
UNIVERSITY OF NORTH TEXAS
HEALTH SCIENCE CENTER AT FORT WORTH
1970

CLINICAL RESEARCH: DRUG STUDIES AND DEVICE TRIALS, THEORY AND APPROACH

Timothy Chad McCormick, B.S.

APPROVED:

Rustin Reeves, Ph.D. (Major Professor)

Don Pesca, D.O. (Committee Member)

Della Weis, R.N., B.S.N. (Committee Member)

Michael Forster, Ph.D. (University Member)

Victoria Rudick, Ph.D. (Graduate Advisor)

Thomas Yorio, Ph.D. (Dean, Graduate School of Biomedical Sciences)

CLINICAL RESEARCH: DRUG STUDIES AND DEVICE TRIALS, THEORY AND APPROACH

INTERNSHIP PRACTICUM REPORT

Presented to the Graduate Council of the

Graduate School of Biomedical Sciences

University of North Texas

Health Science Center at Fort Worth

in Partial Fulfillment of the Requirements

for the Degree of

MASTER OF SCIENCE

By

Timothy Chad McCormick, B.S.

Fort Worth, Texas

July, 2002

TABLE OF CONTENTS

Chapter

I. INTRODUCTION.....1

II. JOURNAL OF INTERNSHIP PRACTICUM.....8

III. DISCUSSION.....23

IV. SUMMARY.....28

REFERENCES.....30

CHAPTER I

INTRODUCTION

A Clinical study is defined as a prospective study comparing the effect and value of intervention(s) against a control in human beings (Friedman, 1996). This is very important because these studies are set up and based on results of numerous laboratory tests using many *in vitro* as well as *in vivo* experiments. Animal research is usually a prerequisite to clinical studies, but in some cases these experiments may be created from previous human findings in another clinical trial. It is important to understand that clinical trials are essential to the understanding of drugs and devices that may be used on human patients. If a drug, for example, is capable of being used in rats to reduce the amount of post-operative pain, it is worth testing in humans if that drug is safe and effective in the human system. How do we determine whether or not the drug is safe and effective?

A clinical research trial must be set up to determine whether or not a drug or device is safe and effective. To understand the safety issues first, the laboratory experiments must be analyzed and evaluated for the safest calculable response or dose in humans. Next, these must be placed into action in a phase I clinical trial. Phase I clinical trials utilize a small number of subjects (20-30), who are usually healthy individuals, or individuals having the disease that the prospective drug/device will be treating. The patients that have the disease to be tested are usually incurable without the possible procedure; therefore, their risk factors do not change as significantly as the healthy

individuals. This is done so that adverse events (AE's) may be documented and understood (Friedman, 1996). An adverse event is defined by Mosby's medical dictionary as any harmful, unintended effect of a medication, diagnostic test, or therapeutic intervention (Mosby, 1998). After the adverse events have been evaluated and the AE's are documented and shown to be safe in a small generation, the study drug/device must go through a Phase II clinical trial.

A phase II study uses a larger subject population (100-300) than a phase I study. All of the study population has the condition/disease that the new drug/device is intended to treat. A phase II clinical trial is the basic efficacy and safety study and is also considered the pivotal trial (Bulpitt, 1996). This clinical trial period allows researchers to use a larger population to determine safe dosing ranges for drugs and the use of the drug/device on the preferred population. A Phase II study also allows researchers to implement what is discovered in the phase I study into a larger population to understand the variance and effect of the drug/device.

After a phase II study is completed, a phase III study must take place. A phase III study is usually a multi-center study in populations of 1000 to 3000 patients or more for whom the medicine/device is intended (Friedman, 1996). Phase III trials are useful for generating additional safety and efficacy data from large populations in controlled and uncontrolled designs. Phase III studies provide much of the information that is needed for the package insert and labeling of the particular drug/device. Phase III studies take place during the period between submission for approval and receipt of marketing authorization (Gallen, 2002).

Phase IV studies are conducted following the release of the drug/device onto the market. The Phase IV study occurs after the study drug or device has been deemed safe and efficacious by the Food and Drug Administration (FDA), and has been approved for mass sales. A phase IV study follows the drug/device in a large-scale market, and it allows for increased understanding of the adverse events and/or possible adverse events. Phase IV studies are very important for comparison studies. A comparison study allows one FDA approved drug/device to be compared to another. The phase IV study may last for many years to obtain as much information as possible about a certain drug/device. The phase IV study is usually the longest of the studies and is the hardest to control, because it is in the general population, and allows for a great amount of statistics and valuable information.

In clinical trials, there are two main areas that are observed. These areas are drug studies and device studies. The drug studies may range from antibiotic studies, anti-diuretic studies, or pain analgesic studies, as will be mentioned later. Drug studies are very complex, because many of the drugs that are tested are capable of causing chemical changes within the human body. It is important that all of the drug studies be closely monitored to ensure the existence of safety and efficacy without the complications of serious adverse events. Drug studies are typically developed by pharmaceutical companies due to the expense of the studies themselves. A drug study entails many different facets of medicine. It may include one of many different disciplines found within medicine such as; surgery, geriatrics, or internal medicine. A drug study also utilizes pharmacokinetics, biochemistry, immunology, and biostatistics to name a few.

The complexities involved in the protocol design, the inclusion/exclusion criteria, and the rationale behind the results of a drug study are usually decided upon by the pharmaceutical company providing the funding for the study. If a drug study is funded by a pharmaceutical company, the company usually reserves all the rights to publish the findings of the study at their own discretion.

Device studies have a range of applications involving a variety of items. A device is defined by Mosby's medical dictionary as an item other than a drug that has application in the healing arts (Mosby, 1998). The term is sometimes restricted to items used directly by, on, or in the patient, as opposed to surgical instruments or other equipment used for diagnosis and treatment. The types of devices include; orthopedic appliances, crutches, artificial heart valves, pacemakers, prostheses, wheelchairs, cervical collars, hearing aids, and eye glasses. Many device studies are based on a pre-existing device that has only been modified to make it better. The FDA decides whether or not the device must undergo all phases of clinical trials depending on the similarities and differences of the device with the previously marketed device. Depending upon the complexity of the device itself, some device studies are created by certain institutions, which may not be large producers of medical devices. A certain institution, a hospital for example, may create a protocol to test for differences between two types of laparoscopic cutting techniques (as will be discussed later). This is possible because the protocol is not complex and the techniques have been previously approved by the FDA. Most device studies are not as complex as drug studies, but some may be due to the nature of what they treat and where and how they act upon the human body.

A phase III, randomized, double blinded, dose controlled, parallel group, dose-ranging study to evaluate the safety and efficacy of a single epidural dose of sustained-release encapsulated morphine (SKY0401) for the management of post-operative pain in patients undergoing lower abdominal surgery is the subject of the prospective drug study to be carried out in the surgery department of The University of North Texas Health Science Center. The objective of this study is to evaluate the safety, efficacy, and pharmacokinetic profile of a single epidural dose (5,10,15,20, or 25 mg) of sustained release encapsulated morphine (SKY0401), compared with unencapsulated morphine for the treatment of post-operative pain in patients undergoing lower abdominal surgery (i.e. surgery via an abdominal incision below the umbilicus) under general or regional (intrathecal) anesthesia. The study design allows for the observation of efficacy of the pain medication in decreasing post-operative pain up to 48 hours following the study.

The Skye- Pharma pain study utilizes a pain scale to allow subjects to convey their own levels of pain following the performed surgical procedures. This pain scale is an effective way of determining the efficacy of the study drug (Graven-Nielson et al., 2000). It allows the patients to display their own pain level to the study personnel while participating in the study. The patients are also allowed fentanyl in a patient controlled analgesia (PCA) pump for any pain that is not controlled by the study drug. Fentanyl has been shown to be effective for post-operative pain analgesia when given by a patient-controlled analgesia pump (Camu, 1998). The amount of fentanyl used will be recorded and this should correlate with the amount of pain that was present in the patient. Therefore, the correlation between the amount of fentanyl used and the time it was used

in for determining what dose of the study drug, if any, was more effective in controlling the post-operative pain should be effective.

It is important to understand that mental alertness will also be evaluated throughout the study to determine the safety of the different doses of the study drug. Mental alertness will be tested using a small battery of questions pertaining to the patient and their abilities to stay awake and alert. The mental abilities of the patient are to be evaluated by the surgeon, or primary investigator, in most cases.

The surgical procedures that are used in this study include lower abdominal surgeries. The possible surgeries include; sigmoid colon resection, total abdominal hysterectomy, salpingoophorectomy, or myomectomy, radical prostatectomy, or cystectomy. All of these surgical procedures occur through incisions below the umbilicus. If the surgical incision reaches above the umbilicus, this is grounds for exclusion, and all questions regarding inclusion and exclusion may be challenged. The clinical research coordinator is given the opportunity to call the monitor and request a waiver. If a waiver is given, the subject may be used.

A phase IV device study was also followed for six weeks to observe the efficacy and differential analysis of two types of FDA approved laparoscopic cholecystectomy techniques. Laparoscopic cholecystectomy is a minimally invasive procedure in which the gallbladder is removed (Gadacz, 2000). The two possible techniques that are currently approved by the FDA and used by many surgeons include electrocautery and harmonic scalpel as the cutting elements (Zucker, 2001). Electrocautery has been FDA approved and used in practice for a longer amount of time than the harmonic scalpel, but research

points to the increased use of the harmonic scalpel (Lange, 1996). The efficacy of each of these two devices has been established in previous studies (Power, 2000), but what is in question here is if one technique is better than the other for the patient's well being and recovery time. Nausea, vomiting and pain are evaluated up to 7 days post-operative to understand which of the two techniques are most advantageous to the patient. This study is randomized in that the surgeon is trained in both techniques, but does not know which of the two will be used until the box is opened immediately pre-operative.

The laparoscopic cholecystectomy device trial will be evaluating a number of parameters to be able to efficiently recognize a difference, if any, between the two commonly used techniques for laparoscopic cholecystectomy. The parameters that will be monitored will be operating time, blood loss, and injury to adjacent organs. The internal temperature during surgery was to be monitored, but the manufacturer of the ultrasonically activated scalpel was unable to provide the University of North Texas Health Science Center with sterile thermal probes. Post-operative monitoring of pain will be accomplished by using a pen and paper, visual analogue pain scale. Nausea and emesis (vomiting) will also be monitored along with post-operative complications such as bile leaks and bleeding.

CHAPTER II

JOURNAL OF INTERNSHIP PRACTICUM

05/20/02 Monday

Today I arrived at the Patient Care Center (PCC) at 8:00 a.m. I was very excited to begin the summer's internship. Della was also very excited that she would actually have a little help for a few weeks. Della spent most of the day introducing me to the faculty and staff on the surgical floor. I was really excited to meet all of the surgeons, because I will hopefully have the opportunity to work with them in a couple of years in my rotations. I spoke with Dr. Don Peska, Dr. German Berbel, and Dr. Adam Smith about the summer internship, and all of them were pleased to allow me to be present during any surgeries pertinent to the studies, as well as, any other surgeries for experience. Della then escorted me over to the Osteopathic Medical Center (OMCT). We talked to the right people so that I would be able to attend surgeries and then we both walked over to human resources to get badges. After all of this, Della and I went back to her office and discussed the protocols for each of the studies that I will have the opportunity to observe.

05/21/02 Tuesday

Today, I reported to the operating room (OR) at 6:30 in the morning. It was a little too early, but it gave me time to change into sterile scrubs and chit-chat with some of the surgeons and anesthesiologists. At 7:30 a.m., I entered OR room 5 to observe a laparoscopic cholecystectomy (lap chole) being performed by Dr. Berbel. To my

surprise, an emergency exploratory hemicolectomy was already in progress. The surgery was being performed by Dr. Smith, with Dr. Berbel assisting. Immediately following the surgery, the study patient for the lap chole was brought into the OR, and I observed my first laparoscopic cholecystectomy. It was a work of art. Dr. Berbel explained to me the differences between electrocautery and the harmonic scalpel as he had experienced them as a surgeon.

05/22/02 Wednesday

Yesterday's lap chole study patient returned today at 10:00 a.m. for the follow up exam and blood draw. The patient complained of moderate pain, but no nausea. Della suggested that the patient use a pillow or something similar to apply pressure to the area that was painful to relieve some of the pain. I drew some blood from the patient without any sign or complaint of pain. I knew those couple of years of phlebotomy would pay off some time. The patient was instructed to return in another 48 hours to obtain a 72 hour assessment. So we set the time of return at 10:00 a.m. on Friday the 24th. The remainder of the day I utilized the free time to review surgical procedures for the Skye-Pharma pain study.

05/23/02 Thursday

Today, Della and I reviewed a couple of charts of possible pain study participants. This was actually very easy to tell whether or not they met the inclusion and exclusion properties as described in the study protocol. One of the patients seemed perfect for the study based on age and the type of surgery to be performed. Della called the patient and set up a time to come in and discuss the study.

05/24/02 Friday

The lap chole study patient arrived at the Patient Care Center (PCC) around 10:00 a.m. for the 72 hour assessment. I drew blood again and chatted with the patient concerning pain and nausea. The patient told me that pain only occurred during movement, and during coughing periods. The patient also said that eating was not a problem and that there had been no experiences of nausea. The patient was quite chipper in comparison to their 24 hour assessment. In the afternoon, the possible pain study patient arrived at the office for a pre-operative assessment and to discuss the study itself. Della and I discussed the study, the protocol of the study, and the informed consent with the patient. The patient was then left alone for a while to read the informed consent. Upon reading and signing the informed consent vitals, and an electrocardiograph (ECG) was taken. A medical history was also taken and blood drawn. During the medical history, the patient told Della and I about a slight case of sleep apnea that had been experienced. This was important to us because sleep apnea is an exclusionary factor. Della talked to the patient about it and telephoned the monitor. The monitor said to continue with the enrollment. After all of this Della and I escorted the patient to the hospital for the pre-operative assessment. Later we decided to drop the patient from this study due to possible AE's (adverse events) that may occur in association with the sleep apnea.

05/28/02 Tuesday

I arrived at the OR at 7:00 a.m. for two lap chole study patients to be operated on back to back by Dr. Berbel. The two patients were successfully operated on and each was assessed four hours post surgery. However, one of the patients was released prior to the 4

hour assessment, so we had to contact that patient for the assessment. The patient returned to the hospital, but refused to enter. I then drew the blood outside in the parking lot. Della told me the study patient that we dropped because of sleep apnea was opened up and closed automatically due to increased cancer growth. The patient was given 6 months to live, so we decided to visit the patient and give our condolences.

05/29/02 Wednesday

The two lap chole study patients from yesterday (Tuesday the 28th) returned today for their 24 hour assessment. The two patients complained of pain, but only one patient complained of any nausea associated with post surgical treatment. Della and I talked to the patients about how to move, lay down, and apply pressure to their abdominal regions to reduce the pressure of the pain. The day ended with a couple of hours in the library reviewing notes and literature regarding surgery and clinical research.

05/30/02 Thursday

Today, Della and I talked to two different patients about their interests in the pain study. Each of the patients were happy about the idea, because Della and I would be at their bedsides following the surgery for 48 hours on and off. The patients were allowed to ask any questions regarding the study, and then given the informed consent. After the informed consents were signed, Della spoke to one of the candidates while I took the vitals, history, etc., from the other. The ECG was abnormal for the patient that I spoke with, and this abnormality had to be viewed and OK'd by Dr. Spellman in Internal Medicine. He looked at the ECG and said that surgery would be OK. One of the patients

was escorted to the hospital for pre-op, while the other was asked by his doctor to go to pre-op tomorrow on Friday.

05/31/02 Friday

Today, Della and I went over everything that needed to be done next week with the two study patients because she is leaving town. We reviewed the protocol and flagged all of the charts. I manufactured small pocket size protocol reminders for all of the involved personnel. Della was starting to have a great deal of anxiety regarding the study, but I explained to her that I would be able to handle everything while she was gone. This may not have comforted her, but it made me a little more confident in myself, and what I would have to do next week.

06/03/02 Monday

I arrived at the OR at 5:30 a.m. to change into my scrubs and to get ready to see our two study patients that arrived in out patient at 6:00 a.m. I asked the nurses if the pharmacy had been notified on the arrival of the study patients according to the protocol and flow sheet provided in the patients chart. I was told that yes they have been notified, but in reality they had not. So, I asked them to call and tell the pharmacy so that the randomization could take place, and the study drug could be thawed and readied for the administration. We had two patients for the Skye-Pharma drug study and both were undergoing different surgeries. One underwent colon resection and the other underwent a radical prostatectomy. The colon resection case was Dr. Smith's and the study drug was administered at 7:56 a.m. The radical prostatectomy was performed by Dr. Rittenhouse, and the study drug was administered at 8:13 a.m. The surgeries were to start at least 30

minutes. following the study drug administration, and each did, give or take a couple of minutes. Dr. Rittenhouse was not very happy with the tardiness of the surgery due to the time delay of drug administration. Following the surgeries, the patients were taken to the post anesthesia care unit (PACU), and Della and I accompanied the patients to ensure proper protocol procedures. At this time, the fourth floor tower declined to accept the patients if they were going to be on fentanyl pumps, because they had not been notified of the study. This sent everyone into a frenzy. After Dr. Smith was notified of this, he called the right people and we were able to take the patients up to the floor. At this time, the patients were transferred to the floor, and we monitored their vitals hourly for the first 24 hours to ensure safety and to monitor the usage of fentanyl. We ended the day at about 7:00 p.m. and explained to the floor nurses how to fill out our patient report flow charts and asked them to perform these tasks until we arrived the next day.

06/04/02 Tuesday

Today I began the day at 7:00 a.m. in the morning, seeing each of our study patients and greeting their families. I took the necessary assessments and noted them where necessary. A problem developed with the usage of fentanyl by one of our patients. The dosage shows to be too much, but in reality it was not. What actually occurred is that the pharmacy doubled the concentration of the fentanyl to be given in the PCA pump, but they failed to inform any of the nurses which were setting the PCA pumps. This caused a greater amount of fentanyl to be released each time the patient pressed the button (q time). This was remedied with the pharmacy realizing they must place into action a specified concentration q time / study protocol. The two patients dosages or rate of

dosages were decreased due to the possibility that fentanyl may cause pulmonary distress. However, we have not witnessed this in our patients. Our staff pharmacist warned us of this, but the protocol allows for higher doses than those that are actually being given. This remained at our discretion, but the importance of clinical studies is the safety of the patient. Therefore, we decreased everything and they were still comfortable. I have read through the protocol numerous times and we are right on schedule. We will have to calculate the differential statistics that the pharmacy mistake may cause to the study, but that is actually not our problem. Our patients are fine and that is what counts. This study has shown us everyday that Della is in need of assistance and also that we must coordinate our studies with everyone who might be effected by them; patients, surgeons, nurses, anesthesiologists, floor directors, floor specific nurses, pharmacists, etc.

06/05/02 Wednesday

I began the day about 7:00 a.m. at the hospital checking on overnight measurements that were taken for us by the "great" nurses on 4 tower. They have treated us great so far, and take exempliary care of their patients. At 7:56 a.m., I took one patient's 48-hour stats and these were his last measurements for the study. The other patient's stats were taken at 8:15 a.m. Both study patients seemed to be doing much better than the previous day. Later that day, Dr. Smith performed the final study physicals. Della was gone today. She has left to New York City to a conference and also for a small amount of "R & R" with her family. I am glad she took a little time for herself, she needed it desperately.

06/06/02 Thursday

At 8:00 a.m., I visited our study patients in their rooms. Both of them were cheery and happy to see me. Their pain medications had been changed off of fentanyl and they were feeling well. I made copies of their hospital charts to add into the source documents for the study. I ventured back to the office to piece together parts of the information that had been taken down in various places and to transport them to the case report form. It was a successful day and I believe that the study went well even though there were a few flaws. However, these were the first two Skye-Pharma pain study patients and the next ones should be a little smoother.

06/07/02 Friday

Today, I visited our study patients at 8:30 a.m. in the morning. Each of the two patients were doing well. One patient explained to me that the doctor told him that he would probably be going home that day. I asked the nurse to contact me at the patient care center when this patient was released so that I would have the opportunity to capture any documents in his chart that may need to be recorded in the case report form. The nurses notified me upon release of this patient and I copied all of the patient's information that I did not previously have to add to the Case Report Form.

06/10/02 Monday

The last pain study patient that was in the hospital was dismissed this morning and I captured all of the pertinent information needed for the Case Report Form. Della is back from New York today. I took a little time to explain to her some of the things that

happened while she was away. There was nothing bad, but I thought it would be important to inform her of the daily things which occurred in her absence.

06/11/02 Tuesday

Today we had a patient come in for the laparoscopic cholecystectomy study. We allowed the patient to read and sign the informed consent. This was followed by me performing a medical history on the patient and taking vitals and drawing blood for the necessary lab work. The patient's history and labs were satisfactory for inclusion into the lap chole study. After we performed all of the necessary measurements and questions with the patient, Della and I escorted the patient to the pre-operative area in the hospital. Della and I went back and flagged the patients chart so that all of the nurses and everyone involved would know that this was a study patient.

06/12/02 Wednesday

Most of today I transferred information from the source documents to the Case Report Form (CRF) for the Skye-Pharma pain study. The CRF is very redundant, but I guess it is necessary to understand and statistically evaluate the study and the actual effects of the drug. Writing down the concomitant medications seemed like it took forever. I had to document every type of medicine other than the study drug that was taken 24 hours previous to the surgery and all medications taken 48 hours post study drug dosage. I know that this is a very important part though, to ensure that it is the study drug that is relieving pain and not another type of medication. Today, I left the office at about 4:00 p.m. and I will finish this work tomorrow.

06/13/02 Thursday

Today I arrived at the PCC around 8:00 a.m. so that I could finish as much as possible on the CRF before the weekend, because the pain study monitor will be here on Monday to look over the CRF's and to make sure that the data is the same as in the source documents. I finished transcribing about 1:30 p.m. When I finished, I began to look over the source documents for the lap chole study and make sure that all of them are in order. All of them seemed to be OK and I left around 4:00 p.m. to go to the library to read a little and write.

06/14/02 Friday

A possible lap chole subject was screened and blood was taken. The patient was accepted to the lap chole study and was scheduled for surgery the following Tuesday. Later, I took one last look over the CRF and asked Della to double check so the monitor would not be upset with me. So we did and I left about 5:00 p.m.

06/17/02 Monday

Today I began at 8:00 a.m. At 8:30 a.m. a monitor for our pain study arrived to go over everything that we had done for our last two subjects. She stayed all day and only finished looking over one patients case report form. She was very thorough and found a few mistakes that I had made in transcribing the CRF from the source documents. We also had a possible candidate for the pain study. The patient will be having a colon resection done due to a diagnosis of colon cancer. This patient presented very healthy and willing to participate in the study, because it meant "extra special care" in the patient's words. All of the pre-operative regime were carried out after the patient signed

the informed consent. This included history, vitals, ECG, lab draws and an escort to the hospital for pre-op.

06/18/02 Tuesday

I arrived at the OR at 6:30 a.m. this morning to attend a lap chole with Dr. Berbel. The lap chole lasted about an hour and following the procedure, I briefly talked to the subject in post anesthesia care unit (PACU). At 12:30 p.m., I performed the 4 hour post operative assessments which include a nausea scale and a lab draw. The out patient nurses were then given the OK to allow the patient to go home.

06/19/02 Wednesday

Our Tuesday lap chole patient came in for a 24 hour assessment that consisted of a regime of basic questions regarding post surgery nausea and pain. I also extracted blood to run a couple of labs that are composed of a complete metabolic profile and a complete blood count. Prior to the arrival of this study patient, Della and I made sure that everything was ready for tomorrow's pain study patient. We went over to the hospital to talk to the hospital's pharmacy staff about the study drug and the administration of fentanyl and its concentration. After this we walked over to surgery to find out what time the surgery was set for and found out that it was set for 2:30 p.m. The procedure that will be done is a right hemicolectomy, taking 2 to 2.5 hours to perform. We wondered if we might be able to get Dr. Berbel to change this to an earlier case, so the study may begin at an earlier time. This surgery was moved to second case and it will start around 8:30 or 9:00 a.m. This time we made sure that the nurses in tower 4 knew that a study case will be coming their way, so that they do not "freak out" like last time. I ended the day about

4:00 p.m. by escorting some blood over to the lab for an assessment, and will begin tomorrow very early.

06/20/02 Thursday

My day began at 7:30 a.m. this morning, and I was actually late. Our pain study that was in the OR this morning was supposed to be a second case, but was switched to first case. That was OK with me because it will be over quicker; however, it made me late. The surgery was performed by Dr. Berbel and surgical resident Dr. Ferrara. The surgery consisted of right hemicolectomy the removal of the ascending colon, as well as a portion of transverse colon. This day went much smoother than did the first day of pain studies three weeks ago. Today was a very strange day indeed. Our study patients whole family was here, which was very nice. They were all great. The family insisted on buying me dinner that night since I had been there all day with the patient and the family. That was not the strangest thing though. Soon after the arrival of the patients granddaughter, the entire family kept trying to hook me up with her, for lack of better words. They were very persistent, but I could not do it. It seems a little unprofessional to me, even though she was very beautiful. I finished the day at about 6:00 p.m.

06/21/02 Friday

Today, I arrived at the hospital at 7:15 a.m. and walked in on our study patient. The patient was in high spirits and was feeling no pain upon questioning. My first thought was that the patient was using a great deal of fentanyl, but to my surprise, he had only used 100 μg more than he had the previous day. I asked the patient all of the pertinent study questions and visited with the family to see how the night was. Each family

member present kept telling me that the patient really wanted to go home all night long, but that they were able to reason with the patient, convincing the patient to relax. Upon asking the family a few questions, they said that the patient had not complained of any pain all night long. I stayed in the hospital most of the day and checked vitals and performed assessments when necessary according to protocol. The nurses that are on duty today were great with helping us when we needed it. They also allowed us to leave whenever we wanted, because we could trust them to perform what they needed to, when they needed to. One of our lap chole patients came in today for the 72 hour assessment. There did not seem to be a great deal of pain in the patient and the nausea they once experienced had subsided. I talked to Dr. Berbel's resident and he said that he would be available in the morning to perform a 48 hour assessment physical examination on our study patient. The study patient's family was arriving by the droves, so I decided to leave the hospital about 3:00 p.m. and go over to the library to work on my thesis.

06/24/02 Monday

I arrived at the clinic at 8:00 a.m. and put some things away, then decided to go over to the hospital and talk to our study patient. When I arrived at the room, Della was there with some of the family members and she wanted me to help her to get the patient up and walking. We then helped the patient out of bed and walked around the room and out into the hall. I was relieved to see the patient walking and moving without much pain medicine intervention. After walking the patient, Della and I returned to the clinic to follow up on some of the paperwork regarding this patient's chart for the first 48 hours on study.

06/25/02 Tuesday

Today was not very exciting. We did not have much to do at the clinic, so I sat in the library most of the day reading about clinical research and talking to people.

06/26/02 Wednesday

A new patient came in today for pre-op for the pain study. This patient qualified for the study by meeting all inclusion/exclusion criteria. The patient was given the informed consent and asked to read it and ask question if there were any. I left the room as the patient read the consent form so that I would not seem to pressure the patient. After a few minutes I returned and explained the study to the patient and allowed the patient to ask any questions. Next, I took a family history and patient history, then drew blood according to study protocol. Della and I then escorted the patient to pre-op at the hospital. Later that day, we received word of a couple more possible pain study candidates. These candidates were the patients of a few doctors who had not been added as sub-investigators, and must complete a clinical research tutorial prior to patient admission into the study. Della told me that it is like "pulling teeth" sometime to get the surgeons to complete the tutorials, because of their busy schedules. It is necessary for IRB protocol for each of the sub-investigator's to take the tutorial previous to performing any surgery that is linked with the study drug.

06/27/02 Thursday

Today's work consisted of transcribing concomitant medications and fentanyl usage from the source documents and chart that were used to the CRF. It was so much easier this time than it was the first, because the new flow sheets that Della received for this study

are excellent and they trap the needed information in a well defined report. It did not take a long time to transcribe the work this time either in comparison to the last time, because we only used concomitant medications up to 48 hours, not passing that time frame as we did in the previous two study patients.

06/28/02 Friday

Today, is my last day. Della and I began the morning by finishing the CRF of the previous patient and getting some paperwork ready for the new patient coming in next Monday. Later, Della treated me to lunch at an Italian restaurant down the street. It was great. After lunch, Della let me leave early so that I could drive home and see my son for a couple of days. I took a few minutes to write and I really enjoyed this experience. Then I was off like a bullet.

CHAPTER III

DISCUSSION

With regard to the usage of clinical research in surgery, it is important to understand that without this research it would be nearly impossible to make advancements in techniques and patient care without first applying the proposed drug/device to study patients and then observing the outcome. Everyone must understand human research is as necessary as animal research. Techniques involved in surgery must be tested in an animal model first if applicable, but must also be observed in humans before it is used to ensure safety and efficacy. An epidurally administered, encapsulated form of morphine was previously tested for safety in dogs, before human trials began, and it produced a sustained clearance of morphine, and a prolonged period of analgesia (Yaksh, 2000). Another study in dogs allowed scientists to determine that an extended release of encapsulated morphine corresponded with an extended duration of pain relief without an increase in the incidence of side effects (Yaksh, 1999). Studies such as these allow for the primary effects and reactions of a living system to a drug to be evaluated before a drug study may proceed into phase I of a clinical trial. Clinical trials require many hours of previous bench work research, as well as many hours of clinical work. Who does all of the work?

Many people and positions are needed to allow clinical research to be possible in the surgical department of the University of North Texas Health Sciences Center. First, it is necessary to have a Clinical Research Coordinator (CRC), which is responsible for all

of the work involved in the research makeup. The CRC makes sure that all of the studies run as smoothly as possible. The CRC is required to coordinate the studies, evaluate the possible patients, and keep up with all of the data and information that comes in as the study progresses. Basically, the CRC is the backbone of any clinical research program.

Next, the primary investigator is the person that is ultimately held 100% accountable for the study itself. The primary investigator must be able to understand the rationale behind the study, and be able to carry out the study. In the prospective drug/device studies in this paper, the primary investigator's role is to carry out the study protocol and communicate with the CRC. This work is also given to the other members of the clinical research team.

Last, the other members of the team are the secondary investigators. The secondary investigator's roles are to work under the primary investigator in the study. In the surgical department at the University of North Texas Health Science Center, the secondary investigators are usually any of the surgeons other than the primary investigators that are involved in any of the surgeries that are capable of being used in the studies. Between the CRC, the primary investigator, and the secondary investigator, the team that is responsible for clinical research in the surgery department of the University of North Texas Health Science Center is very competent and capable of controlling a large amount of research in that department.

During the six week time period in which the internship practicum lasted, there were many questions that were raised about the protocol developments and how they could have been changed. The Skye-Pharma drug study utilized information about a

certain drug and the way that it was given to understand the efficacy of an encapsulated morphine like drug for post-operative pain. This study's protocol lacked the time that seemed to be needed to understand the true efficacy of the drug. A 48 hour post dose time period was observed which may not allow complete dispersal of the study drug. Various study patients complained of high amounts of pain within the 48 hours post dose, but then did not even fill their pain medication prescription upon leaving the hospital. This leads to the question of whether or not the pain medication had taken effect within the 48 hours post dose or after dismissal from the hospital? Another protocol exclusion factor came into question when two of the patients had their abdominal incisions extended above their umbilicus. According to the protocol, these patients should have been excluded, but upon calling the monitor and the company, these patients were accepted without waiver. Does the extended incision matter, or was it a mistake in the protocol exclusion list? Questions such as these were raised during the processes of the study itself, but it is not understood whether or not factors such as these will effect the overall outcome.

In the laparoscopic cholecystectomy study, many of the protocol designations kept a large number of eligible participants from being accepted. The first protocol exclusionary factor was age. The oldest a study patient could be was 65. This left out many healthy 66, 67, etc., year old people that would have been great for the study. The developer of the study was contacted about this and has decided to amend the age limit for an increased number of patients. According to the protocol, the internal temperature was to be tested during the two procedure techniques. This did not occur because of the

lack of thermometers. The sponsoring company did not supply the thermometers as they had previously planned on doing so. This loss of quantitative data may be a detriment when the results of the study are published for peer review. All in all though, the protocol design of this study was very interesting as a phase IV study.

In comparing the complexity of the drug study versus the device study, there are many aspects that should be looked at. First, the Skye-Pharma encapsulated form of morphine is not FDA approved as of yet; therefore, it is a Phase III study. The laparoscopic cholecystectomy device study is using only devices that have been FDA approved, and are on the market making it a phase IV study. The drug study must be more thorough to ensure patient safety, because complete safety is one of the things being monitored in the study. However, the device study may be more lax, because each device being studied has been studied for safety and approved. Next, more pre-operative precautions must be taken into consideration for the drug study in comparison to the laparoscopic cholecystectomy study. This is necessary because the drug study patients are undergoing more invasive procedures than those patients in the laparoscopic cholecystectomy study. Any slight problem that takes place during surgery or post surgery may be considered an adverse event. If there are too many adverse events, the drug will not be considered safe enough for distribution. All of the pre-operative precautions allow investigators to "weed out" potential adverse events. Adverse events are also monitored in the laparoscopic cholecystectomy study, but these are capable of being used to promote one device over another. The AE findings in the device study should not be used particularly as a safety issue.

Finally, looking at the phase III drug study versus the phase IV device study, it is evident that the drug study is more expensive to carry out. The drug study is sponsored by Skye-Pharma pharmaceuticals, while the device study is an in house study that has partial backing by a device manufacturer. Elements of the drug study, which may be costly include labs, EKG, cost of study drug, payment to pharmacy, payment to secondary surgeons involved in the study, and payments to the anesthesia department for drug delivery. The laparoscopic cholecystectomy study on the other hand involves only payment for labs, and occasional payment to secondary surgeons. It is not always the case that a drug study is more expensive than a device study, but on average, device studies are not as complex and demanding, making them cheaper in most cases. (Bulpitt, 1996).

CHAPTER IV

SUMMARY

A clinical trial is composed of four different phases. Each of these phases serves a purpose such as testing safety, efficacy, and dosage. These phases are essential to provide the best possible model for mass use of a drug or a new device. Drug studies differ from device studies in their design and their delivery. In this case, a post-operative pain medication was tested, as well as a differential study between two types of cutting devices used in laparoscopic cholecystectomy. The post-operative pain study is a phase III study that is testing the efficacy, safety, and the pharmacokinetics of a proposed drug. The device study is considered a phase IV study because it is evaluating two commonly used techniques for laparoscopic cholecystectomy. Both of these techniques have previously been approved by the FDA and are mass marketed.

These two studies were followed for six weeks and evaluated for protocol design, differences and similarities, and for hands on experience in the clinical research arena. Upon completion of the six week opportunity, it is evident that clinical research is a viable piece of medicine today. Following these two studies allowed for an understanding of the differences and similarities encountered when executing a drug study, as well as a device study. The complexities of the two studies were evaluated, and without doubt, the drug study included much more paper work, patient testing, inclusion/exclusion criteria, study evaluation, and most of all, man hours. All in all, this

was a very rewarding experience that allowed for a greater understanding of the implementation and value of today's clinical research.

REFERENCES

"Adverse Event." Mosby's Medical, Nursing, & Allied Health Dictionary. 5th edition. 1998.

Bulpit, C.J. Randomised Controlled Clinical Trials. 2nd edition Norwell, Massachusetts: Kluwer Academic Publishers, 1996.

Camu, F., Van Aken, H., Bovill, J.G., (1998). Postoperative analgesic effects of three demand-dose sizes of fentanyl administered by patient-controlled analgesia. *Anesthetic Analgesia.* 87(4): 890-5.

"Device." Mosby's Medical, Nursing, & Allied Health Dictionary. 5th edition. 1998.

Friedman, Lawrence M., Furberg, Curt D., DeMets, David L. Fundamentals of Clinical Trials. 3rd edition St.Louis: Mosby, 1996.

Gadacz, T.R., (2000). Update on laparoscopic cholecystectomy, including a clinical pathway. *Surgery Clinician of North America.* 80(4): 1127-49.

Gallin, John I. Principles and Practice of Clinical Research. San Diego, California: Academic Press, 2002.

Lange, B., Millott, M., Dahshan, H., Eilers, D., (1996). Ultrasound scalper—initial experiences with use in laparoscopic surgery. *Chirurgische.* 67(4): 387-93.

Power, C., Maguire, D., McAnena O.J., Calleary, J., (2000). Use of the ultrasonicdissections scalpel in laparoscopic cholecystectomy. *Surgical Endoscopy.* 14(11): 1070-3.

Yaksh, T.L., Provencher, J.C., Rathbu, M.L., Kohn, F.R., (1999). Pharmacokinetics and efficacy of epidurally delivered sustained-release encapsulated morphine in dogs. *Anesthesiology.* 90(5): 1402-12.

Yaksh, T.L., Provencher, J.C., Rathbun, M.L., Myers, R.R., Powell, H., Richter, P., Kohn, F.R., (2000). Safety assessment of encapsulated morphine dilevered epidurally in a sustained-release multivesicular liposome preparation in dogs. *Drug Delivery.* 7(1): 27-36.

Zucker, Karl A. Surgical Laparoscopy. 2nd edition Philadelphia, PA: Lippincott Williams & Wilkins, 2001.