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Lung cancer remains a major contributor of cancer-related deaths and account for more than half of lung cancer deaths. In the U.S., lung cancer accounts for almost 25% of all U.S. cancer deaths and certain population groups bear a disproportionate burden. Immunotherapy is a novel treatment for lung cancer that has shown improvements in stalling disease progression and overall survival. But these treatments are associated with a plethora of adverse events that can affect any organ in the body. Most of the evidence on the adverse effects associated with immunotherapy is documented from clinical trials which often exclude the socioeconomically marginalized population. Hence little evidence exists on the incidence and range of adverse events in this population group. This study contributes to the evidence on the frequency and types of immunotherapy side effects experienced by socioeconomically marginalized populations.

ADVERSE EFFECTS OF LUNG CANCER IMMUNOTHERAPY AMONG SOCIOECONOMICALLY MARGINALIZED LUNG CANCER PATIENTS

INTERNSHIP PRACTICUM REPORT

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MASTER OF SCIENCE

IN CLINICAL RESEARCH MANAGEMENT

By

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CHAPTER I: INTRODUCTION

Immunotherapy has become an important treatment strategy for various types of cancers. It harnesses the capacity of the human immune system to recognize and destroy cancer cells and is a promising treatment option, particularly for late stage lung cancer (Laparra *et al*. 2021; Berti A *et al*. 2021; Borghaei H *et al*. 2015; Cheng, Zhang, and Xu 2021; Tabatabai *et al*. 2016). Clinical studies have documented various therapeutic mechanisms of immunotherapy, for example, immune checkpoint inhibitors (ICI) trigger the body's antitumor immune responses thus enhancing the body's resistance to cancer (Tan *et al*. 2020). Other less common strategies include cancer vaccination that activate effector immune cells, and oncolytic virus immunotherapy which uses engineered viruses to directly kill cancer cells (Farkona, Diamandis, and Blasutig 2016). While these immunotherapy strategies are effective, they can cause adverse effects often distinct from other cancer therapies (Kennedy and Salama 2020). For example, checkpoint inhibitors are associated with a spectrum of side effects involving a variety of organs. These effects include pruritus, pyrexia, decreased appetite, nausea, and asthenia (Wills, Brahmer, and Naidoo 2018), and other side effects including dermatologic toxicity, hypophysis, hypothyroidism, and pneumonitis, have been recorded in clinical studies (Kennedy and Salama 2020)

Most of the existing evidence on adverse effects (AE's) of immunotherapy is documented from clinical trials, and little is known about the incidence and range of adverse effects of lung cancer immunotherapy among socioeconomically marginalized populations. Socioeconomically marginalized populations include racial/ethnic minorities, the uninsured/underinsured, and the

homeless. These populations are underrepresented in clinical trials and may have different incidences of adverse events due to higher prevalence of comorbidities and barriers to healthcare.

CHAPTER II: BACKGROUND AND LITERATURE REVIEW

Histologically, lung cancers are divided into non-small cell lung cancer (NSCLC), found in about 85% of patients hence the most common, and small cell lung cancer (SCLC) which makes up about 15% of lung cancer cases. Non-small cell lung cancer has the highest incidence and mortality worldwide, and in 2020, there were about 2,206,771 new cases of NSCLC and 1,796,144 deaths (Global Cancer Observatory, 2020). Known risk factors for NSCLC includes exposure to urban air, cigarette smoking (including passive smoking) and exposure to silica and asbestos (De Mello, 2021)

Globally, lung cancer remains a major contributor of cancer-related deaths and low- and middle-income countries account for more than half of lung cancer deaths (Lubuzo, 2020). In the U.S., lung cancer accounts for almost 25% of all U.S. cancer deaths (Siegel, 2022). Substantial variations exist in trends and rate by age, sex, socioeconomic status, race/ethnicity, and geography (Torre, Siegel, and Jemal 2016). In the U.S., certain population groups bear a disproportionate burden, for example, people with lower socioeconomic status, males, blacks, and those living in the mid-South (Tabatabai *et al*. 2016; Torre, Siegel, and Jemal 2016). Although lung cancer incidence has been on the decline since 1990 (1990 to 2007: annual percent change, -0.9 [95% CI, -1.0%, -0.8%]; 2007 to 2015: -2.6 [-2.9%, -2.2%]), notable variations were observed amongst groups. A higher incidence was noted for females between the ages of 20-39 years during 1995 to 2011. An overall decline in the incidence of lung cancer resulted to lower incidence amongst females (males: -2.5% [-2.8%, -2.2%]; females: -3.1% [-

4.7%, -1.5%). Since 1987, a higher incidence of small cell carcinoma was recorded amongst white population compared to blacks (Zhong YJ *et al*. 2019).

Immunotherapy is a novel treatment for lung cancer and has the potential to improve lung cancer therapeutic outcomes. Immunotherapy utilizes agents that increase immune responses to tumor antigens or inhibit the ability of cancers to evade the body's immunological surveillance (Cappelli, Shah, and Bingham 2017). Compared to cytotoxic agents, immunotherapy can be considered a mild therapy, yet can still present side effects that affect several body systems (predominantly those that involve the kidney, liver, skin and GI tract) (Steinel *et al*. 2020). Adverse events severity and organ specificity vary by immunotherapy agent type, dose and tumor type. Growing recognition of AEs has become more important with the increase in use of immunotherapy. Therefore, a critical need exists for characterization of AEs in underrepresented population groups. Characterizing the adverse effects of lung cancer immunotherapy is important for informing clinical decision-making for immunotherapy use.

Currently, three classes of immunotherapies are approved by the FDA, those that inhibit cytotoxic T-lymphocyte antigen 4 (CTLA-4) - ipilimumab, programmed cell death protein 1 (PD-1) - cemiplimab, nivolumab, pembrolizumab, and the programmed cell death protein ligand 1 (PD-L1) - atezolizumab, avelumab and dirvalumab. These immunotherapy agents have been useful in the treatment of various types of cancers for example, Pembrolizumab, is one of the most widely used immunotherapy in lung cancer treatment, as a single agent and in combination therapy and has shown significant benefits compared to traditional chemotherapy (Borghaei H, 2015), while atezolizumab was also found to prolong overall survival in patients with NSCLC compared to platinum-based chemotherapy (Kinoshita, 2021).

Immune-related AEs result from the activation of the immune system against normal tissues and can trigger autoimmune diseases (Laparra *et al*. 2021). Adverse events require rapid detection and management to avoid progression to severe complications. Various clinical trials have characterized AEs according to agents used. Colitis and pneumonitis were more commonly reported with ipilimumab and nivolumab while pneumonitis and hepatitis were associated with pembrolizumab and endocrinopathies common in all immune checkpoint inhibitors (Ali & Watson, 2017). Overall, cutaneous (rash), endocrine (thyroiditis, hypothyroidism and hyperthyroidism), hepatic (hepatitis), gastrointestinal (diarrhea, colitis), and pulmonary (pneumonitis and interstitial lung disease) effects are common (Berti A *et al*. 2021). A systematic review of adverse events in phase 3 clinical trials for lung cancer checkpoint inhibitors found that 27.1% and 7.7% of study subjects had mild to severe immune related adverse effects, respectively (Berti A *et al*. 2021). Gastrointestinal, skin, and endocrine toxicities were most frequently reported followed by pulmonary and hepatic toxicities. Another study assessing the effects of nivolumab versus docetaxel for advanced non-squamous non-small cell lung cancer found that 10% of subjects treated with nivolumab reported 3-5 treatment-related adverse events while 54% reported same for docetaxel, a 2nd line of immunotherapy treatment for lung cancer (Borghaei H *et al*. 2015).

Little evidence exists on the incidence of adverse events in socioeconomically marginalized populations. Various trials on adverse effects of immunotherapy have underrepresented racial/ethnic minority groups. For example, in the trial to assess the efficacy of pembrolizumab versus docetaxel for advanced non-small-cell lung cancer, about 72% of patients were non-Hispanic white, 21% were Asian, and only 4% were non-Hispanic black (Herbst *et al*. 2016). Another trial on the safety and efficacy of Nivolumab versus Docetaxel, 92% of patients

were non-Hispanic white while only 3% were Asian and 3% were non-Hispanic black (Herbst *et al*. 2016; Borghaei H *et al*. 2015). The pattern is similar for various other trials (Jotte *et al*. 2020).

Information on the adverse events of immunotherapy among socioeconomically marginalized populations is critically important in informing clinical decision making. This population group often carries the disproportionate burden of risk factors for diseases and chronic conditions, for example, trends in obesity have shown socioeconomic disparities at individual and community level (Anekwe *et al*. 2020). High incidence of tobacco use and cardiometabolic diseases are associated with socioeconomic factors such as household income, education, and race (Apovian 2016; Benusic and Cheskin 2021; Cornelius *et al*. 2020). These factors could also contribute to this patient population potentially experiencing substantially higher incidence of adverse effects of immunotherapy compared to results from clinical trials.

The present study contributes to the evidence on the frequency and types of immunotherapy side effects experienced by socioeconomically marginalized populations. The findings may be useful to inform strategies aimed at addressing health equity and improving cancer disparities and outcomes.

Specific Aims

The specific aims of this study include the following:

1. To evaluate the demographic characteristics of patients treated with lung cancer immunotherapy at a safety-net cancer center.
2. To assess adverse events of lung cancer immunotherapy among socioeconomically marginalized patients within two years of immunotherapy initiation.

Significance

Immunotherapy is a novel treatment modality for late-stage lung cancer and little evidence exists on associated adverse effects among socioeconomically marginalized populations. It is unknown if underrepresented population groups experience differences in in incidence and range of adverse events following immunotherapy treatment. Furthermore, few studies have documented adverse effects using real-world data; current evidence relies mostly on clinical trials that target highly selected patient populations. Real-world evidence can provide more generalizable information that applies to patient populations that are underrepresented in trials.

This study utilizes data from routine clinical practice and provides evidence to help understand the adverse effects of lung cancer immunotherapy in socioeconomically marginalized populations. The results provide new knowledge that could help inform interventions to optimize early detection of adverse events and help advance health equity for lung cancer outcomes.

Materials And Methods

Study design and data source

- The study was a retrospective observational study using institutional cancer registry and electronic health record (EHR) data from JPS Health Network. The JPS Oncology and Infusion Center is a Comprehensive Community Cancer Program facility accredited by the American College of Surgeons Commission on Cancer. The cancer registry has been maintained since 2008 and includes information on cancer patient's demographics, diagnosis, treatment, and follow-up information, etc. The registry maintains at least 90% follow-up for vital status through 5 years after cancer diagnosis for Commission on Cancer accreditation. The EHR at JPS Health Network is held in the Epic system, which captures information on all inpatient and outpatient encounters, medications, procedures, imaging and laboratory tests, and provider notes, etc. for all patients that interact with the JPS healthcare system. Provider notes were the main source for patient-reported AEs used in this study.

Eligibility criteria

- Eligible individuals included adults diagnosed with first primary lung cancer from 2016 to 2019 who received the immunotherapy of interest. We included only two immunotherapy agents; a PD-1 inhibitor and a PD-L1 inhibitor because these are the first line immunotherapy treatments for patients with late-stage lung cancer. We excluded patients that did not receive any of their first course treatment at JPS.

Variables of interest and data collection

- Patient's demographic information including age, gender, race/ethnicity, cancer stage, immunotherapy agent, insurance status, marital status, body mass index (BMI), tobacco use, alcohol use, preferred language and vital status were retrieved from the institutional oncology registry. Other variables of interest such as patient's reported symptoms, first date of symptom onset, specific infections after immunotherapy initiation (i.e., pneumonia, hepatitis and anemia etc) were abstracted from JPS EHR through chart review. Information was also obtained on whether immunotherapy treatment was interrupted due to AE and whether patient completed the immunotherapy treatment. Death was not considered an adverse event in this study hence was not included as immunotherapy interruption in the results.
- Prior to data collection, a chart review manual was developed to guide data collection. The manual details the process of abstracting data and the location of each information category in EPIC system to ensure consistency and that the correct information was being obtained for each subject. An Excel template for data collection containing a list of the most common adverse events associated with the immunotherapy agents of interest was created. Other adverse events as documented in the provider notes were added to the list as they were being abstracted.
- Adverse effects was defined as any sign, symptom or disease condition that are associated with the use of immunotherapy (Martins *et al*. 2019). Initial list of adverse effects from literature was used to create a database for abstraction, new conditions following immunotherapy initiation were abstracted.

Sampling and sample size

- Convenience sampling was used to select patients who met the inclusion criteria. A total of 46 patients were retrieved from the registry. Seven patients were excluded because they did not receive the 2 immunotherapy agents of interest, another three patients were excluded because they received their treatment outside of JPS facility. A total of 36 patients who met the eligibility criteria were included in the chart review. The medical record number (MRN) of these patients were used to identify them in EPIC and review their medical charts.

Statistical analyses

- Data was analyzed using Stata 16 (StataCorp, College Station, TX). Descriptive statistics was used to describe sociodemographic characteristics (e.g., race/ethnicity, age, gender, and insurance status) of patients who received immunotherapy for lung cancer treatment. Descriptive statistics were also used to summarize the frequency of adverse events including proportions, medians, and subgroup differences by race, gender, and insurance status.
- This study was approved by the North Texas Regional Institutional Review Board (IRB# 2017-103).

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Results And Discussion

Patient characteristics

Respondents were mostly middle-aged (median age = 58 years), with almost an equal proportion of male (47.22%) and female (52.78%). Forty two percent were non-Hispanic white, 39% were non-Hispanic black, 8% were of Hispanic ethnic group, and 11% were of" other" race/ethnicity. About 94.12% of patients were diagnosed with stage 4 lung cancer. Fifty percent were uninsured, 22.22% had Medicare, 3% had Medicaid, and 25% had other insurance. Almost half (47.22%) were never married, 30% were married, and 22% were separated, divorced, or widowed. Fourteen percent of patients were obese and 22% were overweight. More than a third (36%) reported current or past alcohol and 83% reported current or past tobacco use. The language of preference for most of the patients (90%) was English, followed by Spanish (6%), and Vietnamese (3%) (Table 1).

Immunotherapy agent used and proportion of patients who experienced adverse events

The two immunotherapy agents included in this study were a PD-1 inhibitor and a PD-L1 inhibitor. In this study, 83.33% of the patients received PD-1 inhibitor and 16% received PD-L1 inhibitor. All patients experienced at least one type of adverse event following immunotherapy initiation. Overall, the median number of adverse events was 6.5 AEs. Median number of adverse events was 6 and 11 for patients receiving PD-1 and PD-L1, respectively. By race/ethnicity, non-Hispanic white had the highest number of AE with a median of 8 AE's, followed by "other" race/ethnic group (7.5), black (6), and Hispanic ethnic group (4) (Table 2).

In one-third of patients (33.33%), their immunotherapy treatment was interrupted at some point due to the severity of their adverse event. By the end of the 2-year follow-up period, about 36% had died, while a third (33.33%) had completed their immunotherapy treatment. A quarter (25%) did not complete treatment.

The overall median time to onset of first adverse event was 18 days but varied by the type of immunotherapy agent used. The median time to first onset of an AE was 16 days for patients receiving PD-1 and 29.5 days for patients receiving PD-L1 (Table 2).

Types of adverse event by immunotherapy agent

Overall, various types of AEs were experienced by patients. Anemia was the most commonly reported AE (83.33%), followed by fatigue (72%), acute kidney injury (AKI) (50%) and arthralgia (50%), and nausea (36%). A quarter of patients experienced myalgia and constipation. Other AEs were reported in <25% of patients including diarrhea (19.44%), rash, (19.44%), hypothyroidism (16.67%), dizziness (13.89%), vomiting (11.11%), pneumonitis (11.11%), and arthritis (0%) (Figure 1).

The frequency of most common adverse events differed by type of immunotherapy agent used. Among patients receiving PD-1, the top 3 most common AE were anemia (83.33%), fatigue (66.66%), and AKI (50.00%). Among patients receiving PD-L1, the top 3 most common AE were fatigue (100%), anemia (83.33%), and arthralgia (66.66%) (Figure 1).

Most common adverse events by gender, race/ethnicity, and insurance status

By gender, a higher proportion of female patients (58.49%) had AEs and by race/ethnicity, a greater proportion of non-Hispanic white (32.50%) and non-Hispanic black (41.50%) patients

experienced adverse events compared to Hispanic (6.60%) or "other" race/ethnicity (11.32%). By insurance status, a greater proportion of uninsured patients (61.32%) had AEs followed by those on other type of insurance (25.47%), Medicare (19.81%) and Medicaid (2.83%) (Table 3).

Time to onset of first AE by gender, race/ethnicity, and insurance status

The median time to onset of first AE was highest (21 days) for patients of "other" race/ethnicity and lowest (15 days) for white non-Hispanic patients. By insurance status, patients with Medicaid or Medicare had the greatest length of time to onset of first AE (21 days for both). Uninsured patients and those with a hospital-based insurance plan (i.e., JPS Connection) had the lowest length of time to onset of first AE (10.5 days). Females also had a longer length of days to onset of AEs (21 days) compared to men (15 days) (Table 4).

Immunotherapy interruption and completion by gender, race/ethnicity, and insurance status

A higher proportion of females (42.10%%) compared to males (23.52%) completed their immunotherapy while a higher proportion of males (47.6%) compared to females (21.05%) had immunotherapy interruption due to AE (Table 5).

By race/ethnicity, an equal proportion of non-Hispanic black and white patients (33.33% for both) completed their immunotherapy treatment. Completion was 66.66% among Hispanics and 0% among non-Hispanic other. For immunotherapy treatment interruption, about 33.33% were whites, 28.57% black, and 75.00% from "other" race. No Hispanic patient has immunotherapy interruption (Table 5).

Based on insurance status, about a third (33%) of those uninsured and 44.44% with other insurance completed immunotherapy, while no one on Medicaid and a quarter on Medicare completed immunotherapy. More people on Medicare (50%) had their immunotherapy interrupted due to AE compared to those on Medicaid (0%). About a third of those uninsured and with other insurance (33.33% for both) had immunotherapy interruption.

DISCUSSION

This study investigated adverse events following immunotherapy among socioeconomically marginalized lung cancer patients. It was observed that a high proportion of patients experienced AEs within 2 years of immunotherapy initiation. In addition, the most common types of adverse events observed were not similar to those from clinical trials that underrepresented socioeconomically marginalized populations (Herbst, 2016, Jotte, 2020). Furthermore, only 33% of patients in this study completed their immunotherapy treatment and 33% experienced interruptions in their immunotherapy treatment.

Collective Evidence

Adverse events are common with the use of immunotherapy and vary widely in severity, by type of therapy and by characteristics of individual patients (Martins *et al*. 2019). Current evidence on incidence of AEs originates mostly from clinical trials, systematic reviews, and meta-analysis. This study is one of the few accounts that is based on real-world evidence. We found that all patients treated with PD-1 and PD-L1 immunotherapy agents experienced at least one type of adverse event, with a median AE of 6. Although more patients were treated with the PD-1 inhibitor, patients who received the PD-L1 inhibitor had a greater number of AEs per

person and had more time before the onset of symptoms. Overall, the most common AEs were anemia, fatigue, arthralgia, and acute kidney infection (AKI). Similar pattern was observed across the two immunotherapy agents used. This finding contrasts with what was reported by Coschi *et al*, where the most common immunotherapy related AEs (IrAEs) were pruritis, rash, diarrhea, colitis, hypo- or hyper-thyroidism, and pneumonitis (Coschi and Juergens 2021), although this finding was for all ICIs they studied. Another study using pooled data for ICIs from clinical trials reported that rashes were the most common AE occurring in about 35% of study subjects while colitis and pneumonitis are less common, with incidence ranging from 1% to 5% in patients treated with anti-PD-1 (Cappelli, Shah, and Bingham 2017). A trial on metastatic non-squamous NSCLC using atezolizumab reported that treatment related AEs occurred in 94% of one patients group (atezolizumab plus carboplatin plus paclitaxel) and in 95.4% in the other patient group (atezolizumab, bevacizumab plus carboplatin plus paclitaxel) (Socinski, 2018). Berti *et al*, also found that in patients with stage III and IV NSCLC in phase 3 trial, the most frequent organ-specific irAEs (any grade) were diarrhea (15.1%), skin rash (11.7%), hypothyroidism (9.0%), elevated liver enzymes (6.2%), and pneumonitis (5.3%), while the most represented severe irAEs were pneumonitis and elevated liver enzymes (both 1.7%), Any grade and severe irAEs for ICIs in lung cancer were 27.1% and 7.7%, respectively (Berti A, 2021).

Most patients in this study were uninsured or had Medicare or Medicaid. Furthermore, a majority were diagnosed with advanced-stage lung cancer, which may be related to SES factors. Low SES is associated with advanced stage of cancer at diagnosis, which has substantial implications for treatment decisions and patient outcomes. People of a lower SES generally have worse outcomes, have lower cancer survival, due to the lower likelihood of receiving both

traditional and next-generation treatments, and the higher likelihood of being admitted as emergency (Redondo-Sánchez, 2022). Early-stage lung cancer confers the best chance for survival with surgical resection of a localized tumor, in contrast to later stages with poorer prognosis due to possible metastases. Studies on cancer outcomes in people of low SES as indicated by occupation, education and income acknowledge that low SES is a risk factor for higher rates of co-morbidities which exacerbates the occurrence of immunotherapy AEs, hence low SES is an independent prognostic factor for poor survival in lung cancer patients (Redondo-Sánchez, D., *et al*. 2022, Ou *et al*. 2008).

We observed unfavorable lifestyle behaviors among lung cancer patients in this study that may contribute to higher frequency of adverse events of immunotherapy. Thirty six percent were overweight or obese, 83% were current or former tobacco users, and 36% were current or former alcohol users. Obesity, smoking, and alcohol use are modifiable risk factors for many chronic conditions and certain types of cancers. Unhealthy lifestyle behaviors such as alcohol and tobacco use during cancer treatment have an impact on patients' cancer treatment outcomes (Clark *et al*., 2007, Peppone *et al*., 2011). Studies have shown that continued tobacco use adversely impacts on the liver metabolism of many cytotoxic agents thus increasing the rates of complications (Jassem, 2019). Nicotine may impair the efficacy of chemotherapy in patients with head and neck cancers, and there was an observed lower rate of complete response to radiation therapy (Jassem, 2019). Overall, cancer patients who smoke reported lower quality of life (decreased functional, emotional, and physical domains) scores than non-smokers, worse treatment related AEs such as fatigue, pain, depression, and an overall higher mean burden of side effects. (Peppone *et al* 2011). Higher incidence of severe side effects can result to dosage

reductions and treatment interruption which compromises treatment efficacy and result in lower survival rates (Peppone, *et al*., 2017).

There are variations in the time course for developing AEs, while some can occur as early as after the first dose of immunotherapy, others could manifest after several months of treatment. Skin manifestations tend to present early in therapy, usually during the first few weeks of treatment, diarrhea and colitis tend to occur between weeks 5 and 10, liver toxicity from week 7 to 14, hypophysitis after 6 weeks while pneumonitis usually presents around week 12 (Khunger, 2017) endocrinopathies and pneumonitis tend to occur later (Berti A *et al*. 2021). In this study, the median onset of AEs was 18 days from the start of treatment, and it varied widely by the immunotherapy agent used, for the PD-1 inhibitor, it was 16 days and for the PD-L1 it was about 30 days post onset of treatment. Other studies have shown that AEs can be as early as one week after treatment is started and can last for up to a year after completion of treatment and that median onset of AEs can range from 2-16 weeks from the start of treatment (Coschi and Juergens 2021). Martins *et al.* reported a median time of approximately 14.5 days for ICI combination therapies and up to 40 days for monotherapies (Martins *et al*. 2019). Across race/ethnicity, gender and insurance status, the highest number of days to onset of AEs were seen for other non-Hispanics (21 days) and the least was for non-Hispanic whites (15 days) compared to other racial categories, females had more days to onset of AE (21days) similar to those on Medicare (21 days) and Medicaid (21 days) respectively (Table 5).

We found that in more than a third of the patients, their immunotherapy regimen was interrupted due to occurrence of AEs. These AE's included side effects of the study

immunotherapy agents excluding deaths. Treatment interruption due to AEs presents some risk including the possibility of compromised efficacy of treatment and disease progression. Although more serious AEs can be fatal, low-grade AEs can often be managed and resolved. Reck *et al*. in their study of atezolizumab versus current treatment found that AEs leading to treatment discontinuation occurred in 46 (8%) patients who received atezolizumab (Reck, 2018), and in another study, discontinuation was due to the occurrence of any grade and severe irAEs in 13.8% and 9.2%, respectively (Berti A, 2021). Most frequently, interruption of immunotherapy may lead to switching to another class of immunotherapy, switching to a single agent (in the case of combined therapy) or restarting the same regimen with a prophylactic immunosuppressive therapy (Coschi, 2021). In these cases, there is still a chance of developing new or recurrent AEs which could be mild or deadly (Santini, 2018). A study on the safety of a continuation with an immune checkpoint inhibitor (ICI) after an immune-related AE found that about 28.8% of patients experienced recurrence of the initial AEs associated with the discontinuation of the initial therapy.

Limitations

Appropriate interpretation of the findings from this study requires consideration of potential biases and limitations. Collection of AE-related data for this study was abstracted from EHR in the absence of standardized data collection on patient-reported symptoms. Therefore, AEs may be underestimated in this study, particularly for rarer AEs. Differential documentation of symptoms by patient gender, race/ethnicity, or insurance status is also possible, which may underestimate symptoms among certain subgroups. This study collected AE within 2 years of immunotherapy initiation; we did not have information on duration of symptoms or long-term AE that may be important for quality-of-life outcomes. Lastly, high mortality among our patient

population was a competing risk to AE following immunotherapy initiation, which limits observation of AE**.**

Implications

This study provides evidence on the frequency and types of the AEs associated with the use of a PD-1 inhibitor and a PD-L1 inhibitor in the treatment of late-stage lung cancer in socioeconomically marginalized lung cancer patients. Capturing information from routine clinical practice is important to guide policy makers and physicians in understanding the performance of medical interventions under usual healthcare practice and can provide information that may not be collected in controlled clinical trials. It could also enable the development of strategies for appropriate management of immunotherapy related AEs in similar population of patients.

Future studies on adverse effects of immunotherapy should include a range of immunotherapy agents and other cancer types to enable a detailed characterization of adverse events across cancer types and immunotherapy agents, and to confirm and further develop these preliminary findings. This will require a larger sample of patients to make meaningful inferences and draw more clinically relevant conclusions.

List of tables and figures

Table 1: Patient characteristics

Variable	N (%)
Age at diagnosis	
Median (IQR)	58 (64.5-53)
Sex (Female)	19 (52.78)
Race/Ethnicity	
Non-Hispanic WHITE	15 (41.67)
Non-Hispanic BLACK	14 (38.89)
HISPANIC	3 (8.33)
Non-Hispanic OTHER	4 (11.11)
Cancer stage at diagnosis	
3	2 (5.88)
4	32 (94.12)
Insurance status	
Uninsured	18 (50.00)
Medicaid	1 (2.78)
Medicare	8 (22.22)
Other insurance	9 (25.00)
Marital status	
1 = Single (never married)	17 (47.22)
2 = Married	11 (30.56)
3 = separated/Divorced/Widowed	8 (22.22)
BMI categories	
Underweight (BMI<18.5)	3 (8.57)
Normal (18.5<=BMI<25)	19 (54.29)
Overweight (25<=BMI<30)	8 (22.86)
Class 1 obese (30<=BMI<35)	3 (8.57)
Class 2 obese (35<=BMI<40)	2 (5. 71)
Mean (SD)	25.25 (5.25)
Tobacco Use	
0 = Never user	6 (16.67)
1 = Current user	21 (58.33)
2 = Former user	9 (25.00)
Alcohol use	
0 = No history of alcohol drinking	23 (63.89)
1 = Current alcohol drinker	11 (30.56)
2 = Past history of drinking	2 (5.56)
Preferred Language	
English	32 (88.89)
Spanish	2 (5.56)
Others	2 (5.56)
Vital Status	
Alive	12 (33.33)
Dead	24 (66.67)

Table 2: **Type of immunotherapy agent used and proportion of patients who experienced adverse events**

Variable	**N (%)**
Type of immunotherapy agent used	
PD-1 Inhibitor	30 (83.33)
PD-L1 Inhibitor	6 (16.66)
Patients experienced adverse events	
Yes	36 (100.00)
No	0 (0.00)
Number of adverse events	
Median (IQR)	6.5 (10-4.5)
Number of adverse events by immunotherapy agent (Median (IQR)	
PD-1 Inhibitor	6 (9-4)
PD-L1 Inhibitor	11 (14-8)
Number of adverse events by population group (Median-IQR)	
Non-Hispanic WHITE	8 (11-6)
Non-Hispanic BLACK	6 (8-4)
HISPANIC	4 (9-2)
Non-Hispanic OTHER	7.5 (10.5-5)
Immunotherapy interruption due to adverse event	
Yes	12 (33.33)
No	24 (66.66)
Completed Immunotherapy	
Yes	12 (33.33)
Died	13 (36.11)
Refusal	2 (5.55)
Other	9 (25.00)
Time to first onset of AE (days) Median IQR	
Overall	18 (25.5-6.5)
PD-1 Inhibitor	16 (21-6)
PD-L1 Inhibitor	29.5 (36-15)

Figure 1: Type of adverse event by immunotherapy agent

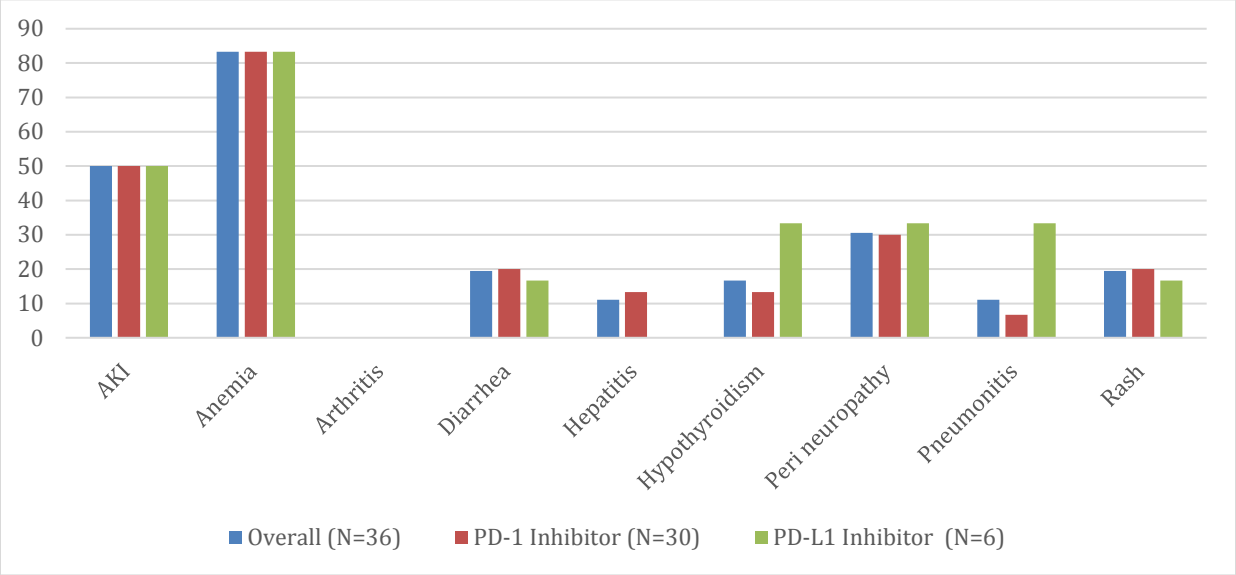

Table 3: Most common adverse events by gender, race/ethnicity, and insurance status

Variable	Anemia N=30	Fatigue N=26	AKI N=18	Arthralgia N=18	Nausea N=13	Peripheral neuropathy N=11	Total N=106
Type of adverse event by gender							
Female	14 (73.68)	15 (78.95)	11 (57.89)	7 (36.84)	8 (42.11)	7 (36.84)	62 (58.49)
Male	16 (94.12)	11 (64.71)	7 (41.18)	11 (64.71)	5 (29.41)	4 (23.53)	54 (50.94
Type of adverse event by race/ethnicity	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Non-Hispanic WHITE	13 (86.67)	12 (80.00)	7 (46.67)	10 (66.67)	5 (33.33)	5 (33.33)	52 (32.5)
Non-Hispanic BLACK	10 (71.43)	11 (78.57)	9 (64.29)	6 (42.86)	5 (35.71)	4 (36.36)	44 (41.50)
HISPANIC	3 (100.00)	0 (0.00)	2 (66.67)	0 (0.00)	1 (33.33)	1 (9.09)	7 (6.60)
Non-Hispanic OTHER	4 (100.00)	3 (75.00)	0 (0.00)	2 (50.00)	2 (50.00)	1 (9.09)	12 (11.32)
Type of adverse event by insurance status							
Uninsured	16 (88.89)	13 (72.22)	12 (66.67)	11 (61.11)	8 (44.44)	5 (27.78)	65 (61.32)
Medicaid	1 (100.00)	1 (100.00)	0 (0.00)	0 (0.00)	1 (100.00)	0 (0.00)	3 (2.83)
Medicare	5 (62.50)	5 (62.50)	3 (37.50)	2 (25.00)	2 (25.00)	4 (50.00)	21 (19.81)
Other Insurance	8 (88.89)	7 (77.78)	3 (33.33)	5 (55.56)	2 (22.22)	2 (22.22)	27 (25.47)

Table 4: Time to onset of first AE by gender, race/ethnicity, and insurance status and duration of Immunotherapy

Variable	**Time to onset of adverse event (days)** Median (IQR)
Gender	
Male	15 (6-21)
Female	21 (9-30)
Race/ethnicity	
Non-Hispanic White	15 (6-26)
Non-Hispanic Black	16 (5-25)
Hispanic	19 (10-145)
Non-Hispanic Other	21 (15-27)
Insurance status	
Uninsured	10.5 (3-21)
Medicaid	21 (21-21)
Medicare	21 (10-31)
Other Insurance	17 (10-33)

Table 5: Immunotherapy interruption and completion by gender, race/ethnicity, and insurance status

	Completed immunotherapy? N=12	**Interrupted due to AE? N=12**
Gender		
Female	8 (42.10)	4 (21.05)
Male	4 (23.52)	8 (47.06)
Race/Ethnicity		
Non-Hispanic White	5 (33.33)	5 (33.33)
Non-Hispanic Black	5 (33.33)	4 (28.57)
Hispanic	2 (66.66)	0 (0.00)
Non-Hispanic Other	0 (0.00)	3 (75.00)
Insurance status		
Uninsured	6 (33.33)	6 (33.33)
Medicaid	0 (0.00)	0 (0.00)
Medicare	2 (25.00)	4 (50.00)
Other Insurance	4 (44.44)	2 (33.33)

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CHAPTER III: INTERNSHIP EXPERIENCE

Internship Site

The internship site is the Office of Clinical Research (OCR), at the JPS Health Network facility located at Fort Worth. JPS Health Network provides Tarrant County, one of the largest counties in Texas, access to quality medical care, and is the only Level I Trauma Center in Tarrant County. The hospital has an Emergency Department, Trauma Services Department, Urgent Care Center and is home to the county's only Psychiatric Emergency Center. The Office of Clinical Research (OCR) was established in 2017 to provide support and build centralized infrastructure for clinical research endeavors at JPS. The OCR is made up of three (3) teams handling clinical trial operations, biostatistics, and research integrity. The Clinical Trials Operations oversee industry sponsored clinical trials, research integrity provides risk management and regulatory support and biostatics provide quality and effective statistical support for all research projects.

The site conducts novel drug, medical device and biologic clinical trials spanning pulmonary, oncology, cardiovascular, infectious diseases, wound care, Podiatry therapeutic areas etc Within the OCR, there are different clinical research staff including a pool of coordinators, data analysts, and regulatory personnelles. These staff fall under clinical operations, data analytics and research and integrity respectively.

Since its inception, OCR has formed networks with various departments and leadership within JPS, encouraged resident research, integrated with different physician groups, partnered with UNTHSC for research approvals, developed community research partnerships, and conducted successful Research Symposiums one of which is the just concluded Research and Quality Symposium held in June, 2022.

Journal Summary

My internship started on the 3rd of January 2022 at the Office of Clinical Research, JPS Fort Worth. My internship was carried out under the supervision of my on-site mentor Andrew Adorboe who is the Manager, Research Integrity. I started out with shadowing the different personnel involved in clinical research at the OCR to understand their roles in research. I had the opportunity to interact with the research coordinators, regulatory personnel, program coordinator, and clinical trial manager. I spent the first few weeks sitting with the coordinators and observing the various aspects of their work. I observed subject screening and recruitment, process of informed consent, sample collection, processing and storage, source documentation, data entry in EDC systems, resolution of queries and documentation of adverse events. I was involved to work directly on a study that assesses the efficacy of a product for toenail fungus. I obtained informed consent from subjects, provided information on how the study product works and how they are to use it, documented each patient's research visit in the appropriate software, scheduled subject's appointments, and assessed for any appearance of adverse reaction to the product at each subject visit. The study requires enrollment for 24 weeks, biweekly submission of pictures and 5 visits overall per patient through the study period.

I also worked with the team from academic affairs on their project on cancer health disparities, from this broad project, I carved out my research focus which is to examine the adverse events experienced by lung cancer patients who received immunotherapy from JPS hospital. The project involved the review of eligible patients' medical charts for two years from the initiation of immunotherapy treatment. The purpose was to abstract information on the adverse events they experience while on treatment with the immunotherapy of interest and to analyze this data to see

if there are trends within groups and if this group of patients experience the same adverse events as those documented in clinical trials given that they are socio-economically marginalized group who are often underrepresented in clinical trials.

During this internship period, I got the opportunity to learn from excellent people in clinical research, my on-site supervisor who has a wealth of knowledge and experience in all aspects of clinical research and the coordinators who were always available to answer my questions and impact knowledge. Beyond what is taught in classroom it is important to get a hands-on experience on how clinical research is operationalized and this internship period availed me of that opportunity. During this internship, I got to learn and use different EDC systems for documenting clinical trial records and resolution of queries, obtaining research records from patients and filling out the source document. I got the opportunity to directly interact with patients and obtain informed consent and conduct and complete the research processes.

APPENDIX A: DAILY JOURNAL

Daily Journal for CRM internship at JPS Forth Worth
By Ogo Nwaogbe
Site Mentor: Andrew Adorboe
Duration: 1/3/2022 – 06/31/2022

1/3/2022

I started the internship on the 3rd of January 2022 at the Office of Clinical Research, JPS Fort Worth. I arrived at the facility at 8am and was met by my on-site mentor, Andrew Adorboe, who is also the Manager, Research Integrity at the office of Clinical Research. He took me to the office and briefly introduced me to the staff present. Later, he took me on a quick tour of the JPS facility pointing out the pertinent sections I needed to be aware of. Back at the office, more staff introduction was done. I proceeded to have an orientation with the Clinical Experience Cordinator who gave me a run down about working at JPS and the necessary resources that I would need. She provided me with my name badge with access to the facility and informed that an official email address will be set up and a read-only access to EPIC software the Electronic medical Record in use at the facility would be provided.

I continued the day with Andrew who explained the organogram of the OCR to me, and it includes a director, three (3) managers overseeing the different subunits namely, clinical operations, data analytics and research integrity respectively. He further introduced me to the clinical regulatory Specialist, responsible for regulatory aspects with central IRB. She briefly talked to me about her roles and responsibilities within OCR. Not all staff were present at the facility today because of the current rotated work schedule at the office due to Covid-19. Andrew discussed with the staff present mostly the CRCs on how best I can shadow them to gain knowledge on the different aspects of their work. The various staff showed readiness to work with

me. The CRCs provided me with a book; the "CRC's guide" to help me get a grasp of the day-to-day CRC role and an abridged study protocol they're currently working on.

I had various brief meetings with Andrew on how we'll go about the internship period, and to have me involved in one or 2 cancer related clinical trials from where I could carve out my thesis. He suggested to use the first month to shadow the different clinical research roles to have a good understanding of things and then get more involved with doing tasks.

1/4/2022

I had a phone meeting with Andrew about the activity for the day. He assigned me to work with a CRC. He also informed me that he had initiated to have a meeting with one of the PIs for a cancer disparity study that I was interested in and was waiting to hear back. He further assigned to do some fact finding on biospecimen research & Moncrief Cancer Institute. The OCR has some ongoing cancer biospecimen studies. These studies are used to obtain information about a patient's tumor markers and is helpful to predict the treatment that is most likely to be effective given the unique characteristics of the cancer. Also found out that the Moncrief Cancer Institute which has some collaborations with OCR is a non-profit Centre with expertise in various cancer services. It is also part of UT Southwestern

Later in the day I worked with a CRC. I observed as patient data was being entered on the source document as part of a study on acute gastritis. She explained to me how the source document is used and its importance in the data collection continuum. The CRC used information collected from the clinic and the patients EMR to populate the source document which will later be transferred to ECRF. Also observed as data for an oncology patient was being entered in the EDC (iMednet). Before the close of work, I registered with IRBNet via the link provided by Andrew.

1/5/2022

I worked with the coordinators on processing blood samples. The blood was collected from a patient with acute gastritis. I learnt how blood samples were centrifuged and how plasma was pipetted into vials and stored according to protocol. They explained the different materials eg tubes, pipettes etc used in sample collection and how they're being used. I later observed a subject's research visit at the clinic, the patient was part of a study on head trauma. He was on his 60-day visit which corresponds to the 2nd visit per the study protocol. Assessment was done at the urgent care clinic; his vitals were taken, and blood drawn for lab. He was assessed for physical function and balance. Later, I observed as the blood samples were processed in the lab within the specified time and refrigerated.

I attended the weekly office meeting which is the first since I started. I was introduced to the group by Andrew. He explained the purpose of the internship and the need for other staff to work with me during the internship period. After the meeting, I proceeded to the Behavioral Health Center which is part of the OCR. I worked with a coordinator and observed as potential study subjects were identified from the medical record. The studies are on childhood trauma and youth depression, two different but related study. The identified patients were invited via telephone to participate in the study. Three patients were recruited for the study.

1/6/2022

My on-site supervisor and I had a meeting in the morning with the PI for one of the cancer research projects at OCR titled "Health outcomes & disparities among underserved cancer patients" that I am interested in. Andrew had reached out to her and requested for a meeting to discuss the possibility of involving me in her study and to work on a part of the project for my

thesis. She indicated interest during the meeting to have me in the study and shed some light on some of their ongoing cancer projects. Most of the mentioned projects have IRB approval which is more suitable given the limited time to pursue a completely new IRB approval. She mentioned she'd send some of these projects to me so I can see which one is a good fit for my need. She requested to see the proposal and thesis guideline from UNT which I sent to her, and I'll be joining her team in their upcoming meeting around next week Friday.

Later on, I observed data entry by a coordinator. The data was from an oncology patient and was entered into the EDC (iMEDNet). Patient is on cycle 3 of the treatment drug (14 days per cycle). Patients' vitals, AE, and dose information were entered into the EDC. Some of the information were obtained from the EMR. Patients daily log from last cycle was obtained and filed in the patient folder.

1/7/2022

I received some articles to review from Rachel Meadows on immunotherapy treatments for lung cancer which is the potential project that I'll be part of. She mentioned that they will initiate the process of getting me added to the IRB. I did some research on lung cancer immunotherapy and reviewed some of the papers I received from Rachel. Then after lunch, went on to observe the collection of lab samples from a patient from the Admissions Holding Unit. Observed as sample was processed and stored away.

One of the CRC's walked me through the CTMS-Realtime which is being used at the OCR. She showed me how to find patient information and navigate through projects. Later in the day I had a meeting with Andrew, he provided me with elaborate details on the scope of what the CTMS could do and why it's a superior tool when compared to others that are somewhat limited in scope.

He talked about HIPAA compliance, safety and user friendliness of the systems and buttressed with examples. We discussed about various other topics including the different career pathways in clinical research. He gave me a book by Carl Newport on Deep work (rules for focused success in a distracted world) which I believe will be very valuable to me. Work ended around 5 pm.

1/10/2022

Observed data entry into the CTMS. Data from various studies collected earlier were entered. I later proceeded to join the collection of samples from a patient. Sample was taken to the lab and allowed to sit for some hours per protocol. The samples were later processed. The study lab manual was used as a guide to process and store the sample. It contains step by step instruction on how to process sample including the required autoclave settings, labelling of vials, quantity of serum to pipette and instructions on storage. I proceeded back to the office and read a study protocol.

1/11/2022

Had a meeting with the PI for Health outcomes disparity research. The meeting was to discuss what aspect of their study that I can work on to develop my thesis. She gave me an overview of what type of data will be required and where the data will be obtained. We agreed on the aims of the study. The study will focus on the adverse effects of immunotherapy on lung cancer patients that are being treated at the JPS facility. We deliberated on the scope of study and agreed on a title. Other issues discussed included the eligibility and the benefit of data from patient records "(real world), versus those from controlled trials. I observed data entry into the EDC.

11/12/2022

Observed the coordinators document and report an adverse event (SAE). Later on, I set up and organized patient binders for an ongoing study. Observed a coordinator work through the CTMS

11/13/2022

I worked on reviewing documents for my practicum project. Several documents were retrieved and reviewed including –

- Kennedy LB, Salama AKS. A review of cancer immunotherapy toxicity. CA Cancer J Clin. 2020;70(2):86-104.
- Cheng Y, Zhang T, Xu Q. Therapeutic advances in non-small cell lung cancer: Focus on clinical development of targeted therapy and immunotherapy. MedComm (2020). 2021;2(4):692-729.

11/14/2022

One of the coordinators briefed me about a new study. I was assigned to contact patients to obtain their addresses so a shipment of their payment cards for study will be shipped to them. I reviewd some documents listed below

- Torre LA, Siegel RL, Jemal A. Lung Cancer Statistics. Adv Exp Med Biol. 2016;893:1-19.
- Tabatabai MA, Kengwoung-Keumo JJ, Oates GR, Guemmegne JT, Akinlawon A, Ekadi G, *et alet al*. Racial and Gender Disparities in Incidence of Lung and Bronchus Cancer in the United States: A Longitudinal Analysis. PLoS One. 2016;11(9):e0162949.

- Cappelli LC, Shah AA, Bingham CO, 3rd. Immune-Related Adverse Effects of Cancer Immunotherapy- Implications for Rheumatology. Rheum Dis Clin North Am. 2017;43(1):65-78. S

1/17/2022

Spent most of the day with a coordinator at the wound care clinic for patient follow-ups. Patients received skin graft in the clinic and the study was assessing the spray-on skin product called RECELL. The spray-on is used to make a piece of skin stretch much more than it normally would thus helping the plastic surgeon to harvest much less skin for performing skin graft. Three patients with varying degrees of skin graft were seen. It was a blinded randomized study where one part of the wound is the control. Various documentations and pictures of the wound was taken. Later, I performed phone call to study subjects that were enrolled in a study. The call was regarding a change in payment card to update their mailing address.

1/19/2022

Worked with a coordinator on resolving queries raised by a sponsor. The queries were mostly about a few data mismatch, request to update information and processing lab sample out of the given time range. Some of these are regarded as protocol deviations and documented. I access to EPIC system, the Electronic Health Record for the hospital. This will enable me to view patient information when needed but not to make changes. A coordinator briefly worked me through EPIC and its features, including how to assess patient chart, vitals, treatment received etc. also how and where to assess provider note. Also observed how patient information is obtained from EPIC.

1/20/2022

Worked with a CRC at the healing hands clinic observing patient recruitment for a study on the medical record based and non-medical record-based community pharmacy. I observed as patients were consented for the study. An explanation was made by the coordinator to the patients of what the study was about, including the risks and benefits and conditions that qualified them to be included. They were asked if it sounded like something they would want to be a part of and then given the option to consent or decline. If willing to participate, they sign the consent form. Patients were also given a copy of the form and told the study is voluntary so they could change their mind anytime if they no longer wish to be in the study. I observed data entry into the EDC.

1/21/2022

I helped prepare and arrange study binders, later on, I had my 1st committee meeting with my major professor, on-site mentor and advisor. Presented my internship proposal and received feedback. Later, I observed data entry into REALTIME, a site operations management system used to document and track clinical research activities from start to finish. Had a phone meeting with Andrew. We talked at length about various concepts in clinical research eg. cold calls, phone visits, study recruitment calls, interview study and ALCOA. He explained these various concepts and how they are used in a study, elucidating with examples where these can or cannot be used. For the last part, ALCOA which means attributable, legible, contemporaneous, original and accurate, denotes the stipulated elements of quality that source document should follow to be acceptable per FDA recommendation. He noted that a C was added to main acronym and it stands for Complete meaning that source documents should be up to standard throughout every study.

1/24/2022

Had a meeting with the lead coordinator on an upcoming cosmetic study that I'll be involved in. The study is on the effectiveness, safety, and tolerability of a topical gel for improving appearance of toenails affected by Fungus. This treatment used in the study is not regulated by FDA but requires IRB approval. My role will be to organize study documents, consent patients. I set up the documents for the patients. 15 patients will be recruited. Recruitment will start next week Tuesday. I made calls to the rest of the patients for the Asthma study to obtain information. I contacted 23 patients before the close of work.

1/25/2022

I worked with a coordinator at the Oncology & infusion center. The study is a phase II study to evaluate the efficacy of drug A with drug B in the treatment of patients with metastatic HER2 breast cancer. Observed collection of patients vitals, lab assessment. Patients daily log from the last visit was collected. Treatment with the medication was withheld for this visit because patient had adverse effect (reduced neutrophil count beyond a set point). Patient will be seen on next visit to determine the best course of action based on the lab results at that point. Observed data entry in Realtime.

1/26/2022

I navigated through Epic to continue to get familiar with the features. I looked through some patients charts and the different features in Epic. Later had a zoom meeting with the IRB regulatory specialist, she handles mostly the investigator-initiated studies, chart reviews, survey studies etc. She walked me through the different regulatory documents used for different research for example retrospective chart reviews, registry type studies etc. She explained when a study is

exempt, expedited or requiring full board review. She talked about other forms including chart review protocol synopsis, and waiver of HIPAA authorization.

1/27/2022

I spent some time on the Epic system. Later observed as documents are uploaded on Real-Time and data entry on EDC. We had a meeting with the coordinators and Clinical Trial Manager on some office related issues. Then proceeded to observe a patient follow up visit as part of the study on brain injury. Patient filled out the self-administered questionnaire and some answered the researcher -administered aspect. Blood sample was collected from patient and vitals taken. Sample was processed at the lab and stored.

1/28/20

I joined a meeting via zoom held by the regulatory unit of OCR for Psychiatry house officers. The meeting was on responsible conduct of research, pointing out the bad research practices in the past and their consequences and the need to conduct research in human subjects according to guidelines. I observed data entry in Medidata I shadowed the office administrator in the morning. She explained her roles and responsibilities to me which is mainly to coalesce information from the various clinical studies conducted by the OCR into a format that is easy to read (such as graphs, one pagers etc) and provide a complete but a snapshot view of the project. She organizes one pager documents to be used for grant pitch and for other presentations. I read protocol for the study on assessing the effectiveness of a topical gel for toenail fungus which should be starting next week. I worked with a coordinator at the lab, crosschecking boxes of blood sample vials to ensure that they're stacked in the right order and corresponds with source document to get

them ready to be shipped to sponsor. Had a review meeting with Andrew where we discussed about when data collection is considered research and when it's not, various aspect of research including data ruled by HIPAA and data not ruled by HIPAA.

1/31/2022

I worked on developing an Excel sheet template. This template will be used to abstract information on lung cancer patients who received immunotherapy from the Electronic Health Record (EPIC). Observed a coordinator place orders in EPIC for patients. These orders are procedures, tests and labs that will be performed on Asthma patients as part of the CHRONICLE study. Contacted additional patients to obtain their addresses as part of the study.

2/1/2022

Observed data entry into the EDC (ESOCDAT) for the Remap-CAP study. I read a study protocol and consent document. Set up patient study binder for the CARPO study

2/2/2022

I contacted some study subjects on the phone as part of the CHRONICLE study. I assisted a coordinator to look up patient's lab results from their electronic Health Record and documented the information on paper. We later had a monthly meeting in the office and various topics were discussed. Work resumes back Monday 2/7/2022 due to snowstorm on 3rd and 4th.

2/7/2022

I worked with a coordinator and observed data entry. I reviewed an article from Andrew on the use of non-physicians as principal investigators. The article tends to make the case that involving non-physicians as principal investigators in research is a more cost-effective approach than using physicians and should be encouraged especially for those trials with tight funding. These non-physicians are qualified to be PI's because they have the right education, training, and experience. Furthermore, regulatory guidelines do not specifically require PIs to be physicians but recommend that physicians should be part of the research team when the PI is not a physician. Even though there's no empirical basis for the cost-effectiveness claim in the article about using non-physicians as PI, the assertion is based on the notion that physicians rarely have time to provide the necessary oversight needed to lead research teams and effectively run a clinical trial due to their busy practice. This will be an advantage for a non-physician PI, say someone with a health-related PhD and the right experience. This is an important topic and one that should be backed up with evidence of cost-effectiveness of using non-physician PI's and improvement in overall success of clinical trials.

2/8/2022

We started the study on the effectiveness and safety of a topical gel for toenail fungus. I arrived in the morning at the Podiatry clinic where the subjects will be recruited. The study will last for 12-24 weeks. Patients with toenail fungus will be recruited and given the study medication for daily application on their toenail(s) with the actual fungal infection, this will be identified by the PI. They will be assessed biweekly through a review of the picture of the toenail to see any changes in appearance of the fungus and if any appearance of side effects. They will make a total of 5 visits after which they exit the study. I worked with a coordinator on the project, we talked to

patients about the study and administered informed consent, took pictures and updated study visits in Realtime software. I also helped with patients in other studies assessing the effectiveness of different kinds of skin grafts. These studies are going on at the clinic and mainly involve patients with diabetic wounds getting various kinds of skin grafts.

2/9/2022

I set up binders for study subjects as part of the CARPO study. I read the protocol for the RheSolve study since I'll be assisting the coordinator on the study tomorrow.

2/10/2022

Worked with a coordinator on the RheSolve Study, an evaluation of product X for the treatment of the symptoms of chronic bronchitis in patients with COPD. This is a randomized double-blind study involving the treatment and sham group. I observed informed consent process and observed collection of patients vitals. Patient had EKG and MRI. Patients in the treatment group will undergo a bronchial procedure in both lungs during the course of the study. A cough counting device was set up for the patient to take home and use for the next 24 hours.

2/14/2022

I set up patient binder for the CARPO study. I observed data entry for the RheSolve study.

2/15/2022

I worked at the Podiatry clinic at Ben Hogan on the toenail fungus study. We recruited three subjects today for the study. These subjects had their toenail fungus treated with the study product at the clinic and are required to continue daily treatment at home for the 12-week duration of the study. Bi-weekly follow up visits were scheduled for the patients. A total of 5 visits will be done by each patient before the end of study. I entered the data on RealTime software and set up payment cards for the subjects.

2/16/2022

I observed data entry into the EDC for the oncology study (INSIGHT). I assisted a coordinator to review patients for the oncology study in Realtime and enter some data for some of the patients.

2/18/2022

I observed data entry on the EDC for the CARPO study then spent some time learning the many features of Real-Time software.

2/21/2022

I called subjects enrolled in the toenail fungus study to remind them of their follow-up visit tomorrow. I had my weekly meeting with Andrew, and he touched on different important topics. He gave me feedback from one of the coordinators I worked with and highlighted some areas that need improvement. We talked about other issues in research including the pros and cons of having a physician PI and non-physician PI, roles of the PI and where the Co-Pi comes in, and usefulness of publishing in impact factor journals. He explained how the cancer IRB works with institutions

and PIs interested in clinical trials. Finally, he also completed the resubmission of an IRB document requirement on my behalf and requested for the review to be expedited.

2/22/2022

I worked at Ben-Hogan clinic on the toenail fungus study. We conducted follow up assessments for 4 subjects recruited two weeks ago and enrolled 3 new subjects. I entered the visit data in Real-Time software, set up their payment cards and next study visit. I reviewed subject logs and checked them for any AE/SAE. I uploaded consent doc in RealTime**.** I created schedule for follow-up of subject's appointments and reminders to take and email pictures. I read the Stark Law and Anti-kickback law.

Stark law also known as physician self-referral law prevents the physician from referring patients to entities that they have financial ties with, for certain services payable by Medicare and Medicaid, unless the applicable exception applies. Failure to adhere to the law attracts penalties including fines and exclusion from Federal healthcare programs.

Anti-Kickback statute is a criminal law that prohibits the willful remuneration (in form of cash, expensive hotel stays etc) for patient referrals to services paid for by federal healthcare programs. Both payers and recipients of kickback are liable under this law based on their intent. Penalties include fines, jail terms and exclusion from participation in Federal healthcare programs.

2/25/2022

I read the form 1572 -statement of investigator form. It is an agreement signed by the investigator before the start of a trial to provide certain information to the sponsor. specifically, it provides the sponsor with information about the investigator's qualifications and the clinical site that will

enable the sponsor to establish and document that the investigator is qualified, and the site is an appropriate location at which to conduct the clinical investigation. It is also used to inform the investigator of their obligation and obtain their commitment to follow through with the trial. I observed documentation of AE in REALTIME and data entry on MEDIDATA. I received some of the dataset for my project from the PI and reviewed the variables.

2/28/2022

I called patients to remind them of their follow-up visits tomorrow at BenHogan podiatry clinic for the toenail fungus study. I observed data entry in REDCAP and worked in the lab with a coordinator to store samples. I joined the 90-minute virtual IDP meeting with other CPRIT researchers and with mentors from UNT.

3/1/2022

I worked with a coordinator at Ben Hogan podiatry clinic for the toenail fungus study. We recruited new patients and had subject follow-ups. Patient recruitment was completed today, and follow-ups will continue till week 24. For the new patients we obtained consent and applied the trial product on their toenails with fungal infection and took pictures. For the follow-up subjects we assess for side effects and took pictures. I joined the North Texas regional IRB meeting, they discussed the protocols under review, the PI of one study was present to answer the questions they had for him. Afterwards they asked for the boards opinion on the issues they raised and decided on the status of the protocols under review.

3/2/2022

I entered data on REALTIME and set up subjects' appointments.

3/3/2022

I worked with a coordinator for the HIV study. We recruited a patient and obtained informed consent for the patient. I observed documentation of an SAE on the source document for the RECELL study, the SAE was also entered in the EDC (iMedidata) and in RealTime software.

3/4/2022

I joined the bi-weekly meeting of the Research Integrity team and later had a one-on-one with my supervisor, Andrew. We talked about the IRB and the need to form a quorum, what happens when a quorum is not formed and situations that require an alternate to fill in., he explained the limits of the IRB and some of the conditions that will trigger IRB audit of a site. We discussed protocol deviations and he explained implications for the various types of protocol deviations. He talked about non-compliance which could fall under serious or continuous non-compliance and when it can trigger for-cause audit.

3/7/2022

I called patients who are on their week 2 schedule for the toenail fungus study to remind them of their follow-up appointment tomorrow. I also made reminder calls to those needing to send in their pictures for the same study.

3/8/2022

I worked at the podiatry clinic on patient's follow-ups. Five (5) patients were seen today. We assessed their logs to confirm they are using the study products as stipulated and if they had any adverse reaction. We provided additional product to those likely to run out before their next visit and took pictures of the study toenail. I uploaded their logs and updated other visit information in Real-Time.

3/9/2020

I reviewed an SAE form and observed how the form is being entered in different EDC. I observed the completion of a case report form (CRF) for an Oncology study and worked with a coordinator at the oncology and infusion clinic to consent a patient.

3/10/2020

I had a meeting with the PI of the cancer immunotherapy study, and we discussed the template for chart review. They talked about creating a protocol for chart review to ensure accuracy and consistency in data collection, they loaned me a laptop with the software for data analysis (STATA).

3/11/2022

I read through the chart review protocol and reviewed some charts in Epic. Later on, I joined a coordinator for a training on a protocol, TRIDENT for a brain cancer study. The training covered screening, randomization, and treatment procedures. Procedure for tissue collection and AE reporting.

3/14/2022

I had a meeting with the Clinical Trial Manager, and she walked me through her roles and responsibilities. She talked about contracting with sponsors and PI's, regulatory requirements, and site qualification procedure. She talked through the budgeting process, budget line items and how the final study budget is agreed on with the sponsor. I asked if the budget accounts for inflations and she said it doesn't but that she'll check with other sites to see if they do that. I also asked if the sponsor pays for screen fails as I didn't see it reflected in the budget and she said yes and that its same amount as consenting patients. She explained how she works through RealTime to do quality control (QC) and we scheduled another meeting for next week Monday.

3/15/2022

I worked at the Ben-Hogan podiatry clinic for the toenail fungus study. We saw 4 patients for their follow up visits. I took pictures of their toenails and uploaded in Real-Time, updated their study visits, and formatted all of week 1 and 2 pictures and sent to the sponsor.

3/17/2022

I called 5 subjects to remind them about sending their week 4 pictures, then I received the corrected dataset for lung cancer patients from the CoPI. Some of the discrepancies that I noticed from the earlier dataset was corrected and they clarified some of the questions I had with respect to patients that discontinued taking immunotherapy and swapped to some other medications without completing the immunotherapy dose.

3/18/2022

I reviewed some patient charts and discovered some discrepancies with some information on file. I pointed this out to the study Co-PI, and they agreed to verify the info. Some other things that I found was that some patients were switched from one immunotherapy to another if they had side effects, I inquired if I was to continue reviewing their info if they were switched to another agent outside of the ones, we were interested in.

3/21/2022

I reviewed 2 patient charts. Both patients were diagnosed with lung cancer in 2018. One was deceased in 2010 and the second patient is still alive and so far, has had 35 cycles of immunotherapy treatment. This was an interesting finding for me because this patient no longer has any viable disease in the lungs despite being stage 4 at diagnosis.

3/22/2022

Worked at Ben Hogan podiatry clinic on the toenail fungus study. Four (4) patients showed up for their week 6 visit. I took pictures of their study toenail, uploaded them, and uploaded subjects' daily logs to Real-Time. I assessed the subjects for the occurrence of adverse events and updated the visits in RealTime. I had a brief meeting at UNT with other cancer researchers and the grant coordinators.

3/23/2022

I worked at the pulmonary clinic with a coordinator for the RheSolve study. I observed a coordinator consent a patient for the study. This was a somewhat complicated study and the consent process was in stages and required some procedures.

3/24/2022

I reviewed patient charts in EPIC and started writing up the method for chart review in my thesis

3/25/2022

I reviewed patient's chart in EPIC, these cancer patients have quite a number of visits and each patient is followed up for 2 years, so it takes quite a while to complete for one patient to ensure that all necessary data is abstracted.

3/28/2022

I reviewed patients' medical charts in Epic. I called subjects due for week 6 study visit tomorrow to remind them about it. Also called the subjects with outstanding week 4 pictures to email it. I observed a coordinator build source document on Real-Time CTMS.

3/29/2022

I worked at the Podiatry clinic on the toenail fungus study. Four (4) patients were scheduled to visit today. I observed their study toenail, took pictures, and updated study visits in Realtime

3/30/2022

Reviewed Patients' charts in EPIC.

3/31/2022

Reviewed patients' charts in EPIC

4/1/2022

Reviewed patients' chart in EPIC

4/4/2022

I called study subjects who have appointments tomorrow to remind them of their visits. I also called those subjects needing to just send in photos of their toenail tomorrow.

4/5/2022

I worked at Ben-Hogan podiatry clinic for the toenail fungus study. I saw five (5) subjects for follow-up. None has had any adverse reaction. some have had some changes to the appearance of their toenail while some have no noticeable changes. A subject inquired about how long it'll take to observe changes and I told them they'll have to be patient till the end of the study to see as it might be different from everyone. Also reminded them there's no guarantee that the product will work for everyone.

4/6/2022

I worked with a coordinator and observed patient consent for the CHRONICLE study. This study is a longitudinal study on the treatment patterns and health outcomes of individuals with severe uncontrolled asthma. I observed data entry

4/7/2022

I reviewed patients' chart in EPIC

4/8/2022

I reviewed charts in EPIC. I had weekly update meeting with Andrew. He talked about documents in clinical trials that can or cannot be modified and the reason for such, for example, investigator brochures, CRF etc are not modified. Source document is modifiable and values on the source doc and EDC must match but there could be additional comments when more is needed about a value or result. Source document also must be written excellently and must be ALCOA compliant. This means that the records in the documents must be traceable to a person or system that collected or generated it, it must be legible and clear, it must be contemporaneous meaning that there should be a record the activity and the time it takes place. The records must be original rather than copies or transcriptions, should be accurate and error free and represent the reality of what happened and finally all records must be complete. At the end of the meeting, I was assigned to read up on note to file and regulatory documents.

4/11/2022

I reviewed several EDCs with a coordinator**;** IBM clinical development, ESOCDAT, RedCap, and iMedidata, we looked at the different features, how queries are resolved in each and

how each of them is being used for data entry. I called patients for their follow-up appointments tomorrow.

4/12/2022

I worked at BenHogan podiatry clinic and saw 3 subjects for their follow-up visits. I updated study visit information in the software and documented pictures and logs appropriately.

4/13/2022

I reviewed patients' chart in EPIC

4/14/2022

I reviewed patients' chart in EPIC

4/15/2022

I reviewed Patient charts and I later had weekly update meeting with Andrew. We discussed essential trial documents eg protocol, consent form, regulatory docs/binder, pharmacy manual etc. He stated that the documents in a regulatory binder and this is a collection of all documents including all IRB docs, FDA documents, monitor logs, investigator brochure, CRF, 1572 etc. The 1572 is a form that must be filled by an investigator running a clinical trial. it is an agreement to follow the FDA code of regulation in running the trial and verifies that he/she has the training and experience to run the trial. He also talked about the patient binder, which contain the scheme of events for patient eg patient's schedule of visits and procedures; the source document which is a mirror image of the CRF that the CRC creates; the patient's physicals and other things such as ECG readings, CT, MRI all signed and dated by the PI/Sub-I. He added that the CRF does not need to be approved by the IRB.

4/18/2022

Reviewed patient charts in EPIC

4/19/2022

Worked at BenHogan podiatry clinic for the Toenail Fungus study. I conducted study update visit for subjects.

4/20/2022

I reviewed patient charts in EPIC. I had a brief meeting with a coordinator on how to proceed with the data entry for the COVID-19 study. She walked me through the different sections of the data abstraction sheet in Redcap software.

4/21/2022

I reviewed patient charts in EPIC and completed the chart review. Sent data to the Sub-I for review. Read the SOP for the COVID-19 registry and validation study.

4/22/2022

Off

4/25/2022

I read up on note to file/note to study file and how it is used in clinical research. It is essentially a written documentation to identify any discrepancy or problem in the conduct of the clinical research study, to note the root cause of the identified problem, to identify the corrective action taken to prevent recurrence of the problem, and document that the corrective action has resolved the problem.

4/26/2022

I called patients to remind them about sending in the pictures of their toenail for the toenail fungus study today. I updated study log.

4/27/2022

I read the SOP for the Covid-19 registry study. I met with the last coordinator who worked on the project to observe how the Covid patient data is abstracted from EPIC.

4/28/2022

I organized and recoded data from chart review on the excel sheet to get them ready for analyses. I worked on data entry for the COVID-19 registry study

4/29/2022

I did some analysis of patient's demographic characteristics for my data. I had our weekly meeting with Andrew, and he talked in detail about various topics. He talked about Note to study file as an important document that shows in detail why some things happened (maybe a discrepancy or error) and what was done to rectify it. It shows the sponsor that things are accounted for. It is not the same as protocol deviation (PD) in that PD can be submitted to IRB but Note to study file is not submitted alone to the IRB, but PD can be supported by Note to study file. Other concepts discussed were progress notes which is a collection of little notes that are made on the chart of what happens during a study visit. Queries: most often flagged by the monitors and must be resolved while the study is still in progress, cannot be resolved after the end of the study. Data Clarification Log (DCL); a list of all identified issues needing clarification and mostly used by monitors. Financial conflict of Interest (COI): a documentation signed by the PI and study personnel indicating that they do not have any financial COI with the sponsor or their affiliates. May be updated once or periodically.

5/2/2022

I worked on analyzing data for the Lung cancer immunotherapy project.

5/3/2022

I worked at BenHogan Podiatry clinic for the toenail fungus study. Conducted follow-up of subjects for their week 12 visits. Four subjects were seen today. I took pictures of the subjects' toenail and updated study visits in Real-Time.

5/4/2022

I worked on analyzing data for the Lung cancer immunotherapy project.

5/5/2022

I read up on Medical Coverage Analysis (MCA), which is a review done by those running clinical trials to determine if a research study is eligible to receive Medicare coverage or not and outlines what items and services performed as part of the research study should be billed to Medicare. When the analysis is done, the investigator receives a study-specific billing summary that lists all items and services to be provided as part of the clinical trial with notations of what should be billed to the research sponsor and what can be billed to Medicare. This kind of analysis is usually outsourced to a third-party agent with the requisite expertise in the conduct of the analysis. Improper billing could result to fines and heavy settlements as stipulated in the False Claims Act.

5/6/2022

I worked on entering data for the Covid-19 registry study. Later on, I looked up patient information from Epic and populated the required files in Redcap EDC system.

5/9/2022

I called study subjects who have their scheduled visit tomorrow to remind them of their appointment. I also called those needing to send in their pictures this week to email them.

5/10/2022

I worked at BenHogan podiatry clinic to see subjects scheduled for appointments today. I took pictures and updated their study visits in Realtime. We had a team meeting for the RI group.

5/11/2022

I did some data entry for the Covid-19 registry study

5/12/2022

I did some data entry for the Covid-19 registry study

5/13/2022

I entered data for the Covid-19 study, I worked half day due to an office event.

5/16/2022

I made calls to study subjects to remind them of their visit and to send in pictures as required.

5/17/2022

I worked at BenHogan podiatry clinic to see subjects scheduled for appointment today. Took pictures and updated their study visits in Realtime software.

5/18/2022

I had some subjects who missed their follow up appointments re-scheduled for today at BenHogan and had to work there for some hours to attend to those subjects. Then I came back to the office and reviewed some literature for my thesis.

5/19/2022

I finalized my analysis and finished making the tables. I started writing part of the result section for thesis.

5/20/2022

I completed writing the result section. I had a meeting with Rachel and her team to discuss the result section and see if there are additional analyses that could be done. We agreed that due to the small sample, there's a limit to the level of analysis that could be done, so I'll go ahead and continue with writing the discussion section of the thesis based on what I currently have.

5/23/2022

I spent some time writing up my practicum report, later in the day, I made reminder calls to patients whose appointments are scheduled to hold tomorrow at Ben-Hogan clinic.

5/24/2022

I worked at Ben-Hogan podiatry clinic to see research subjects on appointment. I collected the required information from subjects and updated in RealTime software.

5/25/2022

I worked on writing my practicum report. Worked half day due to a medical appointment.

5/26/2022

I called study subjects whose pictures were due and reminded them to send them in then I updated the picture drive. I entered data in Redcap software for the COVID-19 registry study.

5/27/2022

I entered data in Redcap software for the COVID-19 registry study.

5/30/2022

Memorial Day

5/31/2022

I spent some time to review some literature and then I worked on my report.

6/1/2022

I worked on finalizing my practicum report

6/2/2022

I made reminder calls to study subjects and reviewed some literature.

6/3/2022

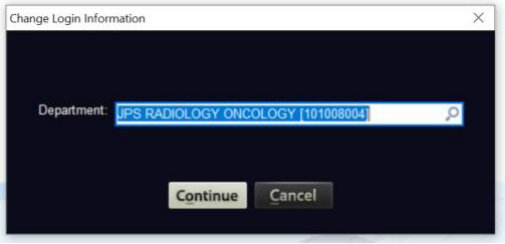
Attended the JPS Health Research & quality symposium 2022, a virtual conference organized by the OCR. It brought together numerous researchers and stakeholders in the field to share findings of their various work. It was a day event.

APPENDIX B: CHART REVIEW TEMPLATE

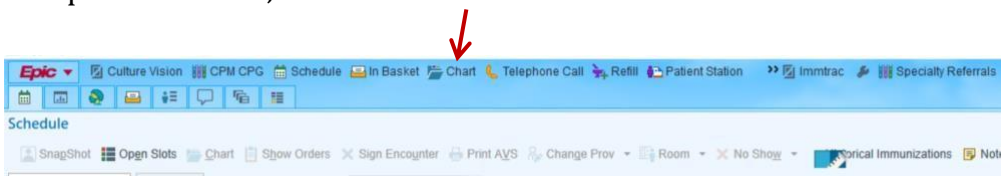
MRNT	Patient_Name	PAT_ID	Interpreter	AKI	Grade_AKI	Date_AKI	Anemia	Grade_Anemia
Date_Anemia	Arthritis	Grade_Arthritis	Date_Arthritis	Diarrhea	Grade_Diarrhea	Date_Diarrhea	Hepatitis	
Date_Hepatitis	Hypothyroidism	Grade_Hypothyroidism	Date_Hypothyroidism	Peripheral_Neuropathy	Grade_Peripheral_Neuropathy			
Date_Peripheral Neuropathy	Pneumonitis	Grade_Pneumonitis	Date_Pneumonitis	Rash	Grade_Rash			
Date_Rash	Tot_AE1	Last_Encounter_Date	Vital Status	Date_of_Death	Others 1	Date_Others1		
Others 2	Date_others 2	Others 3	Date_others 3	Date_First_Immun	Date_Last_Immun	Date_First_AE		
Days_to_onset	Immun_interruption_by_AE	Immun_Completion	Others 4	Date_Others 4	Others5			

Chart Review Protocol – Immunotherapy Adverse Events in Lung Cancer Patients

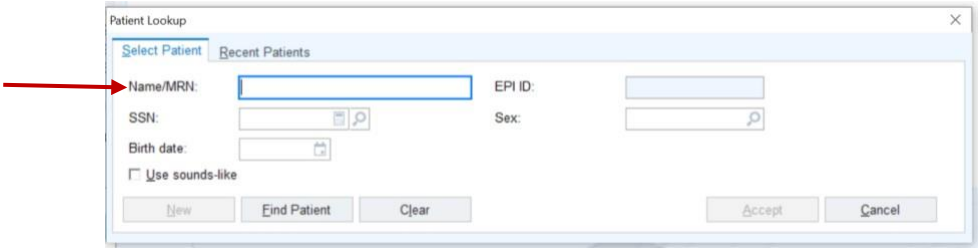
1. Log-on to Epic using your credentials and password
2. When prompted to choose a department, use "**JPS Radiology Oncology**"



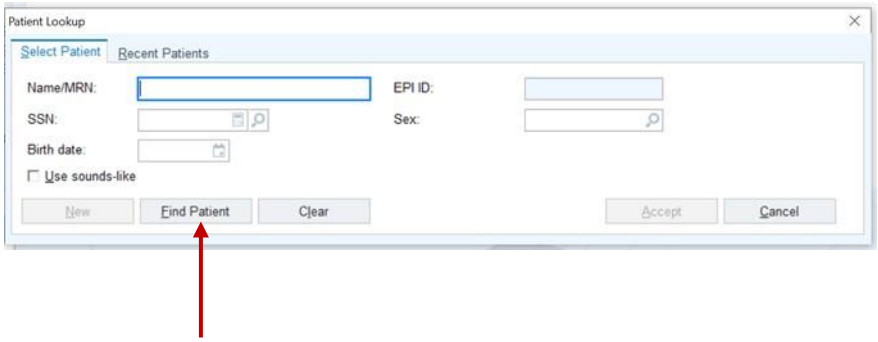
3. At the top of the screen, click on "**Chart**"



4. Copy the MRN number from the Excel document, and paste into the "**Name/MRN**" box.

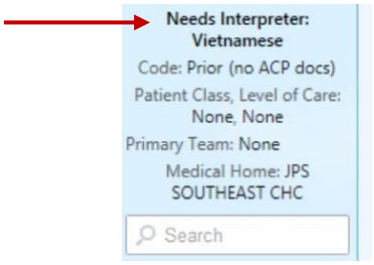


5. Click on "**Find Patient**"

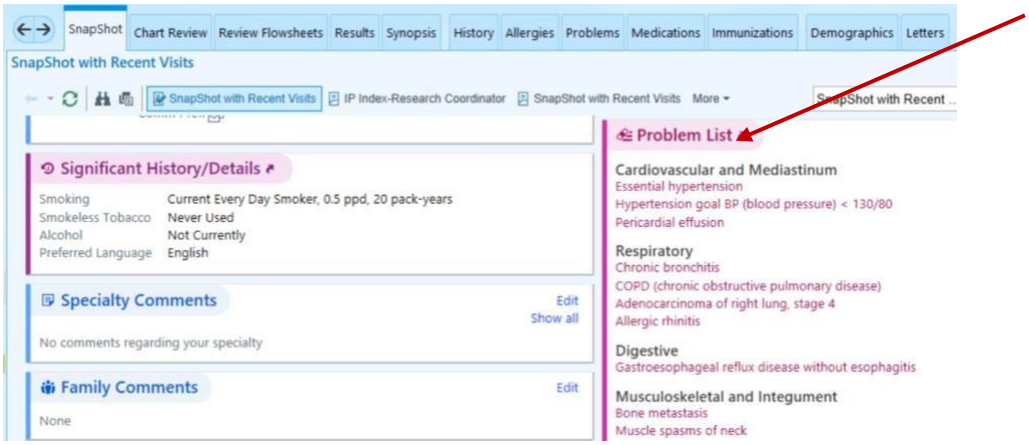


6. A page will appear with the patient's general information – click "**Select**" in the bottom right corner

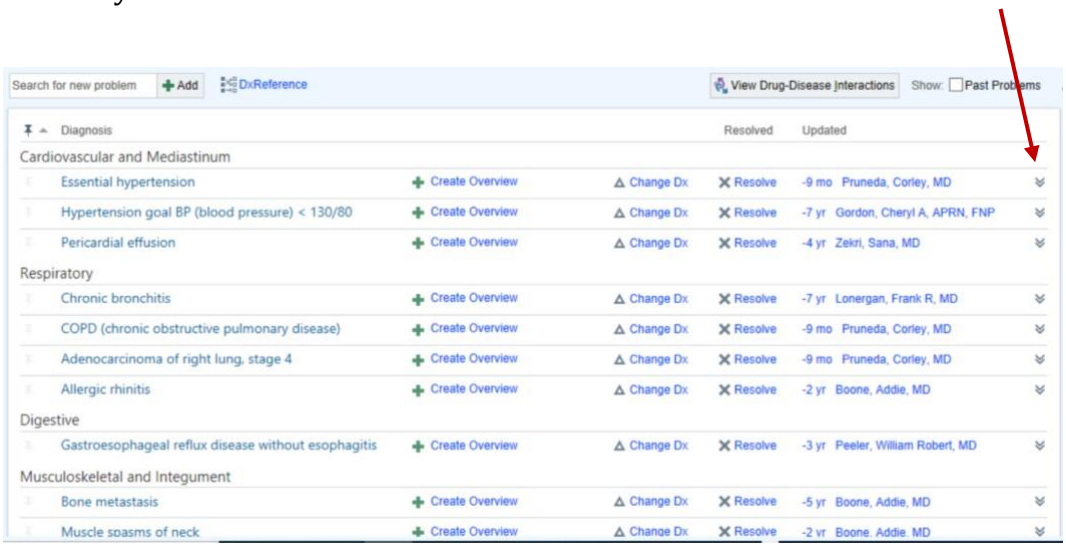
7. Note if the patient requires an interpreter during healthcare encounters. If the patient needs an interpreter, it will be found on the upper left side of the chart underneath the patient's photo and MRN number. Record as "yes" or "no" in the data collection sheet.



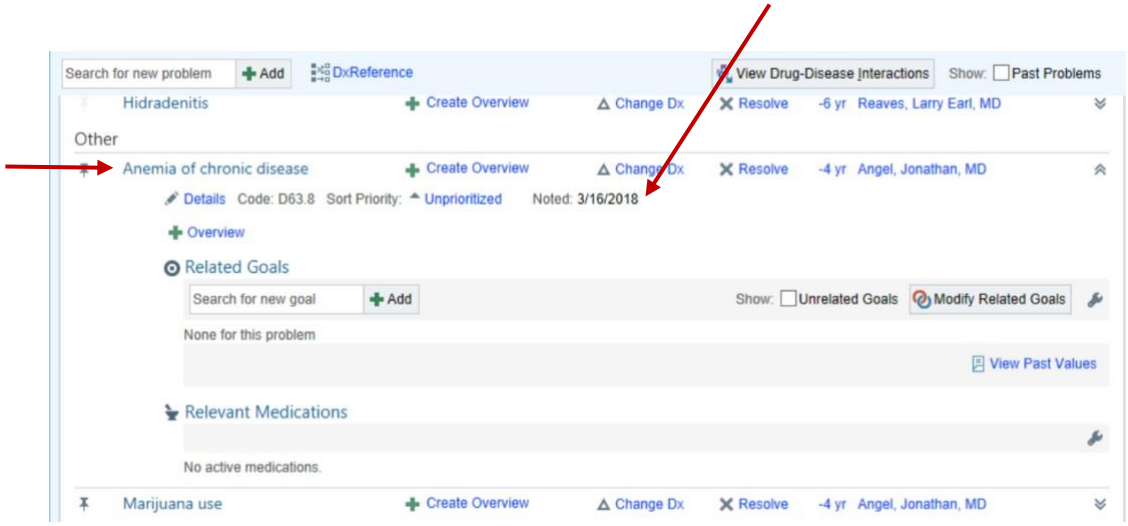
8. Go to "**Problem List**" on the right side of the page (you may need to scroll). Click on "**Problem List**" to expand the details



9. To identify immunotherapy-related adverse events:
    a. From the cancer registry Excel sheet, note the date that the patient started immunotherapy.
    b. The date of diagnosis in the "**Problem List**" can be found by clicking the arrow on the right side of the list (see red arrow).
    c. Identify if the patient has any of the adverse events of interest newly diagnosed within 24 months of immunotherapy initiation and record in the data collection sheet. Mark each adverse event in the data collection sheet as "yes" or "no".

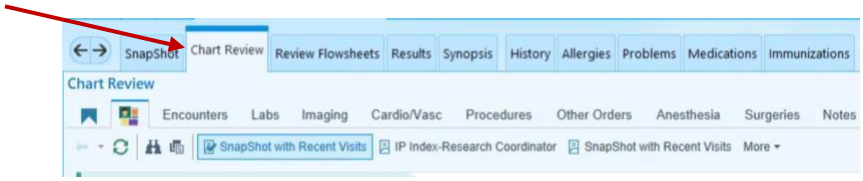


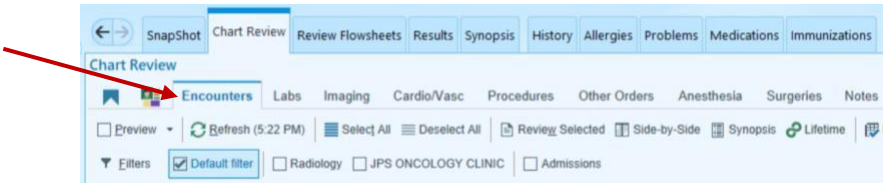
For example, if this patient (image below) began immunotherapy on February 1, 2018, we would mark "yes" for "Anemia" in the data collection sheet because the anemia diagnosis was within 24 months of immunotherapy initiation ("**Noted**" on 3/16/2018). Additionally, add the date (16MAR2018) to the data collection sheet.



*After identifying all adverse events that are being collected from the "**Problem List**" within 24 months of immunotherapy initiation, proceed to #10.

10. At the top of the patient's page, select "**Chart Review**", and then within chart review select the "**Encounters**" tab.





11. Scroll to the date the patient was diagnosed with an adverse event. If no adverse events were identified for the patient in the previous steps, continue to step 13.

12. Click on the encounter that occurred on the date of the adverse event diagnosis, or the next encounter following the diagnosis date.
    a. The encounter may be listed under "**Type**" as "Office Visit", "ED", "Clinical Support", "Care Management", "Hosp-Admission", or "Surgery".

    b. *Ignore* all other "**Type**(s)" listed in the chart, including "Orders Only", "Lab", "Telephone", "Documentation Only", "Nutrition", "Imaging", "Social Work", or

"Imaging"

c. Once the encounter is opened, read the notes written by the healthcare provider and, using the criteria from Schneider et al.,[1] grade the adverse events that were identified in the patient.

    i. Note: You may need to review several encounters or different encounter types to identify the information needed for the adverse event grading.

13. Finally, record in the extraction sheet the last alive encounter date. This will be the most recent in-person encounter type when chart reviewing patient encounters. If the patient is deceased, record the date of death in the data extraction sheet.