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A Descriptive Analysis and Assessment of Predictive Factors for Participation in a Clinical Trial as Front-Line Therapy for Patients Enrolled in the Nebraska Lymphoma Study Group Registry

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Table of Contents

Abstract

Background: Clinical trial participation, especially among cancer clinical trials in adult populations, continues to be low despite the large number of clinical trials available across the U.S. Estimates for clinical trial participation are as low as 5% in some adult cancer populations, however in some lymphoma populations this figure may be as high as 13.9%. This figure can be confusing, given that as much as 70% of Americans are estimated to be willing to participate in a clinical trial. Previous research shows that as much as 95% of surveyed respondents who said they had previously participated in a clinical trial stated they would consider future participation in another clinical trial. Goals and Objectives: This study contains four primary objectives. The first is to provide descriptive statistics for the Nebraska Lymphoma Study Group (NLSG) study population at the University of Nebraska Medical Center (UNMC). The second is to determine associations between demographic and clinical variables and two separate outcome variables: participation in the NLSG study and participate in a clinical trial as front-line therapy. The third objective is to determine the association between participation in the NLSG study and participation in a clinical trial as front-line therapy. The fourth objective is to develop a logistic regression model for participation in a clinical trial as front-line therapy. We hypothesize that patients who agree to participate in the NLSG study will be more likely to select a clinical trial as front-line therapy. Methods: Demographic and clinical information were provided from the NLSG research team at UNMC. Tests for association between categorical variables and two separate outcome variables, participation in the NLSG study and participation in a clinical trial as front-line therapy, were examined using Chi-square analyses. An odds ratio was calculated for participation in the NLSG study and participation in a clinical trial as front-line therapy.

Logistic regression analysis among bivariate predictor variables was modeled for the outcome of participation in a clinical trial as front-line therapy. Results: The sample population consisted of N=2,343 patients. Ethnicity as a multivariate categorical variable and ethnicity as a bivariate categorical variable (White, non-Hispanic and all other ethnicities) were significantly associated with participation in the NLSG study ($p=0.007$ and $p<0.001$, respectively). N=125 patients selected a clinical trial as front-line therapy. Age at diagnosis was found to be negatively associated with participation in a clinical trial as front-line therapy ($p=0.006$). Those who participated in a clinical trial as front-line therapy had 3.48 times the odds of previously participating in the NLSG study, however this was not statistically significant (95% CI=0.47, 25.35). A logistic regression model for selection of a clinical trial as front-line therapy was developed which included two significant covariates, age at diagnosis and diagnosis type. The logistic regression model showed that those who were younger (below the median age at diagnosis) and those with Hodgkin lymphoma diagnosis were at greater odds of selecting a clinical trial as front-line therapy. Conclusions: We found that ethnicity, in particular those who were White, non-Hispanic were more likely to have been enrolled in the NLSG study. Additionally, we found that those who were younger (below the median age at diagnosis of 57 years), and those with a diagnosis of some subtype of Hodgkin Lymphoma, were more likely to have selected a clinical trial as front-line therapy. We found that those who chose a clinical trial as front-line therapy were at 3.48 times the odds of having previously agreed to participate in the NLSG study, however this association was not statistically significant. We recommend that further research be done to investigate the factors associated with registry and clinical trial participation among non-White ethnic groups as well as among older populations. We also

recommend that future similar research be done on lymphoma populations in other geographic areas in the U.S. as well as in other disease states or health conditions to examine predictive factors for participation in clinical trials. Understanding factors that positively influence clinical trial participation may improve clinical trial participation rates.

Key Words & Phrases: Lymphoma, Predictive Factors, Registry, Clinical Trial, Logistic Regression, Nebraska Lymphoma Study Group, Clinical Trial Participation

Service Learning

Service Learning Placement Site

The placement site for the student's Service Learning experience was the Fred & Pamela Buffett Cancer Center (FPBCC) at the University of Nebraska Medical Center (UNMC), located in Omaha, Nebraska. UNMC the only public academic health science center in the state of Nebraska. The university is committed to research aimed at finding cures for a wide variety of diseases, to providing the best possible care for its patients, and to serving the state and its communities through award-winning outreach programs (UNMC, 2018). The mission of UNMC is, "to lead the world in transforming lives to create a healthy future for all individuals and communities through premier educational programs, innovative research and extraordinary patient care" (UNMC, 2018). The FPBCC is the only cancer center in Nebraska with the National Cancer Institute (NCI) designation and is one of 69 NCI-designated centers in the U.S. Additionally, it is a founding member of the National Comprehensive Cancer Network (NCCN), which is an alliance of 19 cancer centers across the world that contributes towards the development of standards and guidelines for the treatment of cancer patients. For over 40 years, the FPBCC has been a leader in the fight against cancer. Physicians and research scientists at the FPBCC collaborate in translational research efforts, which offers their patients the most recent, cutting-edge therapies in their fight against cancer. (UNMC, 2018).

Service Learning Activities

The service learning component of the project focused on the development of a rapid autopsy and tissue banking program, "Fighting Cancer After Death (FCAD): A Postmortem

Tissue Banking Program from Patients with Hematologic Malignancies". Activities that were performed include an extensive literature review on rapid autopsy programs (RAP) across the U.S and Europe, collaboration with pancreatic cancer researchers who have an established RAP to develop standard operating procedures for pre-, during-, and post-autopsy checklists, creation and submission of a complete institutional review board (IRB) application and informed consent form (ICF) for the RAP, development of patient-friendly informational pamphlets regarding tissue donation, and creation of a database for linking of clinical data to tissue samples.

Service Learning Goals and Objectives

1. Perform an extensive literature review of rapid autopsy programs in the United States and Europe and collaborate with pancreatic rapid autopsy program (PRAP) investigators to review features of established programs.
2. Develop standard operating procedures that will guide the conduct of a tissue bank for postmortem tissue donation from patients with hematologic malignancies.
3. Start and complete a full institutional review board (IRB) application and informed consent form (ICF) for submission to UNMC's IRB.
4. Create a database for linking relevant clinical data to tissue sample donations

Capstone Experience Goals and Objectives

The dataset from the NLSG, established by Dr. James O. Armitage in 1982, will serve as the sample population from which statistical analyses will be performed. The NLSG has tracked thousands of patients with hematologic malignancies, particularly Hodgkin's Disease (HD), non-

Hodgkin's Lymphoma (NHL), and other hematologic disorders for several decades; the investigators and supportive staff have collected extensive data in regards to patients' diagnoses, pathological tissue samples, demographics, and treatment regimens. The key objectives for the capstone experience are listed below.

1. Report descriptive statistics such as demographic information, type of malignancy, prior treatments and other relevant clinical data, as appropriate, and conduct comparative analyses on patients enrolled in the Nebraska Lymphoma Study Group (NLSG) database. We hypothesize that those who select a clinical trial as front-line therapy will have greater odds of previously agreeing to participate in the NLSG study.
2. Develop a logistic regression model from the NLSG database from significant covariates for prediction of participation in a clinical trial as front-line therapy.

Introduction & Background

General Cancer Statistics

According to the National Cancer Institute (NCI), in 2018 there will be an estimated 1,735,350 incident cancer cases in the U.S. and about 609,640 people will die from cancer (NCI, 2018). Some of the most common forms of cancer include breast, lung and bronchus, prostate, colorectal, melanoma, bladder, non-Hodgkin lymphoma, among others (NCI, 2018). When looking at men and women combined, the total cancer incidence rate is 439.2 per 100,000 and cancer mortality rate is 163.5 per 100,000, based on 2011-2015 data (NCI, 2018). The estimated number of people living with cancer is expected to grow significantly over the next decade. The

NCI estimates there were 15.5 million people living with cancer in 2016, and that figure is estimated to grow to 20.3 million by the year 2026 (NCI, 2018). The burden of cancer is high among U.S. populations. Based on 2013-2015 data, nearly 2 in 5 people living in the U.S. (38.4%) will be diagnosed with cancer at some point in their life (NCI, 2018). Cancer also creates a massive national economic burden in the U.S. The NCI's Cancer Trends Progress Report, "Financial Burden of Cancer Care", estimates that the national expenditures for complete cancer care, which accounts for those diagnosed with cancer, their families, and society as a whole, was $137.4 billion in 2010 and has grown to $147.3 billion in 2017 (NCI Cancer Trends Progress Report, 2018).

Hematologic Cancer Statistics

The Service Learning section of this project aimed to develop a rapid autopsy program (RAP) for patients with hematologic malignancies including lymphoma, leukemia, and multiple myeloma. Lymphoma is a term that encompasses cancers that originate in lymphocytes (B- or T-cells), which are disease-fighting cells that are a part of the lymphatic, or immune, system (NCI, 2015).

Lymphoma. Lymphoma is grouped into two main types: non-Hodgkin Lymphoma (NHL) and Hodgkin Lymphoma (HL). In 2015, which is the most recent year for which incidence data are available, there were 67,522 new cases of NHL and 20,154 deaths in the U.S. (CDC Data Visualizations, 2015). There were roughly 18 new cases of NHL reported per 100,000 persons in the U.S. The lifetime risk of developing NHL, based on 2013-2015, data is approximately 2.1% for men and women combined (NCI, 2015). The most recent prevalence estimates for NHL

show that there are roughly 686,024 people living with NHL in the U.S. (NCI, 2015). According to the National Cancer Institutes, based on SEER 18 data from 2008-2014, the estimated five-year survival rate for NHL diagnoses is 71.4% (NCI, 2015). The survival rate varies by stage. For stage I, five-year survival rate is 81.8%, II is 75.3%, III is 69.1%, IV is 61.7%, and unknown stage is 76.5% (NCI, 2015).

Hodgkin's Lymphoma. Hodgkin's Lymphoma is less common than NHL. In 2015, there were 8,332 new cases of HL and 1,120 deaths in the U.S. (CDC Data Visualizations, 2015). There were about 3 new cases of HL reported per 100,000 persons. The lifetime risk of developing HL, based on 2013-2015 data, is approximately 0.2% for men and women combined (NCI, 2015). The most recent prevalence estimates for HL show that there are roughly 208,805 people living with HL in the U.S. (NCI, 2015). The estimated five-year survival rates for HL diagnoses, based on SEER 18 data from 2008-2014, is 86.6%. Interestingly, when five-year survival rate is broken down by stage at diagnosis, stage II has the best survival rate of 92.3%, followed by stage I (92.3%), stage III (83.0%), and stage IV (72.9%); unknown stage has a survival rate of 82.7% (NCI, 2015).

Leukemia. Leukemia is a type of cancer that originates in tissues of the bone marrow that facilitate blood cell formation. These abnormal cells do not form solid tumors, but rather accumulate in the blood and bone marrow, which may take up space for normal blood cells (NCI, 2015 (1)). The four most common groups of leukemia are based on how the rate at which the disease worsens (acute or chronic) and on the type of blood cell in which the cancer originates (lymphoblastic or myeloid) (NCI, 2015). In 2015, there were 47,601 new cases of

leukemia and 22,847 deaths in the U.S. (CDC Data Visualizations, 2015). There were roughly 13 new cases of leukemia reported per 100,000 persons.

Multiple Myeloma. A type of cancer that originates in plasma cells, cells that develop from B-cells that assist in antibody production, is referred to as multiple myeloma (NCI, 2015) or plasma cell myeloma. Myeloma cells, otherwise known as abnormal plasma cells, accumulate in the bone marrow. Multiple myeloma tumor formation occurs in bones throughout the entire body. In 2015, there were 24,265 new cases of multiple myeloma and 12,231 deaths in the U.S. ((CDC Data Visualizations, 2015). There were 6 new cases of multiple myeloma reported per 100,000 persons.

Lymphoid Cell Differentiation and Tissue Analysis

Immune cells develop through a complex process of differentiation starting from hematopoietic stem cells (HSC), yielding multiple myeloid and lymphoid cell types that can differentiate and polarize towards distinct subtypes. Different hematologic malignancies can be aligned with "normal counterparts" within the immune system based upon histologic and immunophenotypic characteristics. For example, B-cell lymphomas are characterized according to their alignment with distinct stages of B-cell development. Marginal zone lymphoma (MZL) aligns with marginal zone B-cells, mantle cell lymphoma (MCL) aligns with mantle zone B-cells, and multiple subtypes including follicular lymphoma (FL), Burkitt lymphoma (BL) and diffuse large B-cell lymphoma (DLBCL) align with the germinal center B-cell stage of development (Kuppers, 2005). Patterns of genomic evolution in common B-cell malignancies have been characterized (Green et al., 2015; Green et al., 2014) and modeled the stepwise acquisition of

genetic alterations that give rise to this disease. However, it remains unknown whether specific lymphoid malignancies align with discrete stages of differentiation because that is the stage at which they acquired the transforming genetic event, or because the transforming event drives alterations in cell differentiation. In order to address this question, each stage of lymphoid differentiation will need to be analyzed at high resolution with sufficient sample volume to capture rare events; this will require the acquisition of tissues from multiple sites, including hematopoietic stem cells from the bone marrow, as well as nearby normal tissue counterparts from the same patients.

Service Learning Background

There is a lack of postmortem tissue banking services for hematologic malignancies, especially in adult populations across the United States. The Service Learning component of the student's project aimed to develop policies and procedures for the rapid obtainment of tissue from patients who have died from hematologic malignancies for use in basic science research, as well as to develop a clinical database for capturing clinical and pathological data. The Capstone Experience component of the student's project aimed to provide descriptive statistics on patients enrolled in the Nebraska Lymphoma Study Group (NLSG) Registry & Tissue Bank Study, significant associations for participation in the NLSG Registry & Tissue Bank Study and for participation in a clinical trial as front-line therapy, and a predictive logistic regression model for clinical trial participation as front-line therapy.

The tissue collected from the "Fighting Cancer After Death" study will be stored in the Lymphoma Precision Medicine Tissue Bank, which is part of the James O. Armitage Center for

Leukemia and Lymphoma Research at the University of Nebraska Medical Center. The purpose of this study is to rapidly obtain tissue from patients who have died from hematologic malignancies for use in basic science research. It is essential to procure these tissues within a few hours of death due to rapid destruction of the tissue by enzymes. Defining the premalignant compartments in hematologic malignancies will allow strides forward in the treatment of this disease. In many cases, complete response can be achieved following treatment of these malignancies; however, most patients ultimately relapse and show diverse patterns of genomic evolution. This suggests that premalignant compartments that possess only a subset of the oncogenic events that are detected in the clinically evident tumor propagate relapses. By identifying the oncogenic events in separate compartments (marrow, lymph node, or organ), tissue available from this project may be able to develop research strategies to better characterize this process.

Factors Associated with Participation in Registry Studies

Outcome, a Quintiles company, in their 2012 report "Standards in the Conduct of Registry Studies for Patient-Centered Outcomes Research", prepared for the methodology committee of the Patient-Centered Outcomes Research Institute (PCORI), defined a patient registry as "an organized system that uses observational study methods to collect uniform data (clinical and other) to evaluate specified outcomes for a population defined by a particular disease, condition or exposure, and that serves one or more predetermined scientific, clinical, or policy purposes" (Gliklich et al., 2012; Gliklich et al., 2010). Registries serve as important sources of data for patient-centered outcomes research (PCOR), especially those that enroll patients with specific diseases or those who have exposure to specific treatments or other

therapies (Dreyer & Garner, 2009; Dreyer et al., 2010). Registries provide the opportunity to study populations that may not typically be enrolled in standard clinical trials such as children, elderly, those with multiple or severe comorbidities in addition to the clinical data that are of importance to investigators and potentially the patients themselves. Factors for participation in registry studies, specifically factors that are positively associated with participation, as well as barriers for participation, vary depending on the disease of interest.

A survey by Solomon et al. examined the patients' experience between two chronic disease registries, one focused in rheumatoid arthritis (RA) and another in inflammatory bowel disease (IBD). Among 150 completed surveys from the RA registry and 169 from the IBD registry, the top three factors for participation in the registries were very similar. These factors were the desire to help others, the desire to improve care of their own disease, and the ease of volunteering (Solomon et al., 2017). The investigators made several key conclusions from their results. The first of which was that successful recruitment of patients to participate in a registry study likely depends on the appeal to altruism. Many patients responded that their willingness to participate was based on a desire to help others as well as the potential of improved care for their own disease. A second factor, the ease of participation, was noted among respondents. The surveys were easy and quick to complete, which was favorable for participants, especially those who were older (Solomon et al., 2017).

Another type of registry that is becoming increasingly more common in the U.S. is donor programs. A 2013 study by Switzer et al., examined race and ethnicity as factors for unrelated hematopoietic stem cell (HSC) donation. The donor program that was examined was the National Marrow Donor Program (NMDP), which is the largest registry in the world that focuses

on matching unrelated donors with patients that are in need of an HSC transplant; the NMDP has assisted in over 50,000 successful transplantations from its unrelated donor program in its 25-year history (Switzer et al., 2013). Despite the fact that the NMDP has more than 10 million registrants and that thousands of new volunteers are signing up each month, the NMDP and similar registries across the world experience difficulties in identifying matched donors for certain populations, particularly racial and ethnic minorities (Dehn et al., 2008). Additionally, according to NMDP program statistics, donor attrition rates within the NMDP registry are much higher for racial and ethnic minority groups when compared to non-minority groups (about 60% compared to 40%), and reasons for this disparity in attrition rates remains unanswered. (Switzer et al., 2013). Significant factors for attrition included patients' doubts and worries, feeling unsure about donation, and hoping that someone else would donate instead of them (Switzer et al., 2013). As we are going to assess the relationship between participation in a registry study and participation in a clinical trial as front-line therapy, it is important to understand factors that are associated with clinical trial participation.

Factors Associated with Participation in Clinical Trials

Clinical trial participation, especially in cancer clinical trials in adult populations, continue to be low despite the large number of clinical trials available across the U.S. Some studies estimate that fewer than 5% of adult cancer patients will enroll in a cancer clinical trial (Murthy, Krumholz, & Gross, 2004; Tejeda et al., 1996). However, this figure may be higher in lymphoma populations. The National LymphoCare Study, which was conducted as a multicenter, prospective, observational study examined treatment regimens and associated outcomes among N=2,728 follicular lymphoma patients. The investigators for this study

reported that 13.9% of patients participated in a clinical trial as front-line therapy (Friedberg et al., 2009). This figure can be confusing, especially when considering that as much as 70% of Americans are estimated to be willing or inclined to participate in a clinical trial (Comis et al., 2003). Barriers that have been previously researched include structural (clinic access), clinical (patient eligibility), behavioral (physician's decision to discuss trial with a patient and whether or not the trial is offered; patient's decision to enroll, if offered), demographic, and socioeconomic (Unger et al. 2017).

A retrospective chart review study, conducted from 14 years of patient data, analyzed sociodemographic, clinicopathologic, and treatment characteristics of 558 advanced-staged ovarian cancer patients that were treated at a single institution at one point. Seventy one percent (339/558) of patients did not participate in a clinical trial. Of those that did participate, the majority (78.75%) participated at the time of recurrence. Factors that were significantly associated with clinical trial participation included younger age (58 years v. 63 years, $p < 0.0001$), type of insurance ($p < 0.0001$), receipt of neoadjuvant chemotherapy treatment ($p = 0.014$), and gynecologic oncologist as adjuvant chemotherapy treatment provider ($p = 0.005$) (Mallen et al., 2018). Factors that were not significantly associated with clinical trial participation include race, educational level, religion, marital status, and distance traveled for care.

Another investigation into patient participation in clinical trials listed lack of awareness about clinical trials, assumptions about their eligibility, afraid of the unknown outcome of a clinical trial, and confusion regarding insurance as factors for why patients do not participate (Lopienski, 2014). Factors that were in favor of clinical trial participation included an altruistic

attitude towards the advancement of medical knowledge among 86% of surveyed patients, access to promising treatments (89% of respondents), recommendation from a trusted person such as their doctor, a family member or friend, and if they had a previous positive experience with a clinical trial (Research!America, 2013) Previous experience in a clinical trial was shown to be a very significant factor; 95% of respondents who said they had previously participated in a clinical trial stated that they would consider future participation in another clinical trial (CISCRP, 2013).

A prospective patient survey among Gastrointestinal and Lymphoma Unit patients at the Royal Marsden specialty cancer center in the United Kingdom was conducted between August 2013 and July 2014 to examine patients' willingness to participate in clinical trials and their overall views on certain aspects of cancer research. The most frequent answers in response to the main reason for trial participation were "the trial offered the best treatment available" and "the trial results could benefit others" (Moorcraft et al., 2016). Interestingly, age played a factor in the sense of altruism of the participants. Patients that were less than 65 years of age were more likely to state that their primary reason for participation was "the trial results could benefit others" when compared to those greater than or equal to 65 years of age (64% compared to 39%, OR = 2.77 (1.62-4.74), $p < 0.001$). Additionally, those who had participated previously in a clinical trial (72%) compared to those who had not (50%) were more likely to state an altruistic reason for their participation (OR = 2.65 (1.21-5.83), $p = 0.012$). Factors that were found not to be statistically significant included gender and the total number of previous treatment regimens. There were also several interesting results regarding patients' views on cancer research and biopsies. Of the patients who completed the first questionnaire, 96%

reported that they were happy having been approached to participate in cancer research and 99% believed that cancer research would help future physicians and investigators better understand and treat cancer (Moorcraft et al, 2016). The majority of patients (74%) disagreed or strongly disagreed with the statement: "I have concerns about the use and storage of blood and tissue samples for research". Perhaps most importantly, in terms of future tissue donation, 78% of patients agreed or strongly agreed and another 11% were neutral in regards to the statement: "I would agree to donate tissue for genetic research even if I was not told my genetic results" (Moorcraft et al., 2016).

Overview Rapid Autopsy Programs

Rapid autopsy technology and programs have been available for physicians and researchers for several decades. A group of researchers at the University of Washington have been using rapid autopsy technology to investigate prostate cancer since 1991, and the University of Nebraska Medical Center's pancreatic rapid autopsy program (PRAP) was established in 2002. In a Kaiser Health News article published in April, 2018, Dr. Jody Hooper, the director of the Legacy Gift Rapid Autopsy Program at Johns Hopkins University in Baltimore, Maryland, estimated that there are currently 14 similar autopsy programs in the U.S. (KHN, 2018). This figure shows that the launch of new programs has been slow over the past two or three decades. The value of rapid autopsy programs is massive, especially in cases where the disease has metastasized to several distant locations, sometimes locations that are difficult or impossible to reach in a living patient. These tissue samples, possibly obtained from all over the patient's body, are able to be quickly frozen or fixed in other preserving methods; these samples are then able to be accessed in the future by investigators looking to conduct research

on these cancer tissues. Rapid autopsy programs may also be expanded to other diseases, such as HIV and other diseases where viruses other pathogens may hide throughout the body (KHN, 2018). To date, there are no rapid autopsy programs in the U.S. solely dedicated to patients with hematologic malignancies.

Factors Associated with Tissue Donation

Research has shown that postmortem tissue donation may be a positive opportunity not only for investigators, but also for the families of deceased patients. A two-year pilot project in multiple sclerosis showed that, of families that authorized the donation of tissue samples for research, the respondents to a short questionnaire indicated that they were not further distressed by the approach, and the majority were of the opinion that research donation should be offered to all bereaved families (Millar et al., 2008). Other research has shown that there are other forms of obtaining informed consent by either the patient, while still alive, or family members of the deceased. A prospective, comparative cross-sectional study in Spain by Rodriguez-Villar was performed that included telephone interviews during the tissue donation application process. Of the potential donors, 29% (222/770) of interviews were held over the phone. A positive family answer was obtained 27% of the time. Although this result was less than that of in-person interviews, a calculated donor generation efficiency rose 16 percent to 59% when telephone interviews were added to in-person interviews (Rodriguez-Villar et al., 2007). There are several factors that may influence the decision of patients or their families regarding organ or tissue donation. Factors that were significantly associated with organ donation include knowledge, attitudes, and beliefs about donation (Matten et al., 1991). Other research showed that females, younger individuals, and those with higher knowledge levels

were more likely to have attitudes that favored organ donation; within that same study, individuals who described themselves as having stronger religious beliefs and those with poor knowledge had less favorable attitudes toward organ donation (Wakefield et al., 2011). Tandon showed that, in a prospective study, level of literacy, socioeconomic status, and prior knowledge of organ donation were not associated with corneal tissue procurement (Tandon et al., 2004). A systematic review by Irving involving 18 studies and 1,019 participants showed eight major themes regarding organ donation. The decision to be an organ donor was influenced by relational ties, religious beliefs, cultural influences, family influences, body integrity, previous interactions with the healthcare system such as medical mistrust, the individual's knowledge about the organ donation process, and major reservations about the process of donation (Irving et al., 2011).

Despite the research highlighted above, there seems to be a lack of research on factors associated with participation in a registry and tissue bank study in lymphoma populations, specifically in a Midwestern metro area, as well as a lack of research on factors associated with participating in a clinical trial as front-line therapy in lymphoma populations.

Methods

Nebraska Lymphoma Study Group

The Nebraska Lymphoma Study Group (NLSG), established in 1982, has tracked thousands of patients with hematologic malignancies, particularly Hodgkin's Disease (HD), non-Hodgkin's Lymphoma (NHL), and other hematologic disorders for several decades; the investigators and supportive staff have collected extensive data in regards to patients'

diagnoses, pathological tissue samples, demographics, and treatment regimens. The NLSG is a unique collaborative effort between oncologists and pathologists in the community, as well as their colleagues at UNMC. A unique aspect of the NLSG is that the majority of the patients enrolled in the study are previously treated and may be the most likely to benefit from the treatment regimens offered through the study. One example of the collaborative effort between the medical oncologists and the pathologists is that, in several cases, fresh tissue samples are collected from the patients are delivered to the pathologists at UNMC so that they may perform complex, detailed histopathologic, immunologic, and molecular characterization (UNMC, 2018).

Data Delivery, Cleaning, and Manipulation

The NLSG maintains an electronic database that contains clinical, pathologic, and genetic data on lymphoma patients as well as other patients of interest. A request for data was submitted to the lead data coordinator for the NLSG for cases that contained basic demographic information (sex, ethnicity, date of birth, age at diagnosis) as well as clinical and treatment information (diagnosis, subtype, consent status to the NLSG, first line therapy regimen, and whether first line therapy regimen was a clinical trial). Additionally, it should be noted that the database did not capture information on whether a clinical trial was available at the time the patient received front-line therapy. When the request for data was submitted, the electronic database was in the midst of some technical issues. The dataset therefore only captured cases through February 2018 that had data entered for their diagnosis. The dataset was delivered in an Excel spreadsheet.

Extensive data management activities, including data cleaning and data manipulation, were conducted in Excel. Examples of data cleaning and manipulation that were performed include running procedures in SAS to check for missing and duplicate data, as well as data that would not make sense clinically (i.e., date of diagnosis the same as date of birth). Other data manipulations included adding new variables (i.e., whether the diagnosis fell under non-Hodgkin lymphoma, Hodgkin lymphoma, or other, and recoding age at diagnosis to round down ages that included a decimal to the nearest whole number). All data cleaning methods, data manipulations, and responses to data clarification requests were discussed with the lead data coordinator for the NLSG to ensure appropriateness and accuracy before any analyses were conducted.

Study Design

This study used the Nebraska Lymphoma Study Group Registry & Tissue Bank Study clinical database to perform a descriptive analysis on patients enrolled in the study. In addition, this study used case-control study design to measure the association between consent status to the NLSG study and participation in a clinical trial as front-line therapy. Exposed individuals were considered those who consented to the NLSG study, and unexposed individuals were considered those who did not consent to the NLSG study (did not agree to have tissue from lab samples, biopsy procedures, etc. to be stored) but allowed their clinical data to be followed. The outcome of interest was selection of a clinical trial as front-line therapy (yes/no). Cases were identified as those who selected a clinical trial as front line therapy, and controls were identified as those who selected a front-line therapy regimen that was not considered as a part of a clinical trial. There were 5 cases that were missing an NLSG participation status and were

therefore not included in this analysis. Controls were selected from this sample population for a few different reasons. The first of which was the time frame of the student's project. As the capstone project is conducted in one semester, the selection process of several hundred or thousands of control patients would have been too large of a time constraint on the student's project. The second reason was convenience. The control data was already available in the database that was delivered to the student.

Statistical Analysis

Data management and manipulation was conducted in Microsoft Excel software. Chi-square analyses were conducted between select covariates and two outcome variables: participation in the NLSG registry study and participation in a clinical trial as front-line therapy. Fisher's Exact Test was performed when expected cell counts were less than five. The covariates that were tested for association included sex, ethnicity, age at diagnosis, and diagnosis class. An odds ratio calculation with a 95% confidence interval was perform to measure the association between participation in the NLSG registry study and participation in a clinical trial as front-line therapy. To develop the logistic regression model, odds ratio calculations were conducted between different covariates to determine if any interactions or confounding existed. No interactions or examples of confounding were identified. Therefore, only significant crude odds ratios were incorporated into the logistic regression model. Only covariates with a significant association ($p < 0.05$) were included in the final model. The final logistic regression model for predicting selection of a clinical trial as front-line therapy is reported in Table 5. SAS® 9.3 Software was used for Chi-square analyses, odds ratio calculation

with 95% confidence interval, and logistic regression modeling. An alpha level of 0.05 was used for significance.

Results

Descriptive Statistics

There were 2,343 patients identified in the Nebraska Lymphoma Study Group dataset. The median age at diagnosis was 57 years (14 to 101 years) with a mean age at diagnosis of 55.2 years (+/- 17.3 years); 34 patients did not have a documented age at diagnosis. Patients included in the NLSG dataset were diagnosed from December 1973 through February 2018. N=1,271 (54.2%) of patients were male and N=1,072 (45.8%) were female. White, non-Hispanic participants were the majority (N=2,144, 91.5%), followed by Black, non-Hispanic (N=86, 3.7%) and White, Hispanic (N=36, 1.5%); N=40 observations contained a missing ethnicity (1.7%).

There were 102 distinct diagnoses included in the NLSG dataset. Some of the most common diagnoses were: diffuse large B-cell lymphoma, noncleaved (B-DLCL-NC, N=199, 8.5%), composite lymphoma (CL, varying percentages, N=133, 5.8%), diffuse large B-cell lymphoma, not otherwise specified (B-DLCL-NOS, N=120, 5.1%), nodular sclerosing Hodgkin lymphoma, grade 1 (HD-NS-1, N=102, 4.4%), B-cell chronic lymphocytic leukemia (B-CLL, N=97, 4.1%), extranodal marginal zone B-cell lymphoma, MALT type (B-EMZL, N=97, 4.1%), and follicular lymphoma, grade 2 (B-FL-2, N=97, 4.1%). There were N=48 observations that did not have a diagnosis included in the dataset, and the NLSG staff could not clarify these missing data. When encompassing all common subtypes, diffuse large cell lymphoma was the most common type of diagnosis with N=527 cases, followed by follicular lymphoma (N=342), nodular sclerosing

Hodgkin lymphoma (N=216), composite lymphoma (N=133), and non-Hodgkin lymphoma, not otherwise specified (N=108).

Table 1: Demographic Information

Demographic Characteristic	N (%)	Median Age at Diagnosis (Years)	Mean Age at Diagnosis (Years, SD)
Age at Diagnosis	2,309	57	55.2, 17.3
Sex			
Male	1,271 (54.2%)	56	54.5, 16.7
Female	1,072 (45.8%)	59	56.2, 18.1
Ethnicity			
Asian	18 (0.8%)	51	50.7 (12.1)
Black, non-Hispanic	86 (3.7%)	50	49.3 (16.9)
Missing	40 (1.7%)	61	61.9 (13.5)
Other	19 (0.8%)	45	47.2 (17.9)
White, Hispanic	36 (1.5%)	44.5	44.9 (18.7)
White, non-Hispanic	2,144 (91.5%)	58	55.7 (6.5)

Table 2: Diagnosis Subtypes, Listed Alphabetically by Abbreviation (N=2,343)

Diagnosis Subtype	N	%	Diagnosis Subtype	N	%	Diagnosis Subtype	N	%
B-BL	25	1.07	DL-C	9	0.38	MC	20	0.85
B-BLL	26	1.11	DL-ML	3	0.13	MF	2	0.09
B-BMCL	22	0.94	DL-NC	61	2.60	MZL	1	0.04
B-CLL	97	4.14	DL-NOS	30	1.28	NHL-NOS	80	3.41
B-DFL-1	5	0.21	DM-C/NC	4	0.17	NK/T-NL	5	0.21
B-DFL-2	6	0.26	DM-NOS	9	0.38	NK/T-PL	1	0.04
B-DLCL-AP	11	0.47	DSC	8	0.34	NOS	22	0.94
B-DLCL-C	43	1.84	FL-C	1	0.04	NS-LD	11	0.47
B-DLCL-EBV	4	0.17	FL-NC	15	0.64	NS-M1	34	1.45

B-DLCL-INOS	13	0.55	FM	32	1.37	NS-M2	22	0.94
B-DLCL-IP	17	0.73	FSC	22	0.84	Other	4	0.17
B-DLCL-LG	1	0.04	HD-IF	9	0.38	SL	22	0.94
B-DLCL-NC	199	8.49	HD-LD	2	0.09	SL-CLL	1	0.04
B-DLCL-NOS	120	5.12	HD-LP-N	11	0.47	SL-PC	3	0.13
B-DLCL-PB	8	0.34	HD-LR	6	0.26	SNC-B	3	0.13
B-DLCL-THR	8	0.34	HD-MC	39	1.66	SNC-NB	13	0.55
B-DMCL	35	1.49	HD-NOS	25	1.07	SUS	4	0.17
B-EMZL	97	4.14	HD-NS-1	102	4.35	T-CCD4SML	5	0.21
B-FL-1	84	3.59	HD-NS-2	29	1.24	T-EATL	2	0.09
B-FL-2	97	4.14	HD-NS-CP	15	0.64	T-HSGDL	5	0.21
B-FL-3	91	3.88	HD-NS-S	3	0.13	T-MF	3	0.13
B-LPL	16	0.68	IBL-C	4	0.17	T-PGDL	1	0.04
B-NMCL	56	2.39	IBL-E	1	0.04	T-PLL	2	0.09
B-NMZL	31	1.32	IBL-NOS	9	0.38	T-PTCL-AI	15	0.64
B-PLL	1	0.04	IBL-P	10	0.43	T-PTCL-LC	15	0.64
B-SLL	71	3.03	IBL-P/A	4	0.17	T-PTCL-LE	2	0.09
B-SMZL	11	0.47	IBL-PC	23	0.98	T-PTCL-MC	19	0.81
B-UCL	16	0.68	LB-C	7	0.30	T-PTCL-UC	10	0.43
B-UCL-HD	5	0.21	LB-NC	2	0.09	T-SPTL	1	0.04
B-UCL-HG	14	0.60	LD-R	2	0.09	T/N-ALCL	10	0.43
B-UCL-LG	15	0.64	LP-D	1	0.04	T/N-ALCL-ALK	3	0.13
BP-ALL	25	1.07	LP-N	6	0.26	T/N-ALCL-NEG	8	0.34
BP-LBL	4	0.17	MALT	7	0.30	TP-ALL	9	0.38
CL	133	5.67	MB	5	0.21	TP-LBL	12	0.51
						Unknown	48	2.05

The most common front-line therapy regimens were R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; N=457, 19.5%), CNOP (cyclophosphamide, mitoxantrone, vincristine, and prednisone; N=168, 7.2%), ABVD

(doxorubicin, bleomycin, vinblastine, and dacarbazine; N=135, 5.8%), non-anthracycline-containing regimen, not otherwise specified (N=122, 5.2%), and rituximab (N=113, 4.8%). Other options besides chemotherapy were offered to the patients as well. Radiation therapy for NHL patients was selected in N=122 (4.8%), and radiation therapy for HL patients was selected in N=38 (1.6%). Some patients did not require immediate treatment at the time of their diagnosis. "Watch and Wait" was chosen for N=299 (12.8%) of patients.

Tests for Association

Two thousand, one hundred and one patients (N=2,101; 89.7%) provided consent to the NLSG study, N=234 (9.9%) did not provide consent but agreed to have their clinical data be followed, and N=8 (0.3%) had a missing consent status and were therefore not included in the analysis. Sex, ethnicity, age at diagnosis, and diagnosis class were tested for association among participation in the NLSG study using Chi square analysis. Ethnicity (all ethnicities, X^2=14.02, p=0.007) and Ethnicity (White, non-Hispanic and all others, X^2=11.09, p<0.001) were found to be significantly associated with participation in the NLSG study.

Table 3: Tests for Association between Select Covariates and Participation Status in the NLSG Study (N=2,335)

Covariate	Chi-Square Statistic	p-value
Sex	0.16	0.687
Ethnicity[1]	14.02	0.007
Ethnicity[2]	11.09	<0.001
Age at Diagnosis[3]	2.04	0.152
Diagnosis Type[4]	0.23	0.898
Diagnosis Type[5]	0.09	0.758

[1]All ethnicities (5 levels; missing ethnicity was not included in the analysis); [2]White, non-Hispanic compared to all other ethnicities; [3]At or above median age (57 years) compared to below median age; [4]NHL, HL, Other (3 levels); [5]NHL, HL

One hundred twenty five patients (N=125, 5.3%) patients chose a treatment regimen that was coded as a clinical trial for their front-line therapy, and N=1,919 (81.9%) did not. "Watch and Wait" selections were excluded from this analysis. The same covariates as above were tested for association among participation in a clinical trial as front-line therapy using Chi square analysis. Age at diagnosis (X^2=7.37, p=0.006) was significantly associated with the selection of a clinical trial as front-line therapy.

Table 4: Tests for Association between Select Covariates and Selection of Clinical Trial as Front-Line Therapy Status in the NLSG Study (N=2,044)

Covariate	Chi-Square Statistic	p-value
Sex	0.02	0.881
Ethnicity[1]	2.58	0.629
Ethnicity[2]	0.29	0.585
Age at Diagnosis[3]	7.37	0.006
Diagnosis Type[4]	5.75	0.056
Diagnosis Type[5]	5.76	0.016

[1]All ethnicities (5 levels; missing ethnicity was not included in the analysis); [2]White, non-Hispanic compared to all other ethnicities; [3]At or above median age (57 years) compared to below median age; [4]NHL, HL, Other (3 levels); [5]NHL, HL

An odds ratio calculation was conducted between two bivariate categorical variables: participation in the NLSG study and selection of clinical trial as front-line therapy. Exposed individuals were considered those who consented to the NLSG study, and unexposed individuals were considered those who did not consent to the NLSG study (did not agree to have tissue from lab samples, biopsy procedures, etc. to be stored) but allowed their clinical

data to be followed. The outcome of interest was selection of a clinical trial as front-line therapy (yes/no). Cases were identified as those who selected a clinical trial as front line therapy, and controls were identified as those who selected a front-line therapy regimen that was not considered as a part of a clinical trial. There were 5 cases that were missing an NLSG participation status and were therefore not included in this analysis. Controls were selected from this sample population for a few different reasons. The primary reason was the time component of the student's Capstone Experience project. In a classical case-control study design in the context of cancer populations, we would ideally use individuals with cancer diagnoses as "cases" and those without cancer diagnoses as "controls". As the NLSG study does not maintain an active list or subset of controls for its patients, the student would have had to submit a full IRB application to search UNMC medical records for appropriate controls. The student was limited by the semester parameters, and therefore this would not have been achievable. "Watch and Wait" selections were omitted from this analysis. Those who selected a clinical trial as front-line therapy were 3.48 times the odds to have previously agreed to participate in the NLSG study, however this result was not statistically significant (OR=3.48; 0.47, 25.35).

Table 5: Two-by-Two Table for Odds Ratio Calculation between NLSG Study Participation and Selection of Clinical Trial as Front-Line Therapy

	Cases (Clinical Trial as Front-Line Therapy – Yes) (Column %) (Row %)	Controls (Clinical Trial as Front-Line Therapy – No) (Column %) (Row %)	Totals
Exposed (Nebraska Lymphoma Study Group – Yes)	119 (99.1%) (5.6%)	1,982 (97.1%) (94.4%)	2,101
Unexposed (Nebraska Lymphoma Study Group – No)	1 (0.9%) (1.7%)	58 (2.9%) (98.3%)	59
Totals	120	2,040	2,160

Logistic Regression Model

Odds ratio calculations were conducted between different covariates to determine if any interactions or confounding existed. No interactions or examples of confounding were identified. Therefore, only significant crude odds ratios were incorporated into the logistic regression model. Age at diagnosis, categorized into "at or above median age at diagnosis" and "below median age at diagnosis" (OR=0.6; 0.41, 0.87), and diagnosis type categorized into "non-Hodgkin's lymphoma" and "Hodgkin's lymphoma" (OR=0.58; 0.37, 0.91) were independently associated with the outcome of selection of a clinical trial as front-line therapy. The final logistic regression model for predicting selection of a clinical trial as front-line therapy is reported in Table 5.

Table 5: Logistic Regression Model for Predicting Selection of a Clinical Trial as Front-Line Therapy in Patients Enrolled in the Nebraska Lymphoma Study Group Study

ln(odds) = -2.8051 + 0.2121*(Median Age at Diagnosis) + 0.1676*(Diagnosis Type)

Median Age at Diagnosis is coded as: At or Above Median Age at Diagnosis = (-1); Below Median Age at Diagnosis = (1); Diagnosis Type is coded as: non-Hodgkin's lymphoma = (-1); Hodgkin's lymphoma = (1)

Discussion

This study provided comprehensive descriptive statistics on patients enrolled in the NLSG study. Additionally, front-line therapy regimens, as well as whether those regimens were a part of a clinical trial, were examined in detail. An odds ratio was reported between two bivariate categorical variables: participation in the NLSG study, and selection of a clinical trial as front-line therapy. Lastly, a logistic regression model for predicting participation in a clinical trial as front-line therapy was developed. It is interesting to note that White, non-Hispanic patients, when compared to all other ethnicities were more likely to have participated in the NLSG study. One reason that may explain this result is that the state of Nebraska, as well as the sample population for this study, is overwhelmingly White (91.5% in this study). Also, decades of research on different ethnic populations show that persons who are White may have higher levels of education, higher socioeconomic status, and tend to have higher rates of insured persons, all of which may positively influence their decision to seek care at UNMC and participate in studies outside of their regular care. We also found that those who were of younger age, defined as below the median age at diagnosis of 57 years, were more likely to participate in a clinical trial as front-line therapy. One possible explanation of this result is that younger individuals may be more willing to take a chance on an unapproved treatment

regimen, in the hopes that it may have a better chance at curing their cancer or extending their life expectancy. Older populations may opt more for approved treatment regimens to treat their cancer for their front-, second-, or third-line therapies. It is possible that once older populations have exhausted approved their therapy options that they may shift their focus on palliative care rather than participating in a clinical trial with unknown adverse event and response data. One final observation of interest was that those with Hodgkin lymphoma were more likely to participate in a clinical trial as front-line therapy. It is possible that those with HL were more likely to participate in a clinical trial as front-line therapy due to more availability of clinical trials at their time of diagnosis, however we do not have information to assess this possibility. Another possible reason for this difference is that the clinical trials that were available at the time of diagnosis could have been showing promising results and were therefore recommended by the treating physician. The dataset for this study did not include data on the number of clinical trials that were available or the number of FDA-approved therapies for NHL or HL at the time of diagnosis for each patient. It is possible that the number of clinical trials and number of approved therapies fluctuated throughout the recruitment period for the NLSG study, which therefore may affect the likelihood of selection of a clinical trial or approved therapy. We recommend that the landscape of available therapies, both standard of care and experimental, be documented so that this may be adjusted for in future studies.

Conclusions

This study aimed to provide comprehensive descriptive statistics on the participants included in the Nebraska Lymphoma Study Group Registry & Tissue Bank study, to examine

associations between selected demographic and clinical variables and two key outcome variables, and to develop a predictive logistic regression model for selection of a clinical trial as front-line therapy. This study addressed the lack of research performed on factors that are associated with participation in a registry and tissue bank study, as well as selection of a clinical trial as front-line therapy, in a large lymphoma population enrolled at an academic medical center located in Omaha, Nebraska.

We found that participants who were White, non-Hispanic were more likely to have agreed to participate in the NLSG study when compared to all other ethnicities. We also found that participants who were below the median age of 57 years were more likely to select a clinical trial as front-line therapy. Lastly, we found that those who selected a clinical-trial as front-line therapy were 3.48 times the odds of previously agreeing to participate in the NLSG study, however this result was not statistically significant; a logistic regression model using two significant covariates, age at diagnosis and diagnosis type, was developed for predicting selecting a clinical trial as front-line therapy. The dataset used in this study was graciously provided by the NLSG study staff. All data management activities, including clarifications on ambiguous data, re-coding of select variables, and creation of new variables from the existing data were discussed with and confirmed by the lead data coordinator for the NLSG study. Chi-square tests for association between select covariates and two outcome variables, participation in the NLSG study and selection of a clinical trial as front-line therapy, were performed. An odds ratio was calculated for the association between participation in the NLSG study and selection of a clinical trial as front-line therapy; the results showed that those who selected a clinical trial as front-line therapy were at nearly 3.5 times the odds of previously participating in the NLSG

study, however this result was not statistically significant. Lastly, a predictive logistic regression model was developed for selection of a clinical trial as front-line therapy.

One key strength of this study includes the large sample size provided by the NLSG study dataset (N=2,343), which included detailed data on sex, ethnicity, age at diagnosis, diagnosis subtype, and front-line therapy regimen. Another strength of this study is the sample population represented over 100 distinct subtypes of lymphoma. Some subtypes may have more clinical trials available than others, so analyzing a dataset with a wide variety of subtypes may reduce this potential source of bias.

Several limitations exist within this study. First, this study was only conducted with patients enrolled at one academic medical center in Omaha, Nebraska. It is possible that other regions in the U.S. that have a different prevalence distribution of subtypes of lymphoma may see different results for participating in registry studies and selecting a clinical trial as front-line therapy. Previous literature has shown that patients who have had positive experiences with clinical trials in their past are more willing to participate in future studies. This study did not take into account whether the participants in the NLSG study had ever been previously offered to participate in a clinical trial for their cancer, whether that be a non-interventional registry study or an investigative therapeutic clinical trial. Additionally, the NLSG study database did not have data available for whether its participants had ever previously been approached for participation in a study for any other disease or condition other than their cancer. It is therefore theoretically possible that some of the participants in this study may have had previously participated in clinical research, which may skew their attitudes or beliefs positively about participating in this study. This study also did not examine attitudes and behaviors of its

participants towards participating in registry studies as well as clinical trials, which has been previously shown to be significantly associated with participation. Another limitation of this study is that clinical trials were not as ubiquitous in the early 1980s and 1990s as they are in present-day. Some patients enrolled in the NLSG study at the beginning of the recruitment period for the study may not have had any, or very few, clinical trials available to them, whereas patients enrolled within the past year may have had several clinical trials available. With the advent of the Internet, in particular clinicaltrials.gov, patients have much more information available to them regarding the availability of clinical trials across the country, so patients may be more likely to actively seek out care at institutions that offer therapies that are currently involved within a clinical trial as they are able to research the trials in-depth at their discretion. One last limitation that is of note is that the database did not collect information on whether subsequent therapy regimens after the first-line therapy were clinical trials. It is certainly possible that patients had enrolled in the NLSG study, selected an FDA-approved, standard of care treatment first to treat their cancer and then elected to participate in a clinical trial as a second- or third-line regimen. This study did not take this possibility into account, however that may be of interest for future investigations.

Several recommendations are provided for future investigators. It may be beneficial for similar research to be conducted in other cancer populations, as clinical trial participation may vary widely depending on the type of cancer. The sample population in this study was overwhelmingly White (91.5%), so it may be worthwhile to conduct further investigations focusing on non-White populations such as Asian, Black, Hispanic, and Native American populations. This study did not take into account the number of clinical trials that were

available at different time points throughout the period where patients were enrolled into the NLSG study. Repeated studies into populations that have been recruited into registry studies, and subsequently offered clinical trial participation, within the past decade may be beneficial due to the increase in number of clinical trials available nationwide. This study was conducted at only one center in the Midwest U.S. There could be geographic differences in cancer populations across the U.S. that were not accounted for in this study, and perhaps different results would be found in more densely-populated metro areas with larger, more diverse patient populations. Lastly, clinical trials are available for nearly every known disease; therefore, more research is needed into factors associated with clinical trials across the disease spectrum such as cardiovascular disease, diabetes, and respiratory diseases.

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Service Learning/Capstone Experience Reflections

My experience with my placement site, the University of Nebraska Medical Center, was one of the experiences of my educational career. UNMC is committed to furthering the education of not only those in the state of Nebraska, but of those across the U.S. As I have been an employee at UNMC for over four years, I knew a great amount about UNMC prior to starting my education and prior to starting my Service Learning & Capstone Experience (SL/CE) projects. One of the key aspect that I learned more about was the collaboration between investigators at UNMC. In the development of our rapid autopsy program, I collaborated frequently with a basic scientist, Dr. Paul Grandgenett, who oversees the Pancreatic Rapid Autopsy Program (PRAP) at UNMC, to learn about how their program was started, how they currently run their program, and what their goals are for the future. In addition to collaborating with Dr. Grandgenett, I worked weekly with my committee preceptor, Dr. Matt Lunning, to provide updates on how the program development was progressing. He provided great insight to the clinical and pathological aspects of how a rapid autopsy program for patients with hematologic malignancies should be run. Some other individuals that I collaborated with include Emily Gale, who assists with the Nebraska Lymphoma Study Group program, as she was a great resource for the IRB application process and the informed consent form (ICF) development.

One aspect that I was different than what I expected when I started the project was the rate at which new projects at UNMC are developed. I anticipated that we would move much faster than we were able to, but quickly found out that collaboration across many different departments and professionals takes a tremendous amount of effort, and perhaps more importantly, time. I now have a much better understanding as to the amount of work that is

required to start new programs or even improve upon existing programs at UNMC, and therefore also have a much greater appreciation for the programs that currently exist.

Some of the SL/CE activities have been highlighted previously. Throughout the semester, I spent time during the regular business day, as well as evenings, working through a list of activities that Dr. Lunning and I developed together. A few of the key activities that were performed include: submission of an IRB application, including an informed consent form, to UNMC's IRB. This submission alone took nearly 40 hours of work, as a great deal amount of collaboration with other UNMC professionals was required. Other SL/CE activities that were performed include meeting with Dr. Grandgenett on a few different occasions to discuss how the PRAP program was started back in the 1990s, how the program has progressed over the past few decades, how the program currently functions, and what the program's goals are for the future. I shadowed Dr. Grandgenett for a few hours to learn how they order supplies, how they prepare several "autopsy carts" so that they are ready for up to three autopsies at a time, and what the process is like for tissue sample preparation after the autopsy is completed and how the samples are stored for future use by investigators. Another major activity that was performed was an extensive literature review on existing autopsy programs across the U.S. and U.K. to learn about some of they key aspects of their programs. This literature review, along with the knowledge learned from Dr. Grandgenett, set the foundation for our autopsy program. Lastly, some other activities that were performed include the development of a presentation for key stakeholders at UNMC about our proposed program, the development of pre-, during-, and post-autopsy checklists, and the start of the development of a clinical database for linking key clinical data and pathological tissue samples.

As stated above, a presentation for UNMC stakeholders was developed. This presentation is important because high-level administrators at the university need to be informed of the importance of a rapid autopsy program for this patient population as well as the enormous potential impact on future scientific research for investigators at the university. The checklists were developed in a similar manner to those of the PRAP group as theirs were clear and easy to follow. Additionally, the IRB application was developed according to UNMC's IRB guidelines. The clinical database is still under development and a final product has not been achieved. The sustainability plan is still in progress as how to continue to track data.

Some of my greatest contributions to the SL activities were the IRB application, the creation of the autopsy checklists, the ongoing development of the clinical database, and the development of a presentation for UNMC stakeholders. One of my greatest accomplishments, which goes hand-in-hand as a strength, was my ability to manage my time along with several different aspects of this project at the same time. Another consideration is that I consider myself a "part-time" student in the MPH program as I maintain full-time employment at UNMC. Not only was I focusing a great amount of energy and detail to my SL/CE projects, but I was maintaining my focus on my employment as well.

One of the biggest challenges that I faced was the need to collaborate with several different professionals at UNMC. Though it is a great pleasure to work with many great people at UNMC, it was difficult to work around everyone's schedules to schedule meetings. Another challenge was balancing my time between work and the SL/CE activities. I was able to overcome these challenges because I had a great support system at home with my wife and my family members who were able to take care of many different responsibilities outside of work

and school. Another way I was able to overcome some of these challenges was staying late at UNMC's campus several nights per week as well as spending countless hours on the weekend in the UNMC computer lab working on SL/CE activities, in particular my statistical analysis.

My views of public health practice have been greatly impacted by my experience with the SL/CE project. Throughout my MPH education in the College of Public Health, I have had to collaborate with other students on class projects every semester. These collaborations gave me good practice for future collaborations in more of a "real world" setting. One view that has changed since the start of my SL/CE project is realizing the amount of hard work and collaboration that is required for a new program to be successfully developed. A new program could take several months, perhaps even over a year, to be properly developed, even with full-time commitment to the development of the program. One view of public health practice that has stayed the same is knowing that, despite the hard work and countless hours spent towards new or ongoing initiatives, public health professional's efforts are worthwhile as they have the potential to positively impact the lives of the others in their communities, across the country, or even across the world.

The only ethical issues that were required to be addressed were managed through the IRB application for the rapid autopsy program. The IRB provides oversight, including ethical oversight, for all research involving humans or human biological material (HBM) at UNMC. Another ethical issue that was identified in the development of the project was the process of approaching a patient regarding discussing the possibility of participating in the rapid autopsy program. It was appropriately decided that the physicians and nurse program coordinators included on the IRB application would be responsible for approaching eligible patients. This was

decided as the best course of action because they have extensive experience with approaching patients for other clinical trials at UNMC and have navigated difficult situations with patients who are nearing the end of their lives before.

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