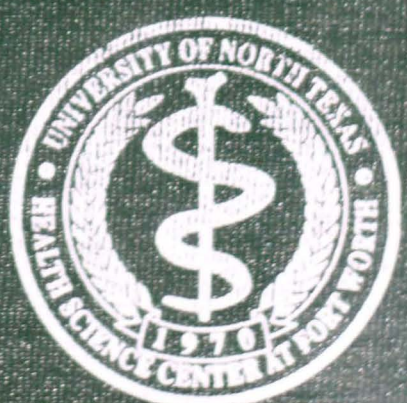
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A CLINICAL RESEARCH STUDY INVOLVING THE USE OF ERYTHROPOIETIN IN PERIOPERATIVE PATIENTS UNDERGOING SURGERY FOR GYNECOLOGIC CANCER

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A CLINICAL RESEARCH STUDY INVOLVING THE USE OF ERYTHROPOIETIN IN PERIOPERATIVE PATIENTS UNDERGOING SURGERY FOR GYNECOLOGIC CANCER

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

SHARON BETH LARSON, B.A.

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HYPOTHESIS

Introduction

The purpose of this internship practicum report is to analyze the pathophysiology and impact of anemia in low-income gynecologic cancer patients. The report also assesses the impact of erythropoietin on hemoglobin levels prior to gynecologic cancer surgery. This report is based on a clinical research study to determine whether or not erythropoietin will mitigate the suppression of bone marrow inherent to the gynecologic cancer population and alleviate some of the symptoms and side effects of the anemia.

Background

The focus of this clinical study is anemia in the newly diagnosed gynecologic cancer patient undergoing primary surgery. The clinical study is investigator initiated and is sponsored by a pharmaceutical company. The principal investigator is a gynecologic oncologist and was approached by the pharmaceutical company to write the protocol for the clinical research study.

Some gynecologic cancer patients may occasionally suffer from preoperative uterine bleeding that may be exacerbated by older age and the cancer disease in its advanced stages. Disease states combined with poor nutritional status and the treatment with surgery, radiation, or chemotherapy may contribute to anemia in the cancer patient.

Blood loss during surgeries to treat cancer may be extensive. In addition, preoperative anemia combined with intraoperative blood loss deplete the stores of healthy, red blood cells in the gynecologic cancer patient requiring some form of treatment such as blood transfusion. Similarly, several additional factors may increase the risk that a gynecologic cancer patient will require a red blood cell transfusion. These factors include presentation of anemia at the time of gynecologic cancer diagnosis, surgical procedures required for disease treatment that may result in an increased blood loss, poor tissue oxygenation due to anemia that may worsen with cardiovascular and peripheral vascular disease, and hemoglobin and hematocrit levels that should be increased prior to radiation therapy and chemotherapy (8). In most patient populations, allogeneic blood transfusions are given to cure the anemia. As a result, patients with anemia associated with gynecologic cancer experience an increased risk of receiving a red blood cell transfusion preoperatively, intraoperatively, or postoperatively to correct the anemia (1). Due to the nature and characteristics of the disease, however, the prognosis for patients with gynecologic cancer is negatively affected by red blood cell transfusion performed perioperatively (2-7). Side effects associated with red blood cell transfusion include alloimmunization, allergic reactions, hemolytic reactions, iron and circulatory overload, immunosuppression, decreased measures in quality of life, insufficient energy levels, overall fatigue, the transmission of infectious disease, and fever (32).

Infectious agents such as the hepatitis virus, Epstein-Barr virus, and exotic microbes cause concern when considering blood transfusion (32). Table 1 summarizes the infections that compromise disease free blood transfusion (15).

Risk factor	Estimated frequency per million units	Number of deaths per million units
Viral Infection		
Hepatitis A	1	0
Hepatitis B	7-32	0.14
Hepatitis C	4-36	0.5-17
HIV	0.4-5	0.5-5
HTLV types I and II	0.5-4	0
Parovirus B19	100	0
Bacterial Infection		
Red blood cells	2	0.1-0.25
Platelets	83	21
Acute Hemolytic Reaction	1-4	0.67
Delayed hemolytic reactions	1000	0.4
Transfusion-related acute lung injury	200	0.2

Table 1: Risks of blood transfusions. Goodnough LT, Brecher ME, Kanter MH, AuBuchon JP. Transfusion medicine. First two parts-blood transfusion. New England Journal of Medicine 1999; 340:438-47.

Because of the risks associated with blood transfusion, such procedures are reserved for patients with serious emergencies, those who are severely anemic with very grade 3 or 4 anemia, and those for whom underlying illness puts them at risk for adverse cardiac events in the mild to moderate anemia range (30). In order to decrease the frequency of red blood cell transfusions for patients undergoing major surgical procedures, supplemental iron therapy, preoperative autologous donation (PAD) of blood, and preoperative hemodilution are performed. Due to preoperative anemic states,

gynecologic cancer patients are ineligible to donate their own blood prior to their own surgery (1). Since several limitations are placed on the treatment of anemia in gynecologic cancer patients, there are few options to pursue.

A number of alternative suggestions have been made for the treatment for anemia. These include the use of a cell saver and natural hormones. A cell saver is a surgical device that separates the plasma fraction from the blood, returning the patient's own red blood cell fraction back to the body, reducing the need for blood transfusion. While the intraoperative use of the cell saver has been suggested as an alternative, it cannot be utilized for patients scheduled for major gynecologic oncology surgery due to the low perioperative red blood cell counts of anemia and fear of spreading cancerous cells to naïve tissue (1).

The administration of erythropoietin, a natural hormone, is another treatment that has been used to treat anemia. The Food and Drug Administration (FDA) has already approved the use of erythropoietin for the treatment of chronic renal failure patients, zidovudine (AZT)-treated human immunodeficiency virus (HIV)-infected anemic patients, cancer patients who are anemic due to chemotherapy with nonmyeloid malignancies (9,10), and anemic patients planning to have elective, non-cardiac, non-vascular surgery to reduce the requirement of an allogeneic red blood cell transfusion (11-13). Erythropoietin is also indicated for the treatment of anemia in patients undergoing elective, non-cardiac, non-vascular surgeries with hemoglobin levels > 10 to

≤ 13 g/dL. In addition, erythropoietin is used to treat anemia and to reduce transfusions in patients with nonmyeloid malignancies in which chemotherapy may be the cause of the anemia (13).

The use of erythropoietin for patients undergoing surgery has been evaluated in four major studies including 869 patients undergoing major, elective, orthopedic surgery. These studies demonstrated that treatment with erythropoietin increases preoperative hemoglobin, hematocrit, and reticulocyte levels, resulting in significantly less exposure to allogeneic blood transfusions, and that erythropoietin is safe and well tolerated. In addition, these studies showed that baseline hemoglobin is one of the strongest predictors of transfusion risk, patients with a baseline hemoglobin > 10 to ≤ 13 g/dL benefited most, and if the period prior to surgery is ≥ 3 weeks, 600 U/kg can be administered once weekly for 3 weeks and on the day of surgery (33, 36-38).

Treatment of Anemia

Because anemia has such detrimental effects on the prognosis of gynecologic cancer patients, treatment to correct these patients' anemia is of utmost importance. As previously mentioned, supplemental iron, preoperative autologous blood donation, and the use of a cell saver all attempt to reduce the frequency of blood transfusions in patients scheduled for major operative procedures. Supplemental iron therapy demands 6 to 8 weeks to correct an iron deficiency anemia in the absence of active bleeding. The time delay from diagnosis to surgery required for supplemental iron to take effect prevents this

treatment form from becoming a reasonable solution for the problem of preoperative anemia. Anemic patients may not donate their own blood due to their pre-existing, preoperative anemic states, so autologous red blood cell donations are infeasible for gynecologic cancer patients wishing to correct anemia prior to the date of their surgery. The fear of circulating cancer cells in the cell saver forbids the use of intraoperative blood saving devices in cancer surgery (35).

The management of anemia may vary depending on the intensity of the chemotherapy. Treatment options include replacement crystalloids, red blood cell transfusions, and the administration of erythropoietin, or a combination of all. Replacement crystalloids are isotonic solutions that are meant to replace blood volume including interstitial fluid and blood plasma. Symptomatic transient anemia due to blood loss or symptomatic chronic anemia may be treated with replacement crystalloids to replace volume in the cardiovascular system (30). Patients with persistent anemia for whom crystalloid treatment has not been effective should be considered for a red blood cell transfusion. Anemia caused by acute blood loss in patents with cancer should be treated with a red blood cell transfusion when crystalloid treatment does not correct vascular volume deficiency adequately. These transfusions are also indicated for patients with chronic anemia who do not respond to iron replacement therapy. Because erythropoietin, often used to treat mild to moderate anemia, requires time in order to take effect, some patients may need transfusions to correct their anemia immediately (30). The incidence of red blood cell transfusion is as high as 50-60% in anemic gynecologic cancer patients

undergoing chemotherapy (31). Although red blood cell transfusions are champions in the correction of anemia, as previously mentioned, complications and risks are not absent from this procedure.

Gynecologic Cancer

Gynecologic cancers may include ovarian, endometrial, and cervical cancer. The leading cause of death from gynecologic malignancies is ovarian carcinoma. Women aged in their sixties and seventies represent the group with the highest frequency of ovarian carcinoma diagnoses. In order to improve survival, several different modes of therapy are employed. The methods for treating ovarian cancer include surgery, radiation therapy, and chemotherapy. Surgical procedures performed in order to aggressively combat ovarian carcinoma incorporate total abdominal hysterectomy, bilateral salpingo oopherectomy, complete staging, and debulking. Because there are few early symptoms and no successful screening tests, most ovarian cancer patients present with advanced stage cancer and significant debility that often includes anemia (3,6).

Endometrial cancer affects the innermost layer of the uterus and is the second most common gynecologic malignancy. Patients diagnosed with endometrial carcinoma average 57 years of age. Abnormal uterine bleeding, or postmenopausal bleeding, is the hallmark symptom of this disease. This bleeding contributes to the anemic state of the patients presenting with endometrial carcinoma. Surgery in the form of total abdominal

hysterectomy and bilateral salpingo oopherectomy acts as the most significant treatment of endometrial carcinoma (10).

Cervical cancer stands as the third most common malignancy of the female genital tract. Patients with cervical cancer may present with vaginal bleeding that may exacerbate the anemia in these women. Surgery treats invasive cervical cancer and recurrent cervical cancer, but only in early stages of the cancer (7).

A common symptom of all gynecologic cancers is abnormal bleeding due to the cancer disease. This loss of blood contributes to the anemia present in most gynecologic oncology patients. Surgery conducted to treat and remove the cancerous tissue from the female genital tract may be accompanied with perioperative blood loss, further contributing to the anemia gynecologic cancer patients exhibit. Therefore, patients of gynecologic oncology experience a double threat to the maintenance of normal red blood cell counts. The anemia that results from the cancer disease and surgery is substantial and a serious threat to the disease prognosis (7).

In addition to the anemia that results from gynecologic cancer bleeding and surgery, chemotherapy-induced anemia occurs as a common complication associated with the treatment of gynecologic cancer. The progress of the gynecologic cancer disease and the intensity of the chemotherapeutic treatment combined, may escalate the severity of the anemia. Multiple cycles of chemotherapy may completely debilitate the process of

erythropoiesis, cumulatively and permanently, leading to the most severe grades of anemia (14). Anemia exists as a debilitating disease that decreases the amount of daily activities a gynecologic cancer patient may endure, limiting their functional capacity. Thus, anemia diminishes quality of life for gynecologic cancer patients. Clinical studies have shown that even the mild to moderate grades of chemotherapy-induced anemia may reduce a gynecologic cancer patient's energy level and quality of life, due to the impact of fatigue (1,15). These mild to moderate cases of anemia, however, are rarely managed and never aggressively treated (1). Standardized toxicity grading systems help to assess the severity of anemia and its effects on quality of life (QOL). The World Health Organization and the National Cancer Institute recommend similar toxicity criteria to classify the varying degrees of anemia ranging from grade 0 anemia severity to grade 4 anemia severity. Table 2 describes the grading system for anemia of the National Cancer Institute (14).

Severity	Toxicity Grading System (grams of hemoglobin)
Grade 0 (within normal limits)	12.0-16.0 g/dL (women), 14.0-18.0 g/dL (men)
Grade 1 (mild)	10.0 g/dL to within normal limits
Grade 2 (moderate)	8.0-10.0 g/dL
Grade 3 (serious/severe)	6.5-7.9 g/dL
Grade 4 (life-threatening)	<6.5 g/dL

Table 2. Anemia grading system of the National Cancer Institute. Groopman JE, Itri LM. Chemotherapy-induced anemia in adults: incidence and treatment. Journal of the National Cancer Institute 1999; 91(19):1616-34.

In the future, the classification systems of chemotherapy-induced anemia may guide physicians in seeking appropriate treatment and intervention based on hemoglobin levels and anemia grade profiles (15).

Clinical studies show that chemotherapy-induced anemia reduces a gynecologic cancer patient's energy level and quality of life (14). Symptoms of anemia such as fatigue and dyspnea upon exertion can impair the quality of life for gynecologic cancer patients and decrease the gynecologic cancer patient's ability to perform the activities required for everyday life (14). Of those gynecologic cancer patients undergoing chemotherapy, 80-100% complain of fatigue because of their anticancer treatment, making fatigue the most highly reported symptom in gynecologic cancer patients in general (16-18). Fatigue poses a serious threat to the cure of gynecologic cancer patients. Due to the emotional and physical drains that anemia-induced fatigue places on gynecologic cancer patients, motivation to seek, continue, or complete treatment is diminished (19). Therefore, the most detrimental adverse impact on the quality of life of cancer patients is fatigue. Fortunately, higher hemoglobin levels are associated with less fatigue and better quality of life (14). Therefore, it is vital that gynecologic cancer patients and health care providers seek treatment for anemia to preserve the quality of life the patients desire.

The severity of anemia resulting from chemotherapy depends on the particular therapeutic agent administered and the patient's history of exposure to previous chemotherapy, radiation therapy, or a combination of both. With successive, multiple cycles of chemotherapy, the proportion of patients with anemia increases from 17% before the first cycle to 35% before the sixth cycle, and the average measure of hemoglobin decreases with each chemotherapy visit (14). For gynecologic cancer

patients with advanced ovarian cancer, the chemotherapeutic agent and regimen may differ based on whether the patient has a recurrent case of ovarian cancer or whether it is the patient's first regimen of chemotherapy for the disease. Combination regimens are used more frequently in cases of initial chemotherapy, and those with recurrent disease usually undergo treatment with a single chemotherapeutic agent (20,21). Paclitaxel and topotecan are two widely used chemotherapeutic agents in ovarian cancer cases. Paclitaxel combined with a platinum compound is considered the standard of care for the management of ovarian cancer (21). Increased doses and longer exposures to paclitaxel not only cause immunosuppression, but also increase the prevalence of more severe forms of anemia in chemotherapy-treated patients (22).

The chemotherapy that gynecologic cancer patients receive to treat their cancer may induce anemia due to the suppression of erythropoiesis caused by the chemotherapeutic agent. The severity of anemia that results from this treatment depends on the intensity of treatment and brand of chemotherapeutic agent. This chemotherapy-induced anemia in addition to the anemia caused by cancer disease-induced bleeding and surgical blood loss contributes to the overall commonplace presence of anemia in gynecologic cancer patients (22).

Erythropoiesis

The process by which red blood cells differentiate, mature, and proliferate is called erythropoiesis. In the bone marrow, a pluripotent hematopoietic stem cell gives rise to

committed progenitors of white blood cells, red blood cells, and megakaryocytes. These cells then give rise to recognizable precursors of the cells found in the bone marrow. In the case of erythropoiesis, there is an early progenitor that can be recognized called the burst forming unit erythroid. The late progenitor that stems from the burst forming unit erythroid is the colony forming unit erythroid. The proliferation of the burst forming unit erythroid and the colony forming unit erythroid is regulated by the hormone erythropoietin. The colony forming unit erythroid then gives rise to the proerythroblast that in turn gives way to the erythrocyte, the mature red blood cell (35).,

Erythropoietin

Erythropoietin may treat anemia in gynecologic cancer patients in order to avoid perioperative blood transfusion. Erythropoietin is a growth factor hormone produced by the human body that stimulates the production, maturation, and release of red blood cells. This process of erythropoiesis is controlled by the kidneys detecting changes in oxygen delivery to the tissues and increases the secretion of erythropoietin. The kidneys produce erythropoietin to counter tissue hypoxia. Blood plasma carries the hormone from the kidneys to the bone marrow where erythropoietin then stimulates the division and differentiation of erythroid precursors. When erythropoietin travels to the bone marrow, it binds to a receptor on the surface of a red blood cell precursor. Erythropoietin action on an anemic patient causes the kidneys to produce even more erythropoietin that in turn causes even more proliferation and maturation of red blood cell precursors. This positive feedback system can be interrupted by cancer. The disease of cancer itself can suppress

erythropoietin secretion and progenitor cell proliferation. A single gene on the human chromosome 7 holds the code for erythropoietin production. The protein product is heavily glycosylated and has a molecular weight of 30,000 daltons. Erythropoietin is manufactured by recombinant DNA technology to possess the same biological effects as endogenous erythropoietin. Natural erythropoietin and erythropoietin have the same 193 amino acid sequence, with slight differences in the carbohydrate region of the protein molecule (14).

When injected intravenously at a dose of 10,000U, erythropoietin is cleared from the plasma with a half-life of 10 hours. The stimulatory effects of the drug on erythropoiesis, however, is sustained so that an anemic cancer patient does not need to receive erythropoietin more than three times a week to respond significantly (14).

Preoperative anemia in gynecologic cancer patients results from the bleeding that occurs from the gynecologic cancer disease. Intraoperative blood losses that result from surgery performed to cure the cancer also contribute to the anemia in these female patients. Postoperative chemotherapy compromises the process of erythropoiesis, resulting in increasing anemic states in these patients with gynecologic cancer. Blood transfusions that are used to correct anemia present significant risks to patients already suffering from a debilitating cancer disease. Therefore, it is necessary to develop a treatment to correct anemia in gynecologic cancer patients that will not require red blood cell transfusions (30).

The proposed study will use erythropoietin perioperatively to correct anemia in gynecologic cancer patients so that red blood cell transfusions may be avoided.

Study Procedures

This phase II study examines the efficacy, or the ability to improve hematological parameters and reduce exposure to allogeneic blood, and the safety of the perioperative administration of erythropoietin in adult women undergoing major surgery for gynecologic cancer (40).

A complication associated with this particular clinical trial lies within the patient population that will be enrolled as subjects in the study. The majority of patients that will be recruited from a county hospital are poor, or indigent, patients. Preexisting anemia, due to nutritional deficiencies caused by their low income status, may cause these patients to be too weak to seek medical care. Moreover, should these indigent patients desire medical care, they may not have the strength to get themselves to the clinic where they will be treated.

The typical time course for erythropoietin action requires three doses of 10,000 U in a week. The results of a 2-dose scheme in a radical prostatectomy study suggest that this increased dose of erythropoietin administration is both efficacious and safe (33, 34). To avoid undue delay from cancer diagnosis and study initiation to surgical therapy, a 3-

dose, 40,000 U regimen (preoperatively on days -12±2, -5±2, and day of surgery) is proposed. Therefore, by increasing the dose from 10,000 U to 40,000 U and increasing the amount of time between each dose (7 days between each dose compared to three time weekly), it is hypothesized that the patient will benefit from increased hemoglobin levels without suffering from hypertension caused by raising blood volume too quickly. It is hoped that the added benefits will include no delay in surgical therapy and decreased patient inconvenience. Overall, the patients in the prostatectomy study were anemic preoperatively (33). An additional dose, in the recovery room on the day of surgery, is planned for this population of anemic gynecologic surgery patients to maximize the postoperative hematocrit in anticipation of possible radiation or chemotherapy (40).

Further support for the dosing regimen comes from a recent placebo-controlled study that evaluated the use of recombinant human erythropoietin (3 preoperative doses of 600 IU/kg of body weight) in patients undergoing major head and neck cancer surgery (35). Patients in the erythropoietin group exhibited a significant increase in hemoglobin, hematocrit, and reticulocyte count values from baseline to the day of surgery. Additionally, the erythropoietin group had decreased transfusion requirements (35).

The objectives of the study are to study the efficacy and safety of a 3-dose erythropoietin regimen -12±2, -5±2, and the day of surgery, and its impact on hemoglobin levels in patients with gynecologic malignancies undergoing major surgical procedures, and to examine the number of patients who require allogeneic red blood cell transfusions (40).

This is an open-label pilot study. All patients are to receive adequate oral iron replacement from the time they enter the study to the day prior to surgery. A polysaccharide-iron complex supplement, Niferex 150 mg, two capsules per day, is suggested (35).

Inclusion criteria include 1) adult females with known or suspected cancer of the female genital tract 2) who are scheduled to undergo a major surgical procedure 3) with hemoglobin ≤ 13 g/dL at pre-study evaluation 4) aged 18 years or older, 5) who have read and signed an informed consent form after the nature of the study has been fully explained, 6) with lead time to surgery of at least ten days. Exclusion criteria include 1) patients with the presence of any primary hematological disease, 2) uncontrolled hypertension after adequate anti-hypertensive therapy, 3) new onset of seizures within the last 3 months and seizures not controlled by medications, 4) recent, significant gastrointestinal bleeding within 3 months of the study entry, 5) recent history of deep vein thrombosis within six months of study entry, 6) patients with previous exposure to erythropoietin within six months prior to study enrollment, 7) patients with known sensitivity to mammalian cell-derived products, 8) and patients with known sensitivity to human albumin (40).

Prestudy screening procedures will be performed within 21 days prior to entry into the study. These procedures are medical history, complete physical examination, complete

blood count (CBC) with differential and reticulocyte count, and an iron profile, blood chemistry, and informed consent (40).

The study drug-dosing schedule begins with patients receiving erythropoietin 40,000 U subcutaneously at 12±2 days prior to the scheduled surgery. At 5±2 days prior to surgery, patients will receive a second dose of erythropoietin 40,000 U subcutaneously. Patients will receive a final dose of erythropoietin 40,000 U subcutaneously on the day of surgery, following surgery in the recovery room. The sponsor will provide the 40,000 U/mL preserved solution vial (40).

Evaluation on the day of surgery will include a hematocrit, hemoglobin, and reticulocyte count that will be obtained prior to surgery (40).

During the intraoperative period, the following information will be collected: type of procedure, estimated blood loss, duration of procedure, use of blood product with amount given, type of anesthesia, preoperative diagnosis and cancer staging, and American Society of Anesthesiologists (ASA) status (40).

During the postoperative period, hemoglobin, hematocrit, and reticulocyte counts will be measured on post-operative day 1, day 3±1, and day of discharge, if the patient remains longer than 4 days. An iron profile will be measured prior to discharge. Every effort will be made not to transfuse patients except where clinical symptoms warrant. The type of

blood product and amount must be recorded. The reason for transfusion must be documented. Use of intermittent pneumatic compression devices as prophylaxis for deep vein thrombosis or other prescribed therapy for deep vein thrombosis prophylaxis will be prescribed. Patients will be followed throughout their postoperative course until discharge. Documented information should include treatment for any adverse events. Total length of the hospital stay and time in the intensive care unit will be documented (40).

A patient may be withdrawn prematurely from the study for any of the following reasons: development of a significant intercurrent illness or adverse event, patient request, investigator request, significant delay in surgery ($\geq$ 10 days), and significant protocol violations (40).

The primary endpoint for this pilot study is the mean change in hematocrit from baseline to the value available on the day of surgery, drawn prior to the surgical procedure. The secondary endpoints for this pilot study are the mean change in hemoglobin from baseline to the value drawn preoperatively on the day of surgery, the mean change in reticulocyte count from baseline to the value drawn preoperatively on the day of surgery, the incidence of transfusions, the number of units transfused, and the incidence of adverse effects (40).

Over 3,000 patients have received erythropoietin in clinical trials and adverse events reported were consistent with the underlying disease state and are not necessarily attributable to erythropoietin therapy. Constipation, pyrexia, and nausea were the most common adverse events (33, 36-38).

As mentioned previously, the primary endpoint of this study is the change in hematocrit between baseline and the day of surgery. Data across four FDA-approved indications suggest that this patient population will experience an increase in hematocrit. Thirty patients will be enrolled in this study and will be included in the analysis of this study. This number was chosen since it is adequate for applying the Central Limit Theorem to these analyses. In addition, this is a pilot study where the mean change and its corresponding standard deviation are unknown (40).

A summary of adverse events will be presented. A listing of the patients reporting one or more adverse events will be summarized by severity, body part, and condition. In addition, any potential relationship to erythropoietin as well as discontinuation of erythropoietin therapy will be recorded. For statistical analysis, each patient will contribute only once for events occurring at the same location in the body. For reoccurring adverse events in the same location in a single patient, the particular event will be reported only once. However, for events occurring in different parts of the body each subject may contribute more than once (40).

It is hoped that erythropoietin will demonstrate the ability to improve hematological parameters and reduce exposure to allogeneic blood for adult women undergoing major surgery for gynecologic cancer.

Summary

Bleeding occurs because of the cancer disease progression in the patient with gynecologic cancer. This preoperative bleeding reduces the levels of healthy red blood cells in gynecologic cancer patients, and therefore, anemia arises. Surgery is performed to remove cancerous tissue. Intraoperative blood losses caused by the surgery also reduce healthy red blood cell levels, and anemia is further propagated. Chemotherapeutic agents administered to treat cancer postoperatively undermine the process of erythropoiesis. Without the natural action of red blood cell maturation, proliferation, and differentiation, anemia will emerge. Anemia, therefore, is unavoidable and presents a serious threat to the health and recovery of gynecologic cancer patients. Blood transfusions, although a treatment for anemia, possess serious risks to the safety and recovery of these patients. Erythropoietin will be studied for its ability to correct anemia in gynecologic oncology patients and avoid blood transfusion. By correcting anemia and avoiding blood transfusions, the energy levels of these female cancer patients will be increased, and fatigue levels should decrease. Therefore, this study presents a potential benefit in the quality of life of gynecologic cancer patients.

Little attention has been given to cases of patients with gynecologic malignancies scheduled for major surgery and treated with erythropoietin. Patients with cancer of the female genital tract generally have two weeks from diagnosis to the day of surgery. Gynecologic cancer patients that receive treatment with erythropoietin preoperatively may benefit from an improvement in their anemic status and a reduction in the exposure to allogeneic red blood cell transfusions.

INTERNSHIP PRACTICUM JOURNAL

The time spent during my internship practicum at the University of Texas Southwestern (UTSouthwestern) Medical Center at Dallas was filled with various clinical and research related activities. This journal is a record of the activities that I participated in during my internship practicum at UTSouthwestern. The following account of my daily accomplishments is a requirement of the internship practicum report. Each date of the internship practicum is listed with a time frame in which these activities were performed.

04/30/2002

1:00 p.m.: Met with the thesis committee to discuss overall internship practicum goals and thesis subject. The principal investigator (P.I.), a member of the committee, presented a clinical study involving gynecologic oncology patients who would undergo surgery and chemotherapy for their cancer and would be given erythropoietin preoperatively in hopes of increasing hemoglobin levels and preventing blood transfusions postoperatively. The study would be examining a new indication for erythropoietin that is already approved by the Food and Drug Administration (FDA). The group determined that during the internship I would receive exposure to the Institutional Review Board (IRB), be involved in the recruitment and consent process of patients, become familiar with the clinic, and interact with residents, study nurses, and data managers.

05/03/2002

1:30 p.m.: Met with my mentor, a member of the thesis committee, to discuss anemia and erythropoietin. My mentor explained the physiology of the disease and the different types of anemia affecting patients. My mentor then suggested I read some background information about anemia and gave two sources from which to study.

05/10/2002

2:00 p.m.: Met with the P.I. and a data manager for Gynecologic Oncology to discuss the internship practicum schedule and to review the study protocol and informed consent forms (ICF). The group determined I should develop the case report forms (CRF) to be used in the study.

05/13/2002

7:30 a.m.: Filled out the University of North Texas Health Science Center (UNTHSC) forms for declaration of graduation, research proposal, committee designation, and intent to graduate in anticipation for the committee to sign.

1:00 p.m.: Reviewed information regarding erythropoietin including the generic and trade names of the drug, the FDA approval of the drug, and the unapproved use of the drug in this study, which is the dosing schedule for gynecologic oncology surgery patients. The sponsor of the study bears the Investigational New Drug (IND) application. The drug will be provided by the sponsor and given to subjects by the principal investigator at no cost to the subjects. There is unknown risk of fetal death, breast milk contamination,

congenital anomalies, or infertility with the use of erythropoietin. The drug is not known to be teratogenic, mutagenic, or carcinogenic.

05/14/2002

7:30 a.m.: Wrote the first draft of the research proposal.

10:00 a.m.: Inquired at UTSouthwestern's IRB office about the necessity of a translated consent form in Spanish due to the high percentage of the patient population who speak only Spanish. Since there is a short-from consent form that is in Spanish that explains what the required elements of a consent form should be, the accompanying English consent form would suffice as long as there is a translator present to answer questions and translate the English version into Spanish at the time of consent. However, the IRB office responded saying that they prefer to have a full length Spanish consent form to give to their patients, although it is not a requirement at this time.

1:00 p.m.: Contacted the clinical research coordinating offices at Aston Ambulatory Care Center, Parkland Memorial Hospital, Zale Lipshy University Hospital, and St. Paul Medical Center, the participating sites in the study of erythropoietin, to determine what forms needed to be submitted before study initiation at these sites.

05/15/2002

7:30 a.m.: Reviewed the budget worksheets, all correspondence, statistical analysis methodology, the sponsor and principal investigator contract, and the list of sites to be involved in the study of erythropoietin.

10:00 a.m.: Wrote a letter to the study sponsor to introduce myself and begin correspondence regarding the study of erythropoietin.

1:00 p.m.: Read through the purpose and background information regarding the study of erythropoietin. The main goal of the study is to examine the efficacy and safety of the perioperative administration of erythropoietin in gynecologic oncology patients undergoing surgery for their cancer. A secondary aim is to examine the number and frequency of blood transfusions the patients might receive. Patients with gynecologic cancer may have anemia resulting from bleeding caused by their disease. Blood loss may also occur during their operation. These blood losses may require allogeneic blood transfusions that might cause the patients to contract infectious diseases or experience immunosuppression. Erythropoietin may help correct the anemia and avoid transfusion.

05/16/2002

7:30 a.m.: Met with the P.I.'s research nurses and a data manager for Gynecologic Oncology. Reviewed the protocol and informed consent form for the study of erythropoietin. Studied the required informed consent document elements and examined the study of erythropoietin ICF to ensure that all required elements were present.

10:00 a.m.: Designed a CRF layout using spreadsheets for the study.

11:00 a.m.: Reviewed the website of the IRB of UTSouthwestern. Read The Belmont Report, Title 45 Code of Federal Regulations Part 46, and the Multiple Project Assurance M-1304. Completed training in the ethical principles, federal regulations, and university

policies protecting human subjects in research, was tested over the material, and was granted certification in the policies protecting human subjects in research.

2:00 p.m.: Developed CRFs to be used in the study capturing data as specified in the protocol.

05/17/2002

7:30 a.m.: Reviewed the elements of an informed consent document and verified that the consent form used in the study had all required and suggested information.

8:00 p.m.: Explored the IRB web site and found that payment to research subjects for participation in clinical research is not considered a benefit; it is an incentive to participate.

9:00 a.m.: Read the regulations regarding consent forms for patients who do not speak or read English and reviewed the short form written consent document in Spanish.

10:00 a.m.: Read an article in the monthly publication of UTSouthwestern, *CenterTimes*, about a new biomarker that a sub-investigator (sub P.I.) found that should lead to an early stage ovarian cancer test. This is substantial given that ovarian cancer is the most deadly of gynecologic cancers. This biomarker for ovarian cancer utilizes osteopontin, a protein found in bodily fluids, whose levels are elevated in all stages of ovarian cancer. The study that was conducted found that osteopontin levels in blood plasma were significantly higher in patients with epithelial ovarian cancer compared with healthy controls, patients with benign ovarian disease, and patients with other gynecologic cancers.

11:00 a.m. Worked on research proposal by researching literature collected for the protocol of the study.

1:00 p.m. Researched the Internet, specifically PubMed, to find articles pertinent to the study.

05/20/2002

7:30 a.m.: Read the Gynecologic Oncology Group (GOG) information on the Internet. Searched the National Cancer Institute's (NCI) clinical trials database for other similar cancer studies.

9:00 a.m.: Read information regarding the disease process, treatment, staging, and side effects of breast cancer. Read information regarding the disease process, risk factors, diagnosis, staging, treatment, and side effects of cancer of the uterus. Read about cervical cancer prevention. Read about the disease process, risk factors, detection, treatment, side effects, and follow-up care of ovarian cancer. Read about the disease process, stages, and treatment of endometrial cancer. Read about the disease process, stages, and treatment of vaginal and vulvar cancer. Gathered notes on these cancers to use as references for research.

2:00 p.m.: Searched the NCI website for information on gynecological cancers and current clinical trials. Corresponded with the sponsor to request a package insert and a copy of FDA form 1572 for work on the study. Inquired about the length of time for patient follow up after the study has been completed.

3:00 p.m.: Asked the P.I. how to capture information regarding the incidence of blood transfusions. Since the secondary endpoint of the study is to determine the number of blood transfusions during treatment with erythropoietin, those blood transfusions that might occur several weeks or months after study completion would not be considered in the statistical analysis.

05/21/2002

9:00 a.m.: Collected references and made notes from the NCI web site.

11:00 a.m.: Read the Physician's Data Query (PDQ) for uterine sarcoma, ovarian epithelial cancer, cervical cancer, and vaginal cancer.

2:00 p.m.: Informal meeting with P.I and data manager. Discussed the Office of Grants Management (OGM) procedures in initiating a study and reviewed the Clinical Trials Worksheet. Spoke about the length of the follow up period for patients enrolled in the erythropoietin study. Contemplated following patients through to their first postoperative visit, their first chemotherapy or radiation therapy visit, or up to three months after the date of their surgery.

3:00 p.m.: Filled out the OGM form 1 and submitted to the P.I. for approval. When submitting the OGM1 form to the Clinical Trials Office (CTO), it must be accompanied by the sponsor and investigator contract.

3:30 p.m.: Visited the Obstetrics and Gynecology (Ob/Gyn) clinic at Parkland Memorial Hospital. Noted that the doctors and nurses were very busy taking care of many patients. The waiting areas were full of patients in obvious discomfort and pain. Due to the

enormous population of Spanish speaking patients, the nurses interacting with the women in the clinic spoke Spanish.

4:30 p.m.: Corresponded with the sponsor to request a conflict of interest form and financial disclosure document.

05/22/2002

7:30 a.m.: Went to tumor board where doctors and nurses discuss treatment plans for those patients undergoing chemotherapy and radiation treatment for gynecologic cancer. Gynecologists, radiologists, pathologists, stenographers, oncologists, nurses, fellows, and pharmacists collaboratively determine what should be done in regards to the treatment plan for other cases. The P.I. led the discussion and asked questions regarding the reasoning behind methods of treatment. A physician gave an informal lecture over reproductive endocrinology to give further insight into a particular endometrial cancer case.

9:30 a.m.: Reviewed terminology introduced in the tumor board.

10:30 a.m.: Prepared contract to be sent to the OGM. Reviewed requirements of submittal. The sponsor writes the contract. The OGM makes sure all legal issues are in accordance with UTSouthwestern's legal department and approves the contract. The investigator then signs the contract.

12:00 p.m.: Attended grand rounds discussion about cervical cancer screening given by a visiting physician. The physician is from the University at Alabama at Birmingham School of Medicine. Cervical cancer is the second most common cancer in women

worldwide. 250,000 women die each year from cervical cancer worldwide. In the United States, 14 women die each year from cervical cancer and fifty percent of women diagnosed with invasive cervical cancer had a recent Pap smear. The Pap smear is the best known screening test for cervical cancer, but it only evaluates collected cells. If abnormal cells are not collected, then those cells will not be detected. Direct inspection with acetic acid is also performed to detect cervical cancer. Speculoscopy uses light to directly examine the cervix and is better at detecting cancer than magnified direct inspection. A new technique combines a Pap smear and speculoscopy that more than doubles the detection rate of cervical disease. Real time visualization combined with screening techniques is a thorough examination for cervical cancer and should be performed on more women. In the future, a technique that would detect cervical cancer with very high accuracy the first time a sample is taken from the cervix could save many women's lives.

1:00 p.m.: Prepared proposal submission and award administration for the study. This included contacting the OGM, the Chair of the Department of Ob/Gyn, and the IRB coordinator.

1:30 p.m.: Spoke to the IRB office to confirm that no new submission forms were needed. Response was that the ICF only needed to be sent in with the amendments and changes. The ICF had been approved with stipulations over a year ago.

2:00 p.m.: Spoke with the Conflict of Interest Office to ensure that all financial disclosure forms were up to date for the investigative team. Emailed sub P.I.'s office for pending financial disclosure to be sent to the Conflict of Interest Office.

2:30 p.m.: Delivered the OGM1 form to the Chair of Ob/Gyn to be signed and dated.

3:00 p.m.: Corresponded with the sponsor to request their section on risks and caution for inclusion in the ICF. Also informed the sponsor that the contract submitted was the latest agreement and budget.

05/23/2002

10:00 a.m.: Collected and copied curriculum vitae (CV) and medical licenses for the P.I. and sub P.I.s to send to the sponsor. Also printed the letter to send to the sponsor regarding the UTSouthwestern's policy on not releasing an IRB membership list.

11:00 a.m.: Filled out the Clinical Trial Worksheet for the CTO.

1:00 p.m.: Contacted the CTO to verify the information contained in the Clinical Trial Worksheet.

3:00 p.m.: Asked the P.I. about the anticipated start and end date for the study and asked who was the originator of the protocol. The start date would be as soon as the study is approved and would end as soon as the last patient completed the treatment protocol. The P.I. wrote the protocol and is therefore considered the owner of the protocol.

4:00 p.m.: Corresponded with the sponsor who requested that a copy of the ICF be sent to them before submittal to the IRB.

05/24/2002

9:00 a.m.: Typed the ICF with changes suggested by the IRB for approval.

1:00 p.m.: Sent a copy of the IRB membership letter to the sponsor. Institutional policy forbids the release of the names of the members of the IRB and this letter serves to explain policy and assure that the IRB is in good standing and follows guidelines set by the Code of Federal Regulations (CFR).

3:00 p.m.: Released the sponsor and investigator contract to the OGM containing the signatures of both the P.I. and the Chair of the Department of Ob/Gyn.

05/28/2002

9:00 a.m.: Read an article in the Dallas Morning News about Clinical Research Coordinators (CRC).

11:00 a.m.: Revised protocol and the ICF for submittal.

1:00 p.m.: Developed the per-patient budget for the study of erythropoietin based on the payment schedule.

3:00 p.m.: Organized and placed the contents of the study binder in chronological order separating correspondence, IRB documents, CV and licenses, contracts, protocol, and revisions sections.

05/29/2002

9:00 a.m.: Delivered the Clinical Trial Worksheet, 3 copies of the study protocol, 3 copies of the per patient study of erythropoietin budget, the OGM 1 form, the sponsor and investigator contract, copies of the investigator and sub-investigators' medical licenses and CV to the CTO.

10:00 a.m.: Made photocopies of the ICF to submit to the UTSouthwestern IRB office. Highlighted changes and additions to the original ICF and drew red lines through deletions of the original ICF.

11:00 a.m.: Contacted the UTSouthwestern IRB office to determine how many copies of the revised ICF needed to be sent and which sites needed copies of the revisions.

1:00 p.m.: Sat in an interview with a fellow candidate. Asked about his proficiency in Spanish and how he decided to pursue gynecologic oncology.

3:00 p.m.: Translated the ICF into Spanish. Translated the ICF in Spanish back into English to check if anything had been lost in the translation.

05/30/2002

7:30 a.m.: Went to tumor board. Reviewed computerized tomography (CT) scans and pathology slides of a patient with an ovarian cystic mass in her pelvis. Pathology slides showed goblet cells, mitotic bodies, and filiform papillae. Sections of fallopian tubes were found in pathology, although they were not grossly observable. Her status was unstaged and the cyst was removed surgically. A patient with cervical cancer who smokes complained of vaginal pain. Her CT scan showed circumferential thickening of the vaginal wall with accompanying fibrosis. Squamous cell carcinoma spread from her vagina, to her cervix, and into her uterus. A patient was diagnosed with cervical cancer, but had no evidence of invasion. A patient presented with inappropriately rising levels of beta human chorionic gonadotropin (HCG). She had a history of miscarriages and pregnancies. Dilation and curettage (D&C) was reported multiple times with her

pregnancies. There were pulmonary and renal metastases present. The patient experienced regular, monthly menses.

11:00 a.m.: Spoke the sponsor contact about the ICF and CRFs.

1:00 p.m.: Made additions to the ICF that the sponsor requested regarding risks and compensation. Faxed copy of ICF to sponsor for review.

3:00 p.m.: Updated spreadsheets and CRFs.

05/31/2002

8:00 a.m.: Reviewed the primary and secondary endpoints of the study. The primary endpoint will be measured by the difference in preoperative hematocrit and baseline hemoglobin levels. These values will be compared to historical controls measuring the difference in preoperative and baseline hemoglobin. The secondary endpoints are the change in hematocrit and reticulocyte counts, transfusion outcomes, and adverse events. The transfusion outcomes include the number of allogeneic units transfused, the number of patients transfused, transfusions per patient, and complications associated with transfusion.

10:00 a.m.: Examined the statistical analysis to be done for the study of erythropoietin. Historical controls will be matched to the subjects receiving erythropoietin based on age, diagnosis, hemoglobin, and cardiovascular and peripheral vascular comorbidities.

1:00 p.m.: Studied the parameters under which efficacy would be determined. Efficacy will be assessed through changes in hematological parameters including hemoglobin,

hematocrit, and reticulocytes, as well as transfusion rates between baseline, preoperative, and postoperative points in time.

3:00 p.m.: Read about the statistical assumptions to power the study. The standard deviation, the alpha value, the beta value, normally distributed data, and equal variances are all assumptions of the statistical elements of the study of erythropoietin. An independent t-test will be used to assess the statistical significance between the change in hemoglobin in patients receiving erythropoietin and historical controls.

06/03/2002

8:00 a.m.: Read background information on the perioperative administration of erythropoietin and its ability to increase hematocrit levels and decrease the need for a blood transfusion in adult female patients requiring surgery for gynecologic cancer.

1:00 p.m.: Read about the factors that increase the likelihood a gynecologic cancer patient will need a blood transfusion. These factors include anemia, surgery resulting in blood loss, cardiovascular disease that decreases oxygen delivery to the tissues, the need to increase hemoglobin and hematocrit levels in preparation for radiation therapy and chemotherapy, and the combination of preoperative anemia coupled with surgical blood loss.

06/04/2002

10:00 a.m.: Read about the reasons that gynecologic cancer patients develop anemia. The reasons these patients develop anemia is due to preoperative bleeding that may worsen

with age and growing disease, intraoperative blood loss, gynecologic carcinomas not being detected until more advanced stages accompanied with debility and anemia, postmenopausal uterine bleeding associated with endometrial carcinoma, and vaginal bleeding characteristic of cervical cancer.

2:00 p.m.: Read about the ways that erythropoietin can help patients with gynecologic cancer. Erythropoietin can correct anemia preoperatively, help to avoid postoperative transfusions, and increase hematocrit levels for chemotherapy.

3:00 p.m.: Studied hormonal and nonhormonal contraceptives for women. Hormonal contraceptives work by preventing release of an egg from the ovaries into the uterus, and may make the environment in the uterus nonconductive for the successful action of sperm. The birth control patch, the oral contraceptive pill, contraceptive injections, progestin releasing intrauterine devices, and vaginal rings are all hormonal contraceptives. These are all highly consistent and effective means of birth control and all require a prescription from a doctor. Nonhormonal contraceptives prevent pregnancy by creating a barrier against sperm, interfering with sperm movement, or by providing an unfriendly environment for sperm. Condoms, both male and female, intrauterine devices, spermicides, diaphragms, cervical caps, and surgical sterilization are all forms of nonhormonal contraceptives. Most of these methods are reliably effective and some are available without a prescription.

06/05/2002

9:00 a.m.: Read about the hormone erythropoietin that stimulates the production, maturation, and release of red blood cells. Erythropoietin is carried to the bone marrow where it stimulates the division and differentiation of committed erythroid precursors. Erythropoietin is the recombinant DNA form of human erythropoietin.

3:00 p.m.: Studied the package insert of erythropoietin to isolate all adverse events unique to the drug. These adverse events include upset stomach, swelling of hands and feet, diarrhea, blood clots, anxiety, headaches, urinary tract infections, high blood pressure, dizziness, inability to sleep, vomiting, reaction at the drug administration site, fever, nausea, and constipation.

06/06/2002

9:00 a.m.: Reviewed a case of a patient who was experiencing vaginal bleeding especially after sexual intercourse. The patient was diagnosed with squamous cell carcinoma. Upon bimanual exam, there was too much tumor to find her cervix. The doctors who examined her could not find her os. The treatment plan for the patient included a sciad implant and consultation with a radiation oncologist. There was no evidence of periaortic nodes indicating that the disease was focused locally in the pelvis.

11:00 a.m.: Read about kidney problems, anemia, and treatment with erythropoietin for this condition. Patients with anemia feel tired, short of breath, weak, weary, and dizzy. Anemia is the condition of the body when there are not enough red blood cells. Patients with anemia due to kidney problems can take erythropoietin to treat their disease.

Erythropoietin is a substance that the body makes naturally. Erythropoietin stimulates red blood cell production, and with more red blood cells that contain hemoglobin, more oxygen is carried throughout the body, increasing energy levels.

06/07/2002

10:00 a.m.: Reviewed a case of a patient with cancer of the ovaries. At first, the patient was diagnosed with invasive ovarian cancer and was treated with chemotherapy and gene therapy. After this, the patient's quality of life improved.

11:00 a.m.: Read about the GOG. The GOG is a national organization dedicated to clinical research in the field of gynecologic cancer. Gynecologic cancers include breast cancer, cervical cancer, endometrial cancer, ovarian cancer, uterine cancer, vaginal cancer, and vulvar cancer.

2:00 p.m.: Read about the cancer process. When cells divide without control or order, when no new cells are needed, a mass of tissue forms that is called a tumor. If the tumor is not cancerous, then it is a benign tumor. Benign tumors do not spread to other parts of the body and do not present a threat to life. If the tumor is cancerous, then the tumor is malignant. Malignant tumors are life threatening. When cancerous cells of the malignant tumor invade the lymphatic system, the cancer is spread to other parts of the body in a process called metastasis.

06/10/2002

8:00 a.m.: Reviewed a case of a patient in gynecologic oncology who was diagnosed with stage IV endometrial carcinoma. The treatment plan for this patient included exploratory laprascopy (XPL), total abdominal hysterectomy (TAH), bilateral salpingo oopherectomy (BSO) and debulking. The majority of patients who undergo surgery as the primary treatment for stage IV endometrial carcinoma experienced cytoreduction and an increase in survival.

10:00 a.m.: Defined the following terms: menorrhagia is excessive bleeding, CXR is a chest x-ray, TVH is a total vaginal hysterectomy, TAH is a total abdominal hysterectomy, menarche is the onset of menstruation, coitarche is the onset of sexual intercourse, EMB is endometrial biopsy, and ascites is fluid accumulation in the abdomen and pelvis.

06/11/2002

8:00 a.m.: Reviewed the study binder.

10:00 a.m.: Interviewed a fellow candidate.

11:00 a.m.: Reorganized all copies of forms, drafts of the protocol and consent form, and correspondence.

1:00 p.m.: Placed documents of the study binder in chronological order.

3:00 p.m.: Met with P.I. and study nurses to discuss the status of oncology patients, ongoing studies, and submitted contracts seeking approval.

4:30 p.m.: Attended presentation given by a fellow candidate about ETV4 expression in breast and ovarian cancer. This physician came from Brigham and Women's Hospital in

Boston, Massachusetts. ETV4 (ETS Variant Gene 4) is a member of the ETS (E26 Transformation Specific Gene) oncogene family that is regulated by estrogen.

06/12/2002

7:30 a.m.: Attended tumor board where the gynecologic oncology chemotherapy and radiation therapy treatment list was reviewed. Treatment plans for gynecologic oncology patients were also determined through collaboration of attending physicians and residents.

9:30 a.m.: Worked on completing thesis forms.

12:00 p.m.: Attended grand rounds given by a physician who discussed urodynamics in obstetrics and gynecology. The physician is an assistant professor of Ob/Gyn at UTSouthwestern.

06/13/2002

10:00 a.m.: Read about hormone replacement therapy (HRT). HRT is used to prevent osteoporosis and treat vasomotor symptoms associated with menopause, such as hot flashes. Patients who continue to take HRT experience cumulative amenorrhea, the absence of bleeding of spotting, over time.

1:00 p.m.: Checked the study binder for copies of the confidentiality agreement signed by the sponsor, the principal investigator, and the director of clinical research studies.

2:00 p.m.: Reviewed the lab certifications and normals for the study of erythropoietin.

06/14/2002

9:00 a.m.: Reviewed a case of a patient with advanced endometrial cancer whose treatment plan included a combination of carboplatin and doxil. There is evidence that several chemotherapy combinations have an advantage in treating cancer patients over just a single agent being employed.

11:00 a.m.: Reviewed a case of a patient who has ovarian cancer and is pregnant. The patient experienced complications due to advanced maternal age (AMA) and chronic hypertension (CHTN). The patient was observed to have a reduction in the size of her ovaries. This is due to the fact that ovaries become smaller during pregnancy because the placenta takes over as the hormone-producing organ. The delivery will have to be cesarean. Postpartum, the patient will experience extreme menopausal symptoms after the placenta is removed.

2:00 p.m.: Learned about the positron emission tomography (PET) CT scan. This diagnostic procedure costs $3,000 to have it performed. Since very few patients can afford this procedure, and since few insurance companies will approve this new procedure, hospitals can take on compassionate cases for those individuals whose disease prognosis would most benefit from the PET CT scan.

06/17/2002

9:00 a.m.: Called the Clinical Research Office at the Harold C. Simmons Comprehensive Cancer Center to request a Resources Review Sheet for cancer-related protocols that needed to be completed for the study of erythropoietin.

11:00 a.m.: Filled out a new IRB form NR1 for the study of erythropoietin. Originally, the study was approved with stipulations, but since that approval had occurred over a year ago, a new study submission had to be given to the IRB.

2:00 p.m.: Called the CTO at UTSouthwestern to receive an update on the status of contract negotiations with the sponsor of the study of erythropoietin.

06/18/2002

9:00 a.m.: Met with P.I., study nurses, and data managers to discuss plans to move out of the Gynecologic Oncology Research Office in preparation for remodeling. Maintaining confidentiality of patient and study records while in transition was the greatest concern among the group. In order to successfully move without compromising confidentiality, the group decided to place files in the P.I.'s office and find secure, locked storage on campus for the remaining files left.

3:00 p.m.: Called the GOG office in Pennsylvania to request a Spanish consent form for another study that would open soon at UTSouthwestern.

3:30 p.m.: Called the sponsor for the study of erythropoietin, pending initiation, to inquire about the status of the contract negotiations between the sponsor and the CTO of UTSouthwestern.

06/19/2002

7:30 a.m.: Went to tumor board where attending physicians, residents, and nurses discussed the radiation and chemotherapy treatment of gynecologic oncology patients.

Reviewed pathology slides, CT scans, clinical histories, medical histories, physical exams, and diagnostic studies of gynecologic oncology patients in order to develop an appropriate treatment plan. Had P.I., sub P.I.'s, and data manager sign the IRB form NR1, the application for review of new research involving human subjects, for the study of erythropoietin so that the IRB could review the study since the approval with stipulations had been granted over a year ago.

12:00 p.m.: Attended a lunch conference about hydrothermal endometrial ablation for the treatment of menorrhagia, or chronic, excessive bleeding.

2:00 p.m.: Read information about the birth control patch. The patch is used to prevent pregancy and contains hormones similar to those in birth control pills. The patch contains estrogen and progestin. When the patch is applied, low doses of these hormones are transferred through the skin and into the bloodstream. The patch can be worn in four areas including the buttock, abdomen, upper torso excluding the breasts, or upper outer arm. The amount of drug that is transferred into the blood stream is not effected by vomiting or diarrhea, unlike the birth control pill.

06/20/2002

10:00 a.m.: Called the Harold C. Simmons Comprehensive Cancer Center for instructions regarding the resources review sheet that must be filled out for each clinical study requiring resources at the Simmons Cancer Center.

11:00 a.m.: Reviewed correspondence for the study of erythropoietin. Made notes of any outstanding issues that needed to be addressed.

1:00 p.m.: Called the Office of Government Reimbursement at Parkland Memorial Hospital to confirm that a Special Accounts Receivable (SAR) account had been established for the study of erythropoietin.

2:00 p.m.: Watched a UTSouthwestern video on the guidelines for information security and patient confidentiality.

06/21/2002

9:00 a.m.: Completed the IRB Form NR3 Clinical Research and Special Project Impact Assessment for the study of erythropoietin.

1:00 p.m.: Made twenty-five copies of the ICF and protocol for the study of erythropoietin to be given to the IRB when the study is reviewed for approval.

2:00 p.m.: Typed the project summary for the study of erythropoietin to be submitted in the IRB form NR3. The project summary includes the purpose of the study, the background of the study, the inclusion and exclusion criteria for subjects, sources of research material, recruitment procedures, potential risks, special precautions, procedures to maintain confidentiality, potential benefits, biostatistical analysis, and the risk and benefit assessment.

06/24/2002

9:00 a.m.: Documented the names and titles of the research personnel who completed the certification of training for the protection of human subjects in research including the locations where and dates when the training occurred.

10:00 a.m.: Called to request copies of the certificates for training in good clinical practices for the P.I. and sub P.I.s for the study of erythropoietin.

2:00 p.m.: Left a message with the sponsor contact to request the IND# for erythropoietin.

3:00 p.m.: Called the IRB office about the closure of studies with different IRB numbers, but both pertaining to the current study of erythropoietin.

06/25/2002

9:00 a.m.: Called the Investigational Drug Service at Parkland Memorial Hospital in regards to the SAR account for the study of erythropoietin.

11:00 a.m.: Spoke to the IRB office. The IRB said that the study of erythropoietin had two previous IRB numbers but both cases had been terminated.

1:00 p.m.: Read an article in the *Dallas Morning News* about two former University of Texas at San Antonio researchers that are now in jail for stealing gene data from Harvard that would be used to develop anti immunosuppression drugs for use in organ transplantation. The data was sold to a Japanese biotechnology firm.

2:00 p.m.: Submitted the IRB form NR1, certification of training in the protection of human subjects involved in research, certification of training in good clinical practices, the protocol, consent form, and Spanish consent form to the IRB for approval of the study of erythropoietin.

06/26/2002

7:30 a.m.: Attended tumor board to discuss Gynecologic Oncology chemotherapy and radiotherapy treatment for patients with gynecologic cancers. The P.I., who is also the current Division Director of Gynecologic Oncology at UTSouthwestern, the former chairman of Ob/Gyn, and the assistant to the executive director of the American Board of Ob/Gyn, attending physicians, fellows, residents, nurses, and research staff collaborate to discuss disease progression and treatment plans for the patients under their care.

9:00 a.m.: Met with the assistant to the executive director of the American Board of Ob/Gyn.

10:30 a.m.: Reviewed a case about a patient with a molar pregnancy. A molar pregnancy occurs when fetal parts such as hair and teeth attach to the uterine wall and develop. The mass of tissue that results is called a gestational trophoblastic neoplasm (GTN). Pathology shows the presence of scalloped shaped villi extending from samples taken as a biopsy. Normally these samples would present with polar or straight villi. Pretreatment levels of HCG were abnormally high indicating a molar pregnancy. Few patients experience a fall in HCG levels on the day they begin treatment for low risk GTN. Some partial molar pregnancies may gradually terminate, but the patient may immediately become pregnant again with a normal pregnancy. In these cases, the patient almost never presents with persistent disease.

06/27/2002

9:45 a.m.: Reviewed a case of a patient with parakeratosis. An increase in the keratin composition of the cervical epithelium cells is associated with dysplasia and may indicate human papilloma virus (HPV).

12:00 p.m.: Attended a lunch conference about menopause given by a physician of UTSouthwestern. The lecture included topics such as the physiology of menopause, hormonal changes during menopause, the relationship of cardiovascular disease to estrogen deprivation, hormone replacement therapy, osteoporosis, breast cancer, and clinical studies examining quality of life for women in perimenopausal and postmenopausal states. The lecture indicated that the use of HRT has cardiovascular benefit in healthy postmenopausal women.

3:00 p.m.: Contacted the pharmacy at Parkland Memorial Hospital to ensure that the SAR account was established for the study.

06/28/2002

10:00 a.m.: Had a phone conference with the sponsor to discuss the status of the study of erythropoietin approval by the IRB. Talked about the CRFs and statistical analysis for the study as well as planning a study initiation meeting for the study of erythropoietin.

11:00 a.m.: Photocopied the financial disclosure forms for a GOG study and mailed the originals to the sponsor.

1:00 p.m.: Completed the IRB form NR2 to submit to participating sites in the study of erythropoietin.

3:00 p.m.: Submitted the cooperating institution form NR2 to Parkland Memorial Hospital, St. Paul Medical Center, Zale Lipshy University Hospital, and Aston Ambulatory Care Center.

DISCUSSION

The University of Texas Southwestern (UTSouthwestern) Medical Center at Dallas, Department of Obstetrics and Gynecology, Division of Gynecologic Oncology, acted as the host of my internship practicum. Specific guidance was provided by the principal investigator (P.I.), Director of the Division of Gynecologic Oncology, and a data manager. The purpose of my experience at UTSouthwestern was to receive training in the clinical research coordinator's (CRC) role in the process and development of the clinical research study. More specifically, I was in charge of one particular study that initially had attempted approval, required modification, and experienced termination, and needed to be submitted as a new study once again. The activities in which I participated introduced the many responsibilities that a CRC must take charge of to ensure the efficient progression from study development, to study approval, and finally, to study initiation. In addition to the personal responsibilities of the CRC, the interaction with other members of the research team, the sponsor, and institutional departments was introduced. The particular trial in which I was involved became my personal project during my stay at UTSouthwestern, and therefore, the particular requirements to move the study into its initiation phase became my sole responsibility. Thus, the particular study that occupied my time during the internship practicum is of central importance.

I was in charge of a clinical research pilot study examining the safety and efficacy of erythropoietin administered to anemic gynecologic oncology patients undergoing surgery. Erythropoietin is hypothesized to increase hemoglobin levels and decrease the risk of blood transfusion. The Food and Drug Administration (FDA) has already approved erythropoietin for certain indications in patients with other diseases and ailments. The study in which I participated employed erythropoietin for a non-indicated use in anemic patients with newly diagnosed gynecologic cancers about to undergo surgery. Because this particular use of erythropoietin is different from the indicated use, a clinical trial must be performed to assess the safety and efficacy of erythropoietin used to correct anemia and prevent blood transfusions in surgical patients with gynecologic cancer. In this particular case, the P.I. of the study wrote the protocol after being approached by the sponsor who requested that he develop and perform the study. For UTSouthwestern's contract purposes, it is necessary to identify the originator of the protocol. Within UTSouthwestern, the P.I is deemed owner of the protocol. The protocol outlined the disease to be studied, anemia, the investigational product, erythropoietin, and the patient population that would be involved in the study. The protocol included information about gynecologic cancers and the target population of women that would receive the study drug. Background information about previous studies with erythropoietin including safety and efficacy data was collected as justification that the hypothesis of the clinical study is reasonable. Proof that the experimental use of erythropoietin would be of potential benefit is also presented. At the time I entered the internship practicum, the Institutional Review Board (IRB) of

UTSouthwestern had approved the study protocol. The initial approval was terminated due to the lack of response for more than one year on other issues.

The IRB grants approval of the study protocol as well as the informed consent form (ICF). Since the IRB's function is to protect the safety and welfare of study subjects, special attention is given to the ICF that the patients sign. The ICF states that the study involves research, lists the potential risks and benefits of the research, includes the number of participants in the study, gives the duration of the study, states the purpose of the study, describes study procedures, both standard of care and investigational, gives alternatives to the participation in the research, describes the conditions under which the study may be terminated, lists the costs and compensation for participation in the research, states the voluntary nature of participation in the study, presents the measures taken to ensure confidentiality, and gives contact information for questions and concerns (39). Protection of the subjects involved in the trial is critical to the success of the research. Therefore, the IRB will scrutinize every aspect of the study to ensure all possible measures are met that decrease possible risks and maximize potential benefits for the participating subjects. When the study was first submitted to the IRB in the year 2000, approval of the consent form was deferred until the next IRB meeting so that the several suggested changes given by the IRB could be made for the approval process to continue. However, the changes were not submitted in a timely manner and in the year 2001, the study was terminated. Later that same year, the study was resubmitted to the IRB and was approved with stipulations. These stipulations were small details that could

be corrected, and when completed, could be submitted to the IRB office and approved without requiring full board review a second time. Again, the changes were not made in a timely manner, and therefore, the study was again terminated at the beginning of the year 2002. When I entered into the internship practicum, I reviewed all the previous documents and made sure all the suggestions that the IRB had made in the past were applied to the ICF. The sponsor contact requested that particular information and wording be included in the consent document to meet the sponsor's legal department requirements. Among the items to be included in the consent form were additional side effects of the study drug, compensation for study related injury, and alternative treatments. I included this information in the consent document; however, the language of the ICF must be in lay terms so that any subject would be able to understand exactly what was presented. A particular reading level may be suggested based upon each IRB's preferences. Therefore, I had to translate some of the scientific and medical terms into words the common person could comprehend. The sponsor contact requested to review the consent form before submittal to the IRB, so I emailed the finished document to the sponsor for approval. Because the community in which the study would be performed has numerous Spanish-speaking patients, translating the consent form into this language was a consideration. The IRB states that a short form consent form in Spanish is sufficient to present to Spanish speaking subjects as long as there is a translator to translate the English form and answer questions. However, due to the multitude of patients enrolling in studies who speak only Spanish, the IRB office had begun to appreciate full-length Spanish consent forms. Part of my job was to translate the ICF into

Spanish, but this was not submitted to the IRB. It was suggested that the English ICF be submitted for approval to speed the already tardy process of getting this study approved and initiated. Upon completion of my internship practicum, the ICF was in the process of being approved by the IRB at UTSouthwestern.

The majority of my time spent during the internship practicum was devoted to the ICF. Another detail-oriented set of documents that occupied my efforts was collectively referred to as the case report form (CRF). The CRF captures data collected during the study that is utilized in the statistical analysis of the research to determine the significance of the study findings. The case report form was divided into several sections that included pre-study evaluation, intraoperative evaluation, postoperative evaluation, and adverse event reporting. Initially, the CRF I developed aspired to capture too many pieces of information. This is not desirable for statistical analysis. The more data that is captured, the more likely error may enter into analysis. Therefore, I had to skim the CRF and remove superfluous data captures. The CRF is also the document that records patient progression during a study. Monitoring the data in these documents helps to keep the patients safe.

Although patient safety is the greatest concern in clinical research, financial considerations are also interests in clinical research, contracts and study budgets are also considered. The research institutions and sponsor organizations negotiate the terms under which the clinical research study will be performed. The agreement between these

parties must conform to federal, state, and institutional regulations. The sponsor and investigator contract addresses the legal issues associated with the new information and the ownership of such information that will result as the study progresses and finally ends. The legal departments of both the sponsor organization and the investigative institution develop and eventually approve the language and content of the contract before either the sponsor representative or the principal investigator may sign the document. The language of the contract is very different from other study documents, such as the ICF written for the study subject. The language of the contract requires special knowledge of legal terms. The Clinical Trials Office (CTO) and the Office of Grants Management (OGM), both institutional departments, oversee the interactions between the sponsor and the principal investigator. The Clinical Trials Worksheet requests information regarding the study protocol, the study budget, the sponsor contact, and the principal investigator and accompanies the OGM Form 1 Proposal Review that requests additional information about safety and protection of study subjects. These departments review, edit, and approve the sponsor and investigator contract based upon university regulations. The UTSouthwestern CTO submitted a version of the contract with language that met university regulations to the sponsor for approval from their legal department. The contract negotiations had not been settled by the end of the internship practicum, and therefore the contract is still pending. Another business related concern in clinical trials is financial disclosure. There is a potential for bias if the investigators of a study have potential financial gain or loss dependent upon the outcome of the study they conduct. Therefore, the Conflict of Interest Office must have financial disclosure forms

on file for all investigators participating in clinical research trials in order to ensure that methods are in place to reduce bias if financial interest exists. As part of my internship, I requested that the P.I. and sub P.I.s all fill out financial disclosure forms and subsequently submitted those to the Conflict of Interest Office.

The role of a CRC as introduced to me through my internship practicum experience includes submitting the study protocol and ICF to the IRB for approval, making corrections to these documents as suggested, developing and modifying the CRF, facilitating contract negotiations, filing financial disclosures, and managing all these responsibilities to move a study towards initiation as efficiently as possible. In addition to these responsibilities, other activities are beneficial and necessary to coordinate a successful clinical trial study. Frequent correspondence with the sponsor, institutional departments, and all members of the research team is vital to maintain momentum in the initial phases of a clinical research study. Communicating to these individuals frequently reminds the entire group about the specific tasks needed to be accomplished. This correspondence also builds bonds of camaraderie and establishes a good sense of the team goals agreed upon for the sake of the study. The trial proceeds efficiently when the lines of communication are open and frequently used. Documentation of all correspondence and study procedures is not only advantageous, but essential as well. Every bit of information that pertains to the study must be recorded and kept on file. By adopting this habit, correspondence is facilitated. One may easily reference documents they are citing if the copies are easily accessible and dated. The documentation of all

activities also protects individuals when a step in the study process has experienced disturbance. One can be safeguarded when they have proof of exactly what they did and when they did it. All documentation provides an audit trail and tells the story of the activities conducted throughout the course of a study. Most importantly, I learned that organization allows the CRC to do the very best job possible for the clinical research trial. Without the composure and adaptability organization allows the CRC, the work can overtake the individual to the detriment of the study. Fortunately, having only one study to manage allowed me to stay organized. I witnessed great skill and organization in the offices where I spent my internship practicum experience.

The education I received prior to entering this internship practicum granted me a firm foundation in the FDA's Code of Federal Regulations (CFR) and the ethical behavior that research scientists should exhibit. Working in the Division of Gynecologic Oncology at UTSouthwestern presented real world application of the lessons I learned in the classroom. More importantly, the individuals that guided me throughout my internship practicum taught me that patient consideration is the key to successful and worthwhile clinical research. Although I have been taught to have a great appreciation for the administrative requirements of clinical research, I have been endowed with an even greater lesson in the empathy clinical researchers and health care providers demonstrate to their patients.

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