed about the Cook Children’s CCSS recruitment update. Later we spoke about what will be our plan of action for our project. We discussed about the preparation of the database and the statistical analysis of the data.

13th Dec:
Worked on the iRIS access program for Cook Childrens. Added my project in it. Updated Dr. Bowman about it. Met Dr. Gwirtz today and told her about the project.

14th Dec:
Attended Grand Rounds with Dr. Bowman where there was a presentation on a few cases from Cook related to Leukemia and Lymphoma.

17th Dec:
Shadowed with Steve. He told me about the process of tracking records in clinical trials.

18th Dec:
Shadowed with Steve. He told me about the process of tracking records in clinical trials. Updated Dr. Bowman about it.

19th Dec:
Shadowed with Steve. He explained about the way we communicate with patients and the HIPAA policies.

20th Dec to 2nd Jan:
Christmas Break.

Read articles about Obesity and ALL.

3rd Jan:
Started working on my thesis. Updated Dr. Bowman about it.

4th Jan:
Shadowed with Steve in Cook. Learnt a few more aspects about clinical trials.

7th Jan:
Shadowed with Steve in Cook. Learnt a few more aspects about clinical trials. Wrote a few chapters of my thesis related to introduction.

8\textsuperscript{th} Jan:
Met Kathy in the Clinical Research department in Cook. She gave me the information about the access and the database related to my project. Worked on my thesis too. Met Melinda Meacham.

9\textsuperscript{th} Jan:
Updated Dr. Bowman about my thesis work. Informed Dr. Gwirtz about my plan of action for my project. Emailed Kathy for more information about the project related patients.

10\textsuperscript{th} Jan:
Met Dr. Bowman in UNT. We discussed about the results and statistics part of our project. We spoke about the Cook IRB requirements for our project. We chalked out a plan for the next few days. Informed him about my thesis.

11\textsuperscript{th} Jan;
Worked on my thesis. Shadowed with Steve in Cook.

14\textsuperscript{th} Jan:
Contacted Dr. Simecka to take his guidance for my thesis. Spoke with Melinda Meacham in Cook to get information about the database related to my project.

15\textsuperscript{th} Jan:
Updated Dr. Simecka about the TPHA conference. Worked on the introduction part of my thesis based on inputs given by Dr. Simecka. Sent the Significance and Specific Aims sections to Dr. Simecka to get his inputs.

16\textsuperscript{th} Jan:
Met Dr. Bowman in Cook. We discussed about the Cook Children’s CCSS recruitment update. Later we discussed about the plan of action to get the results related to our project. Later met Lisa Bashore and we both looked at the Athena and Meditech access. Later met Dr. Gwirtz to update her about my project and the TPHA conference.

17th Jan:
Worked on my thesis. Read a few articles related to Obesity to work on the background as suggested by Dr. Simecka.

18th Jan:
Worked on my thesis. Later met Lisa Bashore in Cook. We discussed about the database which we can use to track changes related to BMI in my project.

21st Jan:
Worked on preparing my database. Met Lisa Bashore to discuss about the plan of action to prepare the database. Worked on getting access to Meditech.

22nd Jan:
Started preparing the database. Worked on the data of 20 patients related to their treatment time points and BMI. Discussed the plan of action for the database with Lisa Bashore.

23rd Jan:
Worked on the database. Updated the information for 50 patients in the database by taking information via Meditech.

24th Jan:
Worked on the database. Updated the information for 50 patients in the database by taking information via Meditech. Simultaneously worked on my thesis and took inputs from Dr. Simecka on it.
25\textsuperscript{th} Jan:

Met Dr. Aryal to discuss about the statistics and results part of my project and to talk about the plan of action for the statistical analysis.

28\textsuperscript{th} Jan:

Worked on my thesis and got inputs from Dr. Simecka on the background section. Met Dr. Aryal to get his feedback on my database.

29\textsuperscript{th} Jan:

Met Dr. Bowman to discuss about the variables that we would be looking at with respect to trends in BMI changes. Shadowed with Steve and learnt about HIPAA policies.

30\textsuperscript{th} Jan:

Met Dr. Bowman in Cook. Discussed with him about the database and how to track the total doses for each patient for steroids and anthracyclines. Later worked on updating the database. Completed adding the drug doses for all the patients.

31\textsuperscript{st} Jan:

Met Dr. Gwirtz, Dr. Bowman and Dr. Simecka in UNT. Updated them about my thesis progress. Took their signatures to submit the intend to defend form.

1\textsuperscript{st} Feb:

Worked on my thesis. Worked on the results and analysis section of my database.

4\textsuperscript{th} Feb:

Worked on my thesis. Worked on the results and analysis section of my database. Updated Dr. Simecka about the other sections of my thesis.

5\textsuperscript{th} Feb:
Worked on my thesis. Worked on the results and analysis section of my database with the biostatistics professor. Updated Dr. Simecka and Dr. Gwirtz about the other sections of my thesis.

6th Feb:
Used the SAS and SPSS softwares to look at the minute details as far as the statistical sections of my thesis were concerned. Interpreted the results and discussed them with the biostatistics professor.

7th Feb:
Shadowed with Steve. Learnt more about the clinical trials department HIPAA policies and informed consent procedures in Cook. Worked on the last section of my thesis. Met Dr. Bowman in UNT.

8th Feb:
Submitted the results and analysis section of my thesis to Dr. Simecka to get his inputs.
Shadowed with Steve. Attended the Grand Rounds in Cook. Met Dr. Bowman in Cook.
Discussed about the analysis and results with him.

11th Feb:
Worked on the statistics and analysis section as suggested by Dr. Bowman. Divided the patients into 4 groups and interpreted the results for each group.

12th Feb:
Met Dr. Bowman and Lisa Bashore in Cook. Showed them the final version of the results and analysis section and discussed with them about it.

13th Feb to 26th Feb: Worked on the final part of the thesis, prepared my presentation for defense, practiced my presentation, and submitted my thesis to my committee members.