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Views on Clinical Trials

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Clinical Drug Trials have had a significant role in the public health arena dating all the way back to World War II. Although not always apparent to consumers, clinical trials have exerted a strong presence in the health of many individuals today. The purpose of this practicum research project is to understand the attitudes and opinions of individuals with chronic illness, drug related injuries, who are participating in a clinical trials compared to non-participating controls, relative to the risks and benefits of pharmacological treatment and clinical trial participation. A survey method was employed to collect attitudes and opinions of subjects from North Texas Clinical Trials and individuals from the general public. This survey was designed to illustrate potential differences in the perspectives of the two groups of subjects in a quantifiable manner. These clinical trials research materials have been designed and approved by the appropriate Institutional Review Board (IRB) committee. Upon the completion of this study we hope gain a deeper understanding of the perception of Clinical Trials and, hopefully, this knowledge may prove to be insightful towards developing innovative methods to obtain a stronger recruitment turnout.

VIEWS ON CLINICALS TRIALS

Bryan Tran, B.S., M.S.

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VIEW ON CLINICAL TRIALS

INTERNSHIP PRACTICUM REPORT

Presented to the Graduate Council of the

Graduate School of Biomedical Sciences

University of North Texas

Health Science Center at Forth Worth

in Partial Fulfillment of the Requirements

For the Degree of

MASTERS OF SCIENCE

IN

CLINICAL RESEARCH MANAGEMENT

By

Bryan Tran, B.S., M.S.

Fort Worth, Texas

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ACKNOWLEDGEMENT

I would like to express gratitude to my committee members, Dr. Patricia Gwirtz, Dr. Geoffrey Guttmann, and Dr. Brian Maynard for allowing me this wonderful opportunity to explore a new field in medicine. I am grateful that each person has had the patience to continually express support this endeavor.

Dr. Gwirtz has been monumental in my introduction into this arena because she not only welcomed me with open arms but gave me the tools to succeed in this internship. She has been there every step of the way, no matter how frustrating I'm sure it was for her. I sincerely appreciate your kind and generous efforts in getting me on track of my true goal. As a mentor, as a counselor, and as my saving grace there a not enough "thank you" to ever repay you for the kindness you have bestowed upon me. You have been instrumental in my motivation to succeed.

Dr. Maynard has been exceptional in showing me the operations of a clinical research site. He allowed me under his wing to gain valuable hands on experience. Being patient and kind have been the best qualities that I have learned and chosen to exemplify in my daily life.

Dr. Guttmann, thank you for sacrificing several minutes out of your busy schedule to meet up with me on several occasions and talking to me about areas of improvements.

Thank you to my mom and dad for giving life. I love you.

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CHAPTER I. INTRODUCTION

Clinical Drug Trials are defined by the United States government as a method a company uses to test the safety, efficacy, and life-span of a specific drug before releasing the drug to the public[8]. From discovery to treatment, development of one specific medication can take up to 10 to 15 years[7,8,13]. The estimated development cost from pre- discovery to post marketing surveillance is around 800 million to 1 billion dollars[6, 7,8,13]. Unfortunately, only 1 out of every 10,000 compounds that are discovered will become approved as a new drug[8].

The first stage in the development of a new drug is the pre- discovery stage. At this stage scientists analyze and evaluate a specific disease state. They examine how the disease affects certain structures of the human body. After adequate research of the disease a "target" can be chosen[7,8,13]. This target may be a single molecule that is necessary in the mechanism of the disease[7,8,13]. One consideration is whether the target is susceptible to a drug molecule[7,8,13]. To validate this target, molecular scientists study the target's relevance when living cells and animal models are infected with the disease[7,8,13].

Paired with a thorough research of the disease and a target molecule, scientists begin to either search or create a lead compound[7,8,13]. The purpose of the lead compound is to affect the target molecule in some way that alters the course of the disease[7,8,13]. There are 4 methods in which lead compounds can be obtained[7,8,13]. Nature provides a variety of substances which can act as lead compounds[7,8,13]. De novo discovery is the method of creating a lead compound from scratch with the use of a computerized model[7,8,13]. Biotechnology is a method where genetically engineered organisms produce disease-fighting biological molecules[9,13]. Finally, the most

common method of drug discovery is called high-throughput screening where many compounds are tested to see which has the greatest activity towards the target[13].

Once a lead compound is found, its pharmacokinetics will be investigated[7,8,13], including the mechanisms in which the drug is absorbed into the bloodstream, distributed to necessary tissues, metabolized efficiently and effectively, and excreted, and characterized. If the compound shows signs of toxicity, the drug may be altered structurally to reduce its potential risk for side effects. During the optimization stage the drug delivery method will be determined. At the preclinical testing stage the drug will be tested in biological assays, including whole animal studies where observations can be made of the drug's safety and efficacy. After analyzing the data and determining that the drug is safe and potentially effective, the drug will be referred to as a candidate drug.

The drug development process starts upon approval of the Investigational New Drug application (IND) by the Food and Drug Administration (FDA) to begin human trials[13].

The main purpose of Phase 1 Clinical Trials is to assess the safety of the "candidate drug"[13] in man. The drug is tested in a small sample of around 20- 100 healthy volunteers[13]. Observations and evaluations will be made regarding the pharmacokinetics and the pharmacodynamics of the drug. Pharmacokinetics is defined as what the body does to the drug. Pharmacodynamics is defined as what the drug does to the body. These evaluations inform researchers about the safe range for dosing and the degree to which side effects are present.

Phase 2 Trials have a slightly larger sample population of around 100 to 500 subjects who suffer from the condition that the drug is intended to treat[13]. The Phase 2 Clinical Trials is the first test of efficacy. For novel compounds Phase 2 trials are often referred to as "Proof of

Concept", as they will assess the ability of the compound to affect some measure of the disease state.

Phase 3 Trials contains a significantly larger sample population ranging from hundreds to thousands of affected patients[13]. Phase 3 trials provide data on the drug's safety, efficacy and overall risk /benefit. Phase 1,2, 3 Clinical Trials are then submitted along with a New Drug Application (NDA)[13] to the FDA for approval. If the results from the studies show the compound to be efficacious and have a tolerable risk profile, the drug will receive marketing approval.

After the drug has been introduced to the market, Phase 4 trials are initiated. The main goal of Phase 4 trials is to observe and evaluate the drug's safety for extended periods of time, usually around 2 years[13]. This is a component of the larger field of Pharmacovigilance, and a critical part of ongoing drug safety.

The earliest documented concept of Clinical Trials started with King Nebuchadnezzar circa 562 BC[14,15]. His military leader devised an experiment examining the dietary intake of his subjects. The hypothesis was people who ate a strict diet of meat and wine would become healthier[14,15]. A group of vegetarians refused to eat meat so they were given legumes and water as an alternative. The results of this experiment surprised even the King. The individuals who consumed only legumes were at a better state physically than those who had only consumed meat and wine. Even though this was the earliest documentation of a clinical trial, King Nebuchadnezzar was not given the title of "the father of the clinical trial". That honor was bestowed upon a British doctor by the name of James Lind[14,15]. In 1747 many sailors suffered symptoms of scurvy, including "putrid gums, the spots and lassitude, with weakness of knees" Dr. James Lind's "Treatise on Scurvy" published in Edinburgh in 1753) [14,15]. Through his

method of grouping, he made 6 different treatment plans for 12 sailors[14,15]. Eventually the pair of sailors who had consumed his citric treatment recovered miraculously.

The first use of a placebo in a clinical study was 1863 by Austin Flint[15]. He treated his patients for rheumatism with an herbal extract and compared the results with patients who were treated with the real remedy[15]. Before 1938, a drug could be introduced to market without proof of effectiveness or evidence of toxicity[20]. That changed with the introduction of "elixir of sulfanilamide" [20]. At that time Sulfanilamide was considered an effective treatment for infectious disease[20]. However, as facilitation method to children, ethylene glycol (a component of antifreeze) had to be used to dissolve Sulfanilamide. Ultimately, around 107 children died as a result of the ethylene glycol poisoning[20]. Amendments were added to the Food, Drug and Cosmetic Act of 1906, making toxicity testing mandatory before any drug is introduced for public consumption[20]. In 1943 an investigation for treatment methods for the common cold gave rise to the first double blind controlled trial[15,17]. Neither physicians nor patients knew if the treatment or placebo was administered[15,17].

Ethics became a significant issue in clinical trials because of the dangerous cases of abuse pertaining to human experimentation during the second World War[14,15,16]. In response, the Nuremberg Code was created to emphasize the ethical principals of human experimentation[15,16]. In 1962 the Kefauver-Harris amendments were approved which gave the federal government a stronger hold on drug testing and made the informed consent process mandatory[15]. This was in response to the thalidomide incident[15,19]. In 1956 Thalidomide was introduced as a treatment for nausea in pregnant woman in Europe[15,19]. It was not yet approved for use in the U.S. However serious congenital deformities occurred because of the pharmacological effects of the drug[19]. Thus, Thalidomide was banned by 1961[19].

Another historical event which became a powerful reason for public mistrust in clinical trials was the Tuskegee Syphilis Study[15,16,18]. From 1932 to 1972, the United States government sanctioned study, denied to treatment to 399 black men from Alabama for syphilis for the sole purpose of observing the natural course of the disease[15,16,18].

Since 1938, the FDA required a larger expectation of drug companies to adhere to a stricter set of safety regulations. However, a more complex safety concern of long term drug use was not considered until the introduction of Vioxx (Rofecoxib) a cyclooxygenase- 2(COX-2) inhibitor[3]. Vioxx was a specific type of pain killer, non steroidal anti-inflammatory drug (NSAID)[3]. In 1999 Vioxx[3] was heavily marketed and approved for release for public use. For five years Vioxx[3] exploded onto the drug market with its strong adventurous campaign that emphasized the reduced gastrointestinal side effects it had on the body. Annual sales of Vioxx had reached well over $2.5 billion[3] and an estimated 84 million[3] people globally had received prescriptions. After one year of public use, studies started surfacing that indicated that compared to other NSAIDS like Naproxen[3], Vioxx[3] did have significantly fewer side effects on GI tract. However, an unexpected outcome appeared, the increased risk of heart failure and death. On September 30, 2004 Vioxx[3] was banned from the global market. The Vioxx case has placed an increased emphasis on the need for long term studies and improved Pharmacovigilance.

A representation of an injury from medication was the discovery of Tardive Dyskinesia. Tardive Dyskinesia (TD) is a movement disorder which occurs from prolonged exposure to neuroleptic medications such as those used to treat conditions including schizophrenia, bipolar disorder and depression. Multiple classes of drugs have the ability to also cause TD. These include antidepressants[4], calcium channel blockers[4], antiemetic[4], antiepileptic[4], antiparkinsonian[4], anticholinergic[4], mood stabilizers[4], and others.[4] During the 1950s, movement

disorders were observed following the use of anti-psychotic medication treatment. Ten years later the term Tardive Dyskinesia appeared in the literature. [Tardive refers to the delayed onset of motor disturbances following treatment with psychotropic medications.] [4]

Theories explaining TD manifestation include: an imbalance between dopamine and cholinergic function; noradrenergic dysfunction; dysfunctions of striatonigral, gamma-aminobutyric acid (GABA)ergic neurons; and excitotoxicity.[4] Although multiple theories exist, the pathophysiology for Tardive Dyskinesia is still not fully understood.

Two approaches have been proposed with regards to eliminating the occurrence of Tardive Dyskinesia. The first was prevention and the second suggested pharmacological treatment options. Upon further evaluation of TD, prevention was seen as a less viable method of thwarting the disease. Since TD is a side effect of antipsychotic medication, the use of antipsychotics would have to be prohibited. However, patients who require the use of antipsychotics continue to deteriorate in mental health without treatment. Thus antipsychotic treatment involves consideration of both risks and benefits. Often time with the most ill patients, the benefits outweigh the risk of developing TD. Therefore several medications, including biperiden[4,10], trihexyphenidyl[4,10], benzotropine[4,10], and procyclidine,[4,10] which are normally used to treat acute EPS (Extrapyramidal symptoms), have been used as a temporary measure to treat light cases of TD. However, there is presently still no FDA approved treatment for TD. Until newer antipsychotics with zero risk of TD are discovered, this side effect will occur in this population.

According to the World Health Organization (WHO) Pharmacovigilance is defined as "the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem."[3] Clinical trials not only work to get a drug to

market but once the drug is available to the public, clinical drug trials can be used to analyze and observe the health risk of patients involved in a long term period in comparison with other drugs.

Drugs are obviously very important, however, for healthcare management; many factors are involved in making drugs available to prescribers. Clinical Trials require hundreds to thousands of volunteer participants, without whose willingness to participate in clinical trials, the investigational medication could not be completed. Drug developers and clinical investigators are entrusted with the health and well-being of trial subjects. Therefore, the general public's perception of drug development and ongoing safety of medications is crucial. Thus, understanding the attitudes and opinions towards the pharmaceutical industry and the clinical trials process is important to learn and understand because there are various implications on how future drugs will be pushed to the global market.

CHAPTER II. HYPOTHESIS/SPECIFIC AIMS

The hypothesis of this research is that the population of people who have chronic illness and injury from taking certain medications (sample 1) will possess a different risk/ benefit equation than the general public (sample 2). Therefore, the opinions of Sample 1 on clinical trials will differ from those of the Sample 2 because of the conditions that they have endured due to the treatment. It is possible that these opinions will overvalue pharmacological effects of clinical drug trials to a greater degree than those of the matched population.

Hypothesis 1: Individuals in Sample 1 are more likely to feel differently than individuals in Sample 2 regarding to the importance of clinical trials.

Specific Aim 1.1 – To determine if there is a statistically significant difference between Sample 1 and Sample 2 regarding feelings of importance about clinical trials and individuals in sample 1.

Hypothesis 2: Individuals in Sample 1 have a different level of trust towards medication prescribed by their doctor than individuals in sample 2.

Specific Aim 2.1 – To determine if there is a statistically significant difference between Sample 1 and Sample 2 regarding higher level of trust in medications prescribed by their doctor.

Hypothesis 3: Individuals in Sample 1 are more likely to have a different perception on the pharmaceutical industry than individuals in sample 2**.**

Specific Aim 3.1 – To determine if there is a statistically significant difference between Sample 1 and Sample 2 regarding a more positive perception of the pharmaceutical industry.

SIGNIFICANCE

Attitudes about the value and risk of pharmacological intervention and participation in clinical trials will shape the future of new medication development. In light of the growing field of pharmacogenomics (understanding genetically why some individuals respond to some medicines when others do not, same thing for side effects) and individualized medicine, these attitudes could affect the nature in which new medications are brought to market.

CHAPTER III. MATERIALS AND METHODS

HUMAN SUBJECTS

The subjects targeted for this study comprised of individuals 18 years of age or older regardless of gender and ethnicity. Since two populations (stratum) were analyzed independently, a method of Stratified Sampling was performed. The first population (Sample1) were patients at North Texas Clinical Trials (200 West Magnolia Avenue, Fort Worth, Texas. Suite 102, 76104.) The second population (Sample 2) comprised of individuals from various locations: University of North Texas Health Science Center (UNTHSC), University of Texas in Arlington, Lifetime Fitness, Hulen Mall, and Northeast Mall.

INFORMED CONSENT

A consent form was produced and approved by the UNTHSC Institutional Review Board (IRB) to ensure appropriate and thorough comprehension to survey participants regarding the specific details of the survey. Each participant was given ample time to read and discuss their involvement with this study. The student investigator provided and collected each consent form. A copy of the consent form was made available to each participant upon the discretion of the individual. The subjects were given the option to withdraw from the study at any time. There was no direct benefit/risk to participate in the study. Participants were not compensated by any means to complete the survey. Each survey was completed on a voluntary basis.

Inclusion Criteria

- Individuals 18 years of age or older

- Male and Female
- Any Ethnic background/Race
- Patients from North Texas Clinical Trials (and controls)

Exclusion Criteria

- Any individual under 18 years of age

Procedures-

First population (location: North Texas Clinical Trials)

North Texas Clinical Trials is a site dedicated to clinical trials work. Currently there are two ongoing studies pertaining to Tardive Dyskinesia. North Texas Clinical Trials is located on 200 West Magnolia avenue, Fort Worth, Texas. Patients, regardless of which study they were involved, were approached during their clinic visit and asked to take part in a study by the student investigator. If they verbally agreed, the student investigator began the informed consent process. Each informed consent form detailed the specifics of the survey and explained factors of interest to each subject. (i.e compensation, health risks, and benefits.) After the process of informed consent, subjects answered 7 questions. Each response was recorded and securely kept by the student investigator. (Survey questions are shown in Appendix B)

Second population (location: University of North Texas Health Science Center, University of Texas at Arlington, Lifetime Fitness, Northeast and Hulen Malls)

Random individuals were selected based upon which location the student investigator was present at that specific point in time. Any individual of an affable nature was approached and asked to participate in the study. Once a verbal affirmation was confirmed, the inform

consent process and survey process described above began. Each response was recorded and kept by the student investigator.

Data Analysis

Descriptive and inferential statistics were evalated to calculate comparison between two independent populations using Microsoft Excel.

Hypothesis 1: Individuals in Sample 1 are more likely to feel differently than individuals in Sample 2 regarding to the importance of clinical trials.

Specific Aim 1.1 – An Unpaired T-test was used to determine if the difference in means of Sample 1 and Sample 2 reflects an "actual" difference in the population from which they were sampled. This test was used to analyze data to test Hypothesis 1, 2 and 3.

The first part of the survey was to assess and evaluate demographic information: age, gender, and ethnicity. The second part of my survey assessed and evaluate characterization behaviors. Since categorical data was obtained Chi-Squared tests were used to calculate and determine if there was a significant difference detected between Sample 1 and Sample 2. Any significant differences would possibly represent confounding variables for results of Hypothesis 1, 2, and 3.

CHAPTER IV. RESULTS/DISCUSSION

The purpose of this study was to assess, evaluate and compare the attitudes and opinions of individuals from a population (Sample 1) where medication has been a source of injury to the perception of a control population (Sample 2) regarding clinical trials. A total of 9 subjects in Sample 1 and 61 subjects in Sample 2 were asked 3 demographic identifiers, 4 categorical characterization questions, and 3 scaled opinion questions. The primary hypothesis is focused around results and calculations of the last 3 scaled opinion questions. However, to eliminate confounding variables, 3 demographic identifiers and 4 categorical characterization questions were developed and tested for significant differences between Sample 1 and Sample 2. Each participant was asked to write their age, gender and ethnicity. The demographics data (Table 1.) reflected that there was no significant difference detected in the gender and ethnic categories. However, the difference in mean ages between the two samples are approximately 17 years apart. Mean age (Figure 1) was the only section in the demographic data to reflect a "significant" difference between Sample 1 and Sample 2. There was a difference in mean ages between Sample 1 and Sample 2 because the population of people who are diagnosed with TD generally came from an older generation.

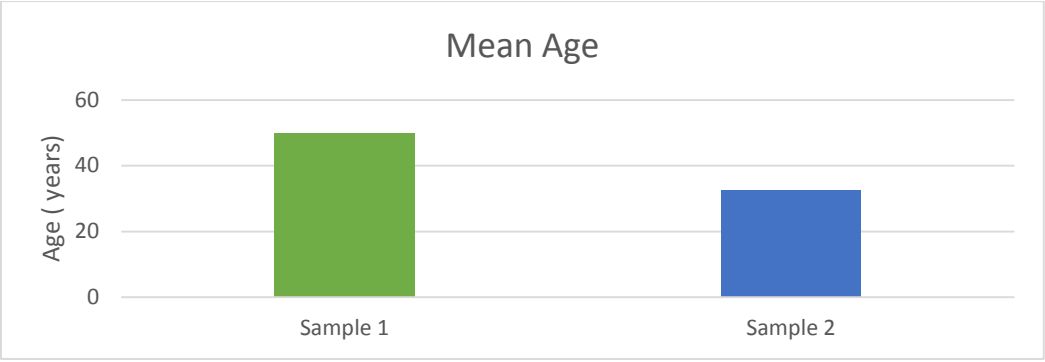

Figure1. Graph of the mean ages in years of Sample 1 and Sample 2.

Table 1. Demographics Data

	Sample 1	**Sample 2**	**Test used/ (T-statistic or p-value)**	**Significant Detection (yes if p-value< 0.05 No if p-value > 0.05)**
Mean Age (years)	Mean age is 49.9 years	Mean age is 32.4 years	Unpaired T- Test P-value = 0.0014	Yes, Age was significantly different between two samples
Gender	77.8% Male	55.6% Male	Chi- Squared Test/ P-value = 0.210	No significant difference detected
Ethnicity	66.7% White 33.3% Black	39.3% White 29.5% Asian 14.8% Black 9.8% Hispanic 3.3% Middle Eastern	Chi- Squared Test/ P-value = 0.122	No significant difference detected

Each participant was asked 4 characterization questions to assess and evaluate long term health issues, duration of medication usage for longer than one week, Clinical Trial participation, and injury by medication. The characterization data (Table 2) revealed two areas in which detection of significant differences occurred: Long term health issues and Clinical Trial Participation. No other characterization factors revealed significant differences through statistical calculations. An astonishing result was data present about the answer to question 4 by the individuals in Sample 1. Question 4 asked "Have you ever been injured by medication? (Y/N)." Having prior knowledge that Sample 1, all are patients of North Texas Clinical Trials having been diagnosed with TD. (TD is an injury from medication), the result should have been 100 percent. The result

is not 100 percent because these individuals probably do not consider or lack the knowledge that TD is an injury due to medication they are taking.

Table 2. Characterization Data

	Sample 1 (Percent who answered Yes)	**Sample 2 (Percent who answered Yes)**	**Test used/ p- value**	**Significant Detection (yes if p-value< 0.05 No if p-value > 0.05)**
Long Term Health Issues	88%	26%	Chi- Squared Test/ P-value = .002	Yes there is significant difference between two samples
Duration of Medication Usage (over 1 week)	100%	72%	Chi- Squared Test/ P-value = 0.06	No significant difference detected
Clinical Trial Participation	88%	1.6%	Chi- Squared Test/ P-value = 0.000288E-9	Yes there is significant difference between two samples
Injury by Medication	0%	9.8%	Chi- Squared Test/ P-value = 0.325	No significant difference detected

To address Hypothesis 1, the survey asked subjects to provide an answer to the question "How important do you feel Clinical Trials are?" on a scale of 1- 10 (1= not very and 10 = very). The results are shown in the first row of Figure 3. This data indicated that a calculated p-value is greater than 0.05 (alpha significance level). Thus, no difference was observed between the two samples. The hypothesis was not accepted. A difference in opinions in the importance of Clinical Trials between Sample 1 and Sample 2 was expected because individuals from Sample 1 were

patients of North Texas Clinical Trials. These individuals received direct benefit from participating in clinical trials from monetary compensation for a clinical visit to the improved health conditions from the effects of pharmaceutical treatment. On the other hand, some individuals from Sample 2 have the misconception that clinical trials treat human subjects as "guinea pigs". Public value for clinical trials may have increased because of the growing concern for better drugs, which could be a reason for no difference observed.

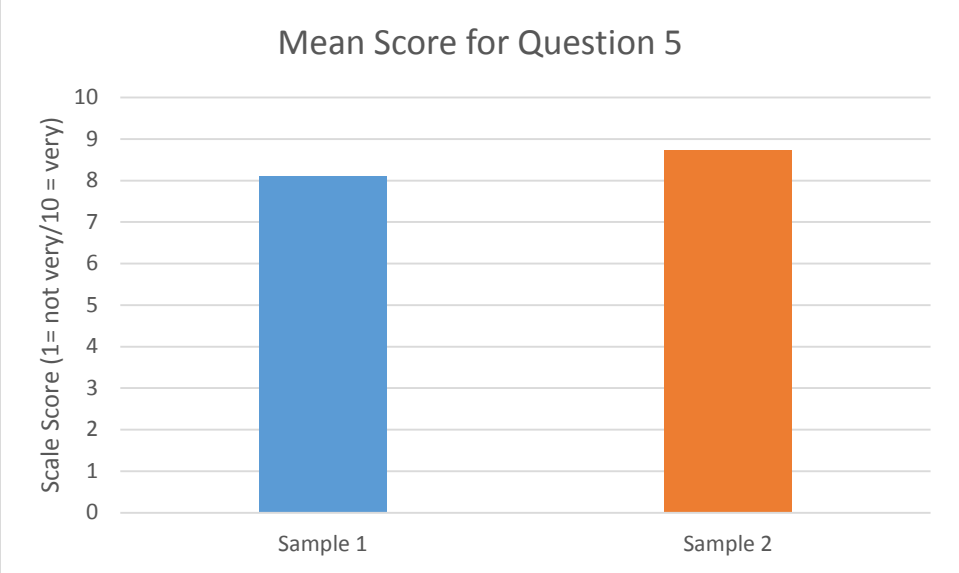

Figure 2. Graph of the mean score for question 5 between Sample 1 and Sample 2.

To address Hypothesis 2, the survey asked subjects to provide an answer to the question "How much do you trust medication prescribed by your doctor?" on a scale (1= Don't Trust, 10 = Trust). The results are shown in the second row of Figure 3. This data indicated that a calculated p-value is greater than 0.05 (alpha significance level). Thus, no difference was observed between the two samples. This hypothesis was not accepted. A difference in opinions in the confidence in medication prescribed by their physician between Sample 1 and Sample 2 was expected because individuals from Sample 1 were people who have sustained injuries from

medication. All individuals have been diagnosed with TD, which is an adverse effect of the use of antipsychotic drugs. On the other hand, most individuals from Sample 2 trust their doctors to make the best decision. A significant difference was not detected because the individuals from this sample had a lot more faith in the medication prescribed by their doctor than what was originally anticipated.

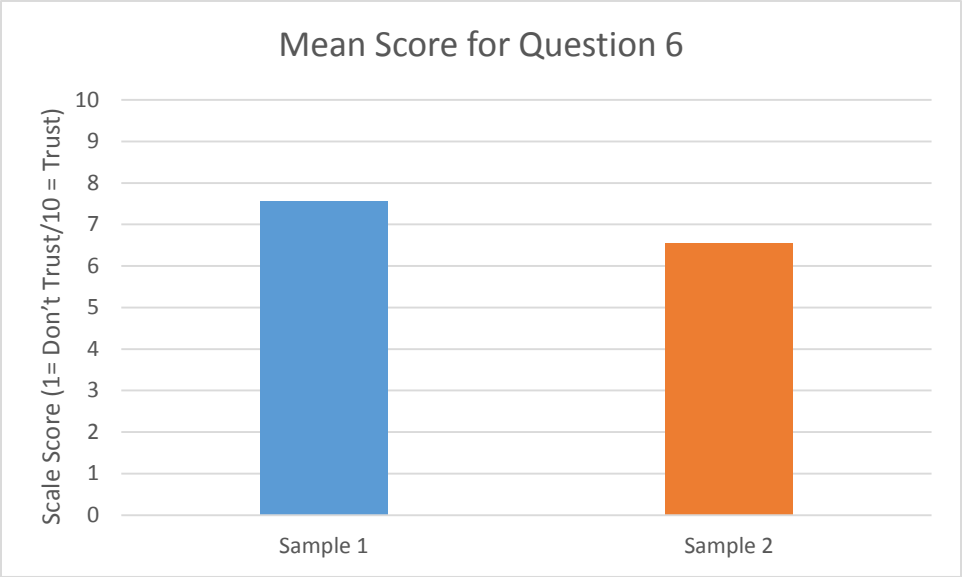

Figure 3. Graph of the mean score for question 6 between Sample 1 and Sample 2.

To address Hypothesis 3, the survey asked subjects to provide an answer to the question "Do you feel the pharmaceutical industry is bad or good?" on a scale of 1- 10. The results are shown in the third row of Figure 3. This data indicated that a calculated p-value is greater than 0.05 (alpha significance level). Thus, no difference was observed between the two samples. This hypothesis was not accepted. A difference in opinions in the value of the pharmaceutical industry between Sample 1 and Sample 2 was expected because individuals from Sample 1 were patients of North Texas Clinical Trials. These individuals received free medical treatment from the pharmaceutical companies. On the other hand, some individuals from Sample 2 have the

perception that the pharmaceutical industry put their profit margin as a top priority. This was not the case as evidently the attitudes and opinions between both samples were more congruent than what was originally hypothesized. A larger sample size for Sample 2 may be a reason.

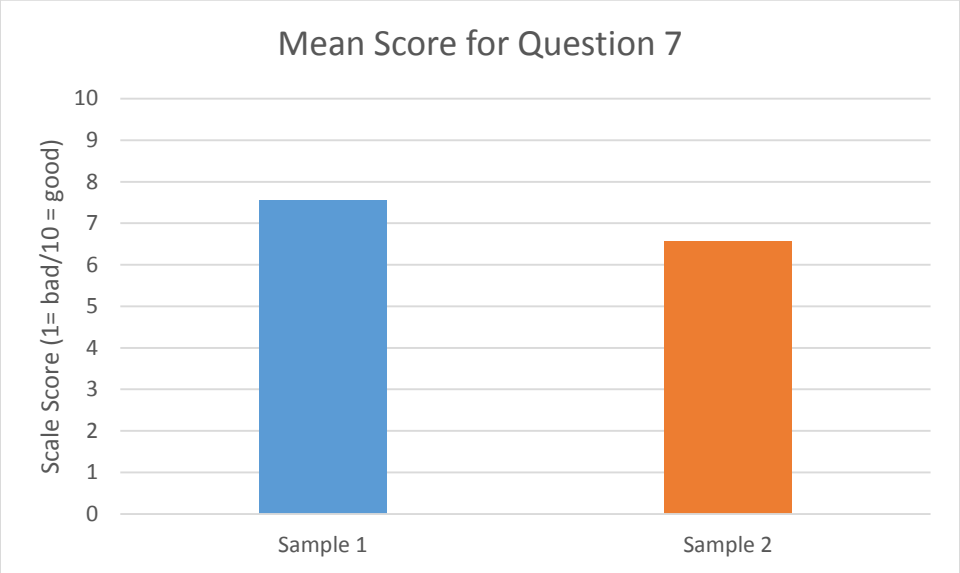

Figure 4. Graph of the mean score for question 7 between Sample 1 and Sample 2.

Table 3. Opinions Data

	Sample 1 (average scale from 1-10, Standard deviation)	**Sample 2 (average scale from 1-10, Standard deviation)**	**Test used/ p- value**	**Significant Detection (yes if p-value< 0.05 No if p-value > 0.05)**
Level of importance in Clinical Trials	Mean – 8.11 Std Dev- 1.05	Mean – 8.73 Std Dev- 1.97	Unpaired T- Test P-value = 0.178	No significant difference detected
Level of trust in medication from physicians	Mean – 7.55 Std Dev- 1.13	Mean – 7.96 Std Dev- 1.99	Unpaired T- Test P-value = 0.274	No significant difference detected
Level of perception in pharmaceutical industry	Mean – 7.55 Std Dev- 2.35	Mean – 6.55 Std Dev- 2.43	Unpaired T- Test P-value = 0.873	No significant difference detected

LIMITATIONS

Of the 70, subjects only 9 subjects represented the sampling size for sample 1. Had more subjects been surveyed, then a more accurate representation of each population may have been presented. The student investigator believed that the wording of question 4 “Have you ever been injured by medications?” (Y/N) may have been misunderstood as many subjects either lack the knowledge or consideration that TD is an injury from medication. This may have resulted in a very unnatural phenomenon where patients of Sample 1 were not associated with injury by medication. There was also another limitation where the mean age (years) differed between Sample 1 and Sample 2 by 17 years. If a Sample 2 was filtered to contain participants with 40 years and above, better results would have been obtained. The health of Sample 2 was unknown, where the health Sample 1 was documented in volumes of medicals records. Comparison could have supplemented the data set by 100 fold. Furthermore, many participants were deterred from taking the survey due to the abnormally long length of the consent form. The informed consent was 5 pages long and very detailed to meet the requirements of the IRB. More participants could have been surveyed if the consent form was confined to a page.

SUMMARY AND CONCLUSIONS

Historically, Human Medical Testing has developed a negative reputation due to Nazi testing[15], the Tuskegee experiments[16,18], and most recently the Vioxx recall[3]. Each one of these events represents an example of disregard for human life. As such, a series of hypothesis were developed to test whether the general public opinion significantly differ with the opinions of those enrolled in clinical trials. Witnessing the benefits of clinical trial drugs from patients at

North Texas Clinical Trials supports the claim that this population (trial participants) might overvalue the effects of clinical trial drugs to a higher degree than the general population. From the majority of the results, public perception was determined to not be significantly different from the perception of individuals currently enrolled in clinical trials. As populations grow, lifespans become larger, and diseases of life style increase in the western world, (and other regions), there is an ever-increasing need for new medications. With the future of new medication development being greatly influenced by public perception it is imperative to learn and understand the mentality of how people view clinical trial drugs.

V. INTERNSHIP EXPERIENCE

INTERNSHIP SITE

North Texas Clinical Trials is located on the 200 West Magnolia Avenue 76104, Fort Worth, Texas. Relatively humble in staffing size compared to other clinical research facilities, North Texas Clinical Trials offers a unique perspective of clinical trials research in the private sector. Currently there are five mental health studies being conducted here. The site director is Dr. Brian Maynard whose kindred spirit and business acumen provides an optimistic outlook for this facility's dream of expansion.

JOURNAL SUMMARY

Dr. Brian Maynard started this research facility two years ago. He and his assistant are the two coordinators in charge of five mental health studies. When I first arrived, he took me under his wing and gave me the full exposure of the responsibilities of a clinical research coordinator. Most of our mental health studies pertain to Tardive Dyskinesia which at first was the main focus for my research thesis. However, since North Texas Clinical Trials is employed by private pharmaceutical companies I soon realized I would not be able to use any of the data that was right in front of me. Dr. Maynard and I worked together for weeks to find another option to fulfill my internship requirements. We later came to a consensus with another one of my professors to employ a survey. I learned how to develop a survey, submit IRB documents and request approval, and how to run through an informed consent process. In the mean time Dr. Maynard introduced me to exposures I may not get to experience anywhere else. He showed me: how to do drug accountability, how operate ECG machine, how to take vitals, Quality Control, Quality Assurance, manage and maintain patient visit reports, how to report adverse events and serious adverse events. The most exciting experience was when he invited me to

attend an all investigator meeting for new drug study in Las Vegas, Nevada. During the 3 day trip I receive training on data management with the latest software. This internship experience has definitely shifted my mentality and shaped my skill set to possibly pursue clinical research management as future endeavor.

APPENDIX A.
DAILY JOURNAL

Week 1

Monday June 1th, 2015

I met up with Dr. Maynard and began training right away. He showed me which studies I was going to be involved in. I made a few phone calls to a couple of patients to schedule appointment within the upcoming week.

Tuesday June 2nd, 2015

Dr. Maynard and I talked about what I could be research for since I wasn't able to use any data for the studies. I got to see two patients and I worked on their visit reports.

Wednesday, June 3rd, 2015

I began working on drug accountability which was fun at first but then I was bogged down on how many numbers I had to look at. There are currently three studies that I am working on C-20, C-18, and C23.

Thursday June 4th, 2015

I worked on organizing the drug room all day. It was kind of boring but at least now it is in spectacular order. I met Nicholas Keyes a research assistant under Dr. Maynard and he and I worked on Quality Control together.

Friday June 5th, 2015

I went to the library and began research.

Week 2

Monday, June 8th – 19th, 2015

It was pretty slow day. I mainly worked on prepping the visit report for the next few days.

Tuesday June 9rd, 2015

We had three patients come in today. It was super busy. I worked on the headers for each visit. Dr. Maynard allowed me to shadow his coordinator position. I learned what type of scales that our clinic uses for mental ill patients. I got to see a video taping of a patient during his visit. It was amazing.

Wednesday June 10th, 2015

We just worked on cleaning up the visit reports from the last day and prepping for tomorrow.

Thursday June 11th, 2015 – 11 AM

We had two visits today. Dr. Maynard showed how to take ECG and vitals. I got to watch blood being drawn. We randomized a patient for baseline but Dr. Maynard and Dr. Davis (Principal investigator) has doubts that she will be a screen fail. I learned what a screen fail is.

Friday June 12th, 2015

It was a pretty short day, I met a really funny patient. I helped Monica with her visit report and I went to library to study.

Week 3

Monday June 15th, 2015

Dr. Maynard showed me how to upload a video today for the monitors the drug companies to observe. It was a long a painful process. He had to change the password 5 times in order to log in. Nicholas and I prepped the visit reports for the upcoming week.

Tuesday June 16, 2015

Monica was out to Yellowstone this whole week so Nicholas and I had to step up and help out with the other pharmaceutical companies visit reports. We we got done, Dr. Maynard let me go to library and study.

Wednesday June 17th, 2015

Clean up day today. I looked for errors in the visit reports and when I found them, since I wasn't part of the regulatory team yet I had to show them to Dr. Maynard. He had to cross out with one line and initial and date the correction.

Thursday June 18th, 2015

We had a screening visit today. It my first screening visit. I got to see who actually qualifies into the study and what labs have to done. I did not get to process any labs because I am still and Intern but I did get to see different scales than normal. Dr. Maynard showed me when pharmacokinetic samples have to be taken and when then have to be shipped off. I went a picked up dry ice and that was end.

Friday June 19th, 2015

I went to the library to study.

Week 4

Monday June 22nd, 2015

I registered for EDC training. I went through the training and got certified.

Tuesday June 23, 2015

We had one visit today. It was the funny patient again. Hahahha. Nicholas showed me how we had to make phone with a patient and what things we have to ask in our weekly patient report.

Wednesday June 24th, 2015

Clean up day today. Since I am now EDC certified I was able to manually enter data for each visit. I did that pretty much all of today.

Thursday June 25th, 2015

There was pharmaceutical Kinect 4 meeting so Dr. Maynard told me to be off for today and tomorrow.

Friday June 26th, 2015

OFF.

Week 5

Monday June 29th, 2015

Monica the other coordinator came back. So a heavy load was lifted with regards to the other pharmaceutical study. I went and prepped for the patient pre-screen tomorrow. I help organize the scale system. I also received drug shipments and logged them in and organized them again.

Tuesday June 30, 2015

First prescreen today. It was pretty exciting. I hope they will be enrolled. I helped out with a few more phone calls.

Wednesday July 1st, 2015

I had to prepped visit reports for two study visits. I studied for my DAT.

Thursday, July 2, 2015

Busy day. We met with two patients. One was extremely manic. We found out she was off her medication and was hospitalized. I learned how to process and report an adverse event and a serious adverse event.

Friday, July 3, 2015

OFF.

Week 6

Monday July 6h, 2015

I helped prepare for two patient visits tomorrow.

Tuesday July 7th, 2015

We had two patient visits to complete and learned to more on the allocation of funds that our site gets compensate from by the drug companies.

Wednesday July 8nd, 2015

I went to hospital Network breakfast with Monica. I came back to the office and work help with the two visit report we had tomorrow.

Thursday, July 9, 2015

Busy day. We met with two patients. Dr. Maynard was very nice. He even drove one of the patients and her grandkids to the clinic just so they can have their medication dosage adjusted. It has been around a month since I started and Dr. Maynard has patience of an angel.

Week 7

Monday July 13h, 2015

I helped prepare for two patient visits tomorrow.

Tuesday July 14th, 2015

We had two patient visits to complete. I went to study for my DAT.

Wednesday July 15, 2015

We had one visit and I studied. I also helped prep for five more visit reports for tomorrow.

Thursday, July 16, 2015

Busy day. We met with five patients. I was on the constant move. Nicholas and I were on Vitals and ECG duty. Monica was doing scales. Dr. Maynard and Dr. Davis were recording patients for their movements.

Week 8

Monday July 20h, 2015

I helped prepare for four patient visits tomorrow. We met a patient today. I also helped with all the source documentation with Monica. I left early to study for my DAT

Tuesday July 21th, 2015

We had three patient visits to complete. I went to study for my DAT.

Wednesday July 22, 2015

Catch up Day. I Quality Control checked all the patient visit reports we had yesterday and I update EDC with the new information.

Thursday, July 23, 2015

Helped out Monica with source documentation and made about three phone calls to follow up on their health.

Week 9

Monday July 27h, 2015

Helped out with Source Documentation for the other study. Talked to Dr. Maynard about proposal and survey ideas. Prepared for monitor visit.

Tuesday July 28th, 2015

First monitor visit. She was really nice. I honestly she was going to try to make our lives harder but she didn't. We had two visits to complete today.

Wednesday July 29, 2015

Catch up Day. I followed up with a couple of patients via telephone.

Thursday, July 30, 2015

OFF.

Week 10

Monday August 3rd, 2015

Prepped for two patient visits. I entered Drug Accountability in EDC. I went to the library to do some research.

Tuesday August 4th, 2015

Had three patient visits and went to study.

Wednesday August 5th, 2015

OFF. I worked on my proposal.

Thursday, August 6, 2015

Went in for three patients visits.

Week 11

Monday August 10rd, 2015

Prepped for thee patient visits. Studied for DAT.

Tuesday August 11th, 2015

Helped out with three patient visits. Studied for DAT

Wednesday August 12th, 2015

Studied for DAT.

Thursday August 14th, 2015

I helped out with four patient visits and organized the drug shipments and entered them in EDC.

Friday August 15th, 2015

I continued working on my protocol.

Week 12

Monday August 17th, 2015

I worked on my proposal and helped Monica complete all source documentation. I learned how to call in medication for patients and how to store used medication from patients.

Tuesday August 11th, 2015

I learned how to follow up on an SAE. I attended my first Prescreening visits for a new Tourette study. It was kind of long but It was definitely very interesting. Helped out with a screening visit.

Wednesday August 19th, 2015

Catch UP day. Full of paperwork.

Thursday August 20th, 2015

There were four patient visit reports to complete.

Week 13

Monday August 24th, 2015

Worked on my proposal. I also underwent Imedidata training. I prepared for another monitor visit.

Tuesday August 25th, 2015

Worked on my proposal. I complete tasks that the monitor caught.

Wednesday August 26th, 2015

I completed my Proposal.

Thursday August 27th, 2015

There were two patient visit reports to complete. We had a second pre-screening visit for pediatric depression.

Friday, August 28th, 2015

OFF.

Week 14

Monday August 31st, 2015

Worked on prep for three patient visit reports.

Tuesday September 1st, 2015

I helped out with three patient visits.

Wednesday September 2nd, 2015

Catch up day. I reviewed source documentation. Checked for errors and any missing signatures. I worked on my survey. I entered data into EDC.

Thursday September 3rd, 2015

One patient visit and one follow up phone call visit.

Week 15

Monday September 7th, 2015

Worked on prep for two patient visit reports.

Tuesday, September 8th, 2015

Two patient visits.

Wednesday September 9th, 2015

Hospital Networking breakfast with Monica and two patient visits. First time unscheduled visit happened.

Thursday, September 10th, 2015

Followed up with a patient. Worked on Drug accountability and EDC.

Week 16

Monday September 14th, 2015

Worked on three patient visit reports.

Tuesday, September 15th, 2015

Worked on two patient visits. Communicated with UNTHSC about IRB approval.

Wednesday, September 16th, 2015

Two follow up phone calls and got see Last patient visit.

Thursday, September 17th, 2015

Worked on my thesis.

Week 17

Monday, September 21st, 2015

I went through three Regulatory Binders. Worked on five patient reports and followed up on three patients.

Tuesday, September 22nd, 2015

Two patient visit and two follow up phone calls.

Wednesday, September 23rd, 2015

Four patient visits and helped sift through medical records. A LOT of medical records.

Week 17

Monday, September 28th, 2015

Three patient visits

Tuesday, September 29th, 2015

Dr. Maynard out of town and monitor for the drug company came by. So I have step up my game. I helped Monica with calling in medication and one patient visit.

Wednesday, September 30th, 2015

OFF.

Thursday, October 1st, 2015

Went to Las Vegas with the Dr.Maynard, Monica and Dr.Davis for Drug study initiation program.

12-3pm- flight to Las Vegas

5pm- 7 pm Introductory dinner.

Friday, October 2nd, 2015

7aam- 12 am – Meeting with pharmaceutical Company

12am-1pm – lunch

1pm-5 pm – Sat in a lecture with four different speakers talk about Tourette's

Saturday, October 3, 2015

7am-12 am- Training with online component for coordinators with the drug company.

Week 18

Monday, October 5th, 2015

One patient visit and I prepared for four patient visits for tomorrow.

Tuesday, October 6th, 2015

Four patient visits occurred. I communicated with UNTHSC about IRB approval. I made edits and to my submission.

Wednesday, October 7th, 2015

One Patient Visit.

Thursday, October 8th, 2015

First Site Initiation visit and one patient visit.

Week 19

Monday, October 12th, 2015

I QC checked C-23 study binders and corrected errors If I saw any.

Tuesday, October 13th, 2015

Screening Visit for 3 patients and one regular patient visit. Attended Peppers and piñatas event for mental health. I had dinner with Dr. Maynard. Dr. Davis, and Monica.

Wednesday, October 14th, 2015

One regular patient visit.

Thursday, October 15th, 2015

Received IRB approval. Finally!! I went out to lifetime fitness to look for participants.

Week 20

Monday, October 19th, 2015

I worked on getting more participants to take my survey.

Tuesday, October 20th, 2015

Worked with Dr. Maynard on the format of my thesis.

Wednesday, October 21st, 2015

I prepared for two patient visits.

Thursday, October 22rd, 2015

Two patients visits.

Friday, October 23rd, 2015

I tried to work on my thesis. I just had writer's block and failed.

Week 21

Monday, October 26th, 2015

I helped Monica out with sending Praxis some photos, followed up with some patients. Helped enter data for EDC with NBI studies.

Tuesday, October 27th, 2015

Four patient visits. I worked on how I might interpret my results.

Wednesday, October 28th, 2015

Dr. Maynard help me build a structure to my thesis.

Thursday, October 29th, 2015

Three patient visits and practiced taking Vitals.

Week 20

Monday, November 2nd, 2015

Dr. Maynard and I had discussion to hire me on upon completion of this internship.

Tuesday, November 3th, 2015

Three patient visits. I worked on getting more participants.

Wednesday, November 3rd, 2015

Two patient visits, with each visit I got another survey done. Yay!! Me!!

Thursday, November 5th, 2015

I attended a teleconference with NBI drug company and stayed for training purposes.

Week 21

Monday, November 9th, 2015

I helped follow up calls with patients and got Dr. Davis to sign important documents. I edited my essay but I am so unconfident about this thesis.

Tuesday, November 10th, 2015

One patient visit and Monitor visit.

Wednesday, November 11th, 2015

Went to UTA and gave out surveys and informed consent forms.

Thursday, November 12th, 2015

I worked closely with Monica to take over her position when I complete my internship.

Week 22

Monday, November 16th, 2015

I worked on the main portion of my thesis. The pressure is on the finish.

Tuesday, November 17th, 2015

Two patient visits.

Wednesday, November 18th, 2015

Catch up day. Quality Control checked all the binders for any discrepancies.

Thursday, November 19th, 2015

Once patient Visit. I decided I can't wait any longer I have to just work with what I have with limited patient inflow. I began enter my date in excel to try to get my results portion of my thesis done.

Week 23

Monday, November 23th, 2015

Three patient visits. Frantically trying to finish my paper.

Tuesday, November 24th, 2015

Three patient visits. Conducted the Visit on my own for the very first time. Had Monica shadow me and correct any of my mistake. Deadline approaching and apologized to Dr.

Gwirtz because I am not meeting any deadlines. Dr. Gwirtz if you read this. I am so very sorry to put you through this burden.

APPENDIX B.
RECRUITMENT SCRIPT

Hello, my name is _____. I am a graduate student at UNTHSC in Fort Worth. I am conducting research on Views on Clinical Trials, and if I may, would you be willing to donate five minutes to take part in my survey?

Participation in this research includes taking a survey about your attitudes toward Clinical Trials. If participant say “Yes” Proceed with informed consent process.

If participant says” no”. Thank you for your time and please have a wonderful day.

Take 5-10 minutes to walk them through the inform consent process and then provide 5 more minutes to have take the survey.

Thank you so much for your time and please have wonderful day.

APPENDIX C.
INFORMEND CONSENT FORM

University of North Texas Health Science Center Fort Worth, TX

RESEARCH SUBJECT INFORMATION AND CONSENT FORM

Title – Views on Clinical Trial Drugs

Student Investigator - Bryan Tran

Principal Investigator- Patricia Gwirtz Ph.D.

Sub Principal Investigator- Brian Maynard Ph.D.

Site- North Texas Clinical Trials – 200 West Magnolia Avenue Suite 102 Fort Worth Texas, 76104

This is a research study consent form which may contain words that you do not understand. Please ask the study doctor or the study staff to explain any words or information that you do not clearly understand. You may take home an unsigned copy of this consent form to think about or discuss with family or friends before making you decisions.

- You are being asked to be in a research study.

- Your decision to be in this study is voluntary.

- If you decide to be in this study and then change your mind, you can leave the study at any time. However, your response will not be discarded because no name /personal identifiers will be collected

- You will be in this study for one time response .

- Your medical insurance will not be affected.

- You will be in this study for a one time survey.

PROCEDURES

1. You will be Informed of the survey details.

2. You will be politely asked for your participation.

3. You will take survey that will just ask you about your personal views on clinical trials.

4. Your results will be analyzed, no identifiers will be collected for the survey

RISKS /BENEFITS

There are minimal risks with participating in this survey. No personal identifiers will be collected from the survey and all data will kept in a secure location known only to the research personnel. You may receive indirect benefit from participating in this study. The benefits of this survey/interview will allow us to evaluate your opinions on Clinical Trials.

COSTS

There are no charges for this study procedures and methods.

PAYMENT FOR PARTICIPATION

Due to the brevity of duration and minimal risks we will not pay you to participate in this study (no subject fee). You will not be charged for your responses during the period of study.

AUTHORIZATION TO USE AND DISCLOSE INFORMATION FOR RESEARCH PURPOSES

Federal regulations give you certain rights related to your health information. These include the right to know who will be able to get information and why they are able to get it. However, none of your health information will be required. The survey will ask you some questions about your medication and health history. However, no personal identifiers will be linked to this information. All your responses will be presented

anonymously therefore any information you choose to provide will not be linked to your identity.

What information may be used and given to others?

If you choose to be in this study, the study investigator will ask you a seven (7) question survey and your responses will be analyzed and presented in an anonymous fashion.

Who may use and give out information about you?

You have been asked to take part in a research study. There will be no need to observe your health records. Any information that will be shared will purely be of those answered during the survey process.

Authorization to Use Health Information:

NO identifiable health information will be collected or retained and any information will be kept confidential

Term of Authorization:

If you sign this form, we will collect your survey responses.

Who might get this information?

Research personnel will be given your survey responses for their study.

Information about you and your health would only be given to the below listed agencies, as the Law requires.

1. Department of Health and Human Services (DHHS).

2. University of North Texas Health Science Center Institutional Review Board (UNTHSC- IRB). The UNTHSC-IRB is a group of people who perform individual review of research as required by regulations. **Subjects Initials _____** Date _____

Why will this information be used and/or given to others?

Results of this research maybe published in scientific journals or presented to medical meetings, but your identity will not be disclosed.

Is my health information protected after it has been given to others?

No identifiable information will not be involved in the study.

Questions regarding your privacy rights:

Any questions? Please ask the researcher. You can also call UNTHSC Institutional Review Board at 817-735-0409 with questions about the research use of your health information. The researcher will give you a signed copy of this form.

VOLUNTARY PARTICIPATION AND WITHDRAWAL

Your participation in this study is voluntary. You may decide not to participate or you may leave the study at any time. Your decision will not result in any penalty or loss of benefits to which you are entitled.

Your participation in this study may be stopped at any time by the researcher without your consent because:

- you have not followed study instructions;
- the researcher has stopped the study; or
- administrative reasons require your withdrawal.

QUESTIONS

If you have any questions about the study, you are free to contact Bryan Tran, the student investigator, 469-744- 6409 or the Principal Investigator Patricia Gwirtz at Patricia.Gwirtz@unthsc.edu. If you have questions about your rights as research subject, you may contact;

UNTHSC Institutional Review Board 3500 Camp Bowie Blvd, Fort Worth, TX 76107 Telephone 1-817-735-0409

Do not sign this consent form unless you have chance to ask questions or read and received satisfactory answers to all your questions.

CONSENT

I have read the information in this consent form (or it has been read to me). All my questions about the study and my participation in it have been answered. I freely consent to be in this research study.

By signing this consent form, I have not given up any of my legal rights.

_____ Subject Name

CONSENT SIGNATURE:

_____ _____ Signature of Subject Date

_____ _____ Signature of Person Conducting Informed Date Consent Discussion

APPENDIX D.
SUBJECT SURVEY

Perception of the use of Clinical Trial Drugs

(AGE):

GENDER:

ETHNICITY:

1) Do you have long term health issues Y / N

2) Have you ever taken medication for longer than a week? Y / N

3) Do you or have you ever taken part in clinical trial drugs? Y / N

4) Have you ever been injured by medications? Y / N

Please answer the following on a scale based from 1- 10.

5) How important do you feel Clinical Trials are? (1- not very/ 10 – very)

1 2 3 4 5 6 7 8 9 10

6) How much do you trust medication prescribed by your doctor? (1- Don't Trust/ 10- Trust)

1 2 3 4 5 6 7 8 9 10

7) Do you feel the Pharmaceutical industry is? (1- bad/ 10 – good)

1 2 3 4 5 6 7 8 9 10

BIBLIOGRAPHY

1) Notaras M. A role for the BDNF gene Val66Met polymorphism in schizophrenia? A comprehensive review. Neuroscience and biobehavioral reviews. 2015-04;51:15-30.

2) Ryu S. Tardive Dyskinesia and Tardive Dystonia With Second-Generation Antipsychotics in Non-Elderly Schizophrenic Patients Unexposed to First-Generation Antipsychotics A Cross-Sectional and Retrospective Study. Journal of clinical psychopharmacology. 2015-02;35:13-21.

3) Barry A. Adverse drug reactions: The importance of maintaining pharmacovigilance. Canadian pharmacists journal. 2014-07;147:233-238.

4) Lerner P. Tardive dyskinesia (syndrome): Current concept and modern approaches to its management Modern approaches to tardive dyskinesia. Psychiatry and clinical neurosciences. 2015-06;69:321-334.

5) J.A. DiMasi, “New Drug Development in the United States from 1963-1999,” Clinical Pharmacology and Therapeutics 69, no. 5 (2001): 286-296.

6) J.A. DiMasi, R.W. Hansen and H.G. Grabowski, “The Price of Innovation: New Estimates of Drug Development Costs,” Journal of Health Economics 22 (2003): 151-185.

7) Pharmaceutical Research and Manufacturers of America, based on data from Tufts University, Tufts Center for the Study of Drug Development (1995).

8) Pharmaceutical Research and Manufacturers of America, Pharmaceutical Industry Profile 2006,

(Washington, DC: PhRMA, March 2006).

9) Tufts Center for the Study of Drug Development, "Average Cost to Develop a New Biotechnology Product Is $1.2 Billion, According to the Tufts Center for the Study of Drug Development," 9 November 2006, http://csdd.tufts.edu/NewsEvents/NewsArticle.asp?newsid=69 (accessed 18 December 2006)

10) John M Kane, Pharmacologic treatment of schizophrenia, Biological Psychiatry, Volume 46, Issue 10, 15 November 1999, Pages 1396-1408, ISSN 0006-3223, http://dx.doi.org/10.1016/S0006-3223(99)00059-1. (http://www.sciencedirect.com/science/article/pii/S0006322399000591) Keywords: Schizophrenia; treatment; psychopharmacology antipsychotic medication

11) Winston W Shen, A history of antipsychotic drug development, Comprehensive Psychiatry, Volume 40, Issue 6, November–December 1999, Pages 407-414, ISSN 0010-440X, http://dx.doi.org/10.1016/S0010-440X(99)90082-2. (http://www.sciencedirect.com/science/article/pii/S0010440X99900822)

12) Herbert Y Meltzer, What's atypical about atypical antipsychotic drugs?, Current Opinion in Pharmacology, Volume 4, Issue 1, February 2004, Pages 53-57, ISSN 1471-4892, http://dx.doi.org/10.1016/j.coph.2003.09.010. (http://www.sciencedirect.com/science/article/pii/S1471489203002054)

13) Pharmaceutical Research and Manufacturers of America, Pharmaceutical Industry Profile 2007,
(Washington, DC: PhRMA, February 2007).

14) Collier, R. (2009). Legumes, lemons and streptomycin: A short history of the clinical trial. CMAJ : Canadian Medical Association Journal, 180(1), 23–24. http://doi.org/10.1503/cmaj.081879

15) Bhatt, A. (2010). Evolution of Clinical Research: A History Before and Beyond James Lind. Perspectives in Clinical Research, 1(1), 6–10.

16) Mandal, J., Halder, A., & Parija, S. C. (2011). Ethics and clinical research.Tropical Parasitology, 1(2), 54–56. http://doi.org/10.4103/2229-5070.86925

17) Hart, P. D. (1999). A change in scientific approach: from alternation to randomised allocation in clinical trials in the 1940s. BMJ : British Medical Journal, 319(7209), 572–573.

18) Gamble, V. N. (1997). Under the shadow of Tuskegee: African Americans and health care. American Journal of Public Health, 87(11), 1773–1778.

19) Vianna, F. S. L., Lopez-Camelo, J. S., Leite, J. C. L., Sanseverino, M. T. V., da Graça Dutra, M., Castilla, E. E., & Schüler-Faccini, L. (2011). Epidemiological Surveillance of Birth Defects Compatible with Thalidomide Embryopathy in Brazil. PLoS ONE, 6(7), e21735. http://doi.org/10.1371/journal.pone.0021735

20) Skelly, J. P. (2010). A History of Biopharmaceutics in the Food and Drug Administration 1968–1993. *The AAPS Journal*, *12*(1), 44–50. http://doi.org/10.1208/s12248-009-9154-8