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The purpose of a clinical trial is to demonstrate safety, tolerability and efficacy of investigational medications before receiving FDA approval for medical use. The success of clinical trials heavily relies on quick patient recruitment as well as long-term patient retention throughout the duration of the study. Recruitment and retention have been identified as the most expensive components of research, in some instances consisting of up to 33% of the designated budget spanning from phase I to III trials [3]. In light of the rising costs of pharmaceutical research, it is important to investigate factors implicated in patient recruitment and retention throughout a clinical trial. Focusing on a Major Depressive Disorder study, an analysis of the following factors determining patient involvement in clinical trials was proposed: sex, age, weight, distance from site, marital status, concomitant medications, comorbid diseases, and work status, among others. Using logistical regression model, a retrospective study was conducted in order to characterize a profile of an optimized patient. Logistic regression analysis of data revealed that the most significant determinant of patient enrollment into a Major Depressive Disorder study is the use of an antidepressant treatment (ADT) at the time of pre-screening consultation. A closer look revealed that a potential patient was three times more likely to enroll in the study if he or she was on an ADT than an individual without the treatment. Further analysis confirmed model significance and result validity, as well as prompted ideas for further research.

FACTOR ANALYSIS AFFECTING STUDY SUBJECT RECRUITMENT AND RETENSION IN A MAJOR DEPRESSIVE DISORDER STUDY

INTERNSHIP PRACTICUM REPORT

Presented to the Graduate Council of the Graduate School of Biomedical Sciences University of North Texas Health Science Center at Fort Worth In Partial Fulfillment of the Requirements

For the Degree of

MASTERS OF SCIENCE IN CLINICAL RESEARCH MANAGEMENT

By

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CHAPTER I

INTRODUCTION

Background

The purpose of conducting pharmaceutical research is to demonstrate the safety and efficacy of a potential drug designed to treat, cure or alleviate symptoms of a disease. As the pharmaceutical companies race against time and competitors in order to receive marketing approval, the cost of drug trials keeps increasing [6]. According to Tufts Center for the Study of Drug Development from year 2003 to 2013, the cost of bringing a drug to market has risen by 145% [1]. This rapid rise indicates an urgent need for a closer analysis of factors that contribute to the escalation of the costs of research and development of new pharmaceuticals. Recruitment and retention of study subjects have been identified as the main factor responsible for soaring clinical trial costs as nearly 80% of trial sites fail to meet their subject quota deadlines due to slow enrollment [2].

Drug approval is a long and expensive process lasting from 10 to 15 years from the time a molecule is discovered in the lab to the moment it enters the consumer market [7]. Prior to the first phase of clinical trials, a compound or potential therapeutic is purified and extensively tested on animals. On average, one out of a thousand molecules is selected for further testing [18]. A set of properties of the molecule such as pharmacokinetics, pharmacodynamics, dosing, drug delivery, and proof of mechanism have to be determined before the sponsor can file for an Investigational New Drug (IND) approval with the Food and Drug Administration [8]. Once the

FDA determines that the drug is relatively safe, the sponsor may proceed to the first phase of clinical trials. The purpose of Phase I of clinical trials is to determine the safety of a new drug. Over the course of two years, local small scale experiments are conducted on non-targeted populations of 20-30 healthy individuals in order to determine dosing tolerability, pharmacokinetics, and potential side effects as well as safety profiles [9]. In Phase II, efficacy and continued safety are evaluated in targeted populations and disease under study consisting of two to three hundred volunteers. Phase III is the longest and most expensive part of the drug approval process. The number of research subjects may reach in to the thousands as the sponsor initiates nationwide trials encompassing a broader scope of participating races and ethnicities. Upon successful completion of phase three a New Drug Application (NDA) may be filed for market approval.

Since 1996, the number of New Molecular Entities (NME) or NDA filings has been steadily decreasing, reaching a decade low in 2007 with only 23 submitted NMEs [10]. The resulting trend is a consequence of growing costs of research due to a shift toward chronic and degenerative diseases predominant in the growing aging population [11]. While therapeutics may provide a promising source of profits, they also possess a challenge because the clinical trials for those conditions require longer time frames, greater number of patients, and complicated, costly testing [12]. As a consequence, extended trial periods are needed in order to determine the potential long-term effects, which eventually generate large amounts of data that must be processed and analyzed at the expense and time of the sponsor. Furthermore, when entering Phases II/III participants must meet specific conditions under the study, which further limits the potential subject pool. This contributes to the increasing costs of the studies.

Recruitment of an adequate number of participants is essential for the timely completion of a study; however, every clinical trial faces the challenge of meeting recruitment goals within a specified budget. Ideally, participants should be enrolled at a constant rate to complete interim data analyses, predict timelines, and maintain the power of the study by providing an adequate sample size [13]. Furthermore, in order to minimize costs, patients who are likely to adhere to all aspects of the study protocol need to be identified. Representative recruitment of both genders and all racial/ethnic minority groups is also important for the purpose of maintaining external validity of the study and its relevance throughout the process of drug approval.

Any randomized clinical trial or longitudinal study can be divided into two phases, the first one being patient recruitment, and the second one patient retention. Patient recruitment consists of three levels: pre-screening, consenting, and screening. Pre-screening is the initial point of contact often involving a phone call by the site recruitment staff during which a potential patient answers series of surface level questions that may indicate whether an individual is a good candidate for the study. The questions are structured to include some of the study inclusion and exclusion criteria. For example, in the present study of Major Depressive Disorder (MDD), the primary goal is to acquire patients within an 18-75 age range who have been struggling with a formally diagnosed, treatment resistant depression. Some additional requirements eliminate patients who are on a combination of antidepressants or receiving treatment through counseling. Some of the more common factors that contribute to patient loss during the process of pre-screening are age group, gender, income and level of education [14].

The process of informed consent is the second part of recruitment during which an individual is informed in detail about the purpose of the study, the visit schedule, sponsor expectations regarding patient compliance, patient compensation, and potential side effects from

the drug, as well as patient rights and obligations. Once a consent form is signed, the clinical research staff is able to perform screening procedures which verify patient's physical suitability with respect to the inclusionary criteria of the protocol. The most common screening procedures in a MDD study trial involve blood tests such as liver enzymes levels, hematocrit, metabolite profile, as well as medical history review, EKG's and scales including C-SSRS (Columbia-Suicidal Severity Rating Scale), MADRS (Montgomery-Asberg Depression Rating Scale), CGI (Clinical Global Impression scale), and SCID (Structured Clinical Interview for DSM-IV). Each procedure or scale is a tool for evaluating patient's general health, psychological stability, and eligibility for the study. Screening factors which limit patient enrollment are defined by the procedures done during the screen.

Retention of randomized subjects is another component of conducting efficient and timely clinical trials. It is defined as "strategy and tactics designed to keep patients enrolled in clinical trials, and from discontinuing participation and 'dropping out'"[19]. Once randomly assigned to study drug or placebo, retention of the subject in the study becomes the next hurdle for obtaining accurate and statistically significant data. Previous studies identify frequency of visits and their longevity, invasiveness of procedures, distance to trial site, investigational drug compliance, or illicit drug use during the study as some of the more significant factors which affect individual's continued participation. Recent studies have classified these factors into three categorical hurdles to study completion: subject-related barriers, contextual/environmental-related barriers and study-related barriers. A methodological literature review lists and analyzes specific factors within each category affecting retention, for example, a patient's unrealistic expectations of a clinical trial are implicated as subject-related hurdles to completing a study protocol [20]. Such expectations could cause a problem with the informed consent process (ICP),

especially in instances where requirements associated with trial participation are poorly communicated to subjects. However, even in the case of thorough consenting and patient education, subjects do choose to drop out of the trial when they begin to suspect the use of a placebo due to little improvement or lack of desired effect.

Some of the more common contextual/environmental hurdles to patient retention include lack of support from subject's family or a general care provider, mounting side effects from the experimental treatment, exacerbation of concomitant diseases, and lack of dedication from the principal investigator's study team [21]. Staff involvement, commitment and enthusiasm were strongly correlated with subject's willingness to continue their participation in the trial as the staff becomes a primary point of contact and a supporting resource [21]. Lastly, study-related barriers such as protocol design and complexity, number of procedures, frequency of drug dosing, and their psychological impact, have a drastic effect on the level of patient commitment to the trial [22]. Another experimental design with ethical issues which has an impact on patient participation is the treatment-placebo design. Placebo is an inactive substance. Participants may be assigned to the placebo group and as a result miss out on the opportunity to experience the potential therapeutic benefits of the drug. Although the issues associated with patient recruitment and retention have been studied and categorized extensively for over three decades, the effect of some factors remains ambiguous especially in instances where interactions between components clouds thorough understanding of attrition patterns.

As a central component of any successful clinical trial, patient recruitment and retention have been extensively analyzed and a basic model has been proposed in order to identify the pattern of patient dropout rates from initial point of contact through pre-screening, consenting, screening, and randomization [23]. The model suggests that out of a hypothetical pool of 100

potential patients, about 31 of pre-screened individuals qualify. Furthermore, of the 31patients, 13 give consent and of those 13, only 9 are assigned to a group. On average, 7 individuals of the 9 that start the study end up completing the trial. This funneling model can be further segmented into additional phases of the process of enrollment in the instances of stringent inclusion/exclusion criteria.

In order to enroll in the study, a patient must fulfill a set of inclusionary and exclusionary (I/E) guidelines. Specifically, a patient has to be at least 18 years of age but no more than 65, meet DMS-5 criteria for MDD, a minimum MADRS score of 25 or above at screening visit(V1) and baseline(V2), no more than partial response to ongoing typical antidepressant treatment (fluoxetine, sertraline, bupropion, etc.), normal physical examination as well as negative results for blood work and ECG reading at V1. The exclusionary criteria which a patient must fail to meet is: concomitant psychological disorder such as anxiety, schizophrenia, bipolar disorder etc., history of substance abuse within 6 months before V1, history of antipsychotics, anticonvulsant or mood stabilizer use, suicidal attempt or hospitalization within 6 months of V1, lack of psychotherapy for depression within 3 months of trial, and lastly fall outside of the 40kg to 125 kg range on the day of screening. Fulfillment of the I/E criteria guarantees successful enrollment and participation in the trial. There are additional less relevant criteria.

Preliminary data obtained from qualitative observations conducted by the clinical trial site staff indicated correlation with respect to distance travelled by a participant and his or her study completion rate [unpublished data]. Additionally, it was revealed that women are more likely to show interest in participating in an MDD study, while men are more likely to demonstrate compliance. Further database analysis identified secondary and tertiary factors that contribute to patient enrollment in the study.

Significance

Clinical trials are extremely expensive consisting of up to 33% of the research and development budget provided by a pharmaceutical company [3]. Although reports of the cost of bringing a drug to market range from $800 million to $2.6 billion a decade long expense analysis reflected a unanimous steadily rising trend associated with clinical trials [4]. Considering these accruing expenditures due to ever increasing bureaucratic hurdles, and difficulty in patient recruitment among other factors, it is important to investigate and analyze factors that might be directly contributing to the costs. Patient recruitment and retention has been implicated as one of the most challenging aspects of conducting clinical trials in the United States [4]. Low recruitment rates and failure to retain participants results in costly delays and potential cancellation of an entire trial. Any extra expenses incurred by the pharmaceutical company may eventually passed down to the consumer in the form of higher prices which in many cases may limit availability of new and possibly more effective treatments. Due to the staggering average US $1.3 billion cost of bringing a drug to market in the United States, and a yearly 10.2% increase in price of brand name drugs, it is important to identify some of the underlying factors of patient recruitment and retention [5]. Optimization of patient recruitment would provide a steady stream of qualified patients, that are likely to complete the study and provide, accurate, reliable, statistically significant data, without the mounting costs of extending trials into subsequent phases.

Aims and Hypothesis

Due to the mounting drug costs, the time it takes to conduct clinical trials, and the financial burden on the general population, it is beneficial to identify factors impacting

recruitment and retention rate of patients for clinical trials, for example, a Major Depressive Disorder (MDD) study at North Texas Clinical Trials site.

With the purpose of understanding patient acquisition and retention in a Major Depressive Disorder (MDD) clinical trial at North Texas Clinical Trials, a data set was retrospectively analyzed in hopes of providing an insight in to major factors contributing to subject participation. The MDD study protocol consisted of three characteristic parts. Phase A was a double-blind, placebo-controlled, part of the study where neither the subject nor the researcher knew whether the administered substance was the treatment or a placebo. Throughout that period, levels of depression were evaluated using clinically approved scales. When all three weekly administrations of treatment or placebo were completed, the subjects enrolled into part B1, an open-label part of the study where the dispensed substance is known to be the study drug. Subject levels of depression are monitored for a period of 16 to 17 weeks. If a patient achieves a level of stability of depression symptoms within that time frame, they are randomized into double-blind part B2 of the study where they are again either given the treatment or a placebo. In the event that a subject never achieves stability they are enrolled into part C open-label part of the study, in which they continue taking the study drug until the study ends, or the patient withdraws their consent.

It is hypothesized that major loss of potential patients occurs during the prescreening phase of recruitment due to one or more of the following factors: distance from the clinic, age, sex, weight, and use of antidepressant treatment. Further investigation may identify additional factors.

CHAPTER II

RESEARCH DESIGN AND METHODOLOGY

Subjects

The data set, taken from a Major Depressive Disorder (MDD) research study, was compiled from two sources. The first one was IntakeQ (IntakeQ, Hamilton, Ontario) which is an online patient database with de-identified demographics such as race, age, gender, marital status, brief medical history such as diagnoses, emotional and behavioral problems, substance use, hospitalizations, symptoms checklist, prescribed medications, and general geographical location. The second source was Skynet (Microsoft, Redmond, Washington), which contained information on patient progress as well as reasons for not qualifying for study, or for early disqualification throughout the multiple phases of the study.

The sample population consisted of all potential and current participants of the Major Depressive Disorder study conducted at North Texas Clinical Trials. All information was confidential and proprietary. A compiled master dataset served as a source for descriptive statistics such as percentage, mean, standard deviation, and frequency for the analysis of sample demographics.

The study protocol was divided into phases that reflect patient progression throughout the study. The first phase contained all individuals who had shown interest in the MDD study and

were prescreened by the site recruitment department. Within that patient pool a binary answer (yes or no) was recorder based on the IntakeQ data for the following factors: marital status, gender, antidepressant medications and enrollment. For the purposes of data analysis, the dichotomous answers were encoded as yes=1 and no=0, female=0 and male=1, single=0 and married=1. Continuous variables in the sample factor analysis were age, weight, and distance from site.

Analysis

One of the most common problems in psychiatric research is missing data due to patient lack of compliance or failure to complete questionnaires [14]. In order to address the problem of missing data points in the dataset, the method of multiple imputations (MI) was used to analyze the master dataset in categories for weight, age, and distance from site. MI utilizes existing data points in order to fill in missing information based on the patterns present in the dataset. Although the minimum recommended number of imputations is 5[13], the present data was imputed 10 times resulting in 10 separate complete datasets.

Descriptive statistics were used to analyze original and imputed data. The two data sets were then compared and percent difference was calculated. Each dataset was then analyzed separately using logistical regression and the results were integrated into a pooled final result. An Omnibus Test was performed on the imputed data in order to determined presence of any statistically significant factors by comparing observed to expected factorial means, while Nagelkerke R-Square was used to evaluate the goodness-of-fit of the model generated using imputed data. Lastly, the logistical model was confirmed using Hosmer- Lemeshow Goodness-of-Fit Test by failing to reject the null that the difference between observed and expected values is significant. Out of the 218 pre-screened subjects, 21 were selected based on their

randomization into phase A of the study. The randomized sample was then analyzed for significance of concomitant medications, comorbid diseases, work status, depression duration of more than 10 years, and psychiatric hospitalization. All data analysis was done using SPSS (software version 24, IBM software company, Dallas, Texas). Patient data collection lasted from December 1, 2016 to August 15, 2017. All patient-related data was de-identified using patient ID numbers, and any additional identifiable information such as birthdays or addresses were converted into numerical values in the form of age or distance from site.

CHAPTER III

DATA ANALYSIS AND RESULTS

Population Demographics

Out of 503 subjects in the patient database in IntakeQ, only 218 were included in data analysis due to information completion and rate of subject responsiveness. The subject response rate was therefore estimated to be 44%, meaning out of 503 potential patients, 218 were reached and were willing to go through the pre-screening process for the study providing it with personal information and medical history. The pre-screened population was 89% female and 11% male (Table 1).

96 of the 218 subjects disclosed race. Of those who provided information, 70% of subjects were Caucasian, compared to 26% African American, and 2% Asian. There was one individual who identified as other (Table 1). Of the 218 subjects, 90 disclosed ethnicity. Of those who chose to identify, 80% were not Hispanic or Latino, 13.3% were Hispanic or Latino, and 6.6% were Unknown (Table 1). 128 individuals failed to identify their ethnicity.

The preliminary analysis of population demographics suggested that individuals who demonstrated greatest interest in the MDD study and were willing to dedicate some time answering questions during pre-screening phone calls were mostly white Non- Hispanic women. Although parts of the data set were missing information, a large sample (96 patients) provided

substantial amount of information to complete significant analysis. Further investigation of the following factors: age, weight, distance from site, use of antidepressant, and marital status, provided additional information of the sample demographics before data imputation.

Table 1: Demographics

Race	
White	68
African American	25
Asian	2
other	1
Not identified	122
Gender	
Male	24
Female	194
Ethnicity	
Not Hispanic or Latino	72
Hispanic/ Latino	12
Unknown	6
Unanswered	128
Marital Status	
Married	42
Single	114
ADT	
Yes	70
No	148

* ADT =Antidepressant Treatment

Sex was coded in terms of 0 and 1, the former being female and latter being male (Table 1). All 218 subjects were classified as either male or female, with average statistic overwhelmingly favoring females. Out of 218 subjects, 183 provided their age, with the low being 14 years of age and a high of 78. The average was 41.8 years with a standard deviation of 10.6 years. Average distance from site was 18.04 miles with standard deviation of 15.4 miles.

Average weight volunteered by the 71 individuals was 195.1 lb with a deviation of 59.5 lb. The large weight deviation was attributed to one individual whose weight proved to be an outlier at maximum weight of 390 lb (Table 2). For the sake of maintaining the dataset and its completeness, the subject's information was preserved for further analysis. Marital status was provided by 156 individuals, of which 42 were married and remaining 114 were single (Table 1). For the purpose of logistical regression, marital status was encoded as S=0 and M=1. Lastly, of 218 subjects, 70 (32.1%) had identified that they were on an antidepressant treatment (ADT) at the time of pre-screening, while the rest 148 (67.9 %) subjects have never taken or have not taken any ADTs within 30 days of pre-screening.

Table 2: Demographic Data: Continuous Variables

	N	Minimum	Maximum	Mean	Std. Deviation
Age	183	14	78	41.8	10.6
Distance from site	74	0.5	90.0	18.17	15.4
Weight	71	115	390	195.16	59. 5

Multiple Imputation

Multiple Imputation was conducted in order to remedy the gaps present in the dataset. Following text book recommendation, imputation was performed 10 times, meaning that in the case of a missing data point, a derived new value point was inserted based on the patterns present in the original dataset [15]. Four factorial categories were imputed: marital status, age, weight, and distance from site (Table 3) where 62, 35, 147 and 144 values were missing in each category, respectively. Continuous variables were imputed using linear regression whereas categorical variables were imputed using logistic regression. ADT and Sex factors did not require MI.

Table 3: Imputation Model: Missing Values

Variable	Type	Effects	Missing Values	Imputed Values
Age	Linear Regression	Sex, ADT, Marital Status, Distance from site, Weight	35	350
Marital Status	Logistic Regression	Sex, ADT, Age, Distance from site, Weight	62	620
Distance from site	Linear Regression	Sex, ADT, Marital Status, Age, Weight	144	1440
Weight	Linear Regression	Sex, ADT, Marital Status, Age, Distance from site	147	1470

The imputed model was then compared with original sample descriptive statistics in order to determine percent difference between the two sample populations. Percent difference in age, distance from site, marital status, weight, sex, and presence of ADT was 0.47%, 1.12%, 0%, 6.12%, 0% and 0%, respectively (Table 4). Greatest percent difference in weight is explained by 147 cases in which that statistical point was missing. Despite large number of missing data points, percent difference for all six factors was relatively small and thus further analysis on the imputed data was carried out.

Table 4: Descriptive Statistics Imputed Data vs. Original

Imputation Number		N	Mean I	Mean O	Percent Difference
Pooled	Sex	218	0.11	0.11	0%
	Age	218	41.61	41.81	0.47%
	Marital Status	218	0.28	0.28	0%
	Distance from site	218	18.313	18.107	1.12%
	Weight	218	183.11	195.06	6.12%
	ADT	218	0.32	0.32	0%

Omnibus Test of Model Coefficient

Omnibus Test was performed on the imputed data in order to determined presence of any statistically significant factors by comparing observed to expected factorial means. An average Chi-Square value was obtained: $X^2(6) = 14.55$, df =6 with a pooled p-value=0.035. Because at least one of the 6 factors was statistically significant, further analysis used logistical regression in order to identify the significant factor (Table 5).

Table 5: Omnibus Tests of Model Coefficients

Imputation Number		Chi-square	df	Sig.
Original Data	Model	9.561	6	0.089
1	Model	12.855	6	0.045
2	Model	13.714	6	0.033
3	Model	16.686	6	0.011
4	Model	12.837	6	0.046
5	Model	11.894	6	0.064
6	Model	14.200	6	0.027
7	Model	11.049	6	0.087
8	Model	14.871	6	0.021
9	Model	15.184	6	0.019
10	Model	22.215	6	0.001

The Omnibus Test is commonly used in the form of Chi-Square for determining significant difference among independent variables having an effect on the outcome variable. Average Chi-square and p-value was calculated using the imputed dataset. With the exception of original data, which initially was incomplete to a certain degree in each category, and 5th and 7th imputation, all data points are statistically significant with p-values less than 0.05. These imputations are generated based on patterns found in the original dataset, and provide a way to fill in the missing data. Imputation involves regressing each variable with missing data onto all other variables [24]. Each round of imputation provides an entire complete dataset which is then

used in analysis. Since each imputation has a degree of variation from the original data, its level of significance may slightly differ from the original dataset. For that reason multiple imputations are performed (in this case 10 as suggested by PROC MI statistical Analysis System) and their pooled average is considered in the final steps. Pooled imputation average was $X^2(6) = 14.55$, df=6 with an average p-value=0.035.

Variation in the sample

R-Squared method was used to evaluate the model goodness-of-fit generated using imputed data. Table 10 provides Nagelkerke R-Square for original and imputed data. For the original data 100% variation was accounted for by the independent variables in the model; however, in the case of imputed points, the average R^2 for the 10 datasets was 0.12(table 6). This suggests a poor predictability of the independent variables on the outcome variable; however, interpretation of the Pseudo R^2 in logistic regression is difficult because although they are on the same scale as ordinary least square regression, Pseudo R^2 can be interpreted differently [18].

Table 6: R^2 for Original and Imputed Data

Imputation Number		Nagelkerke R Squared
Original data	1	1.000
1	1	0.114
2	1	0.122
3	1	0.147
4	1	0.114
5	1	0.106
6	1	0.126
7	1	0.099
8	1	0.132
9	1	0.135
10	1	0.194

Logistic Regression

Primary analysis on the pre-screened population was performed by including all six of the factors in the model building. Pooled imputed dataset presented a significant finding for only ADT with a p-value of 0.15 (OR=0.293, 95% C.I.0.02-21.54)(Table 7).

Table 7: Logistic Regression Model

Imputation Number	B	S.E.	Sig.	Exp(B)	95% C.I. for EXP(B)		Relative Efficiency
					Lower	Upper	
Sex(1)	-0.674	0.646	0.297	0.510	0.144	1.810	0.998
Age	-0.003	0.025	0.899	0.997	0.949	1.047	0.985
Marital Status(1)	-0.866	0.657	0.193	0.420	0.113	1.568	0.960
Distance from site	-0.002	0.018	0.903	0.998	0.962	1.035	0.963
Weight	0.002	0.005	0.713	1.002	0.992	1.011	0.975
ADT(1)	-1.229	0.507	0.015	0.293	0.108	0.790	0.997
Constant	-0.438	1.773	0.805	0.646	0.020	21.154	0.982

Total pooled data revealed the presence of an antidepressant being the only significant predicting factor on the outcome of being screened into phase A of the study. Furthermore, individuals on antidepressant treatment were nearly 3 times more likely to become enrolled compared to individuals who were not on the treatment.

Additionally, the model was confirmed using Hosmer and Lemeshow's Goodness of Fit Test. The average p-value for all ten imputations was p=0.387 with an average X^2 =9.017, df=8. Since p=0.387>0.05, null was not rejected (Table 8).

Table 8: Hosmer and Lemeshow Test

Imputation Number		Chi-square	df	Sig.
Original data	1	0.000	4	1.000
1	1	8.459	8	0.390
2	1	4.228	8	0.836
3	1	7.807	8	0.453
4	1	8.826	8	0.357
5	1	11.119	8	0.195
6	1	14.144	8	0.078
7	1	13.051	8	0.110
8	1	7.984	8	0.435
9	1	8.147	8	0.419
10	1	6.408	8	0.602

CHAPTER IV

DISCUSSION AND CONCLUSION

Out of 503 potential patients, 219 were pre-screened with the intention of enrolling in the MDD study. The data for the following six factors was collected: Age, Weight, ADT, Marital status, distance from site, and sex. Missing data was filled in by multiple imputation and compared to original dataset. A logistic regression identified ADT as the predictor of patient screening into the trial, which suggests that patients on an antidepressant were three times more likely to randomize compared to individuals who were not taking the medication at the time of pre-screening. This finding can be attributed to the fact that patients who were not on antidepressant at the time of pre-screening but still wanted to participate, had to wait 6-8 weeks before they could randomize into the study. Six to eight weeks is the standard time it takes for an antidepressant to begin working. During that time, patients can become discouraged and fail to follow up at the proper time. Moreover, depression is an episodic disorder where a patient can experience symptoms of depression lasting from one to six months or even longer. Given the 6-8 weeks of delay before being eligible for the study, patients may neglect their disease and lose drive to participate.

With respect to sample demographics, certain statistics cannot be ignored. According to the original data 89% of pre-screen responders were women, suggesting that sex would be a predictor of study enrollment. Further analysis with a bigger sample could shed light on this issue in future studies.

Study Limitations

Limitations due to sample size. One of the major limitations of the of data analysis was the small population size. The preliminary sample size of potential patients was n=218; however, as subjects advance in the trial the sample size was considerably reduced. From 503 subjects, 218 were selected for the initial data analysis. Twenty-four subjects were screened into phase A of the study and only a fraction of that proceeded to phase B1. Small sample sizes may pose issues by increasing probability of errors, decreasing generalizability of results and minimizing accuracy of population estimates. Ultimately, the biggest concern is the statistical power of small samples where smaller effects are harder to detect and thus may go unnoticed [12]. The sample population of 21 subjects for phase B was initially analyzed using logistical regression. Unfortunately, with such a small sample, the analysis loses power and introduces error by failing to show statistical significance where one might exist.

Population Demographic. Another significant limitation of the study may be due to the specific population sample originating from the Dallas/ Fort Worth metropolitan area. Racial distribution in the DFW metroplex composes of 61.1% Whites, 18.9 % African Americans, 34.1% Hispanics, and 3.7% Asians [17]. This presents an issue with ethnic overrepresentation as more than 50% of the potential patient pool identified as Caucasian. Additionally, some patients chose not to identify their racial background or simply did not get far enough in the screening

process to divulge that information. Conclusions drawn from our dataset may pose an issue regarding study generalizability across different geographical centers.

Incomplete Database. While the majority of the information collected originated from phone call screens, some portions of the master database were left incomplete, especially in instances where the screened subject refused to provide an answer, or if the recruitment specialist failed to collect the data point. Unlike a laboratory experiment in a controlled environment, this retrospective study depended on independent subjects who volunteered some of the most sensitive information about their physical and psychological well-being. Although the steps were taken to rectify the problem by using multiple imputation, a 10-fold analysis is a minimum requirement for replicating a statistically reliable dataset.

Limitations of the Source. All information extracted for the purpose of this analysis originated in a broad patient database which largely consisted of subjects' geographical and demographic information. Due to the retrospective nature of this investigation certain factors based on patient opinions or personal inputs among other factors. A carefully drafted survey, specifically catering towards MDD potential study subjects, might have revealed additional factors that may have illuminated some additional reasons for patient successful recruitment and retention.

Future Research

Based on the need of eligible patients for clinical research and aforementioned escalating costs of pharmaceutical investigations, a set of recommendations for further research warrants exploration of most effective online, population specific, advertising strategies which follow MDD specific behavioral trends. For example, during our analysis we discovered that the majority of intake forms filled out by patients through the IntakeQ system were done during late

hours of the night and early hours of the morning usually between 11 PM and 3 AM. This is characteristic of majority of patients suffering from depression where one of associated symptoms is insomnia. Exploring internet habits and interests of affected individuals may provide insight and guidance when developing improved recruiting techniques.

Another point for future analysis would to be to deepen the factor analysis by investigating the type of ADT each patient used and which kind was most popular. Along the same line an analysis of the most common comorbid diseases would give insight into the relationship between depression and other medical indications. This would provide a streamlined way of identifying individuals who are more likely to participate in the study.

Conclusion

Out of the 219 pre-screened potential patients 21 were screened into the study. Logistical regression was performed on the sample in order to identify factors predicting enrollment into phase B1 of the study. The analyzed factors were: concomitant medications, comorbid diseases, employment, 10- year depression longevity, psychiatric hospitalization, and suicide risk. Due to the small sample size, the analysis identified concomitant medication as a significant predictor. For future research a much larger patient population will be needed in order maintain statistical power and allow for meaningful analysis.

CHAPTER V

INTERNSHIP EXPERIENCE

Description of Internship Site

My clinical research internship was completed at North Texas Clinical Trials (NTxCT) in partial fulfillment of the requirements for the degree of Masters of Sciences in Clinical Research Management. Under close supervision from site manager Jessica Anderson and site director Brian Maynard Ph.D, I had the rare opportunity to learn about different aspects of clinical research, beginning with the contingencies of starting a study as measured by feasibility criteria specific to each site, patient recruitment, study design, regulatory proceedings, and IRB approvals being some, of many, tasks and skills. During the six-month internship I became closely familiar with obstacles and challenges of bringing new drugs to market.

North Texas Clinical Trials LLC. was established in 2012 by Dr. Maynard. The site focuses on conducting trials associated with psychological and Central Nervous System disorders. Currently, the site is conducting clinical research for the treatment of Major Depressive Disorder, Schizophrenia, Tourette's Syndrome, Postpartum Depression, Essential Tremors, Bipolar Disorder, Anxiety and Migraines.

Journal Summary

On May 30, 2017 I began my internship at the North Texas Clinical Trials. I had the opportunity to become familiar with the facility's operating procedures. For example, I was exposed to the division of labor and work flow as well as the different types of researches. I was trained to conduct a pre-screen phone call. It is very similar to sales. There are leads provided by a marketing company that consist of names, phone numbers, and emails of individuals interested in our studies. It is our job to reach people on the list and vet them out for the study by following an inclusion and exclusion criteria. The conversations included some very emotionally charged and personal topics, therefore, it was almost an art form to be able to get the information needed without sounding detached. If the candidate sounds promising, we send them North Texas Clinical Trial consent forms that provide us with patient background and medical history. A follow up phone call or a pre-screening visit is scheduled if the patient is interested in joining the trials.

Another responsibility I have been delegated is filling updated consent forms, patient data sources, lab records, and other regulatory material. It is an exercise of attention to detail and concentration. I have learned the way each patient and investigator binder needs to be organized according to sponsor and site rules. It is of upmost importance to keep everything up to date due to interim monitor visits or potential unannounced FDA inspections.

Before each patient visits it is important to inspect the patient binders making sure recent labs, ECGs, and concomitant medications are filled out dated and signed. In addition to filing I am in charge of extracting patient data from source documents and inputting it into the electronic data capture (EDC). An EDC is the central data base that the sponsor uses in order to evaluate the quality of information we are providing. These data bases are checked and analyzed by the

CRA on daily bases. If there is a patient vital statistic or value out of the ordinary they flag it down by forming a query. These queries have to be checked and addressed promptly by our clinical staff. I will eventually be trained to keep those in order.

During patient days I serve multiple roles. In the role of a front desk staff I greet the patients, offer them refreshments, schedule appointments, and provide proper paperwork before they proceed into the examination room. Other times, under direct supervision, I am responsible for taking vital signs such as temperature, blood pressure and pulse. I also had the opportunity to learn how to properly place ECG leads on patients of various ages. As I became exposed to the daily tasks at my research site, it became clear that the most challenging aspects of clinical research was patient recruitment, especially in the area of psychological disorders. I decided to investigate some of the reasons why certain potential participants took part in the trials while others failed to make it through the screening process. As a recruitment team member I had access to the MDD patient database and was able to analyze it with the hopes of finding an easier way to recruit and retain study subjects.

APPENDIX A.

DAILY JOURNAL

Journal Entries

Week 1:

Tuesday May 30th 2017

On May 30th I began my internship at the North Texas Clinical Trials. I had the opportunity to get familiarized with the facilities operating procedures. For example, I was exposed to the division of labor and work flow as well as the different types of researches. The main research focuses on an adjunctive treatment for resistant major depressive disorders under the name of XXXX. This ketamine derivative works on NMDA receptors as an allosteric modulator by weakly binding a subunit glycine residue. The purpose of this drug is to enhance the effect of traditional antidepressants. Furthermore, it is meant to close the 8-week gap between first dose and actual therapeutic effects of the antidepressant. XXXX acts as a cognitive enhancer and may slow down the neurodegeneration of C1 and C3 areas of the dentate gyrus of the hippocampus. I had a had a chance to meet one of the MDD patients and go through the inclusion/exclusion criteria for enrollment in a trial.

Wednesday May 31st 2017

Today was a patient day. On patient days we perform drug infusions as well as drug dispensing. I had a chance to take blood pressure and set up and ECG. I watched my supervisor perform phlebotomy and administer the drug. We went through the steps of admitting a drug into the clinical site. The process is very complicated because the medicines are restricted by narrow temperature ranges and it is important to note any deviations. I had a chance to observe the process of consent and review the binding contract between the site and the participant. Every single page has to be initialed and dated by the subject.

Thursday June 1st 2017

I had a chance to listen to a pre-screen phone call. It is very similar to sales. There are leads provided by a marketing company that consist of names, phone numbers, and emails of individuals interested in our studies. It is our job to get a hold of the people on the list and vet them out for the study by following an inclusion and exclusion criteria. The conversations transverse some very emotionally charged and personal topics therefore it is almost an art form to be able to get the information needed without sounding detached. If the candidate sounds promising, we send them some forms that will give us a little bit of a background and medical history. During this time, it is best to schedule them for a pre-qualifying visit in order to maximize the turn out number. I am noticing some inefficiencies and drawbacks of the process as well as the general on-going struggle to keep potential patients committing to come in for a preliminary visit. This may be an area of future investigation.

Friday June 2nd 2017

Today we focused on making calls in order to acquire new patients for the RAD 03 study which is the major depression study. My task was to call people and question them about the history of their disease in order to pre-screen them for the trial. It was an eye opening experience with a huge learning curve. A lot of the people had been struggling with depression for 20 plus years and had tried every available drug on the market in order to combat their negative feelings. The entire process elucidated an ongoing struggle pertaining to every clinical research topic: the efficiency of recruitment techniques and the ratio of pre-screened patients to the ones who

actually did finish the study. Preliminary data shows that recruitment follows the rule of two. For every person which finished the study there may have been twenty which were pre-screened with a five tiered progression. Second part of the day focused on the Tourette's study patients. Normal procedures were conducted, along with an ECG and a video conference documenting the progress of patients on the experimental drugs. The drug looks very promising.

Week2:

Monday June 5th 2017
Today I focused on filling updated consent forms, patient data sources, lab records, and other regulatory material. It was an exercise of attention to detail and concentration. I learned the proper way each patient and investigator binder needs to be organized according to sponsor and site rules. It is of upmost importance to keep everything up to date due to interim monitor visits or potential unannounced FDA inspections.

Tuesday June 6th 2017
My tasks for the day concentrated on more filing and making phone calls to potential study participants. Many of the people do not qualify for the study because they currently are not on an antidepressant. It is our job to bring those people into the office and figure out if they would qualify for the study if other criteria were fulfilled.

Wednesday June 7th 2017
Through my screening efforts, I was able to personally recruit a patient for the major depressive disease study. Lady X came in today for an ADT (antidepressant visit) and was given an opportunity to discuss the history of her disease. It is our duty to make sure that every patient meets the inclusion criteria for the study. On the other hand, some of the things that do exclude patients are history of drug use or abuse, official diagnosis of a bipolar disorder or schizophrenia, and recent suicidal attempts. Luckily for us, lady X was a perfect candidate and she will proceed into the preliminary phases or our study.

Thursday June 8th 2017
The day consisted of tidying up the office and making sure everything was ready for our patient visit on Friday. We went through all the patient binders making sure recent labs, ecgs, and concomitant medications were filled out dated and signed. There had to be some regulatory articles filed into different sections of the IRB approved protocol sections. Our only patient for the day cancelled last minute. In addition to filing we had to quality control the information from data sources and the EDC. EDC is the central data base that the sponsor uses in order to evaluate the quality of information we are providing. It also registers any adverse events if there happens to be an allergic reaction or any other health related event.

Friday June 9th2017
We saw six different patients today. Two of them were part of the trial due to Tourette's syndrome. The drug they are evaluating right now for it is incredibly effective and will soon be approved. Part of the process evaluating the efficacy is a fifteen-minute video of the patient sitting quietly in a room. The purpose of this exercise is to evaluate the ticks, and compulsivity of movement. The second step consists of scales which determine the overall psychological well-

being of the subject. The other patients on the schedule were part of the depression study which consists of an infusion of XXXX. The only side effects reported with this drug are minor headaches and some nausea. These also happen to be typical side effects of any other antidepressant medication currently on the market. One of the more exciting aspects of the week was learning that the major enzymatic processing of the drug is done by CYP2D6, an enzyme we discussed multiple times in pharmacology. Besides the day to day duties of running a clinical trial's site, we took the time to do some team building activities. I am very fortunate to have such a great group of people.

Week 3

Monday June 12th 2017
The schedule for today consisted of C-20 study filing along with drug logging for the MDD study. My responsibility was to match up all the kit lot numbers with requisition forms and their corresponding sections in the accountability binder. In conjunction with clerical duties I had to make some more screening phones calls. I had the privilege to talk to patient Z who has been struggling with depression for over fifteen years. She suspects a diagnosis of a bipolar depression however according to her symptoms list I believe she might be only depressed. For that reason, I scheduled an in-house visit with our M.D. She will receive proper evaluation and an official diagnosis.

Tuesday June 13th 2017
A game plan for today is to get ready for Wednesday which is a patient day. We made charts by pulling specific source documents for each individual patient. Since everyone is at a different point in the study different data points aka vital points have to be collected. We also have a patient coming in at 18:00 for a late night screening session. She will have her mood and mental cognition evaluated by an independent third party. Those are generally done over the phone in order to avoid rater bias.

Wednesday June 14th 2017
Today was a patient day. Unfortunately, we found out that one of our pre-screens has failed a psychological evaluation. As mentioned before those consist of a phone call to a third party evaluator that assesses levels of depression. A patient that scored a 33 two weeks ago was screened again and her second score was only a 23. The passing score is a 24. As strange as that sounds she is not depressed enough for her to continue with our study. The subject has apparent symptoms of depression some of them being weight loss, lack of appetite, hair loss, apparent sadness, excessive stress, and malnutrition. This particular case really struck me to the core. We have the means to help her but because of some ambiguity she will have to deal with this on her own.

Thursday June 15th 2017
We spend the entire day getting ready for the patient visits. We had to pull patient source documents and compile their visit folders. A little cleaning and rearranging was done to prepare the office for the eleven patients we are seeing on Friday.

Friday June 16th 2017
Today was one of the busiest days I have seen throughout my internship. We had eleven patients. Four of them belonged to the Tourette's study which is its termination phase. It seems that the drug will be getting FDA approval very soon. Next we saw the six major depressive patients which had their vitals, ECG's, scales, and infusions done. The infusions consisted of a randomized dose of XXXX. Our last visit was with our only schizophrenic patient. This was her sixth week with us. Unfortunately, we ran into the problem of compliance. For some reason she could not take her medication for a couple of days. The consequences are yet to be determined but most likely she will be early terminated from the study. We have to obtain an 80% compliance rate with the patient if the generated data is to be meaningful. If she does end up terminating, we will desperately have to scramble and find another schizoaffective patient in order to retain the study in our clinic. Overall, it has been a good week. The work we have done has been satisfying. I cannot emphasize enough how fortunate I have been with my placement. Great people and great line of work.

Week 4

Monday June 19th 2017
I had this day off.

Tuesday June 20th2017
Today was a special day due to the interim monitor visit. We came in early in order to prepare all of the Tourette's binders for inspection. The monitor performed drug accountability and made sure that each study subject has adhered to the dosing protocol. Although we are responsible for noting any protocol deviations, the additional oversight provides the sponsor more credibility and better quality data. Each irregularity has to be addressed and noted in the EDC. As small of a deviation as taking the drug in the morning rather than at night has to be noted. The monitor meticulously went over every single detail in every single binder.

Wednesday June 21st 2017
I had two tasks assigned for the day. The first on consisted of making patient charts; it was the first time I had to compose one on my own and the following documents were included: patient driver license copy and basic demographic information, progress note from previous visit which has to always be dated and signed by the physician, recent copy of laboratory results, ECG, drug assigned note from the sponsor, and appropriate visit document sources that includes basic vitals, drug compliance, scales(used to evaluate subject mental well-being, suicidality scale and symptom checklist). The second task involved compiling a data base of all the patients we have in IntakeQ that have not yet been contacted by the recruiting department. So far we have 320 subjects that have either been contacted and not qualified for the study or some which refused to comply with study requirements. During the last part of the day we had an office meeting where we discussed possible recruitment strategies for the MDD study. In addition, we are going to be acquiring another trial from a pharmaceutical company called SAGE. This study will investigate a drug for dyskinesia. Unfortunately, the inclusion/exclusion criteria are very stringent and will limit the number of subjects for our site. We anticipate only two potential patients.

Thursday June 22nd 2017

As the monitor visit progresses through day three there are some irregularities that had to be immediately addressed on paper and in the EDC. For example, the draw time on one of the requisition forms was written down incorrectly. Minute details like that can impede the smooth operation of the site as the testing laboratory has to be contacted, the mistake rectified, and new results faxed, printed, signed (by the PI who is on site only on Wednesdays and Fridays), and lastly filed. Everything is very time consuming. I also had the opportunity to enter patient results from yesterday into the central data base. Lastly, I made new charts for Friday's visits making sure that all components were ready to be filled out and signed. At the moment the biggest struggle for this site is continuous recruitment. It is the bane of everyone's existence as ideas, energy, and drive run low. As we have found out with our only schizophrenia patient, compliance is very important especially when the inclusion and exclusion criteria are so strict. It is a waste of time, money and resources when you invest all of your energy into a patient whose data may be voided if they decide to start doing illegal, or contra indicated drugs during the study.

Friday June 23rd 2017

Another patient day greets us with three MDD patients that are here for the infusions. Two of them are in the randomized phase of the trials, while the third one has been put on the drug until early termination or completion of the study. The numbers are low regardless. One of the patients for the day was a lady I was able to recruit through the phone screening process. Unfortunately, she was not a good candidate for the the study. Although the issues she was experiencing were not very significant, there were many of the them and the sheer number could cause too much mental instability for her to continue with the trial. Another task I was delegated was reading over medical records of a potential patient who will be enrolled in the RAP 03 study. My job was to look for medications that are exclusionary per protocol as well as any bipolar, schizophrenic, PTSD, anxiety diagnoses that would give us a reason to screen her out of the study. Upon inspection the patient turned out to be a great candidate, and hopefully will get enrolled as soon as the mandatory 8-week period passes.

Week 5

Monday 26th June 2017

The task for the day was to enter patient information into the EDC. Information from the binders had to be transcribed into the patient portal. It was a time consuming activity and it took most of the day.

Tuesday 27th June 2017

I started off the day by going through a spreadsheet of all the patients in IntakeQ, making notes about individuals who expressed interest but still need to be contacted by the recruiting staff. We have invested a lot of capital in this recruitment process and it is important to take as much advantage of it before we decide to do another phase of recruitment. During the second part of the day we had a meeting discussing the future of clinical research and potential for technological advancements that will replace some aspects of the job. The general trend is in the direction of electronic data capture, where study patient information is recorded remotely, completely circumventing the need for trial sites such as ours. We discussed the pros and cons and came to the conclusion that the human component is still needed. For example, in the case of

our study, it is imperative to evaluate patients for levels of depression. It is something that the individual would not be able to asses him or herself considering their mental status. Adverse events are another aspect of the study that need to be evaluated by a third party. While a subject might consider it important to report levels of irritability or anxiety they experience under normal daily conditions, it is the job of the clinical research coordinator to decide whether the side effects are due to regular life stressors such as a fight with a spouse or something that might be attributed to the drug. The rest of the day consisted of making patient charts for the Wednesday visits, tidying up the office, and calling the patients to confirm their appointments.

Wednesday 28th June 2017
Today is another patient day. There was a XXXX infusion for one of our new MDD patients. Among other things, my fellow intern and I had to address additional sticker notes left by the monitor who visited the site last week. Majority of the errors pertained to drug accountability logs and missed doses by the patients. We also had to make new patient files for the tardive dyskinesia study. Those binders are much different from the MDD files because they contain kinesiology assessment scales that are completed by Dr. Maynard and Dr. Davis (site PI). In the next couple of weeks, we are going to acquire a new tremor study that will provide us with another 10-15 patients. In order to prepare the resources and be ready to test patients we had to go through a brief training with the pharmaceutical company's representative. We learned how to properly assemble the accelerometer used to evaluate bodily tremors as the patients perform basic movements. The study is so technologically advanced the data is immediately sent to a central database without any manual data entry. Lastly, we spent about two hours phone screening potential patients for the MDD study. I am becoming very familiar with the daily tasks and the general flow of conducting clinical research.

Thursday June 29th 2017
First activity for the day was preparing for an interim monitor visit from one of our pharmaceutical company representatives. We had to edit patient binders, making sure that every page was accounted for and each procedure had a PI signature. We also had our daily meeting during which we discussed standard operating procedures which have been successful at minimizing mistakes, and ones that might be too burdensome or ineffective. Our clinical coordinator has implemented various fail safes which helps us be thorough in our job; however, even the most detail oriented individuals can miss small things during busy patient days. For example, before we file away any source documents from a patient visit, we have a cover sheet that has to be completed by a staff member who is entering data into EDC. Jessica, the CRC, then double checks our work and signs off on it. I personally find it very effective at keeping us accountable. Throughout the remainder of the day we focused on editing new sets of binders for the SAGE study. Tomorrow, we will have an initiation site visit with this new company.

Friday June 30th 2017
As patient days, Fridays are the busiest. We had six patients, five of them for the MDD study and one for Tourette's termination visit. I was responsible to taking temperature, blood pressure as well as setting up the leads for ECGs. As mentioned in previous notes we had a SAGE site initiation visit which began at 10 and lasted until 12 o'clock. The representatives went over pharmacokinetics and pharmacodynamics of the drug pointing out that the drug is metabolized through CYP3A4 hepatic enzyme. Since the drug acts on GABA receptors at the alpha subunit it

has a tendency to cause severe drowsiness which has been implicated as an adverse event. The protocol will necessitate continuous patient monitoring for a period of 14 days, during which the drug effectivity will be recorded in increments of 2 and 8 hours post dosing. This will also include Saturday and Sundays. It is one of the most advanced studies we have had thus far; it is a big step for our site. I personally feel proud and excited to be part of this advancement.

Week 6

Monday July 3rd 2017
Today was a half day. I spent most of the day arranging documents for the Friday visit. We had our weekly meeting during which we discussed the schedule for the week of July 10th. One of our senior staff will be leaving town and it is going to be my responsibility to perform some of his basic duties. I also found out how to schedule phone call interviews also called MADRS (Montgomery-Asberg Depression Rating Scale) for the MDD patients.

Wednesday July 5th 2017
Today we prepared documents for two MDD visits for that evening. We also had a skills lab practical conducted by our two senior staff members and Jessica who is the site's Clinical Research Manager. One other intern and I were tested on our patient screening visit tasks and procedures. The key component of patient intake is the preliminary consent form which allows us to take their vitals, screen for any illegal drugs, administer rating scales which evaluate depression, and any other initial procedures. The most important aspect of signing that form is the proper date format, writing initials on each page and making sure that there are no stray marks which would question the legitimacy of the document. In addition, we practiced taking vitals, ECGs, body temperatures, and RUSH videos (those consisted of taking a 10-minute video of Tourette's patient documenting any recurring tics or tremors). Unfortunately, the skills lab was interrupted by the arrival of our evening patients.

Thursday July 6th 2017
I had to take the day off due to mechanical problems with my transportation.

Friday July 7th 2017
The day started with an early morning visit by a Tourette's patient. Due to our training earlier in the week, my fellow intern and I had the opportunity to check in the patient and take them through the entire visitation process consisting of basic vital signs, ECG's, RUSH videos, and blood sample processing. Immediately after, we QC'ed the paperwork and entered the data into an EDC. I also learned about the process of informed consent. I had the opportunity to sit in on a meeting during which Jessica explained the study protocol, some of the known side effects of XXXX, particular time commitments and expectations. The patient had an opportunity to carefully go through every page of the paperwork, initialing and dating along the way. Afterwards, the consent form was checked by two members of the staff for any missed signatures or improper date formats. Lastly, we had a Friday afternoon meeting in order to go over the division of tasks and duties for the next week. It was an open floor discussion and we had the chance to comment on anything that has gone wrong or right throughout the day.

Week 7

Monday July 10th 2017
My tasks for the day consisted of preparing binders for an interim visit with Mathew who is the monitor from XXXX pharmaceutical company. He will come in tomorrow and evaluate our paper work, making sure that information entered into an EDC is the same as what has been noted on paper. Due to my colleague's week long absence I have been delegated the task of setting up MADRS phone calls. Later in the evening patient Z will come in to have her depression levels evaluated by an independent third party. As the weeks go by, my daily activities have become repetitive and familiar. It is a good thing. I feel comfortable with the process of clinical trials, at least in the context of a Major Depressive study. As part of our office Randy Randomization Contest, I made a couple phone calls to potential patients. In an effort to increase the number of randomized patients, we have started this contest with hopes that a little friendly competition and a prize (bragging rights) will enhance our recruitment statistics.

Tuesday July 11th 2017
My day started with compiling binders for the evening visits. We had two of those at 6 pm. Two infusions for MDD patients. When the monitor arrived we found out that we were missing essential documents for two of our patients. For the next four hours we searched the office looking for two pieces of paper that had times, collection dates, and pre and post drug infusion vitals. Although all that information has been filed electronically, as a trial site we have to provide a physical copy documenting the fact that the treatment has been done and the patient was stable enough to leave the premise. I was also able to sit in on an ADT visit. An ADT visit consists of a twenty-minute interview with a potential study subject who is not currently on an antidepressant but who is willing to start treatment in hopes of entering the study after the mandatory 6-week period. Patient Y seemed like a good candidate for the study. The next step is to bring her into the office to be evaluated by our site psychiatrist. If the doctor feels like patient Y is a good fit for the study, she will be prescribed an antidepressant and asked to return in six weeks for a screening visit. A screening visit is one of the longest lasting up to 3 hours. During that time, we not only take vitals and ECG's but also draw blood, assess mental stability by administering 6 various scales, collect urine for a pregnancy test, urinalysis, and drug screen.

Wednesday July 12th 2017
One of my activities for the day was to generate a Dear Dr. XXX note. Those are used for patients who during an informed consent process request that their participation in the clinical trials be documented and sent off to their general practitioner. There were three patients who needed those notes. I spent the rest of the day editing folders as well as updating source documents from previous studies. Lastly, we had a late night patient who had her MADRS phone call and rater scales done. She was in a very poor frame of mind. In fact, we had to report a potential suicidality risk. She has been under a lot of stress at work and her personal life. The patient will be closely monitored over the next couple of days via additional visits to our site as well as regular phone calls throughout the day. She will see our psychiatrist on Friday for further evaluation. Her mental stability is the result of circumstantial events rather than the drug. She has been responding and tolerating XXXX since the beginning of the trial, but unfortunately a series of events has thrown her out of balance.

Thursday July 13th 2017
My day started later than usual. After last night's events, we took the morning off to regroup and reorganize the schedule for our Friday's visits. Binders had to be compiled and flagged for all patients. I also spent some time returning phone calls from interested individuals. Interestingly, we had a gentleman call our site, asking about our essential tremors study. This is our newest study, and if he qualifies, he will be our first patient. The protocol for the study lasts 14 days including weekends. It is the shortest, yet most intensive study we have had so far. The experimental drug is administered daily, and the tremors are evaluated throughout an eight-hour period. As mentioned before we will be using an accelerometer to measure tremors in both hands. He is scheduled to come in on Monday for a prequalifying visit. Although the drug we are testing is only in phase II trials, it has been showing some promising results. It is an alpha subunit GABA receptor partial agonist. The reason why this study is especially interesting is because there has been little to no pharmaceutical investigation in the area of essential tremors. There is one FDA approved drug specifically designed to ameliorate the symptoms.

Friday July 14th 2017
Today has been an incredibly busy day. We had eight regular patients, as well as two new ADT visits, and one in screen. The day began with the in screen. I had to collect vitals, perform an ECG, prepare scales, and schedule a MADRS phone call. Jessica conducted the initial psych evaluation, performed the informed consent, and drew the patient's blood. Although the list of tasks was short, it took seven hours to get the patient processed and enrolled in the study. In the meantime, we saw our regular patients who had simple infusions. The day unfortunately ended with one of our patients reporting a suicide attempt. I am not sure what the next step will be with regards to her participation in the study and her general well-being. One of the exclusion criteria for the MDD study is suicidality; regardless, we are worried about her mental status. She moment she entered our study she not only became a patient but also a member of our research family. All of our patients have access to Jessica and other staff members 24 hours a day 7 days a week. If anyone is having problems, we want to know about it, no matter how big or small. The patients should feel comfortable enough to let us know what is going on in their lives. The message has been clear this week, we cater to our patients by operating on an entirely different schedule than any medical office, excluding ER, or course.

<u>Week 8</u>

Monday July 17th 2017
The day started with filing back charts and filling out any source documents that have been left unfinished on Friday. Some phone calls were made in order to recruit more patients and further preparations were initiated for tomorrow's late night visit.

Tuesday July 18th 2017
I began the day by organizing patient charts and faxing medical record release forms. The filing and chart maintenance has become my delegated task. I am responsible for completing and making sure that all the patient charts in the office are up to date and have all of the necessary signatures as well as paperwork in appropriate sections of the binders. Additionally, I had to create new folders for the in-screened patient who came in last Friday. We will have to wait two weeks to get back the lab results and the affirmation from the sponsor to go ahead and enroll this

patient in the study. There were three ADT visits in the afternoon that seemed very promising as potential patients. This month has been very busy and our enrollment rates have increased two-fold. Another new development has been the essential tremors study for which we have already chosen two potential patients. We are going to be screening those on Monday of next week. At the end of the day we had a staff meeting during which we submitted our office supplies requests and discussed the schedule for the remainder of the week. Our Friday is going to be very busy.

Wednesday July 19th 2017
Having been delegated the task of organizing binders, I took the time this morning to inventory all of our current and past studies. I itemized all of the patients in each trial, noting all of the missing documents, signatures, IWRS sheets, lab results, and bracket prints outs. The next couple of weeks are going to be laborious due to new study acquisition and two monitor visits. As August approaches, we are getting ready to close out two tardive dyskinesia and one Tourette's study. On the other hand, as I have mentioned before, we are initiating a SAGE sponsored essential tremor's and post-partum depression study. It is rumored that I might have the chance to lead the PPD trials. I am very excited about this potential opportunity. If chosen to be the CRC for this trial, I will be in direct contact with the pharmaceutical company and their leading physicians who are responsible for designing the study. This would be a small step into the world of clinical research.

Thursday July 20th 2017
My entire day consisted of going through stickie notes left by a monitor, and addressing irregularities/queries that might pose an issue during an FDA audit. There were 26 binders in total. Each one consisting of fourteen sections or more, dividing up the visits, concomitant medications, adverse events log, lab reports and more. We were scheduled to have a screening visit for a potential patient, however she did not show up for her appointment. The evening progressed as usual- two visits with our regular patients supervised by our physician and two ADTs. There was a randomized patient who got infused, thus he could potentially be getting a saline solution or the actual drug. The week seemed promising until we had our second screen fail to show. This is concerning because we are not sure if it is just bad luck or if our recruitment strategies are not effective enough. Both patients would have been excellent candidates for the study. On a different note, I have scheduled a visit at the statistics lab in anticipation of my proposal approval and data collection. I also had a meeting with Jessica during which she assigned me the role of a quality control monitor.

Friday July 21st 2017
Another Friday morning began with patient assessment and drug administration. We experienced one anomaly pertaining to an abnormal EGC. The physician had to evaluate whether the potential artifact had anything to do with the study drug. She decided to continue with the drug treatment. The patient was in good health. The remainder of the day consisted of filling out charts and completing all the data necessary for EDC entry. I did learn the purpose of a Note To File, and was directed to write one up myself. An NTF is a note for the sponsor and potential FDA auditors noting any changes or deviations from SOPs (standard operating procedures) that our trial site has put in place in order to enforce quality control. For example, each time a patient comes in for a visit we are required to perform a list of procedures. Often time there are many items on that list and it is very easy to miss something. For that purpose, we have a check list that

guides us through a visit and ensures that we perform all actions items. We have been employing this QC method since the beginning of the study, however, earlier in the year the site switched to an electronic data entry. This made the check lists, which are often times called study coversheets, obsolete. In the NTF I had to explain why we chose to quit writing out the coversheets.

Week 9

Monday July 24th 2017
Due to a family medical emergency I was out of the office.

Tuesday July 25th 2017
My day at the office began with a meeting with Jessica, the clinical research manager. We discussed my progress and devised a plan for the following month regarding the upcoming studies, specifically the PPD study for which I will be directly responsible. In the evening time we saw three MDD patients, one of which was advancing from Part A (which is a double blind portion of the study) to Part B(the open label investigative drug). Our recruitment efforts have been paying off, after two months of relatively stagnant enrollment we have had three new patients join the study within the last three weeks. In addition to the essential tremors study, and PPD, we will be adding a third new trial- pediatric essential tremors.

Wednesday July26th 2017
Wednesday has been a house keeping day. We saw no patients, but rather focused on filling out essential paperwork for all current studies. I compiled a couple of binders and briefly focused on graduation paperwork. Later that same day I was given one more additional study to coordinate. I have been officially made the lead coordinator for two studies: essential tremors, and post-partum depression. My next steps are going to involve visit schedule development and pre-screening/screening patient visit programs as well as source documents.

Thursday July 27th 2017
I focused on my upcoming study today. I familiarized myself with the minute details of the protocol and the procedures needed to be performed at each visit. As mentioned before the ET study lasts up to two weeks and it concentrates of evaluating safety, tolerability, and efficacy of the investigational drug. Our population encompasses individuals from the age of 18 all the way to 75. The patients have had to be formally diagnosed with an ET by a neurologist or a movement disorder specialist. In order to evaluate the efficacy of the investigational drug, a multitude of scales has been set in place that score the tremor reduction, and the drug's effect on lassitude/sleepiness.

Friday July 28th 2017
Friday was particularly difficult. In addition to an already busy patient schedule we had a monitor and PSSV visit. The PSSV visit stands for Pre-Study Site Visit. This is a visit done by a pharmaceutical representative who evaluates our facilities and approves us for the study initiation visit. Luckily, everything went smoothly and we ended up getting the green light to continue into the next phase. The evening was spent entering data into EDC and organizing the office for next week.

Week 10

Monday July 31st 2017
The day began with filing away all regulatory documents for essential tremors study. As the new CRC I am responsible for updating training logs, and delegation of responsibilities. Additionally, I had to address all action items that had been pending since site initiation visit, one of them being an IRB continuing review form. The purpose of this document is to let the central IRB aware of our ongoing trials. On a more exciting note, we were able to finish screening our first ET patient. The protocol is very confusing and entails many procedures, therefore it took three visits to complete everything. The plan for the next week is to compose source documents for visit Minus One and the next two weeks. Before going on with the study, I will have to submit the documents to our CRA (represents the sponsor). Friday will be our tentative date for setting up visit minus one. In other news, the post-partum study has a site initiation visit scheduled for August 16th. This is the second study for which I am responsible.

Tuesday August 1st 2017
I had the chance to finalize the ET schedule for the next two weeks. We have received every inclusionary data point for our first screened patient and are ready to begin day minus one procedures. I have decided to begin the trials on the upcoming Monday. There are many working components that factor into setting up and carrying out a study. There is a group of vendors which are responsible for each separate component of the study. For example, we had to contract a local laboratory that provides us with STAT labs whenever we are checking drug pharmacokinetics. Another example is XXXX XXXX- vendor that provides the accelerometers and gyroscopes which evaluate severity of tremors. As a CRC I am responsible making data sources and figuring out how to use the EDC in order to capture all points data points of interest.

Wednesday August 2nd 2017
I had the chance to screen some patients for the Schizophrenia study. It is something I have not done before. Essentially, we are looking for people who are relatively stable on their current medication but would be willing to transition to either Olanzapine or Risperidone, depending on their trial randomization. Some of the exclusionary criteria for the study are glucose and HbA1c stability, proper liver enzymes levels and no history of suicidality. In more exciting news, we scheduled our SIV visit for the PPD study. The evaluation will occur in the third week of August. Enrollment of the first patient is expected to occur 30 days later. At that point I will be leading two of my own studies and backing up three other ones. Toward the evening we saw three of our depression patients.

Thursday August 3rd 2017
Today I learned about the regulatory documents necessary before a study can begin. We needed to fill out special request for initiation of research to our central IRB. In addition, we had to provide proof of GCP training, staff CV's, and XXXX waiver. The only remaining items on the action list are EDC training, and laboratory staff certification. On a different note, the rest of the day entailed making binders and preparing for the busiest day of the week which is Friday. We will have three XXXX, three XXXX, and four MDD patients. In the late afternoon there will also be an ADT visit with a potential MDD patient. Throughout the course of the week we have

been going through every single patient binder making sure that all records are up to date and the next monitor visit goes by smoothly. The date for our first ET patient has changed yet again. The trial will start on Sunday. We will perform tremor evaluations, take blood/urine samples and ECG's. Because the subsequent visits will last for the next 14 days, 8 hours each day, we had booked a room for the patient at a nearby hotel. The extent of accommodation and compensation seem limitless on our, and the pharmaceutical company's part.

Friday August 4th 2017
The day began earlier than usually due to the large number of patients. There were final touch ups necessary before we began admitting patients. Overall Friday went by smoothly, with very few issues. The day consisted of multiple infusions, scales, and rush videos (those videos are of Tourette's children- the purpose is to evaluate a number of ticks experienced by the patient in a 10 minute times span). Each patient needed their vitals taken, along with ECG's, blood and urine samples. Lastly, we had and ADT appointment, and a late afternoon phone call assessment for a MDD patient. The final order of business for the day was to finalize all necessary equipment and paperwork for this Sunday day minute one visit.

Week 11

Monday August 7th 2017
Today was the first dosing day for our essential tremor patient. After extended preliminary evaluation of the tremor via XXXX accelerometer and gyroscope, as well as the investigator, we dosed the patient. For the next 8 hours we took his vitals and blood samples for pharmacokinetic testing. Along each step of the way we assessed for any adverse events, or reactions that the patient might be experiencing. We also tracked the levels of sleepiness. Some of the house keeping items on the agenda consisted of filing and making new regulatory binders for the PPD study. We also spent some time preparing for a Tuesday evening patient visit.

Tuesday August 8th 2017
In the light of the evening patient visit, we tidied up the office and made sure that all the lab kits were prepared for the evening. There were three regular MDD patients, one of which ended up rolling over to the next phase of the study. The ET patient got his second dose of the medication. Following the dosing we monitored his vitals, mood and energy levels for about 8 hours. Some additional scales were administered to evaluate the tremor. At the end of the day I updated the EDC.

Wednesday August 9th 2017
The highlight of the day was my conference call with the director of a company that we will being using for the PPD study. They provide certified nurses that pay at home patient visits which include patient dosing as well as vital and blood collection. Having this company at our disposal can potentially make the study a logistical nightmare. There are many dependent variables at play which may end up compromising the collected data. For example, the time lag between blood collection and delivery to our site may become an issue as samples get lost or improperly preserved during the transport. We may have to cut out the middle man and start paying at home visits-specifically for the PPD study-mostly because the dosing has to occur at night. This is a less than ideal situation that might require a different solution.

Thursday August 10th 2017
My number one priority for the day was to finish making the source for our ET patient. As we progress further into the study, the days become shorter, requiring less oversight on our part. For example, after establishing a stable dose for the patient, we collected a few vitals and assessed stability. We were happy to report that the patient was tolerating the medication and seeing some very promising results. His tremors were almost invisible. Some of the basic tasks he was struggling with- like buttoning a shirt- were no longer an issue. It is amazing to see the progress and pharmaceutical advancement right before your eyes. Those moments make up for the never ending rat race that clinical research can be.

Friday August 11th 2017
Friday, like any patient day, was very busy. We had our regular ET and MDD patients. As a backup coordinator for the MDD study, I was responsible for helping with vitals, data capture, data quality control, and completion. I helped my coworker with the process of patient admission and check out, as well as ECG capture. Having finished earlier than anticipated, I took the time to complete my ET patient's EDC. Throughout each day of the study we record many data points and all of them have to be transferred carefully into the electronic record.

Week 12

Monday August 14th 2017
Today was an exciting day in the sense that we got to randomize our first ET patient. As hoped, he showed great signs of improvement with regards to his tremor and was able to proceed to part B of the study. In the second part of the study the patient is either given a placebo or the real drug. Based on XXXX and XXXX scales (scales that evaluate the tremor) we need to report a progression or regression of symptoms. The day consisted of taking blood samples, ECG's, vitals, and blood oxygen saturation levels. As a small diversion from the daily activities we took some time to rearrange the office, providing a more open plan, with better functionality. Other than the ET patient we had no other visitors thus the day consisted of regular paperwork, patient recruitment, set up for Tuesday/ Wednesday patient visits, as well as updating the regulatory binders in anticipation of a monitor visit tomorrow. Our SIV visit for the PPD study got pushed back due to some delayed paperwork, but most of the infrastructure for the study is already in place.

Tuesday August 15th 2017
I spent the day entering new data in to the EDC for my ET patient. Along with paper work I performed all the scheduled procedures for day 9 of the trial. Vitals were taken 6 times throughout the day. There was a blood draw, two ECG's , and all sorts of scales that evaluate patient tremor and sleepiness. I was able to finish my full EDC training, and focus some of my time on patient recruitment. We also had a successful monitor visit. It was a slow and peaceful day before our Wednesday patient day.

Wednesday August 16th 2017
I spent most of my day answering emails from sponsors, monitors, and vendors regarding my essential tremors study. In addition, there were a couple IRB regulatory related issues that

needed to be addressed. In the evening we conducted three MDD patient visits for the Part B part of the study. This is the open-label portion where both the subject and investigator know to be taking the real drug. During this part of the study we see the greatest improvement in patient mood and mental stability. We are also looking into different avenues of patient recruitment. I am scheduled to speak about our essential tremors study during an ET support group meeting that meets in east Dallas every month.

Thursday August 17th 2017
Today was a relatively peaceful day. I spent it finishing up source for the remaining three days of the ET trial as well as completing submissions for the EDC. I made all of the folders for tomorrow's visits and readied the drawing kits for two of our patients' blood work. There was a minor technical issue with an XXXXX band that measures levels of tremor. I had to figure out a way to download the data from the device to the sponsor's database since the computer provided has crashed. Lastly, I contacted the CRA and let her know about our recruiting efforts for the upcoming second ET run.

Friday August 18th 2017
As we are approaching the end of the ET two-week trial period, we are increasing our recruitment efforts to find another person who may be eligible for enrollment. Some of the places we have reached out to were the international ET foundation as well as ET support groups located around the DFW area. We are looking to have at least two patients going through the two-week cycle next time we begin the study. As of right now, the end date for XXXXX is this Sunday. We will have a break of about two weeks before the next round of testing begins. On a different note, today was another easy patient day, consisting of three MDD patients who have advanced from XXXX to XXXX meaning that there are in the open-label portion of the protocol. One of the however, has achieved a level of stability where she is ready to go into the double-blind portion of the trial, meaning that we will not know if she is taking the drug or not. In the past we have seen patients relapse (because they were taking the placebo) and be taken into XXXX which is another portion of the protocol where the individual is taking an open-label product.

Week 13

Monday August 21st 2017
After fifteen consecutive days at work we decided to have Monday off.

Tuesday August 22nd 2017
Today I focused on preparing the ET patient folder for upcoming monitor visit. I had to make sure the source and all paper scales were in order, along will ECGs, and paperwork tracking blood draws. Due to sponsor protocol revisions, all ET associated operations have been put on hold. We anticipate major changes with regards to the protocol due to low patient recruitment and large loss to follow up. The protocol so far requires the staff to be on site for fifteen days straight for at least 8 hours a day. Feasibility is low. North Texas Clinical Trials has been the only site in United States that carried out the protocol to completion.

Wednesday August 23rd 2017
I concentrated on compiling all of the patient binders for Wednesday evening and Friday morning visits. All of our patients this week have been MDD patients.

Thursday August 24th 2017
As a group we spent the day arranging the office and making sure everything was ready for the monitor visit. We had to make a couple patient binders and file all of the regulatory paperwork for essential tremors and post-partum depression studies.

Friday August 25th 2017
On Friday we had a three patient visits. Unfortunately, we had to early terminate one of them due to lack of compliance. Our patients are required to take their antidepressants when being treated with the experimental drug. An individual has a window of 5 days without medication in order to remain in the trial. Our patient has gone two weeks without her medications thus violating the protocol and forcing us to end her participation in the study. It is unfortunate, but necessary. We provide a lot of support to our patients. We offer to cover the cost of their antidepressant medications in addition to providing a weekly stipend with each visit. Although we are responsible for a lot of aspects of the patient's treatment and well-being, there are certain things the individual needs to take care of her/himself.

Week 14

Monday August 28th 2017
With the new additions to the ETD protocol, I have been concentrating on recruiting age appropriate candidates for the study. As mentioned before, the pharmaceutical company SAGE, is planning to cut down the trial protocol to 4 clinical days and 10 additional dosing days, with only two or more 8 hour visits on site. This has been a huge obstacle for us because the two-week time spans which are required by the study are not only tasking on the patient but also on the staff which has to be on site for the entirety of the study. Our personnel consist of the site manager, two study coordinators (my coworker and me) and a regulatory specialist. Within the next two weeks we should we getting the revised protocol and will be ready to start three new patients. In addition, we will finally be having a site initiation visit for the post-partum depression study. This is a second study by SAGE offered to our site. As we move into the fall/winter season we expect to grow two fold.

Tuesday August 29th 2017
Today I pre-screened a potential ETD patient. We had a long conversation about the study schedule and what the patient can expect from us as well as what we will require from the subject. With the new additions, we hope to retain more patients and keep enrolling new ones. In other news we had acquired a new bipolar study which will begin in late October. This will keep us very busy in the upcoming months.

Wednesday August 30th 2017
We had our PPD site initiation visit today. This is another study I will be coordinating in the next three weeks. We are currently waiting IRB amendment approval for the finalized protocol. In the meantime, my time will be spent finding potential patients. This may be difficult due to the fact

that most mothers who are depressed do not have the time or desire to be part of a study. It is a very difficult subject and a sensitive time in their life.

Thursday August 31st 2017
I spent my day preparing binders for patient visits. After our first ET monitor visit, I had to address queries. Queries are generated by the monitor when there are discrepancies in the data entered into EDC and source documents.

Friday September 1st 2017
Today was another patient day. We had three MDD and two Tourette's patients. We were kept busy all day with various procedures and paperwork.

Week 15
Monday September 4th 2017
RMV for MDD study

Tuesday September 5th 2017
Regulatory day

Wednesday September 6th 2017
Patient visits.

Thursday September 7th 2017
Patient visits

Friday September 8th 2017
Patient visits

Week 16

Monday September 11th 2017
Today was an office day during which I made phone calls to potential patients for the depression study. I screened three patients and signed them up for an ADT visit during which they will be questioned about the history of their depression, diagnosis, and the types of medications they have been prescribed over the course of the disease. Afterwards it will be decided whether the patient can proceed in the study and if they will be put on a specific type of antidepressant. In other news, we received an updated version of the XXXX protocol and have been cleared to start enrolling patients in the study. The plan for the rest of the week is to contact all of my ET patients and start their screening process on Friday.

Tuesday September 12th 2017
Tuesday was a regulatory day during which we focused on filing away procedural amendments which have been recently submitted to our central IRB. Most of the time the primary reason for a protocol amendment is done because recruitment and retention of study subjects has been proven to be difficult. This is something we experienced during the ET trial where the protocol required the patient and staff to be on-site for 14 days, 8 hours a day. The protocol proved to be too

tasking on patients and therefore had to been restructured by the pharmaceutical. 14 visits were decreased down to 5, lasting only a couple of hours each time.

Wednesday September 13th 2017
The day consisted of making charts for evening visits. We had four MDD patients. One of them was randomized into the second part of the study. The randomization consisted of general blood work, ECG and scales.

Thursday September 14th 2017
Today I lead three ADT appointments. The purpose of ADT appointments is to go over patient's mental and medical history in order to determine if they would qualify for the study. Secondary reason is to put them on an antidepressant if they haven't taken over within the last 2 weeks. In the afternoon we had three patient visits for the depression study. Some of the procedures consisted of ECG's, blood draws, scales and physician evaluations. We also had a Webex meeting into order to go over the ET protocol changes which have recently been approved by an IRB.

Friday September 15th 2017
Friday was an administrative day. I made phone calls to all of the ET study patients, and then continued to recruit for MDD. I cleared the ET EDC, completed a continuing study IRB forms, uploaded all relevant Et study patient data and contacted the patient recruitment firm which is responsible for helping us find potential study subjects.

Week 17

Monday September 18th
Today we spent most of the day screening patients for MDD and filing paperwork as well as regulatory.

Tuesday September 19th
This was a patient day. We had seven MDD patients with one of them rolling over into second part of the study. Second part of the study is open-label.

Wednesday September 19th
I started the day with answering all emails and providing signed PI forms to CRA's. I then focused on pre-screening patients for my ET, PPD and MDD studies. I was able to schedule two people for tomorrow's visit. In addition, I completed a IRB continuing review submission for PPD, and held a conference call with respect to recruiting materials for the next campaign. Later in the evening we had a remote visit with one of our CRA's for the MDD. We are in good standing with all the pharmaceutical companies.

Thursday September 20th
Our site manager conducted a comprehensive training covering historical leading up to the Nuremberg Code, Belmont Report, development of FDA and ICH regulations, the eight components of informed consent, some of the standard operating procedures and the general lifetime of a study protocol.

Friday September 21st
As a lead CRC on the PPD study I was able to attend a two-day investigator's meeting held in Dallas. With the new additions and amendments to the study, the pharmaceutical company held a conference in order to retrain PI's and coordinators on the protocol changes. It was a great opportunity to put faces to names I have been contacting contacting over the last couple of months. Some of the topics of discussion were Inclusion and exclusion criteria, expectations with regards to recruitment and patient retention. There were some concerns pertaining to the subject population which are post-partum women. Second day material covered pharmacokinetics and dynamics of the drug and major anticipated side effects of the study medication.

Week 18
Monday September 25th
Today we screened a patient for a schizophrenia study. The subject had a complete physical done, including lab work, and an EKG. Some of the other duties included making new source documents for the PPD study, filing and making recruitment phone calls.

Tuesday September 26th
The day consisted of making patient folders for the evening visits. Some patients had to have additional lab work and PK samples prepped. I also filed a continuing review file for our central IRB and set up days of monitor visits for three of our pharmaceutical representatives.

Wednesday September 27th
I worked on completing drug accountability logs, ordering extra lab kits and drugs for the studies. I also entered new data into the EDC and completed a continuing review form for one of our depression studies.

Thursday September 28th
Today was a patient day. We had five depression patients and one Tourette's patient. We focused on completing all visit related procedures in a timely manner.

Friday September 29th
The day was spent on filing away all outstadining paperwork into the patient and regulatory binders.

Week 19
Monday October 2nd
The day began with handling left over paperwork from Friday. We then focused on reviewing all binders in order to prepare for a monitoring visit from a sponsor representative.

Tuesday October 3rd
This was patient day. We completed all patient related procedures. I also began screening patients for our ongoing PPD study. This took up most of the day.
Wednesday October 4th
The day focused on continuing screening for our PPD study

Thursday October 5th
This was the second patient day of the week. We conducted patient related procedures and source documents, while transferring all the data from paper to EDC.

Friday October 6th
Throughout the day I focused on making new source documents for my new PPD study.

Monday October 9th
I spent most of my day answering emails from sponsors, monitors, and vendors regarding my essential tremors study. In addition, there were a couple IRB regulatory related issues that needed to be addressed. We also began screening new patients for our schizophrenia study.

Tuesday October 10th
In the light of the evening patient visit, we tidied up the office and made sure that all the lab kits were prepared for the evening. There were three regular MDD patients, one of which ended up rolling over to the next phase of the study. All patient related procedures were completed and captured in the EDC.

Wednesday October 11th
Day off

Thursday October 12th
Patient day

Friday October 13th
Recruitment day.

Monday October 16th
Recruitment day and office filing.

Tuesday October 17th
Patient day and all the visit procedures.

Wednesday October 18th
On this particular day we screened our second ET patient. The procedures involved taking blood samples, ECG's, vitals, and blood oxygen saturation levels, as well as scales evaluating tremor and the severity of the disease.

Thursday October 19th
Second patient day of the week.

Friday October 20st
Filing, patient recruitment, regulatory and source document day.
Monday October 23th
Patient recruitment day.

Tuesday October 24th
Due to minor adverse events experienced by one of our patients, their medication dose had to be adjusted. Patient had blood work and an ECG done, along with a physical and some scales.

Wednesday October 25th
Patient day

Thursday October 26th
Recruitment day/ Working on my presentation.

Friday October 27th
I spent the day creating additional source documents for our ET study as well as practicing my presentation.

Monday October 30th
Thesis Defense Day

Tuesday October 31st
The office closed earlier due to Halloween.

Wednesday November 1st
We had two patient visits both for ET. The rest of the day consisted of gathering the data and entering it in the EDC.

Thursday November 2nd
Patient Day

Friday November 3rd
Recruitment day

November 6th
My day consisted of entering EDC data, filing away regulatory materials, responding to emails, tidying up loose ends with regards to patient eligibility and participation into the study.

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