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The ability of patients to adhere to treatment regimens is very poor and continues to impede optimal therapy of osteoporosis. The shortcomings in treating osteoporosis are: a) noncompliance and/or lack of continued persistence of therapy, b) efficacy of therapy on bone turnover marker levels and fracture prevalence, and c) tolerability of therapy to patients. Studies have shown that interventions such as education and awareness of bone mineral density promote patient usage compliance. The slightest improvement in compliance allows further understanding of accurate efficacy of medication therapy to fractures, bone marker levels, and overall improvement of bone mass. Increased compliance/persistence allows accurate comparison of bisphosphonates to one another for effectiveness on osteoporosis patients and allows improvement opportunity in treatment modalities that can positively influence the course of osteoporosis. This phase IV study targets compliancy/persistence in bisphosphonate therapy in treatment of osteoporosis.

A STUDY TO DETERMINE IMPROVED COMPLIANCE OF BISPHOSPHONATE TREATMENT IN SUBJECTS WITH OSTEOPOROSIS

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A STUDY TO DETERMINE IMPROVED COMPLIANCE OF BISPHOSPHONATE TREATMENT IN SUBJECTS WITH OSTEOPOROSIS

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Introduction

Osteoporosis is a serious disease lurking as an undetected predator of bone density. It remains latent and virtually unrecognized for years until a fracture occurs and alters a person's active and independent lifestyle. An estimated 30 million people suffer from osteoporosis in the USA and 70 percent of the 1.3 million fractures that occur annually in the USA are attributable to osteoporosis in patients aged 45 years and older [1]. Osteoporosis affects more women than heart attacks, strokes and all female-related cancers combined. [1] An estimated 50,000 Americans (both men and women) die as a result of osteoporotic fractures and complications stemming from those fractures [2]. Hip fractures (15%) have the lowest percentile of occurrence compared to vertebral (32%) and lower arm (16%) fractures, but are the most debilitating due to the person's loss of mobility and independence [2]. The reality of the situation is that one out of every eight women suffers from breast cancer while one of every three women suffers from an osteoporotic fracture [1]. Thus, the risk of a woman dying from a hip fracture is equivalent to that of dying from breast cancer and four times greater than that of dying from endometrial cancer [1, 3].

The World Health Organization (WHO) defines osteoporosis as a "systemic skeletal disorder characterized by a low bone mass and micro-architectural deterioration of bone tissue" resulting in an increase of bone fragility and fracture prevalence susceptibility [1, 2]. WHO bases the definition of osteoporosis on the combination of low bone mineral density (BMD) and fracture prevalence. Specific groups, particularly

postmenopausal women aged 50 years and older, have a higher prevalence of osteoporosis than men, who are more affected at the age of 70 years and older. Racially, Caucasian and Asian persons suffer more frequently from osteoporosis. [2, 4]

The prevalence of osteoporosis among the 50 plus age group and the rising cost of rehabilitation for osteoporotic fractures has bought osteoporosis to the forefront of clinical trial studies and made it a serious medical issue. Annually, osteoporosis accounts for $14 billion in health care cost and is expected to exceed $50 billion over the next 30 years due to the increased aging "baby boomer" population. [5] Postmenopausal women aged 55 years are expected to exceed 45 million by year 2020. [5]

Contrary to previously held beliefs, osteoporosis does not have to be a natural part of the aging process and can be prevented through adequate preventive measures. Factors governing bone strength depend on individual bone mass, shape, and quality. Many studies confirm the connection between bone density, strength, and fracture risk. [1, 3] WHO defines osteoporosis as a combination of low bone mineral density and fracture prevalence; therefore, bone density is the main target for 60-90% of bone strength and reduced fracture prevalence. United States Food and Drug Administration (US-FDA) approved medication therapies for osteoporosis includes: bisphosphonates Alendronate (Fosamax) and Risedronate (Actonel), Raloxifene, parathyroid hormone, calcitonin, and estrogen/hormone therapy (ET/HT). [1] Randomized clinical trials have proven bisphosphonates not only reduce bone loss and achieve the greatest reduction (50%) in fracture risk both vertebral and extravertebral after one year of therapy, but also induce a small increase in bone mineral density. [4] Bone mineral density is a parameter

used to assess the effects of drug treatment on osteoporosis and reflects bone mass and mineral content. There are numerous bisphosphonate therapies approved in countries outside the United States and other estrogen-hormone therapies that are under investigation in clinical trials including naturally occurring therapies that can be included in the diet to treat low bone mass and/or osteoporosis. [5] The most conclusive evidence from randomized control trials for reducing osteoporotic fracture risk includes first priority medications: Risedronate (Actonel) or Alendronate (Fosamax) sodium tablets, Raloxifene (Evista) and/or parathyroid hormone therapy (Forteo/ teriparatide), and calcium and vitamin D supplements.[1, 3]

Osteoporosis can be induced by underlying medical problems through a person's medication regimen. Rheumatoid arthritis and systemic lupus erythematosus are particular autoimmune diseases where steroid treatment of these diseases may lead to steroid-induced osteoporosis, particularly glucocorticoid-induced osteoporosis. Bone loss is evident within months of starting steroid therapy and accounts for 30-50% of induced osteoporosis in persons on long-term steroid therapy. [1] The rate of bone loss is very rapid, resulting in a 20% bone mass loss in the first year, and therefore, considered a high turnover osteoporosis. [1] The prevalent use of oral glucocorticoids in women over the age of 55 increases the potential for glucocorticoid-induced osteoporosis. Due to awareness of the increased incidence of glucocorticoid-induced osteoporosis and fracture prevalence, it is recommended that all patients on chronic glucocorticoid (>6 months) therapy be treated with bisphosphonates for ultimate benefit in reducing vertebral fractures. [6] Therapy recommendations for glucocorticoid-induced osteoporosis are the

same as for postmenopausal osteoporosis, however, preventive measures are highly recommended due to the subject's chronic steroid therapy.

Studies have assessed the appropriate therapy actions against osteoporosis with combination therapies of early prevention, active lifestyles, vitamin D and calcium supplements, bisphosphonates, and possible parathyroid hormone and/or raloxifene. However, the main concern regarding treatment of osteoporosis is not related to effectiveness of these medications with osteoporosis, but rather to the subject/patient's adherence to medication regimen and compliancy in the real world. Under the watchful eye of clinicians and physicians in clinical trials, the subject is enthused and supported substantially by health care professionals. The phase IV clinical trial presented in this proposal aims to determine whether subject knowledge of baseline vertebral fracture prevalence and bone turnover marker levels will improve subject persistence and compliance with Risedronate (Actonel) 5mg daily treatment over a 12-month period in subjects with chronic glucocorticoid therapy. Subjects will be randomized into either informed or not informed in which the informed group will receive test results regarding their bone marker levels and fracture prevalence. Medication Event Monitoring System (MEMS) electronic caps will be placed on each bottle of Actonel and record the date and time the Actonel bottle is opened. Actonel will be self-administered. The primary objective of study is to examine whether there is an increase in compliance in self-administration of Actonel when education of bone marker determinations (BTM) and instant vertebral assessment (IVA) is given to an informed (INFO +) group in the treatment of osteoporosis. The secondary objectives of this study are to examine the

prevalence of vertebral fractures vs. duration of steroid therapy, Actonel persistence vs. vertebral fracture prevalence, and Actonel influence on a) bone turnover marker determinations, b) serum OPG/RANKL measurement, and c) bone mineral density at study finish relative to baseline. Other objectives under investigation in this study include patient overall satisfaction with Actonel 5mg daily and the overall safety of Actonel. Patients will be evaluated at study treatment visits and every three months following the baseline visit for a total of twelve months. Any adverse events will be recorded at treatment visits and data collection from each visit will be used to determine persistence/compliance, safety, and efficacy of Actonel 5mg daily regimen.

Table of Abbreviations

BMD	Bone Mineral Density
BTM	Bone Turnover Marker Determinations
DXA	Dual Energy X-Ray Absorptiometry
INFO-	Subjects w/o knowledge of IVA & BTM
INFO+	Subjects w/ knowledge of IVA &BTM
IVA	Instant Vertebral Assessment
OD	Once Daily
OPG	Osteoprotegerin
RANKL	RANKL binding Protein
PTH	Parathyroid Hormone
WHO	World Health Organization
CFR	Code of Federal Regulations
CRF	Case Report Forms
SAE/SAEs	Serious Adverse Event/s
AE	Adverse Event

CHAPTER II

OSTEOPOROSIS

Background

Bone Composition & Structure

Osteoporosis is the silent stalker of bone causing them to thin, become brittle, and fracture. [7] Understanding the effects of osteoporosis on bone begins with an understanding of bone composition. Bone is composed of essential minerals and matrix proteins that give it strength. Bone mineral accounts for 2/3 of the bone weight and stores 99% calcium, 85% phosphate, and 50% magnesium. [4] Matrix proteins account for 1/3 of bone weight and are composed of 90% collagen (type I) and 10% non-collagenous proteins such as osteonectin, osteocalcin, osteopontin, bone sialoprotein, fibronectin, and glycoprotein. [4, 8] The non-collagenous proteins are deposited exclusively in bone; therefore, clinical measures can be assessed through patient's urinary excretion, plasma or serum levels to determine bone turnover.[4] Bone structure, as shown in Figure 1, consists of outer bone (cortical or compact) and inner bone (trabecular, spongy, or cancellous).

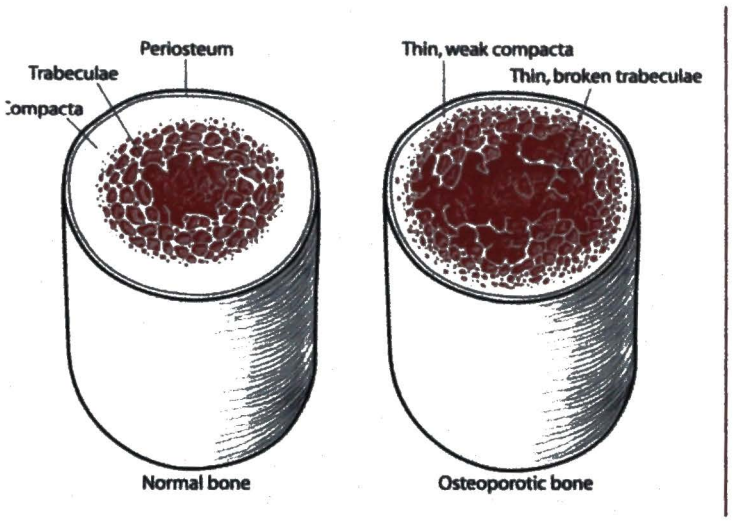


Figure 1: Bone Structure [1]

Trabecular bone is more prone to osteoporosis because of the larger surface area and high bone turnover of approximately 25 percent. Trabecular bone forms a lattice, network-like structure that is optimal for resistance of compressive forces and is responsible for strength and flexibility of bones. Inner bone (trabecular) largely occupies the axial skeleton (cranium, vertebral spine, thorax, and pelvis) that is oriented along lines of stress and weight bearing, and thus is an easy target for fracture along femoral neck, hip and vertebral spine, and lower arm. Outer bone (compact) largely occupies the appendicular skeleton (femur, humerus) that has low turnover of approximately 3 percent annually. Compact bone comprises 80 percent of bone mass and is denser (90% calcified) than trabecular because it is responsible for rigidity and structural integrity of bones.

Remodeling/Turnover

Bone is not a permanent and immutable tissue but undergoes an unceasing process of remodeling (bone turnover) engaged by two classes of cells: osteoblast and

osteoclast. [8] Remodeling is a continuous process that maintains the skeleton as bones age. Remodeling of the skeleton is achieved by mobilizing calcium and maintaining calcium homeostasis, replacing old osseous tissue, repairing damaged bone, and adapting to different loads and weight stresses. *Osteoblasts* are derived from mesenchymal progenitors/stem cells and provide continuous turnover and replacement of interior bone matrix. [4] Bone grows only by apposition, Figure 2 [8], which is lying down of

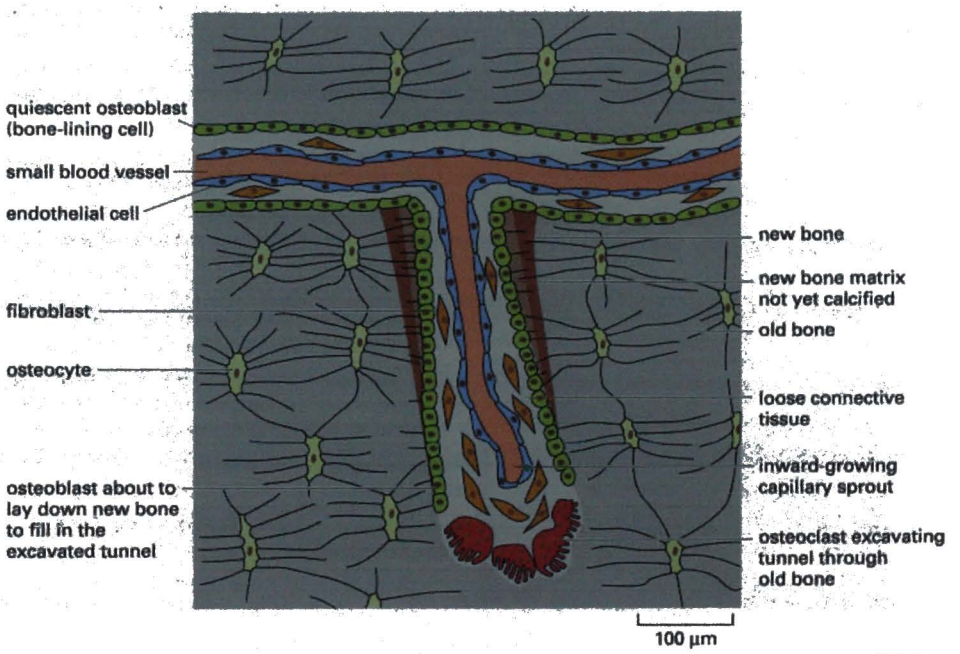


Figure 2: Bone Apposition, Osteoblast, and Osteoclast Activity [8]

additional matrix and cells on the free surfaces of existing bone. Osteoblasts secrete bone matrix and deposit fresh bone onto existing bone. The secreted bone matrix consist mostly of type I collagen and are called osteoid. An osteoid is uncalcified and becomes calcified by deposition of calcium phosphate crystals, thus making it an osteocyte. *Osteocytes* are thereby derived from osteoblasts and remain trapped in bone. Osteocytes

do not divide but continually secrete small amounts of bone matrix while occupying small cavities called lacuna. Lacunas have tiny channels called canaliculi that allow osteocytes to form gap junctions, via connexins, to adjacent osteocytes thus building new bone. Osteocytes have the ability to detect stresses caused by microdamage on bone. Upon detection of these stresses, osteocytes transmit signals to the surface of bone and other bone cells that control the process of remodeling. *Osteoclasts* are derived from hemopoietic stem cells in bone marrow and function to resorb bone and erode bone matrix. Osteoclasts tunnel deep into compact bone and form tunnel-like cavity clearing zones by involving integrins, cell membrane receptors that recognize specific peptide sequences in bone matrix. Adherence of osteoclasts to exposed matrix proteins on the surface of bone gives an appearance of a "ruffled border". The "ruffled border" formed between cell and old bone creates pocket formations that are filled with osteoclastic secretions of hydrochloric acid. Carbonic anhydrase action on H_2CO_3 releases secretion of H^+ ions, which are mobilized by a proton ATPase pump to dissolve bone mineral and protein.[4] Osteoclasts also have various proteolytic enzymes, including cathepsins (cathepsin K) and possible collagenases (metalloproteinase 1) to digest the bone matrix. [4] The cavity/tunnel created by osteoclasts becomes filled with capillaries and osteoblasts, which lay down new matrix and gradually fill the cavity, Figure 4. When osteoclasts are more active than osteoblasts, negative control of remodeling is occurring causing excessive erosion and weakening of the bone leading to osteoporosis.

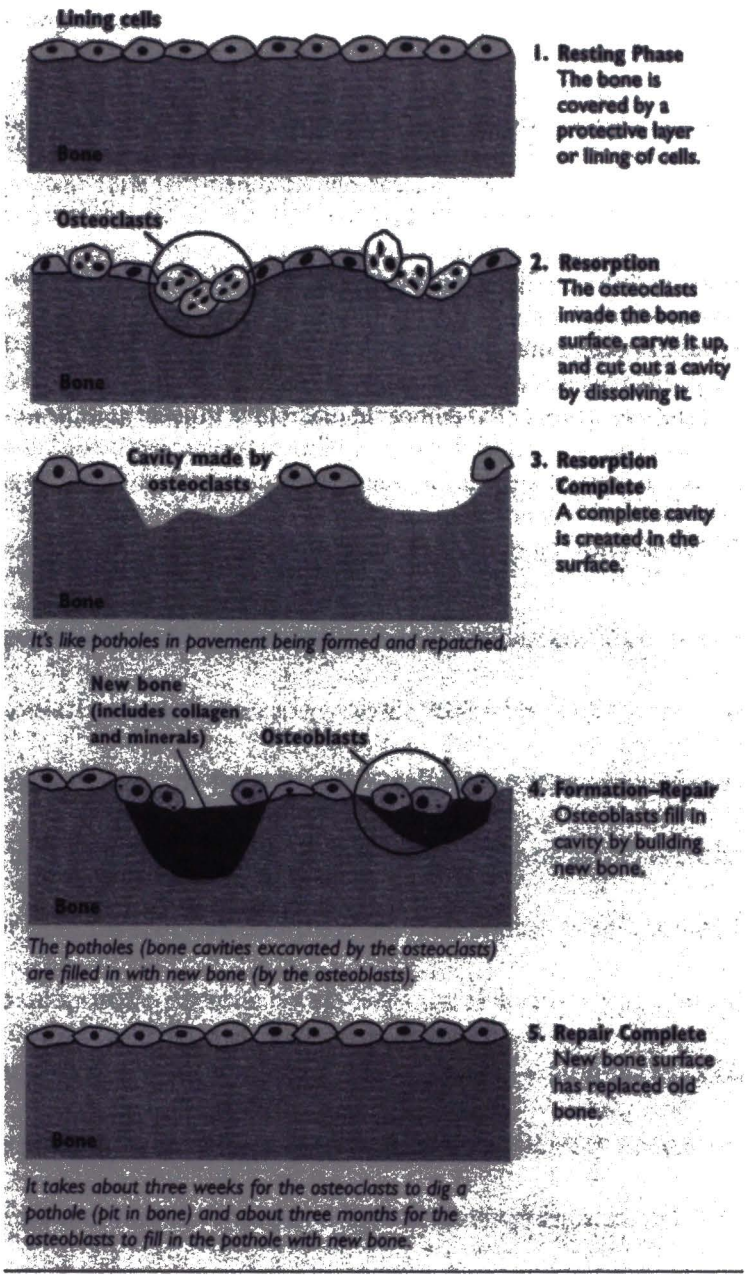


Figure 3: Bone Remodeling/Turnover [10]

Diagnosis of Osteoporosis

Diagnosis of osteoporosis is subject to consideration of genetic and environmental factors and an individual's personal lifestyle of diet and exercise. Osteoporosis is a multifactorial disease that includes highly influenced genetic traits of bone mass and fracture risk. [9] The genetically determined factors of body mass index, age of menarche and menopause, serum PTH levels, vitamin D levels, skeletal geometry, bone turnover/ remodeling rate, and individual BMD levels affect bone mass and strength, therefore affecting fracture risk prevalence. According to the WHO, the standard diagnosis of osteoporosis and fracture assessment is achieved through bone densitometry techniques, particularly, dual energy x-ray absorptiometry (DXA). A DXA scan is a type of bone densitometry that is the most popular, reliable technique used to measure bone mineral density in the most vulnerable osteoporotic areas of spine and hip. [1, 9] DXA is used not only for diagnosis of osteoporosis, but also for the prediction of fracture risk in osteopenic and osteoporotic persons by assesses the risk category an individual belongs. DXA is a noninvasive procedure lasting 5-10 minutes in which patients remain clothed and lie in supine position while two x-rays of different intensity are exposed to the skeletal area. Mineral content is measured by computer programs and the measurement is based on radiation amounts. The low radiation of 1-3mRem (equivalent to 1/10-1/100 of normal x-ray) and high precision and accuracy of DXA make it ideal for follow-up, controlled investigations. [1] DXA bone mineral density (BMD) content is described as a T-score value which "is the number of standard deviations below or above the mean value of BMD for a young 20-30 year old adult" (age of peak bone mass). [1] T-score

range of normal bone is >-1, osteopenia is -1 to -2.5, osteoporosis is >-2.5, and severe osteoporosis is >-2.5 + fracture. [2, 9] DXA allows clinicians to follow both a) progression of diseases affecting BMD and b) efficacy of osteoporosis-specific therapies on bone mineral density.

Epidemiology of Osteoporosis

The public health issue of osteoporosis has become substantially apparent as life expectancy and the aging population increases. Fractures that occur as a result of the effects of osteoporosis on bone mass, strength, and quality are termed fragility fractures. [10] These fractures occur during the course of normal activity or with minimal trauma. The most common types of fractures in osteoporosis are vertebral, hip, and distal radius/ wrist. Fracture risk for aging individuals increases due to increased negative regulation of bone remodeling, which results in decreased bone mass and quality. Also, as individuals age, the risk of falling increases with an estimated 1/3 chance of falling annually in individuals > 65 years old, and 6% of the falls among individuals > 75 years old results in a fracture. [1, 9] Individuals aged 65 and older are more likely to experience a fracture when falling as oppose to young, active individuals. [9] Elderly persons fall differently due to age-related reductions in muscle mass and strength affecting their ability to quickly and strongly extend arms, thus explaining the prevalence of hip and vertebral fractures over wrist fractures. [10] Women are particularly more susceptible to osteoporosis fracture after the age of 50 due to the combined effects of menopause and age on bone mass. Hip and spine fractures among white women after age 50, are 2 to 3

times higher than men aged 50.[9] Men are not as susceptible to osteoporosis until the age of 60 when androgen secretion and age-related bone quality significantly declines. Unfortunately, osteoporosis affects Caucasian and Asian women more than women of color. [10] Although the reasons for ethnic differences are not completely understood, the primary difference in women of color is achievement of higher peak bone mass resulting in a slower bone loss occurrence at menopause. [10] Low bone mass (28 million) competes competitively with other common disorders of hypertension (54 million), hypercholesterolemia (52 million), and diabetes mellitus (16-20 million) making osteoporosis a serious healthcare issue affecting many individuals. [9] Osteoporosis accounts for 1.5 million skeletal fractures annually in the United States with 45% vertebral, 20% hip, 15% wrist, and 20% other sites. [9] Fractures are painful, disabling and cause morbidity and possibly premature mortality. [1, 9] Hip fractures are the most debilitating due to the loss of independence, mobility, quality of life, and sometimes death. Hip fractures account for 75% of cost, disability, and death due to osteoporosis. [10] Hip fractures almost always require hospitalization and are "associated with significant operative & post-operative complications, long-term disability", and adverse events such as thromboembolic events. [9] Approximately 20% of all persons who experience hip fractures require nursing home placement. [9] A reported 30-50% never resume daily physical activities and require mobility assistance with walking devices and wheelchairs. [9, 10] Vertebral fractures cause acute back pain and disability in limitations of activities. A loss of height of approximately 1cm/fracture and kyphosis, backward curvature of dorsal spine, occurs causing impaired pulmonary function and deformed

thorax. [1] Individuals who experience vertebral and hip fractures have greater mortality rate 1-4% (vertebral) and 10-20% (hip) than that of the age-matched normal population. [9] Wrist fractures cause significant pain and decreased activity but are not as troublesome on healthcare cost or mortality rates. The cost of caring for osteoporosis and osteoporotic fractures in the United States in 1995 was approximately 13.8 billion with hip fractures approximating 26,000-37,000 each. [9] In 1997 alone there were a reported 40 million postmenopausal women. [11] The projected number of women in the United States is expected to double over the next 30-50 years, projecting the cost of managing osteoporotic fractures to$64 billion in the year 2025. [9] Osteoporosis is preventable and curable, but proper preventive measures should be implemented years before an osteoporotic fracture occurs. Timely diagnosis and proper recognition of non-influenced and influenced risk factors are imperative for optimal treatment, reduction of cost, and prevention of osteoporotic fractures.

Risk Factors of Osteoporosis:

Non-Controllable:	**Controllable:**
Genetics	Inactivity (chronic),
Age	Excessive exercise
Sex	Diet and nutrition
Race	Body weight
Pregnancy (lactation)	Mental psyche
	Cigarette smoking
	Excessive alcohol
	Excessive lipids
	Medication
	Clumsiness or tendency to fall/imbalance.

Menopause/Andropause

Estrogen targets osteocytes, osteoblast, and osteoclast through estrogen receptors that antagonizes initiation of bone-remodeling by decreasing fusion of osteoclast to bone matrix. Estrogen is in a family of molecules that includes the sex hormone 17B-estradiol, metabolites of the estrogen hormone, and synthetic hormone analogs including environmental estrogens and phytoestrogens. 17B-estradiol has the highest affinity for estrogen receptors and has undeniably increased bone formation on endocortical surfaces and induced new trabecular bone formation in clinical studies with mice. [3] The

principle effect of estrogen is to regulate the rate of bone remodeling and improve remodeling balance while inhibiting bone resorption. Estrogen also increases osteoprotegerin, which is a potent inhibitor of osteoclastogenesis. [3] Osteoprotegerin is related to cytokine TNF and identical to TRANCE/RANKL. Although estrogen is not essential for bone growth, it influences postnatal bone physiology through growth, architecture and turnover and is important for age-related bone mass. The importance of estrogen on bone, Figure 4, explains why postmenopausal women are prone to osteoporosis (type I).

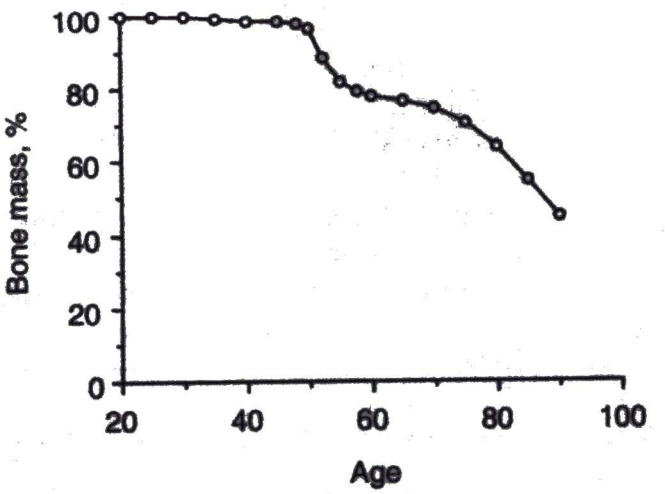


Figure 4: Percent Bone Mass vs. Women's Age [10]

The cessation of ovarian function and estrogen secretion associated at menopause decreases IL-6 and other cytokine activity leading to increased osteoclast activity and chronic high bone turnover (especially on cancellous/trabecular plates). [1] Bone becomes more sensitive to resorption, particularly in trabecular bone in vertebrae and hip, thus increasing the risk of fracture. Even though bone loss begins years before the loss of ovarian function, menopause escalates osteoclasts activity and more bone is lost than built. Thus, an estimated 30% of women develop osteoporosis type I due to menopause. [1] Decreased estrogen results in a 4% annual bone loss causing women to lose 40% of bone mass from ages 40 to 70 years while men only lose a reported 12%. [7] However, men become most susceptible to osteoporosis by age 60-70 years due to age-related complications and primarily due to testosterone deficiency (andropause). Testosterone deficiency causes an increase in bone resorption and decrease in bone formation. Studies show that both testosterone and estrogen play a role in bone formation and that estrogen plays a larger role in bone resorption indicating a stronger correlation in hip fracture in men with the measurement of serum estradiol than testosterone. [9, 10] Men are not only susceptible to trabecular but also to cortical bone loss, which increase their fracture risk. [3] [1] Primary osteoporosis in men is due to genetics and/or age-related testosterone deficiency (andropause), however studies identified that the majority (64%) of osteoporosis in men as a result of underlying conditions such as hypogonadism, alcohol abuse, lower testosterone due to prostate cancer treatment, glucocorticoids, and idiopathic hypercalciuria. [9, 12]

Types of Osteoporosis

Osteoporosis Type I (postmenopausal) is the most common form but there are other forms of osteoporosis that plague people. Involutional osteoporosis Type II (age-related) represents increased osteoclastic activity as according to aging. Commonly, type I merges with type II. Glucocorticoid-Induced Osteoporosis occurs when a patient is subjected to chronic glucocorticoid therapy (> 6 months). Due to underlining diseases such as asthma, inflammatory conditions of joints such as rheumatoid arthritis or osteoarthritis, and gastrointestinal tract and central nervous system diseases, glucocorticoid therapy may be recommended, causing a primary complication of osteoporosis. Glucocorticoids are steroids that affect osteoblasts by reducing proliferation and bone matrix synthesis, via apoptosis of osteoblasts, thus impairing bone remodeling and positive bone formation. [2, 4] Glucocorticoids cause malabsorption of calcium in gut and kidney, and depress testosterone in males causing hypogonadism. Inhibition of calcium absorption, testosterone, and osteoblasts activation leads to glucocorticoid-induced osteoporosis. Approximately one half of all organ transplant patients develop transplantation osteoporosis due to general risk factors of menopause, inactivity, vitamin D deficiency, alcohol, or medication. [1] In most cases, the diseased organ damaged the bone significantly before transplantation occurred. Oncology patients can experience tumor therapy-induced osteoporosis due to effects of chemotherapy and hormone replacement therapy on bones and bone marrow. Drug-induced osteomalacia is caused by drug inhibition of vitamin D system during bone formation and mineralization.

Treatment of Osteoporosis: *Pharmacologic and Non-Pharmacologic*

Bisphosphonates

An overall comprehensive approach to treating osteoporosis includes not only medication therapy but also non-medication practices of calcium-rich diets, essential vitamins, and exercise. [13] FDA- approved therapy for the treatment of osteoporosis includes bisphosphonates (Risedronate and Alendronate), estrogen/hormone therapy, raloxifene, parathyroid hormone, and calcitonin. Nitrogen-containing bisphosphonates (i.e. Risedronate and Alendronate) are clinically proven and usually the first line of defense against osteoporosis as opposed to non-nitrogen-containing bisphosphonates (i.e. Etidronate). [2, 4] Bisphosphonates are the best potent inhibitors of osteoclast activity against bone. Bisphosphonates are derived from pyrophosphate compounds, found in plasma and urine, which inhibit calcium phosphate precipitation. Inorganic pyrophosphates are the simplest compounds in the family of polyphosphates with the ability to bind to calcium phosphate and impair both formation of calcium phosphate crystals and dissolution in vitro, and impair calcification. However, polyphosphates do not possess antiresorptive effects on bone due to susceptibility of hydrolysis through oral administration. Bisphosphonates, analogs of pyrophosphate by changing pyrophosphate P-O-P bond to P-C-P bond, Figure 5, have the ability to resist enzymatic hydrolysis and metabolic breakdown while possessing the physiochemical properties of pyrophosphate. [3, 12] The main function of bisphosphonates is inhibition of bone resorption and bone loss. Bisphosphonates increase bone strength and bone mineral density by binding to calcium and phosphate (hydroxyapatite) crystals, which make up mineral content in bone,

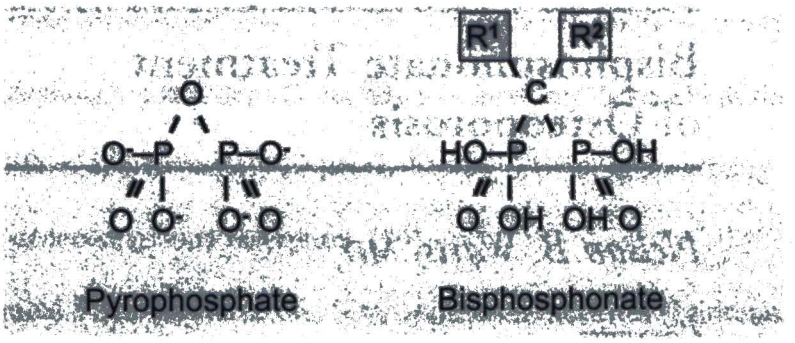


Figure 5: Structure of Pyrophosphate and Bisphosphonate [3]

and inhibit osteoclast-mediated resorption. They decrease bone turnover at the tissue level, inhibit osteoclast recruitment, adhesion, and activity at the cellular level, and form a protective barrier that inactivates osteoclast binding and deposition at the molecular level. Bisphosphonates act exclusively on calcified tissue, especially bone, making them ideal therapy for osteoporosis when administered properly. [4] Studies have shown that intestinal absorption of bisphosphonates is low, and high dosage levels could cause inhibition of bone mineralization and formation of insoluble aggregates impairing kidney function. [1] Absorption is low due to low lipophilicity and high negative charge preventing transcellular and paracellular transport. [4] It is recommended to take bisphosphonates on a fasting stomach, due to their poor intestinal absorption, and preferably when actively moving about. Absorption of bisphosphonates diminishes in the presence of meals, especially those containing calcium and iron, and can aggregate and cause complications when patient is non-mobile during the time of administration. Since

the kidneys excrete bisphosphonates, it is not recommended for persons with renal/kidney failure. [10] Bisphosphonates deposit quickly into bone and have a high skeletal retention half life of approximately 10 years, thereby optimal in promoting bone formation and decreasing bone resorption. [10]

The United States has three oral bisphosphonate therapies (Etidronate, Alendronate, and Risedronate) available for treatment of osteoporosis; however, only two of the three are actually US-FDA approved. Nitrogen-containing bisphosphonates are more potent than non-nitrogen containing and are currently recommended for treatment and prevention of osteoporosis. Risedronate (*Actonel*) was FDA-approved in the year 2000 for prevention and treatment of postmenopausal osteoporosis and corticosteroid-induced osteoporosis. Risedronate (*Actonel*) is administered orally as 5mg daily or 35mg weekly dosage. Clinical trial studies prove nitrogen-containing bisphosphonates may be more effective on bone mineral density than non-nitrogen-containing. [3, 4] Risedronate's efficacy in vertebral fracture prevalence has been proven significant only after one year of treatment with a 33-39% decrease in non-vertebral fractures. Studies also show a significant increase in spine and hipbone mineral density and 70% reduction in new vertebral fractures for persons treated with chronic glucocorticoids. Risedronate inhibits local bone and cartilage resorption, thereby decreasing inflammatory reactions and preserving joint architecture in osteoporotic persons. Risedronate also has good tolerability and offers flexibility with dosage. [3]

Alendronate (*Fosamax*) is a nitrogen-containing bisphosphonate that was FDA approved in 1995, and currently, either alendronate or risedronate are most commonly

prescribed for bisphosphonate treatment of osteoporosis. Alendronate (*Fosamax*) is administered orally as 10 mg daily, 35 mg twice/weekly, or 70 mg weekly dosage. Results from numerous clinical trials showed a 5 % - 9 % increase in bone density with vertebral fracture reduction (59 %) and hip fracture reduction (63 %) after 18-month therapy regimen. [1] Alendronate (*Fosamax*) has been proven in recent studies most effective when given in combination with estrogen/hormone therapy or raloxifene to increase bone mineral density as opposed to estrogen or alendronate alone. [3, 4]

Investigational Bisphosphonates

Etidronate (*Didronel*) is a first generation bisphosphonate investigated for treatment and prevention of osteoporosis. It was introduced in 1977 as an oral, non-nitrogen-containing bisphosphonate for the prevention and treatment of osteoporosis in Canada and Europe. It is not US-FDA approved for osteoporosis but is available in the United States and given as an "off-label" therapy. [10] The recommended dosage for Etidronate (*Didronel*) is 400 mg orally every 2 weeks for 3 months. Etidronate (*Didronel*) is no longer considered the first line of defense due to the side effect of inhibition of bone mineralization associated with it. Dosage manipulation alleviates this problem, however, etidronate is difficult to manipulate and when given a dosage that exceeds 800 mg, inhibition of bone mineralization occurs leading to osteomalacia. [3, 4]

Ibandronate (*Boniva*) bisphosphonate is given as an intravenous infusion or orally. Dosage regimen for orally usage is 0.5-5 mg and intravenous usage is every 2 mg

every 3 months. [4] In clinical trials it has been effective on bone mineral density (BMD) with the intravenous usage proving a BMD of 2.7 - 4.4% increase in spine and 1.8 - 2.9% increase in hip. [9] Ibandronate (*Boniva*) offers flexibility with dosages and ways of administration of therapy. Currently, Ibandronate (*Boniva*) is under investigation for antifracture efficacy and safety in order to gain FDA approval for the treatment of osteoporosis.

Clodronate (*Ostac, Lodromat, Bonefos*) is a non-nitrogen containing bisphosphonate administered both orally and intravenously for type I osteoporosis and corticosteroid-induced osteoporosis. Dosing regimen consist of 200mg infusions every 3 weeks or oral 400 mg daily for 1 month every 3 months or continuous 400 mg daily. [4] This bisphosphonate is generally well-tolerated and in higher dosages (1600 mg daily) was shown to reduce new metastases in breast cancer. [10] Clodronate is available in Europe and Canada but is not FDA approved in U.S. due to questionable long-term efficacy against fracture. [9]

Pamidronate (*Aredia*) is a nitrogen-containing bisphosphonate that is approved in the U.S. for Paget's disease and hypocalcaemia of malignancy, but not for osteoporosis. [1, 10] It is used as an "off label" osteoporosis type I and corticosteroid-induced osteoporosis treatment and administered as an intermittent intravenous infusion of initial 90 mg with subsequent 30 mg infusion every 3 months. [3] Intravenous methods are beneficial for persons unable to tolerate oral bisphosphonates. [3]

Zoledronate (*Zometa*) is a nitrogen-containing bisphosphonate that is administered as a 4 mg intravenous infusion every 6-12 months. Low dosage of twice or

once a year is good for promotion of compliance and for persons unable to tolerate oral bisphosphonates. [3] Zoledronate (*Zometa*) has been proven in clinical studies to effectively increase bone mineral density. [9] It is US-FDA approved for oncology but not approved for osteoporosis.

Non-FDA approved osteoporosis therapies can only be given if written informed consent is obtained, even for "off-label" therapies of *Aredia*, *Zometa*, and *Didronel*. Even though they are available in the U.S., they are not US-FDA-approved and must have informed consent from the patient before administered. Duration of the action of bisphosphonate therapy is not known, however bisphosphonates have long half-lives of 10 years and remain attached to hydroxyapatite (calcium and phosphate) crystals in bone and promote positive effects after treatment is discontinued. [10, 11] Follow-up DXA scans to evaluate bone mineral density (BMD) offer the best indication for clinicians/physicians in determing duration of therapy. Bone repair, rebuild, and maintenance are optimal at 1-3 years with high increase in BMD during the first 12 months.* Consistent maintenance of repaired bone is needed for at least 2-3 years. [1, 10]

Non-bisphosphonate Therapy

Estrogen/hormone therapy (ET/HT) is usually implemented for postmenopausal women due to the rapid decline of ovarian function with regards to estrogen release. ET/HT is used as a standard therapy for prevention of osteoporosis and relief of

postmenopausal symptoms. [5] Estrogen receptors are on both osteoblasts and osteoclasts. When estrogen secretion levels decline (menopause), bone turnover increases, cytokines (promoters of bone resorption) increases, and parathyroid hormone secretion increases causing calcium imbalance and bone loss. [10] ET/HT reduces fracture prevalence significantly in skeletal sites consisting mainly of trabecular bone such as vertebral spine. [7] ET/HT long-term usage, however, has been associated with significant risk such as gall bladder and liver disease, breast cancer, and endometrial cancer. [1] Compliance with ET/HT is poor and benefits of therapy rapidly decline/reverse after discontinuation. Due to safety concerns of ET/HT, other alternatives such as naturally occurring isoflavones, a phytoestogen derived from soy-based products, are being investigated for efficacy. [5]

Raloxifene (*Evista*) is a selective estrogen replacement modulator (SERM) targeting estrogen receptors and acting as an agonist on bone and organ tissue with the exception of antagonistic activity on breast tissue. Raloxifene (*Evista*) is FDA-approved for prevention and treatment of osteoporosis and is recommended at a dosage of 60mg tablets. Evidence exist that Raloxifene (*Evista*) increases bone mineral density 2 - 3% and decreases risk of vertebral fracture prevalence 30 - 50% while also reducing breast cancer by 60-70%.[1] Raloxifene (*Evista*) also increase bone mass by 1.4 - 2.8% in spine, hip, and total body, while reducing bone resorption 12-26%. [10] A MORE study showed that Evista not only prevents and treats osteoporosis, but also decreases the risk of breast cancer and cardiovascular disease in postmenopausal women. [9] Possible side effects of Evista include hot flashes and increased development of venous thrombosis. [9]

[10] Once postmenopausal women have hot flashes under control with estrogen therapy, raloxifene treatment is recommended and is most useful in middle menopausal women aged 55-65.

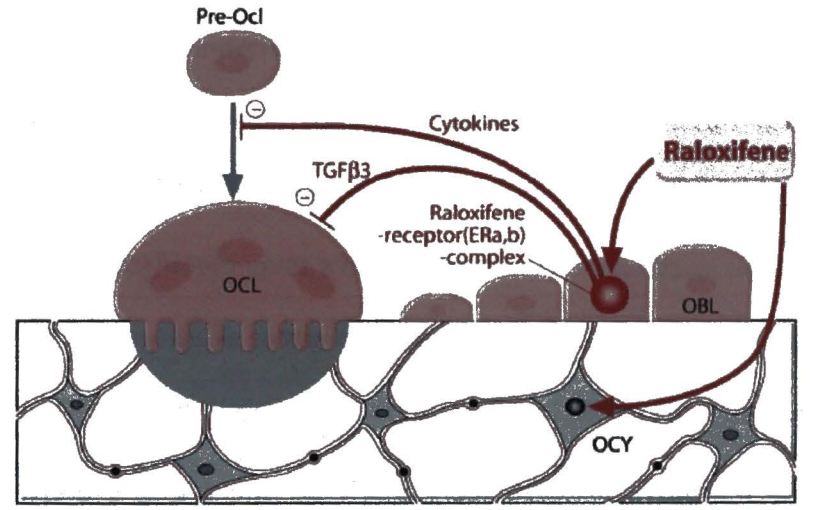


Figure 6: Action of Raloxifene [1]

Calcitonin (Miacalcin, Karil) is a polypeptide hormone produced by parafollicular C cells of the thyroid gland. It is used as an antiresorptive therapy since it binds to osteoclast receptors and inhibits osteoclast activity. Calcitonin is mostly given as a pain inhibitor in the form of a daily 200-400IU nasal spray or daily 50-100IU subcutaneous injections. [9] Nasal and injectable calcitonins are used for the treatment of osteoporosis and both are synthetic salmon-derived calcitonin because human calcitonin is relatively weak. [9] Randomized controlled trials (RCTs) reported 84% reduced risk of vertebral fracture with injectable calitonin and 1-2% lumbar spine BMD increase over 2 year period. [10] The nasal calitonin gives a modest increase in bone mass as compared to the injectable or other antiresorptive therapies; however the injectable calcitonin is limited in use due to the inconvenience of daily injections. [10] Calcitonin is no longer first line therapy for osteoporosis but is used commonly in children and pregnancy.

All current US-FDA approved therapies for osteoporosis are antiresorptive except for parathyroid hormone [PTH (*Forteo*)]. PTH (*Forteo*) is an anabolic therapy that increases bone formation via osteoblast stimulation to increase new bone mass and strength. PTH (*Forteo*) targets osteoblasts on all osseous surfaces while unfaltering the activity of osteoclast and bone resorption. PTH is a regulator of calcium homeostasis in the human body and stimulates the release of calcium and phosphate from bone, reabsorption of calcium in kidneys, and stimulates an increase in synthesis of vitamin D, which increases intestinal calcium and phosphate absorption. [10] Regulation of PTH secretion is determined by extracellular calcium. PTH (1-84) in the body is a single chain polypeptide that has 84 amino acids. The drug PTH (*Forteo*) is a recombinant hPTH(1-

34) with 34 amino acids and has nearly the same biological activity as human PTH(1-84). [9] PTH (*Forteo*) is administered by daily subcutaneous injections and is most efficacious when given intermittently at low dose injections. [14] Evidence demonstrates that PTH induces decreased osteoblast apoptosis and combination therapy of raloxifene and PTH is promising while PTH and bisphosphonate therapy should be administered sequentially and not simultaneously for PTH to effectively stimulate bone formation. [1] Optimal therapy suggests combination of PTH (*Forteo*) with an antiresorptive therapy as well.

Non-pharmacologic

Calcium and Vitamin D are essential for bone growth and maintenance; therefore, supplements of calcium and vitamin D are usually included in prevention and treatment regimens of osteoporosis. Calcium is the most abundant mineral in the body, with 99% of calcium deposited in bone. A recommended dose of calcium for adults is 1000 mg/ day. Higher doses are recommended for men and women over fifty, teenage girls, pregnant or lactating women, and especially postmenopausal women not on estrogen therapy. Fracture risk has been shown to decrease by 40% in numerous studies by taking supplements of calcium and vitamin D alone. [1, 13] Proper calcium build-up in adolescent years decreases the risk of osteoporosis in later years and helps build peak bone mass. A dose of at least 1000 mg/day of calcium suppresses bone breakdown via decreasing PTH secretion. Vitamin D is an important regulator of calcium, which is the reason combined vitamin D and calcium supplementation is recommended. Vitamin D

promotes absorption of calcium and mineralization of it into bone. Vitamin D also increases muscle mass, strength, and coordination, thus lowering falling risk and possible fracture. The therapeutic level of vitamin D recommended is 400-1000 IU. New studies have shown vitamin K to be helpful in prevention of hip fracture and essential for conversion of inactive osteocalcin to active form. [1, 7] Vitamin K is helpful particularly for bone loss in hepatic cirrhosis.

Combination therapy approach to osteoporosis including nitrogen-containing bisphosphonates, vitamin D and calcium supplements, and maintenance of postmenopausal symptoms are crucial when targeting prevention and treatment of osteoporosis. Proper balance between hormones, vitamin D, and calcium are needed to control the remodeling process. Decreasing negative bone turnover and bone resorption of essential minerals decreases incidence of fractures and osteoporosis.

Problem/Hypothesis

The ability of patients to adhere to treatment regimens is very poor and continues to impede optimal therapy of osteoporosis. [15] US-FDA has approved Risedronate (Actonel) as a competitive bisphosphonate that appropriately combats osteoporosis. The shortcomings in treating osteoporosis are: a) noncompliance and/or lack of continued persistence of therapy, b) efficacy of therapy on bone turnover marker levels and fracture prevalence, and c) tolerability of therapy to patients. Studies have shown that interventions such as education and awareness of bone mineral density promote patient usage compliance. [15] The slightest improvement in compliance allows further

understanding of accurate efficacy of medication therapy to fractures, bone marker levels, and overall improvement of bone mass. Increased compliance/persistence allows accurate comparison of bisphosphonates to one another for effectiveness on osteoporosis patients and allows improvement opportunity in treatment modalities that can positively influence the course of osteoporosis. The US-FDA is in the process of investigating new bisphosphonates and other therapies to assess whether they are just as efficacious, if not more, as existing therapies and also ways to promote compliancy in therapies whether it is allocation of once a day, once a week, or once a year. This phase IV study targets glucocorticoid-induced osteoporosis patients, thereby permitting further understanding of glucocorticoid-induced osteoporosis and further understanding of therapy impact with bisphosphonate, Actonel. Actonel discontinuation rate, as observed in clinical trials, is less than 25% and has an advantage of notable rapid onset of fracture efficacy and tolerability. [15] When subjects are advised to treatment regimens of calcium and vitamin D supplements along with Risedronate (Actonel), it is hypothesized that glucocorticoid-induced osteoporosis subjects ***will increase/improve compliance*** when given knowledge of baseline vertebral fracture prevalence and bone turnover marker level results.

Specific Aims (taken from Proctor & Gamble/ Aventis Pharmaceuticals, Actonel Study Protocol HMR4003B/4027)

Specific Aim 1:

- To determine whether subject knowledge of baseline vertebral fracture prevalence and awareness of bone turnover marker results increase persistence/compliance with Actonel 5mg daily

Specific Aim 2

- Evaluate the relationship between prevalence of vertebral fracture vs. duration of steroid therapy
- Evaluate the correlation between baseline vertebral fracture prevalence vs. persistent Actonel 5mg daily
- Evaluate effectiveness of Actonel 5mg daily on bone turnover marker determination (BTM), Osteoprotegerin/ RANKL binding protein (OPG/RANKL) measurements and BMD at end of study vs baseline
- Evaluate subject satisfaction with Actonel
- Evaluate the safety of Actonel with regard to adverse event reporting

Significance

If compliance improves, then therapy with Actonel may prove more efficacious on bone loss, thus proving osteoporosis to be controllable through decreased fracture prevalence and decreased bone turnover marker determinations. Improved compliance allows researchers and physicians the information to improve administration of therapy that is most effective and most compliant to patients, further supporting ways to increase patient's quality of life.

Methods

This study is a phase IV, randomized, multicenter, parallel-group study to determine if knowledge of baseline vertebral fracture prevalence (as determined by Hologic IVA) and bone turnover marker levels improves persistence with Actonel 5mg daily therapy in subjects receiving chronic glucocorticoid therapy. This is a 12-month multi-center open-label drug, single blinded study in which subjects are randomized into one of two groups including informed (baseline vertebral status by IVA and bone turnover marker determination; INFO+) or not informed (INFO-). The number of subjects to be included in this study is approximately 350 at 40 participating investigator study sites. The study consists of a 4-week screening phase and a 52-week treatment phase.

Treatment Regimen

All subjects will be treated with Actonel 5mg daily self-administered by mouth at least 30 minutes before the first food or drink (other than plain water) of the day. The subjects will be given supplements of calcium 500mg and vitamin D 200 units and will be instructed to take each twice a day: one at noontime and other at dinner. All subjects will have a dual energy x-ray absorptiometry (DXA) scan and instant vertebral assessment (IVA) performed prior to or at their baseline visit.

Two randomization groups:

Subjects randomized into informed (INFO+) group will receive results of instant vertebral assessment (IVA) determinations at baseline visit, and bone turnover marker determinations (BTM) measurements will be given via direct phone conversation and letter after baseline visit and all subsequent visits. Subjects randomized into non-informed (INFO-) will **not** receive IVA determinations or BTM measurements until the end of the study via request. However, ***all*** *subjects will receive results of DXA scan consistent with medical standard care.*

Inclusion Criteria

Subjects meeting all of the following criteria will be considered for enrollment into the study:

- Ambulatory male and female subjects, 30-85 years old, inclusive, with a variety of rheumatologic, pulmonary and skin conditions
- Subjects on oral glucocorticoids with a mean daily dose of > or = 7.5 mg prednisone (or its equivalent) and expected (although not required) to remain on a daily dose of > or = 7.5 mg prednisone (or its equivalent) for 12 months after study start
- Women must be at least one year post-menopausal or surgically sterile
- Subjects must have analyzable BMD sites at the lumbar spine and proximal femur
- Subjects on oral glucocorticoids for 8 weeks or less (prevention group), or 6 months and greater (treatment group) prior to screening
- Subjects unable to open study medication with the child-resistant TrackCap closure can be included in the study, provided that an adult in the subject's household will be able and willing to open and close the medication for the patient every morning throughout the treatment period

Informed consent must be read, understood and signed by the subject, and dated.

Exclusion Criteria

- Subject's unwillingness to take Vitamin D, calcium supplements or study medication
- History of cancer: any cancer within past 5 years. Relatively benign skin malignancies, such as basal cell carcinoma or squamous cell carcinoma, are not an exclusion if the subjects has been in remission for at least 6 months prior to enrollment
- History of hyperparathyroidism, hyperthyroidism or osteomalacia or other metabolic bone disease within one year prior to enrollment
- Evidence of clinically significant organic or psychiatric disease on history or physical examination, which in the opinion of the investigator would prevent the subject from completing the study
- History of alcohol or drug dependence within one year of enrollment
- Markedly abnormal pretreatment laboratory findings, except if in the opinion of the investigator, it would not prevent the subject from completing the study
- History of using any of the following medications within 6 months of starting study drug:

  -Estrogen or estrogen-related drugs (tamoxifen, raloxifene, tibolone); low dose vaginal estrogen (estradiol <0.2 mg/day, estropipate < 1.5 mg/day) will be allowed

  -Anabolic steroids

  -Parathyroid hormone

-Anticonvulsants

- History of using any of the following medications within 1 month of starting study drug or for more than 1 month within 6 months prior to study entry:

  -Calcitonin

  -Vitamin D supplements (>1000 IU / day)

  -Calcitrol (> 1.5 mcg/ week

- History of using any of the following medications within 6 months of starting study drug or for more than 14 days within 1 year prior to study entry:

  - Any bisphosphonate

  -Fluoride

  -Estrogen implant

  -Deflazacort

- Have received a depot injection of > 10,000 IU Vitamin D in the past 12 months
- Have a documented history of an abnormal or allergic reaction to bisphosphonates
- Participation in another clinical trial involving active intervention within 30 days prior to enrollment
- History of recurrent nephrolithiasis or a history of one episode of nephrolithiasis within 5 years of study entry
- Severe renal impairment (creatinine clearance of <30 mL/min)
- Subjects on steroid therapy for transplantation
- Subjects on oral glucocorticoids for >8 weeks but <6 months at screening
- Pregnant

- Breast Feeding
- Childbearing Potential (i.e. ovulating, pre-menopausal, not surgically sterile)
- Males planning to father a child within the next 18 months
- History of hypersensitivity to the investigational product or to drugs with similar chemical structures
- Clinically relevant cardiovascular, hepatic, neurological, endocrine, or other major systemic disease making implementation of the protocol or interpretation of the study results difficult
- Mental condition rendering the subject unable to understand the nature, scope, and possible consequences of the study
- Subject unlikely to comply with protocol, e.g., uncooperative attitude, inability to return for follow-up visits, and unlikelihood of completing the study
- Inability to provide informed consent
- History of any known condition that would interfere with the assessment of DXA at either lumbar spine or femoral neck

No subject will be allowed to enroll in this study more than once.

Screening Visit

At screening visit, informed consent will be signed and subjects will be assigned a study subject number, which will be used to identify study subject throughout the study. Also at screen visit, subjects will be given two urine cups to collect the second void fasting urine the day before and the day of their next visit between 5-10 am. After screening, but before baseline visit, the investigator will review all information obtained from the subject, including screening blood and urine test, medical history and physical exam, and make the determination as to whether the subject can be included in the study. The subject will be contacted and baseline visit scheduled if subject meets qualifications of study inclusion and exclusion criteria. The baseline visit must occur within 4 weeks after the screening visit.

Baseline Visit

At baseline visit, the subject will be allocated a treatment number. The unique treatment number will be present on the bottle with Actonel tablets (113 tablets/ bottle). All medication bottles for a given subject (both Actonel and calcium and vitamin D) will have same unique treatment number. It is critical that the investigator removes the original cap of the Actonel bottle and replaces it with the electronic monitoring cap before dispensing both Actonel and calcium and vitamin D bottles to the subject for the next 13-week treatment. The electronic monitoring cap has a serial number printed on the side, which is to be recorded in the case report form. Subjects are not allowed to transfer tablets from the Actonel bottle to any type of tablet organizers. At baseline, the

investigator will collect blood serum OPG/RANKL protein measurements and osteocalcin and two fasting urine samples: one collected the previous morning between 5:00 and 10:00 am and one the morning of the visit between 5:00 and 10:00 am. The subject will receive a bone mineral density (BMD) dual energy x-ray absorptiometry (DXA) of the left hip and the spine. The subject will then be randomized into informed group (INFO+) or non-informed group (INFO-). Informed group will receive information on any vertebral fractures, instant vertebral assessment, and results of DXA scan and lab bone turnover marker determinations. The non-informed lab test results and DXA scan results will be available at the end of the study.

Study and Follow-up Evaluations

Subsequent evaluations following the baseline visit will occur every three months in both treatment groups of INFO+ and INFO-. The schedule of the study events will proceed as follows: visit 1 as screening visit, visit 2 as baseline at month 0, visit 3 at month 3, visit 4 at month 6, visit 5 at month 9, and visit 6 at month 12. Bone marker determination lab test and urine collection by subject will be conducted at every follow-up visit. Visit 6 (month 12) is the last visit and it is critical to the protocol to ask the subject to complete a subject satisfaction questionnaire, place it in a sealed envelope, and give to someone other than the investigator. At final visit 6, an end of study DXA scan is performed and results are given to INFO+ and INFO-. Bone marker determination lab results performed throughout the study are given to INFO- group and final visits lab results are given to

both groups as soon as results are available. All treatment visits are conducted in person with telephone reminder calls of next appointment.

Primary Data Endpoint

The primary endpoint of this study is measurement of persistence/compliance (date and time when Actonel bottle is opened) during the Actonel 52-week treatment period via medication event monitoring system (MEMS). MEMS complies the dosing history of prescribed oral medication with the use of a plastic vial. The vial has threaded opening and closure that contains a micro-electronic circuit that registers times when the closure is opened and closed. The monitoring system has a battery that expires 36 months from initialization, waterproof protection, and memory for data storage that maintains data integrity for years after battery power is loss. The data from the MEMS can be transferred through MEMS V-Communicator via wireless data transfer to a Windows-based computer. Software analyzes displays and prints various formats of patient compliance.

Secondary Data Endpoint

- The level of urinary N-telopeptide, serum osteocalcin and ratio of serum OPG/RANKL protein at the baseline visit and months 3, 6, 9, and 12
- The bone mineral density and instant vertebral assessment determinations at the baseline visit and month 12
- Safety data
- Patient Satisfaction Questionnaire data

**** All methods taken from Proctor & Gamble Aventis Pharmaceuticals Study Protocol HMR4003B/4027 Risedronate Sodium (Actonel) Study*****

Results/Discussion

The Aventis and Proctor & Gamble Pharmaceutical HMR400313/4027 study was conducted in approximately 40 centers in the United States with 350-subject enrollment goal. At site 026, 10 subjects were enrolled and 9 subjects completed the 12-month, 52-week study. Enrollment consists of 6 males and 4 female all randomized into either informed (INFO+) or non-informed (INFO-). Ethnicity of the 10 subjects consists of 9 Caucasian and 1 Hispanic male. Inclusion criteria for the study required subjects, male or female, with a variety of rheumatologic, pulmonary, or skin conditions and on a stable dosage of oral glucocorticoids > or = 7.5 mg for at least 8 week or 6 months prior to screening visit entry. Subjects had to have an analyzable BMD, thus glucocorticoid-induced osteoporosis was expected in these subjects. Enrollment of subjects at site 026 was effective and convenient due to the influx of patients with rheumatoid arthritis who

are on concomitant steroid therapy, directly treating their autoimmune disease and indirectly decreasing their bone mass and strength.

Statistical analysis for subject persistence/ compliance rate with oral bisphosphonate *Actonel 5 mg* daily has not been received. I will discuss the importance of increased compliancy with bisphosphonate therapy in the treatment of osteoporosis, reasons of non-compliance/ non-persistence with therapy, and projected outcomes this compliance/persistence study is attempting to achieve. This discussion is not conclusive as site 026 is awaiting statistical data analysis results from Aventis and Proctor & Gamble on subject persistence and compliance with study therapy *Actonel 5mg* daily.

The Specific Aim of this study is to measure compliance (date and time when Actonel bottle was opened) during the 52-week treatment period via medication event monitoring system (MEMS) inserted into bottle cap of Actonel. The MEMS method is unconventional from pill count or questionnaire in acquiring an accurate measurement of persistence and compliance. MEMS eliminates human interaction errors with data recording because date and time when the bottle is opened is transmitted via wireless data transfer to a Window-based computer, thus providing patterns of non-persistence better than can be identified with pill count only. All randomized INFO+ subjects received DXA scan results from the baseline/ randomization visit and were therefore made aware of their level of bone mineral density. All subjects, whether in informed (INFO+) or non-informed (INFO-) on bone turnover marker determinations (BTM) and DXA scans gained the benefit of routine monitoring visits and telephone contacts in a clinical setting, which has been shown is previous studies to highly influence compliance to medication

as oppose to regular clinic patients whom do not benefit from routine monitoring. Most clinic patients see their primary care physician when things have gone wrong and they are experiencing pain. Asymptomatic disease, such as osteoporosis, will remain virtually unrecognized, predating on bone until a fracture occurs with minimal to no trauma. This chronic condition impedes a person's active lifestyle and quality of life. In addition to routine monitoring and frequent telephone contacts to study participants, perception of necessity of bisphosphonate medication and how it targets bone remodeling is tested by informing and educating one group on their laboratory BTM levels and baseline DXA scan vertebral assessment with the expectation that education of the subject's disease prognosis increases their persistence to the bisphosphonate therapy. Education on the necessity of persistence and compliance in the treatment of osteoporosis is imperative to change patient/subject perception that medication is not necessary simply because they feel no pain and possess no symptoms.

Assessment of secondary aims/endpoints of vertebral fracture prevalence vs. the duration and amount of steroid therapy are assessed by DXA scan at baseline visit 2 month 0 and final visit 6 at month 12. This assessment gives researchers a better understanding of how underlying conditions induce secondary osteoporosis and how severe the bone loss is in relation to duration and amount of steroid usage. Correlation between vertebral fracture prevalence and persistence with Actonel allows researchers assessment of optimal therapeutic targets and how efficacious Actonel therapy is when persistence is maintained. BTM measurements along with baseline and final DXA scans will determine effectiveness of Actonel 5 mg daily on bone mineral density (BMD). The

questionnaire will help assess likeability and ease of compliance to therapy in order to better assess what impedes and/or aids patient/subject compliance to Actonel. Adverse event reporting on-site and at all 39 other sites will determine the safety of Actonel. Site 026 reported two serious adverse events of multiple fracture and right foot surgery bunionectomy and bone removal on right foot toe; both events were definitely not related to study therapy Actonel. The one subject who withdrew from the study was the subject who experienced the multiple fractures as a result of a horseback riding accident. Previous clinical trials have reported Actonel as well tolerated. [6] The 12-month study reported only 8 serious adverse events: 2 definitively not related, 1 probably not related, and 5 possibly related to the treatment.

Compliance is defined in the Oxford dictionary as obedient. [16] Compliancy is the measurement of how often patients take medication correctly and how persistent (amount of time they continue the medication/therapy) and obedient they are to the regimen. Poor compliance to prescribed medication remains a critical concern and accounts for $20 billion a year in medical cost relating to prescription misuse and adverse events. This brings about the question: *Why are patients noncompliant?* A patient's non-compliancy can result from a lack of understanding and/or proper education of medication effects on disease prognosis. [17] As tested in this phase IV trial, the INFO+ group is projected to increase compliancy given education on BTM levels and IVA information, however results are still pending. The issue of the cost for healthcare when incorporating routine visits, proper insurance, drug therapy/medication cost, and transportation to healthcare facilities impedes patient's compliance simply because

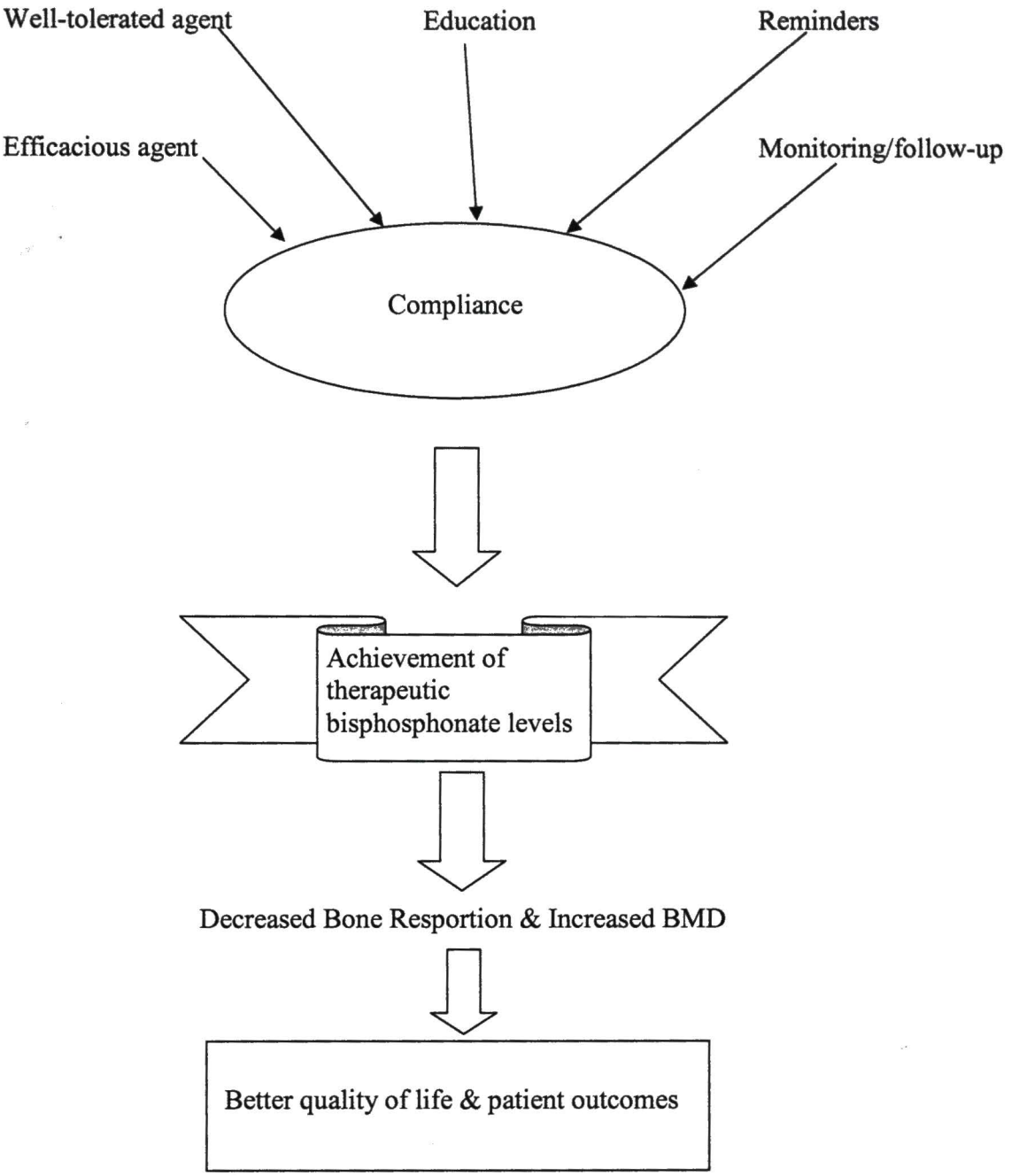
proper maintenance of a disease/disorder is not made a priority, especially if the disease is asymptomatic. Proper therapy administration to ensure full potential of bisphosphonate therapy was reported to decrease in compliance and persistence even in a study where subjects were given counseling on correct dosing. [18] As a result of incorrect dosing administration, the effects of the prescribed medication can cause adverse events such as mild or severe gastrointestinal discomfort. Additional discomfort decreases a patient's compliance and persistence to therapy. Thus, when patients adhere poorly (non-compliant and non-persistence) to bisphosphonate therapy, they experience a greater risk for fracture and an insignificant decrease in the rate of bone resorption causing non-attained therapeutic levels. [18] Psychological variables and physical distresses of pain and discomfort can cause subject/patient noncompliance due to lack of energy or will to comply. [19] Another reason reported in clinical compliancy studies was the absence of pain as a major reason compliancy decreased. The patient feels no pain and thus decreases compliancy to therapy. [19, 20] Inconveinence of frequent dosing of medication affects compliancy such as a patient already on high concomitant usage whom has to remember to take multiple drugs properly. Bisphosphonate therapy, Actonel, has since marketed a more convenient dosage of 35mg once weekly during the duration of this study that aids in patient compliance because the patient only has to remember to take the therapy once instead of daily. Forgetfulness (especially in elderly) must be considered when choosing effective and convenient therapies in order to aid in proper compliance and persistence to therapy regimen.

In clinical trials, compliance measurements have been attempted through such instruments as: questionnaires, pill counts, real-time electronic data capture, and medication event monitoring system (MEMS). Subjects in clinical trials have a higher percentage of compliancy due to frequent visits with health care professionals and increased attention to therapy and adherence to protocol treatment regimen. If side effects or adverse events occur, clinical trial subjects are required to report these events and immediate attention is given to the matter. Therefore, clinical trial subjects are usually healthier individuals and better counseled on disease. [21] Patients not in clinical trials commonly experience increased noncompliance of self-administrative therapy as prognosis worsens. [19] This leads to increased psychological and physical discomforts.

Numerous trials have shown that bisphosphonate therapy provides substantial bone mineral density increases in both hip and lumbar spine. [18] The expected increase in postmenopausal women over age 55 and the continual increase in the aging population by the year 2020 are projected to exceed 45 million. [18] Currently in the US, osteoporosis affects 25 million, thus the expected and projected number of people affected with osteoporosis makes it imperative that increases in compliance/persistence occurs to control disease progression, healthcare cost, and overall patient quality of life. Although Alendronate (*Fosamax*) and Risedronate (*Actonel*) are currently the only US-FDA approved bisphosphonates for osteoporosis, many "off-label" bisphosphonate therapies, Pamidronate (*Aredia*), Zoledronate (*Zometa*), and Etidronate (*Didronel*) are available to give patients non-tolerable to oral bisphosphonates an option of intravenous (*Aredia & Zometa*) and also option on frequency of dosage. More convenient and less

frequent dosing may increase compliance. Improving compliance to bisphosphonate therapy in osteoporosis patients consist of a multifactorial approach consisting of early and accurate diagnosis of osteoporosis, efficacious and well-tolerated bisphosphonate agent, education on prognosis and proper administration of therapy, reminder calls for monitoring/follow-up visits and DXA scans, and reminders of risk factors and good preventive measures to increase bone mass and strength. (See Figure 3, next page)

Figure 7: Improved Compliance *[20]*



Limitations

Subjects are instructed to return their study medication at each visit in the original medication bottle. The compliancy of the subjects to the study treatment is measured according to the number of times the bottle is opened, assuming the medication is taken and not thrown away, or set down, left and forgotten, and only the subject (not a family member) has opened medication only when actually taking the medication. The electronic cap monitoring system allows a way to determine how often the cap of the Actonel bottle is opened with the assumption that one person would not go through all the trouble of opening the bottle just to forget or not take the study medication. This is a good way to monitor subject compliance to study treatment regimen, however, it is not completely full proof.

CHAPTER III

Internship Experience

Internship Site Description

In fulfillment of curriculum requirements for Master of Science in Clinical Research Management, I interned 6 months at the University of North Texas Health Science Center-Patient Care Center in the Department of Internal Medicine, Division Rheumatology under the supervision of on-site mentor/research coordinator, Cynthia Jimenez-Williams, RN, BSN, CCRC. At the start of my internship, 10 clinical studies where ongoing under the supervision of coordinator, Cynthia Jimenez-Williams, which focused on pharmaceutical therapies in the areas of rheumatoid arthritis (4), osteoarthritis (1), osteoporosis (3), gout (1), and cholesterol (1). This internship site dealt with pharmaceutical company sponsors and performed clinical trial research on various biologics and drugs (investigational and/or FDA-approved). The Patient Care Center has a regular clinic of patients that come to see physicians whom specialize in a particular area of medicine (i.e. Rheumatologist, Cardiologist, and Endocrinologist). The facility is not like a hospital; furthermore, there is no emergency room and surgeries are not performed here.

Enrollment of eligible subjects came primarily from regular rheumatology clinic patients and patients from John Peter Smith Hospital who met inclusion criteria of protocol. John Peter Smith Hospital is a facility where the active principal investigator, Dr. Rubin, and sub-principal investigator, Dr. Pertusi, performed regular clinic

visits/rotations. Advertisements (flyers, email, and/or newspaper ads) sent throughout the Department of Internal Medicine, campus-wide, and community-wide aided in recruitment of subjects. All subject visits, laboratory blood draws and packaging, and consenting were conducted on-site in the clinic rooms by the coordinator according to protocol. On-site staff consisting of independent infusion injection RN, independent joint assessor RN, certified DXA radiology technician, PI and sub-PI's, and pharmacist assisted coordinator when needed as per protocol.

The variety of open clinical trial studies allowed me the opportunity to assist/intern all 10 studies in areas of rheumatoid arthritis, osteoarthritis, osteoporosis, gout, and cholesterol. The *Aventis HMR4003B/4027* phase IV trial, which is the basis of my practicum report, had an enrollment goal of 350 subjects at 40 centers. The UNTHSC-Patient Care Center Site 026 met enrollment of 10 subjects screened and randomized.

Other ongoing studies:

- Merck 076, an osteoarthritis study with 2 subjects randomized,
- Centocor C0524T02, a rheumatoid arthritis study with 6 subjects randomized
- Pfizer A3471018, a rheumatoid arthritis study with 4 subjects randomized
- Genentech ACT2847g, a rheumatoid arthritis study with active enrollment
- Novartis CZOL446H2315, an osteoporosis study with 2 subjects randomized

- Tap (Gout) Extension C02-021, a gout study with 2 subjects randomized
- Astra Zeneca 4522IL/0034, a cholesterol study with 1 active subject
- Merck 066, an osteoarthritis and rheumatoid arthritis study with 19 randomized subjects.

The following staff and research persons contributed to my internship learning experience significantly.

- Cynthia Jimenez-Williams, RN, BSN, CCRC – Clinical Trials Coordinator, On-site mentor, Committee Member
- Bernard R. Rubin, DO – Principal Investigator (PI), Committee Member
- Raymond R. Pertusi, DO – Principal Investigator (PI) & sub-PI
- Linda Davis, PA-C – sub-PI
- Dan Hooper - Pharmacist
- Dorothy Corbin, RN – Independent Infusion Nurse
- Anderson Allen, RN – Independent Joint Assessor
- Susan Bitner – Certified DXA Radiology Technician
- Wendy Hammons – IRB Coordinator
- Debbie Ceron – IRB Coordinator
- Sharon Tibola – IRB Coordinator

Specific Aims of Internship

During my internship practicum I was exposed to typical activities in the profession of clinical research, supervised, and guided by my onsite mentor of the purpose of each activity. Detailed day-to-day activities located in Appendix: Journal of Daily Internship Experience.

Institutional Review Board (IRB) Interactions & Communications

The IRB serves to protect the rights of the human subjects. My internship practicum involved clinical trials in a medical clinic setting. Since all of the subjects are human, proper IRB interactions and communications had to be maintained. UNTHSC local onsite IRB receives submissions from the clinical trial coordinators and communicates with the sponsor sites on approvals and/or changes that need to be made. Once UNTHSC local onsite IRB reaches satisfaction with submissions, they are then sent back to the clinical trial coordinator with IRB approval and acknowledgement. The coordinator is responsible for proper filing of documents in regulatory binders and correspondence to sponsor site of IRB approved documents/submissions.

Any material received from a sponsor has to have IRB approval before distribution to the subjects. I corresponded with the IRB by making copies of received materials and submitting them to the IRB for approval. When the approval is received, distribution of the sponsor materials (i.e. subject questionnaires, handbag, exercise

equipment, calendar, and visit reminder note cards) can occur. The IRB makes certain that there is no coercion or misleading information in these materials from the sponsor that could affect the subject.

Continuing Reviews are a requirement of FDA title 21 Code of Federal Regulations (CFR) Part 56.109 for IRB submission of ongoing clinical trial studies. A continuing review must, at a minimum, occur annually; however, some can occur every three or six months as per IRB request. I participated in typing and retrieving information for continuing reviews, which is pulled from source and case report forms, and regulatory binders.

Any amendments to protocol, investigator brochure, or consent forms must have IRB approval. I participated in amending Genentech ACT2847g, Merck 076, Merck 066, and Centocor C0524T02 consent forms and participated in submission of amendments to protocol and investigator brochures for IRB approval. All serious adverse events (SAEs) that occur to subjects in every study both onsite and offsite are documented and sent to UNTHSC IRB for acknowledgement.

Informed Consent

Informed consent has to be obtained on any participant/subject in a study. All informed consents must be approved by IRB as according to title 21 CFR 50.25 and must state the study involves research, purpose of research and timeline, compensation, risk

and benefits involved, number of participants, description of drug, device or biologic, alternative treatments, confidentiality of subject, contact name and number for questions, and emphasize study participation is completely voluntary. During the course of my internship I performed submission of amended informed consents to IRB for approval and witnessed informed consenting process onsite with subjects. I observed that subjects must be able to understand the consent form in its entirety before signing can occur. Once subjects agree to participate in a study, informed consent is signed with date and time, and initialed on each page before any part of the study protocol can be conducted. Informed consent is an ongoing process and participation in the study can be stopped at anytime if the subject wishes to do so, or if the investigator decides it is in the best interest of the subject to discontinue study participation. As witness to informed consenting process, signatures on the consent form included the subject, the PI or sub-PI or coordinator (as approved per protocol to conduct informed consenting process), and myself (witness). The consent form is then filed in the subject source binder. If the consent form is amended in any way, IRB approval must be obtained for the updated consent and the consenting process with the subject occurs again. This is to ensure the subject is informed of changes and that the most recent consent form is signed and filed in subject source binder.

Data Collection and Verification

The first place data is collected is the source. Source binders are made for each subject in each study to collect and document data at the subject visits. I assembled source binders for the ongoing clinical trial studies under the supervision of my onsite mentor and made sure the source binder had all required subject visit sections and forms. The source binder mirrors the case report form (CRF) binders. All collected vital information, routine laboratory sheets, study drug accountability, and adverse event reporting is first documented in the source binder, which is on-hand at every subject visit.

The subject visits consist of screening, randomization, and subsequent follow-up monitoring visits. At each visit, contact information is documented and updated as needed if changes occur, vital signs consisting of weight, pulse, respiration, temperature, height, and blood pressure are recorded as per protocol, and laboratory blood draws and urine collection is performed as per protocol requirements of each particular study. The subject is always asked if any changes to concomitant medications have occurred or if any adverse events have occurred since last visit. The information is then documented in the source binder. Subject is always reminded and given coordinator's contact number at each visit to call if any adverse event happens. The information documented in the source binder is then documented in the CRF binder, which is a master copy of all the subjects' information. The CRF binder can be documented in a paper/binder form or on the computer and transmitted to the sponsor site.

Maintaining Regulatory Binder and Study Files

Regulatory documents are maintained in a binder consisting of records, contracts, reports, and correspondence of the study. Each study has a regulatory binder that details all the information and events of the study. Sections of the regulatory binder were discussed with my mentor and assembled by me. Required sections in the Regulatory binder consist of:

1. Contact Details
2. Study Communications
3. Subject information
4. Subject enrollment log
5. Protocol: IRB approval of most recent protocol and all previous copies
6. Safety Information: Investigator Brochure
7. IRB section: Approvals and submission copies of IRB amendments, protocols, and correspondence
8. Correspondence section: correspondence between sponsor and site
9. Investigator Agreement section: contains 1572's & financial disclosures
10. Site Staff Details: CV's of principal investigator and all required study personnel & licenses
11. Investigational Product section

12. Laboratory section: licenses and contracts with laboratory. CLIA & CAP accreditation and recent dates on licenses

All documents must be maintained with the most recent chronological dates in front and all information current. Any missing information must be obtained from sponsor, IRB, or laboratory. I maintained the regulatory binders and created "Note to File" if any section of the regulatory binder was moved.

Monitoring Visits: Pre-Study Qualification, Site Initiation, Routine, & Close-out

Before any study is conducted, the pre-study qualification process occurs that involves investigator selection, site qualification and operational assessment. I participated in greeting the monitor representative and escorting them to meetings with principal investigator, sub-principal investigator, and coordinator. I assisted in a tour of the facility with the coordinator and monitor. Once the monitor is satisfied with potential investigator and staff, the level of integrity of institution, past research experience, investigator's practice population for desired enrollment achievement, investigator's availability, location, budget, and adequate facility drug room storage, labs, exam rooms, pharmacy, and monitoring space, the site is then approved.

A site initiation visit occurs after a site has qualified for study and before any subjects can be screened into a study. The purpose of the site initiation visit is to clarify requirements and regulations of protocol and review with each staff personnel involved

the actual process of implementing the requirements of protocol. The monitor has a checklist and reviews each area. I participated in the Genentech ACT2847g study site initiation visit and observed the monitor review requirements and regulations of protocol with the pharmacist, infusion nurse, coordinator, principal investigator and sub-principal investigator. I assisted in giving the monitor a tour of the pharmacy facility, lab and exam room facility, drug storage room, and location of crash cart.

A routine monitoring visit occurs periodically through the course of a study's duration to ensure proper progress and integrity of data is conducted. During my internship I prepared for routine monitoring visits by checking the readiness of regulatory binders: IRB submissions and correspondence, updated licenses and CV's as needed, serious adverse event documentation and IRB acknowledgment, and checked/updated laboratory licenses. Source binders were checked and assembled in monitoring consult room with regulatory binders. I greeted monitors and assisted with questions when applicable.

During my internship, I participated in three close-out visits with Aventis/Proctor & Gamble Actonel study, Pfizer/Bextra study, and Merck 076 study. The close-out visit ensures all known data is collected and verified. The final accounts and disposition of investigational test articles (study drug and/or devices) are taken, and study files are verified for completion and accuracy by sponsor representative/ monitor. I assisted sponsor representative/ monitor as needed with verifying safety reports and all other data as applicable.

Drug Accountability

Investigational drugs were stored in restricted, locked facilities at required temperatures as per protocol. Accountability of the study drug was documented (date, time, serial number on therapy) at time of allocation of study therapy and at all follow-up subject visits until end of study/final visit. Subjects were instructed at each visit to return the study drug and bottle even if empty and to never throw any bottle away. Pill counts were done to document subject compliance with study regimen and in the Aventis site 26 Actonel study (basis of practicum report) compliance/ persistence was measured with Medication Event Monitoring System (MEMS) by placing electronic cap on a special communications modem. Subjects in the Aventis site 26 Actonel study were instructed not to transfer tablet to another bottle, only open bottle when actually taking medication, and to instruct family members not to tamper with or open bottle. In accordance with title 21 CFR 312. 62, name of study therapy, type and quantity dispensed, serial number, expiration date, and date of dispense was recorded in subject source binder. All unused study drug are returned/dispositioned to sponsor.

Subject Site Recruitment, Pre-Screening, and Enrollment

During my internship, various forms of pre-screening and advertising for subject enrollment into study were conducted. Subject recruitment was obtained by hanging IRB approved flyers throughout Department of Internal Medicine floors at patient care center

and sending university-wide IRB approved email advertisement of the study. Physicians were given inclusion/exclusion criteria and protocol description of study research and therapy to inform patients of ongoing research study. IRB approved newspaper advertisements were run in the local community and bulletin board information on study and contact number were made available in patient care waiting area.

Pre-screening was achieved by auditing potential patient charts, which allowed me to get medical history on patients interested in participating in ongoing studies. Permission from the patient was first obtained and then chart was audited if applicable. If a patient showed interest in a study but did not have an established chart, then contact information was retrieved and the patient would be phoned. I phoned potential subjects and explained protocol, duration of study, known side effects, description of study therapy, and timeline of study procedures and visits. I reminded potential study participants that trial participation is completely voluntary. If the patient was interested and had an established medical chart at UNTHSC, then I would audit the chart and phone the patient for any subsequent/additional information, and review the inclusion/exclusion criteria of study. If the patient did not have an established chart, I collected medical history over the phone and then reviewed inclusion and exclusion criteria of study with the patient to determine eligibility. If the patient met all inclusionary criteria, I would then review enrollment-screening visit as per protocol and schedule date and time to screen the patient into study with coordinator and principal investigator. I would inform the patient to bring all current medications to screen visit and to fast for fasting blood draw.

Adverse Event (AE) and Serious Adverse Event (SAE) Reporting

Adverse event (AE) reporting is required to be documented in source binder and is defined as any condition unfavorable or unexpected that occurs to subject in study after informed consent is obtained. After informed consent is obtained, pre-existing conditions are documented in medical history and any worsening of pre-existing conditions can be reported as an AE or possible SAE. An AE does not necessarily have a causal relationship with the study treatment/therapy, but must be documented in source binder and case report form.

Serious Adverse Event (SAE) reporting must be documented and submitted to the IRB, sponsor, and FDA. UNTHSC's IRB has a serious event form for occurrences of SAEs onsite and a form for occurrences of SAEs at other sites. Throughout various studies, I documented submissions of SAEs that occurred at other sites and onsite. IRB allows 10 working days to document and submit offsite SAEs. An onsite SAE that is possibly, probably, or definitely related to study drug must be submitted to the IRB within 24 hours as a brief email report specifying the principal investigator's opinion of causality and then submitted on paper form with 10 days to IRB. An onsite SAE with causality not related to study therapy is submitted to IRB on paper form within 10 days. The sponsor company of a study requires all SAE submissions reported within 24 hours to the sponsor site. An SAE is an adverse drug event that results in: death, life-

threatening situation, disability, prolonged hospitalization, congenital anomaly/birth defect, and/or important medical event. The investigator assigns causality of the relationship between study drug and event. If the event has been reported before, previous submissions of the events are recorded. The consent can be amended as a result of SAE reporting due to the frequency of a particular event and the absence of that particular event from the consent form as a potential risk. I participated in the amendment process of adding additional risks to the consents of studies: Centocor C0524T02, Merck 066, and Merck 076.

APPENDIX A

OPEN STUDY SPREADSHEET

Open Studies

Name of Study & # of Patients	Inclusion	Exclusion	Contact Info.
Merck 076: A26-Week, Randomized, Placebo-and Active-Comparator-Controlled, Parallel-Group, Double-Blind, 2-Part Study to Assess the Safety and Efficacy of Etoricoxib 30mg vs. Celecoxib 200mg in Patients With Osteoarthritis (Study 1) - 10 Patients NOTE: Enrollment active: Randomized 1 subject. Ad to come out July 7. These OA studies move quickly. By the time IRB met, contract signed and supplies received, people on vacation..... we are behind. Worldwide enrollment may be met in the next 2 weeks.	*see attachment*	*see attachment*	**Merck & Co., Inc. , One Merck Drive, P.O. Box 100, Whitehouse Station, NJ, 08889-0100, U.S.A.**
Centocor C0524T02: A Randomized, Double-blind, Dose-ranging Trial of CNTO 148 Subcutaneous Injection Compared with Placebo in Subjects with Active Rheumatoid Arthritis Despite Treatment with Methotrexate - 6 Patients NOTE: Enrollment Active. 3 randomized and and a 4th to be randomized July 6. Two more subjects scheduled for screening week of July 5th. Complex trial	*see attachment*	*see attachment*	**Centocor, Inc., 200 Great Valley Parkway, Malvern, PA, 19355**
Pfizer (Bextra) A3471018: Clinical Protocol For a Multicenter, Double-blind, Randomized, Placebo Controlled, Comparison of the Efficacy and Safety of Bextra (valdecoxib) 10mg Once Daily and Naproxen 500mg Twice Daily in Treating the Signs and Symptoms of Rheumatoid Arthritis (RA) in a Severe RA population - 15 Patients Enrollment Active: Difficult to find subjects. Have Randomized 4 subjects. 2 completed and 2 early termination	*see attachment*	*see attachment*	**Valerie Marquino, Senior Clinical Study Manager, 235 East 42nd Street, New York, NY, 10017, (212)733-4483**

Genentech ACT2847g: A Randomized, Placebo-Controlled, Multicenter, Blinded Phase I/II Study of the Safety of Escalating Doses of PRO70769(rhuMAb 2H7) in subjects with Moderate to Severe Rheumatoid Arthritis receiving stable doses of Concomitant methotrexate 15 - 20 Patients Study has not begun at our site. Site initiation July 8th. Complex trial	*see attachment*	*see attachment*	Genentech, Inc., 1 DNA Way, South San Francisco, CA, 94080-4990
Novartis CZOL446H2315: A Multicenter, randomized, double-blind, double-dummy study to determine the rapidity of onset of zoledronic acid compared to alendronate in post-menopausal women with moderate/severe osteopenia or osteroporosis - 8 Patients NOTE: This study may not happen. Novartis and the IRB have been going back and forth on the exculpatory language in the informed consent.	*see attachment*	*see attachment*	Keri Sieh, Lead Clinical Research Associate, 6424 Sprucefield Drive, O'Fallon, MO, 63366, (636)-272-3556
Tap (Gout) Extension C02-021: A Phase III, Open-Label, Randomized, Allopurinol-Controlled Study to Assess the Long-Term Safety of Oral Febuxostat in Subjects with Gout - 3 enrolled into extension NOTE: Enrollment is closed	*see attachment*	*see attachment*	Nancy Joseph-Ridge, MD, Therapeutic Area Head, Internal Medicine/Rheumatology, 675 N. Field Drive, Lake Forest, IL, 60045, (847) 582-5489
Astra Zeneca4522IL/0034: An Open-label, Multinational, Multicentre, Extension Trial to Assess the Long-term Safety and Efficacy of ZD4522 in Subjects in the ZD4522 Clinical Trial Program - 3 Patients NOTE: Only one subject is active. Enrollment closed. Tenatively study is to complete December of 2004	*see attachment*	*see attachment*	James Blasetto MD, MPH, FACC, Astra Zeneca, 1800 Concord Pike, P.O. Box 15437, Wilmington, DE, 19850-5437, (302) 885-1947

Aventis HMR4003B/4027: A Randomized Multicenter, Parallel-Group Study to Determine if knowledge of Baseline Vertebral Fracture Prevalence(as determined by Hologic IVA) and Bone Turnover marker levels improves persistence with Actonel 5 mg Daily Therapy in Subjects receiving Chronic Glucocorticoid Therapy - 10 Patients Enrollment closed. Randomized 10 subjects	*see attachment*	*see attachment*	Robert Kane, MS, MBA, Senior Manager, Clinical Operations, (908) 243-6585
Merck 066: A Randomized, Double-Blind, Active-Comparator-Controlled, Parallel-Group Study to Evaluate the Safety of Etoricoxib in Patients With Osteoarthritis or Rheumatoid Arthritis - 25 Patients 20 subjects were screened and 19 randomized. Enrollment was closed, but then reopened by Merck. Dr. Rubin chose not to open up enrollment at our site again.	*see attachment*	*see attachment*	Merck & Co., Inc. , One Merck Drive, P.O. Box 100, Whitehouse Station, NJ, 08889-0100, U.S.A.

APPENDIX B

NOTE TO FILE

TO: NOTE TO FILE

FROM: CYNTHIA JIMENEZ-WILLIAMS, R.N., B.S.N.
CLINICAL TRIALS COORDINATOR

DATE: October 15, 2004

RE: LOCATION OF CORRESPONDENCE;
QUINTILES/CENTOCOR C0524T02

CORRESPONDENCE IS LOCATED IN BINDER **2** AND **2A**

APPENDIX C

ADVERSE EVENT LOG
MERCK 076

-Adverse Event log: ***Merck Study 076***

Date of Cover Ltr.	Mfr#	Name of Event	Initial or Follow-up
04-09-04	WAES0403SGP00005	Gastritis & Anemia	Initial
04-14-04	WAES0403DEU00181	Cystitis hemorrhagic	Follow-up (1)
04-06-04	WAES0403DEU00181	Cystitis hemorrhagic	Initial
04-09-04	WAES0403DEU00183	Thrombocythaemia & polycythaemia vera	Follow-up (1)
04-05-04	WAES0403DEU00183	Leukemia	Initial
04-09-04	WAES0403COL00038	Blood Creatinine Increase	Follow-up (2)
04-07-04	WAES0311GBR00031	Loss of Consciousness	Follow-up (7)
04-05-04	WAES0403DEU00152	Thrombocytopenia	Initial
04-05-04	WAES0403COL00038	Blood Creatinine Increase	Follow-up (1)
04-07-04	WAES0403BRA00069	Cellulitis	Follow-up (1)
04-05-04	WAES0403BRA00069	Cellulitis	Initial
04-02-04	WAES0312USA50124	Dyspnea	Follow-up (1)
04-02-04	WAES0311CRI00004	Gastritis, duodenitis, reflux esophagitis	Follow-up (4)
04-02-04	WAES0403GBR00258	Left Ventricular Failure	Initial
04-20-04	WAES0403USA50194	Acute Renal Failure & Respiratory Failure	Follow-up (1)
04-16-04	WAES0404GBR00076	Anemia	Initial
04-19-04	WAES0403GBR00258	Ventricular dysfunction & Congestive Cardiac failure	Follow-up (1)
04-19-04	WAES0404USA00864	Atrial Fibrillation	Initial
04-21-04	WAES0310NOR00004	Anemia	Follow-up (1)
04-22-04	WAES0403SWE00020	Epistaxis	Follow-up (1)
04-22-04	WAES0404USA00864	Atrial Fibrillation	Follow-up (1)
04-22-04	WAES0404GBR00126	Rectal Hemmorhage	Initial
04-23-04	WAES0403COL00038	Nephropathy toxic	Follow-up (3)

04-23-04	WAES0312GBR00150	Renal Impairment & Diarrhea	Follow-up (4)
04-30-04	WAES0403USA50194	Acute Renal Failure, Hyperkalaemia, & Respiratory failure	Follow-up (2)
05-03-04	WAES0403SGP00005	Gastritis & Anemia	Follow-up (1)
05-03-04	WAES0403DEU00152	Thrombocytopenia	Follow-up (1)
05-03-04	WAES0404USA50408	Anemia	Initial
05-07-04	WAES0403DEU00183	Thrombocythemia & Polycythemia vera	Follow-up (2)
05-11-04	WAES0310USA50186	Gastroesophageal reflux disease	Initial
5-14-04	WAES0404GBR00076	Anemia	Follow-up (1)
5-14-04	WAES0404USA50408	Anemia	Follow-up (1)
5-18-04	WAES0403SGP00005	Gastritis & Anemia	Follow-up (2)
5-20-04	WAES0310AUS00069	Deep Vein Thrombosis	Follow-up (6)
5-24-04	WAES0405GBR00069	Melena	Initial
5-24-04	WAES0405SWE00007	Gastroenteritis	Initial
5-24-04	WAES0405USA50135	Anemia	Initial
5-26-04	WAES0312GBR00150	Renal Impairment &Diarrhea	Follow-up (5)
5-26-04	WAES0404GBR00076	Anemia	Follow-up (2)
5-28-04	WAES0311GBR00031	Loss of Consciousness	Follow-up (8)
5-28-04	WAES0403SGP00005	Gastritis & Anemia	Follow-up (3)
6-3-04	WAES0311BRA00012	Gastroenteritis	Follow-up (1)
6-1-04	WAES0310AUS00069	Deep Vein Thrombosis	Follow-up (7)
6-1-04	WAES0405GBR00069	Melena, Hiatus hernia, & Esophagitis	Follow-up (1)
6-4-04	WAES0405SWE00007	Gastroenteritis	Follow-up (1)
6-7-04	WAES0405BRA00066	Intestinal hemorrhage	Initial
6-14-04	WAES0406USA50121	Supraventicular tachycardia	Initial

6-14-04	WAES0405GBR00170	Blood Test Abnormal	Initial
6-14-04	WAES0404GBR00076	Anemia	Follow-up (3)
6-18-04	WAES0311GBR00031	Loss of Consciousness	Follow-up (9)
6-21-04	WAES0406USA50148	Gastroesophageal Reflux Disease	Initial
6-22-04	WAES0405GBR00170	Blood Test Abnormal	Follow-up (1)
6-22-04	WAES0310AUS00069	Deep Vein Thrombosis	Follow-up (7)
6-25-04	WAES0312HKG00009	Hemorrhoidal Hemorrhage & Diarrhea	Initial
6-25-04	WAES0405GBR00034	Abdominal Pain & Pancreatitis	Initial
6-24-04	WAES0406VEN00002	Chest Discomfort	Initial
6-30-04	WAES0312HKG00009	Hemorrhoidal Hemorrhage & Diarrhea	Follow-up (1)
7-1-04	WAES0406VEN00002	Chest Discomfort & Hypertensive Crisis	Follow-up (1)
7-6-04	WAES0405GBR00170	Blood Urea Increased & Blood Creatinine Increased	Follow-up (2)
6-28-04	WAES0406USA50134	Dehydration, Hematochezia, Gastroenteritis	Initial
6-28-04	WAES0406FRA00083	Dyspnea & Hypoxia	Initial
6-28-04	WAES0406USA50121	Supraventricular Tachycardia	Follow-up (1)
6-28-04	WAES0403DEU00181	Cystitis Hemorrhage	Follow-up (2)
7-7-04	WAES0311CRI00004	Gastritis, Duodenitis, Reflux Esophagitis	Follow-up (5)
7-12-04	WAES0312HKG00009	Hemorrhoidal Hemorrhage & Diarrhea	Follow-up (2)
7-12-04	WAES0405GBR00170	Blood Urea Increased & Blood Creatinine Increased	Follow-up (3)
7-12-04	WAES0407GBR00001	Anemia	Initial
7-15-04	WAES0403USA50194	Acute Renal Failure, Hyperkalemia, & Respiratory Failure	Follow-up (3)
7-16-04	WAES0407GBR00090	Atrial Fibrillation	Initial
7-16-04	WAES0407GBR00001	Lymphoma	Follow-up (1)
7-19-04	WAES0407CHN00005	Asthma & Lung Infection	Initial
7-20-04	WAES0312GBR00150	Renal Insufficiency &	Follow-up

		Diarrhea	(6)
7-20-04	WAES0406FRA00083	Dyspnea & Hypoxia	Follow-up (1)
7-21-04	WAES0311CRI00004	Gastritis, Duodenitis, Reflux Esophagitis	Follow-up (6)
7-21-04	WAES0308USA50114	Hepatitis	Follow-up (4)
7-28-04	WAES0406FRA00083	Dyspnea, Hypoxia, Wrist Fracture	Follow-up (2)
7-29-04	WAES0401AUS00077	Non-cardiac Chest Pain	Follow-up (3)
7-30-04	WAES0407USA50136	Anemia & Syncope	Initial / Follow-up (1)
8-2-04	WAES0407FRA00017	Pulmonary Edema	Initial
8-6-04	WAES0311GBR00031	Loss of Consciousness	Follow-up (10)
8-6-04	WAES0407BRA00076	Hypertensive Crisis	Initial
8-9-04	WAES0407USA50136	Anemia & Syncope	Follow-up (2)
8-9-04	WAES0406FRA00083	Dyspnea, Hypoxia, & Wrist Fracture	Follow-up (3)
8-9-04	WAES0407CHN00005	Asthma & Lung Infection	Follow-up (1)
8-9-04	WAES0405GBR00034	Abdominal Pain & Pancreatitis	Follow-up (1)
8-9-04	WAES0407FRA00017	Congestive Cardiac Failure	Follow-up (1)
8-11-04	WAES0402COL00034	Hypertensive Crisis	Follow-up (1)
8-11-04	WAES0302USA50106	Cardiac Failure Congestive	Follow-up (4)
8-13-04	WAES0212USA50128	Non-Cardiac Chest Pain	Follow-up (5)
8-13-04	WAES0407BRA00076	Hypertensive Crisis	Follow-up (1)
8-13-04	WAES0406USA50148	Gastroesphageal Reflux Disease	Follow-up (1)
8-17-04	WAES0311CRI00004	Gastritis, Duodenitis, & Reflux Esophagitis	Follow-up (7)
8-20-04	WAES0408HKG00006	Confusional State & Hyponatremia	Initial
8-20-04	WAES0404USA00864	Atrial Fibrillation	Follow-up

			(2)
8-23-04	WAES0408GBR00107	Right Ventricular Failure	Initial
8-23-04	WAES0408USA50133	Dyspnea	Initial
8-23-04	WAES0408HKG00006	Confusional State & Hyponatremia	Follow-up (1)
8-30-04	WAES0311CRI00004	Gastritis, Duodenitis, & Reflux Esophagitis	Follow-up (8)
8-30-04	WAES0408CHN00016	Reflux Esophagitis	Initial
9-1-04	WAES0403SWE00020	Epistaxis	Follow-up (2)
9-7-04	WAES0408USA50133	Cardiac Failure Congestive & Atrioventricular Block Complete	Follow-up (1)
9-9-04	WAES0311GBR00031	Loss of Consciousness	Follow-up (11)
9-13-04	WAES0407GBR00090	Atrial Fibrillation & Atrial Fibrillation	Follow-up (2)
9-13-04	WAES0408GBR00107	Cardiac Failure Congestive	Follow-up (1)
9-13-04	WAES0408HKG00006	Delirium & Hyponatremia	Follow-up (2)
9-14-04	WAES0409CAN00017	Pancreatitis Acute	Initial
9-14-04	WAES0409CHL00004	Hypertensive Crisis	Initial
9-17-04	WAES0308USA50170	Non-Cardiac Chest Pain	Follow-up (1)
9-20-04	WAES0405GBR00034	Abdominal Pain & Pancreatitis	Follow-up (2)
9-20-04	WAES0409VEN00001	Atrial Fibrillation	Initial
9-20-04	WAES0212USA50108	Cardiac Failure Congestive	Follow-up (5)
9-21-04	WAES0409USA50134	Ectopia Cordis (cardiac ectopy)	Initial
9-22-04	WAES0304USA50026	Anemia	Follow-up (2)
9-22-04	WAES0407GBR00090	Atrial Fibrillation & Atrial Fibrillation	Follow-up (3)
9-22-04	WAES0405GBR00034	Abdominal Pain & Pancreatitis	Follow-up (3)
9-23-04	WAES0409CAN00017	Pancreatitis Acute	Follow-up (1)
9-24-04	WAES0403USA50104	Enterocutaneous Fistula	Follow-up (1)
9-28-04	WAES0403USA50104	Enterocutaneous Fistula	Follow-up

			(2)
9-28-04	WAES0311USA50111	Atrial Fibrillation	Follow-up (2)
9-28-04	WAES0409SWE00022	Atrial Fibrillation	Initial
9-30-04	WAES0302USA50126	Lower Gastrointestinal Hemorrhage	Follow-up (4)
10-1-04	WAES0407CHN00005	Asthma & Lung Infection	Follow-up (2)
10-4-04	WAES0308USA50170	Non-Cardiac Chest Pain	Follow-up (2)
10-5-04	WAES0409PHL00011	Dizziness, Blood Pressure increased, Nausea, Hypoaesthesia, Pain, & Vomiting	Initial
10-5-04	WAES0312GBR00150	Renal Impairment & Diarrhea	Follow-up (7)
10-6-04	WAES0409PHL00011	Dizziness, Blood Pressure increased, Nausea, Hypoaesthesia, Pain, & Vomiting	Follow-up (1)
10-7-04	WAES0409VEN00001	Atrial Fibrillation	Follow-up (1)
10-7-04	WAES0409SWE00022	Atrial Fibrillation	Follow-up (1)
10-8-04	WAES0409ITA00034	Hypertensive Crisis, Hypertensive Crisis & Overdose	Initial
10-11-04	WAES0212USA50101	Cardiac Failure Congestive & Pleural Effusion	Follow-up (8)
10-12-04	WAES0409USA50123	Non-Cardiac Chest Pain	Initial to UNTHSC/ follow-up (1)
10-12-04	WAES0409PHL00011	Dizziness, Blood Pressure increased, Nausea, Hypoaesthesia, Pain, & Vomiting	Follow-up (2)
10-13-04	WAES0407GBR00090	Atrial Fibrillation & Atrial Fibrillation	Follow-up (4)
10-14-04	WAES0409ITA00034	Hypertensive Crisis, Hypertensive Crisis, & overdose	Follow-up (1)
10-15-04	WAES0202USA02213	Cerebrovascular Accident,	Initial

		Blood Pressure Increased, & Blood Urea Increased	
10-19-04	WAES0309USA50132	Hyponatremia	Follow-up (2)
10-19-04	WAES0410USA50136	Chest Pain	Initial
10-19-04	WAES0405AUT00006	Toe Deformity, ingrowing nail, skin ulcer, & wound dehiscence	Initial
10-21-04	WAES0409ITA00034	Hypertensive crisis, Hypertensive crisis, & overdose	Follow-up (2)
10-25-04	WAES0405AUT00006	Toe Deformity, ingrowing nail, skin ulcer, & wound dehiscence	Follow-up (1)
10-25-04	WAES0312GBR00150	Renal Impairment & Diarrhea	Follow-up (8)
10-26-04	WAES0309USA50132	Hyponatremia	Follow-up (3)
11-8-04	WAES0404USA50408	Anemia	Follow-up (2)
11-8-04	WAES0409SWE00022	Atrial Fibrillation	Follow-up (2)
11-9-04	WAES0411USA50104	Heart Rate Irregular	Initial
11-11-04	WAES0411ZAF00011	Iron Deficiency Anemia	Initial
11-12-04	WAES0411DNK00007	Alanine Aminotransferase Increased, Aspartate Aminotransferase increased, & overdose	Initial
11-16-04	WAES0411ZAF00011	Iron Deficiency Anemia	Follow-up (1)
11-16-04	WAES0403SWE00020	Epistaxis	Follow-up (3)
11-17-04	WAES0409CAN00017	Pancreatitis Acute	Follow-up (2)
11-18-04	WAES0312BRA00033	Iron Deficiency Anemia	Follow-up (3)
11-19-04	WAES0411USA50104	Atrial Flutter	Follow-up (1)
11-19-04	WAES0409USA50134	Cardiac Disorder	Follow-up (1)
11-23-04	WAES0411DEU00253	Esophagitis	Initial
11-24-04	WAES0403SWE00020	Epistaxis	Follow-up (4)

11-24-04	WAES0411DEU00253	Reflux Esophagitis	Follow-up (1)
11-29-04	WAES0401USA50180	Esophagitis	Follow-up (1)
11-30-04	WAES0411BRA00156	Hypertensive Crisis	Initial
11-30-04	WAES0411USA03294	Raynaud's Phenomenon	Initial
12-1-04	WAES0411DEU00253	Reflux Esophagitis	Follow-up (2)
12-3-04	WAES0411GBR00247	Syncope	Initial
12-3-04	WAES0411USA03928	Atrial Fibrillation	Initial
12-7-04	WAES0411USA03928	Atrial Fibrillation	Follow-up (1)
12-8-04	WAES0411BRA00156	Blood Pressure Increased	Follow-up (1)
12-8-04	WAES0411DNK00007	Alanine Aminotransferase Increased, Aspartate Aminotransferase increased, & overdose	Follow-up (1)
12-8-04	WAES0310DEU00160	Herpes Zoster & Syncope	Initial
12-9-04	WAES0310DEU00160	Herpes Zoster & Syncope	Follow-up (1)
12-10-04	WAES0307USA50104	Palpitations	Follow-up (1)
12-13-04	WAES0412BRA00015	Atrial Fibrillation & Cardiac Failure Congestive	Initial
12-13-04	WAES0411USA03294	Raynaud's Phenomenon	Follow-up (1)
12-13-04	WAES0412BRA00009	Hypertensive Crisis	Initial
12-14-04	WAES0410USA50136	Non-Cardiac Chest	Follow-up (1)
12-14-04	WAES0412USA50106	Hypotension	Initial
12-20-04	WAES0412USA50106	Hypotension	Follow-up (1)
12-20-04	WAES0308USA50159	Colitis Ulcerative	Follow-up (2)
12-21-04	WAES0411GBR00247	Syncope	Follow-up (1)
12-22-04	WAES0310DEU00160	Herpes Zoster & Syncope	Follow-up (2)
12-28-04	WAES0412POL00006	Gastritis	Initial
12-28-04	WAES0412COL00033	Blood Creatinine Increased	Initial
12-29-04	WAES0412COL00033	Blood Creatinine Increased	Follow-up (1)

12-29-04	WAES0412CZE00003	Dyspnea	Initial
1-3-05	WAES0407NOR00019	Arthritis Bacterial & Gastroenteritis	Initial
1-3-05	WAES0412CZE00003	Mitral Valve Incompetence, Coronary Artery Artherosclerosis, Diverticulum, Retroperitoneal hemorrhage, and Arterial Injury	Follow-up (1)
1-4-05	WAES0412USA50161	Dyspnea	Initial
1-4-05	WAES0412POL00006	Gastritis	Follow-up (1)
1-4-05	WAES0407NOR00019	Arthritis Bacterial & Gastroenteritis	Follow-up (1)
1-4-05	WAES0412COL00033	Nephropathy toxic	Follow-up (2)
1-7-05	WAES0412USA03183	Ischemic attack	Initial
1-10-05	WAES0308USA50159	Colitis Ulcerative	Follow-up (3)
1-10-05	WAES0412USA50161	Dyspnea	Follow-up (1)
1-10-05	WAES0403USA50104	Enterocutaneous Fistula	Follow-up (3)

APPENDIX D

NOVARTIS OSTEOPOROSIS ADVERTISEMENT

Osteoporosis Research Study

Participants must be:

Post-Menopausal females

Between 45-79 years of age

Currently **not** taking estrogen hormone therapy

You may qualify for a medical research study to test an investigational medication to treat Osteoporosis. Benefits of being in the study include study medication, calcium supplements, study related physician visits, and lab work.

For further information, Call
(817)735-0256

APPENDIX E

NOVARTIS OSTEOPOROSIS EMAIL ADVERTISEMENT

For Campus Wide Email Ad

OSTEOPOROSIS RESEARCH STUDY VOLUNTEERS NEEDED

The Division of Rheumatology UNTHSC is looking for potential *post-menopausal* female study participants between the *ages of 45-79* who are **not** currently taking estrogen hormone therapy.

We will provide Inclusion/Exclusion criteria upon request. If you would like more information or have a patient you think might be a candidate please contact Cynthia Jimenez-Williams R.N. at (817) 735-0317, Clinical Trials Coordinator.

Raymond M. Pertusi, D.O.
Bernard R. Rubin, D.O.
Linda G. Davis, PA-C

APPENDIX F

JOURNAL OF DAILY INTERNSHIP EXPERIENCE

Internship Practicum Experience & Journal of Daily Activities
August 20, 2004 – February 11, 2004

Monday August 16-19, 2004

- Reviewed ongoing study protocols to familiarize myself, HIPPA certification, and scheduled meeting with committee members.

Friday, August 20, 2004

- Assisted coordinator with subject visits for Centocor C0524T02 study and Merck 076 study by performing vital signs (weight, pulse, respiration, blood pressure, and temperature) and patient questionnaire assembly.
- Learned and assisted coordinator with lab specimen assembly and dry ice packaging for shipment to laboratory for analysis.
- Completed serious adverse events (SAEs) from other sites and sent interoffice to IRB for acknowledgement
- Checked readiness/ audited Merck 076 Regulatory Binder for initial Monitor Visit with coordinator
    a) Reviewed all IRB Correspondence and IRB approvals
    b) Discussed 1572, financial disclosure forms, and purpose of both forms
    c) Reviewed notes to file and discussed importance/need for them
    d) Discussed site responsibility log
    e) Reviewed lab certification forms
    f) Reviewed drug (study drug) accountability logs
- Observed patient electronic data entry as Case Report Form (CRF) from source document for Centocor C0524T02 study

Monday, August 23, 2004

- Assisted in Aventis study subject visit by performing vital signs, helping with compliance questionnaire
- Observed and learned how to operate machinery used to count the number of times bottle of study drug was opened
- Packaged lab specimens and shipment assembly with dry ice
- Input SAEs into Merck 076 Microsoft Word computer log spreadsheet created by me
- Greeted monitor for Merck 076 study, guided her to the appropriate room, and assisted her when needed
- Documentation of SAEs for Novartis & Astrazeneca studies
- Created note to file for Merck 076 & 066 and filed appropriately. (Note to File pertained to location of IRB submitted SAE reports)

- Reviewed Excel Spreedsheet for subject visit window calculations for Merck study 076 and discussed the importance of maintaining protocol window requirements
- Called CRO (Clinical Research Organization) monitor for Novartis CZOL446H2315 study regarding acceptability of Estroven as a concomitant medication. Approval received & conversation documented in telephone log of Novartis Regulatory Binder.
- Subject visit reminder call made to subject KKD of Centocor C0524T02
    a) reminded subject time of visit and which concomitant medication to avoid the day of visit
    b) reminded subject to fast for fasting lab blood draw
- Checked readiness/ audited Astrazeneca Regulatory Binder for monitor visit with coordinator. (Completely checked FDA documentation of 1572 and CV's to insure correct dates on each.)

Tuesday, August 24, 2004

- Participated in 7:20am Centocor C0524T02 subject visit and lab specimen packaging and dry ice shipment assembly
- Assisted with Productivity and Patient Visit Improvement questionnaire for Dept. of Internal Medicine, Division of Rheumatology
- Observed and assisted in initiation account assembly (via computer input) for billing for Novartis CZOL446H2315 study at on-campus IRB office
- Documentation of SAEs from other sites and filing and copying of IRB acknowledged SAEs
- Consultation with Geriatrician by study coordinator and myself to inform of possible patient participation in Osteoporosis study
    a) Discussed study protocol, study drug, inclusion & exclusion
    b) Audited possible study subject chart with coordinator
- Subject visit for Novartis CZOL446H2315 pre-screening
    a) Met potential subject and gave study information, patient interviewing of medical hx, and gave study article on study drug and informed consent for subject to review prior to screening visit.
    b) Scheduled screening visit
    c) Waiver submission to Novartis CRO monitor for newly expired DEXA scan and past medical hx of esophageal dilation
- Assembly and Preparation for tomorrow subject visit for Merck 076, called subject and reminded of visit time and medication to avoid prior to visit.

Wednesday, August 25, 2004

- Documentation of SAEs from other sites for Merck 076 & 066
- Assisted in subject visit for Merck 076
    a) performed vital signs

b) calculation of next visit & electronic entry for visit window
c) drug accountability: counted returned bottles of study drug and dispensed new bottles of study drug

- Library: Online search & library research for research proposal on Osteoporosis study with Aventis Pharmaceuticals

Thursday, August 26, 2004

- Subject visit room readiness by assembly of source documents and preparing lab draw tubes and lab identification stickers
- Subject visit for Merck 066
    a) performed vital signs
    b) witnessed revised informed consent signing
    c) participation in review of cholesterol lab results and explanation of normal levels and abnormal levels
- Utilization of IVRS system for study drug allocation/ dispensing for Merck 066 and review of appropriate study drug medication dosing
- Lab assembly of specimens and delivered lab package to Quest Diagnostics for analysis
- Received fax information regarding waiver exclusion criteria for Novartis study denying subject inclusion into study due to past esophageal stricture history. Filing of fax in correspondence for Novartis study.

Friday, August 27, 2004

- Periodic project review for Gout study: collection of necessary of signatures and routed to IRB office
- Created advertisement for Novartis Osteoporosis study with coordinator
- Created advertisement for campus-wide email for Novartis Osteoporosis study
- Submitted advertisements to Pharmaceutical company (Novartis) for approval
- Reviewed appropriate IRB/UNTHSC language for advertisements
- Observed, listened, and learned from coordinator how to perform phone screenings of potential subjects for the Novartis and Lilly Osteoporosis studies
- Documentation of Centocor & Merck 076 SAE reports
- Filled-out patient/subject prescription refill request form and discussed with nurse.

Monday, August 30, 2004

- Library: research & reading for research proposal (7-9am)
- Copying of source documents for Centocor study and filing in appropriate binder sections

- Room readiness for Merck 066 subject visit by assembly of lab collection tubes, identification stickers, and source documents.
- Merck 066 subject visit
    a) performed vital signs
    b) witness to informed consent signing
    c) conducted IVRS system study drug allocation/dispensing
    d) drug accountability of returned study drug
- Assembly of lab specimens: centrifuge lab samples, collect serum, package, and delivered to Quest Diagnostic for analysis
- Phoned Centocor subjects for visit reminder and reminded them of visit time and which medication to avoid prior to visit
- SAEs: copied and delivered to IRB office for acknowledgement
- Faxed IRB acknowledgement of administrative amendment of protocol Merck 076 to Merck representative (correspondence between sponsor and site) then filed fax and confirmation in IRB correspondence section of regulatory binder

Tuesday, August 31, 2004

- Centocor subject visit (5 subjects, 7am-11am): performed vital signs, assembled source documents for patients, and faxed study visit correspondence to pharmacist for study therapy preparation
- Lab specimen packaging and dry ice shipment to off-site laboratories
- Documentation of SAEs for Merck 066 & 076
- Subject visit readiness for Merck 066
    a) called subject to remind of visit time and medication to avoid prior to visit
    b) assembled lab collection tube/kit for visit
    c) assembled study subject binder
- Copied and delivered SAEs to IRB office for acknowledgement
- Delivered confidential study information from Centocor subject visit to Pharmacist on-site

Wednesday, September 1, 2004

- Subject visit for Merck 066 study (9-12pm)
    a) performed vital signs
    b) witness to informed consent
    c) conducted IVRS system study allocation/dispensing of study drug
    d) study drug accountability: re-dispensing and dispensing of study drug
- Lab specimen assembly (centrifuge samples & collect serum), packaging, and delivered to Quest Diagnostics
- Updated Adverse Event log for Merck 076 on Microsoft Word spreadsheet

- Organization of Merck product supplies in the storage room and inventory on lab kits for expiration dates of all lab supplies
- Scheduled screen visit for first Novartis CZOL446H2315 study visit

Thursday, September 2, 2004

- *Subject visit for Tap/Gout study (7am)* : performed vital signs, assembled lab specimen by centrifuging, collecting, and packaging serum and preparation of hematology slides
- Thermometer setting for Lilly study drug supplies storage
- SAE documentation for Merck 066 & 076 and Novartis study
- Library: Research on proposal topic

Friday, September 3, 2004

- Library: Research on proposal topic

Monday, September 6, 2004

- Labor Day Holiday

Tuesday, September 7, 2004

- Organized and assembled source document binders for Centocor study visit extension post wk. 20
- SAE documentation, copying, and filing
- Astrazeneca SAE update in regulatory binder in preparation for monitor visit
- Preparation for Centocor monitor visit
- Drug supply accountability check/inventory and discard of expired supplies
- Delivery of documents to IRB accounting office
- SAE documentation for Centocor study
- Updated adverse event log spreadsheet for Merck 076

Wednesday, September 8, 2004

- Filing lab reports for Merck 066 in subject charts
- SAE documentation for Merck 066 & 076
- SAE delivery and copying to IRB for acknowledgement
- Monitor Readiness for Centocor study: assembled study binders and appropriate documents
- Research: library research on proposal

Thursday, September 9, 2004

- Performed product accountability for received shipment of Lilly study materials
- Organization of Lilly study binders, case report forms (CRFs), and source documents
- Greeted monitor for Centocor study and assisted monitor when needed
- Organization of office study project binders and study supplies
- Filing of returned SAEs from on-site IRB for Merck 066 & 076 and Novartis studies
- Filing and shredding of old study materials

Friday, September 10, 2004

- Centocor subject visit: performed vital signs, lab specimen assembly and dry ice shipment
- Discussion (coordinator & I) with principal investigator, PI, about investigational drug for Lilly study and which FDA approved drug it is comparable with
- Observed and participated in amendment to agreement between UNTHSC, Principal Investigator, and Radiology Associates contract for Lilly study
- Delivery of contract to Radiology Associates
- Library: Research on proposal and meeting with major professor

Monday, September 13, 2004

- Rheumatology Meeting (8:30am)
- Novartis study subject visit: performed vital signs, observed informed consent and physical examination by Rheumatologist, assisted with source document information retrieval, performed urine dipstick analysis
- Lab specimen: hematology slides and centrifuge and collected serum of samples and packaged for shipment delivery (all ambient).
- Research – library research on research proposal

Tuesday, September 14, 2004

- Subject visit for Centocor (5 subjects) 7am-11am: performed vital signs, faxed subject visit information to pharmacist for proper assembly of study medication
- Dry ice shipment assembly and lab specimen assembly: hematology slides and centrifuge and collected serum of samples
- Subject non-serious adverse event reporting for Centocor patient 109005. Rheumatologist, principal investigator, decided to withhold study therapy due to patient upper respiratory infection.
- Filing and copying of IRB correspondence and study information for Centocor, Astrazeneca, Merck 066, and Lilly studies.

- Research: Library research on proposal topic

Wednesday, September 15, 2004

- Gout subject visit (x2): performed vital signs, performed measurements of pain due to arthritis on Gout subject questionnaire. (used ruler to measure pain assessment)
- Lab specimen packaging: Centrifuge lab specimens and collected serum
- Dry Ice packaging and shipment of lab via Fed-ex
- Reviewed Merck 076 subject visit, study medication/ therapy allocation, and subject reminder call with mentor/ study coordinator and sub-PI.
- Reviewed study reminder call procedure for Centocor Patients:
    - reviewed each patients concomitant medications and noted which medications patient should not take day of visit.
    - Reviewed/noted reminders to pharmacist, nurse, physician assistant, physician, and I.V. infusion nurse to be sent via email and/or call to inform/remind of Centocor subject visits.

Thursday, September 16, 2004

- Faxed Centocor subject patient enrollment log to Centocor monitor
- Research in library on proposal

Friday, September 17, 2004

- Received Genentech study contract from Wendy at on-campus IRB office and marked contract for appropriate signatures.
- Research in library on proposal

Monday, September 20, 2004

- Correspondence with Deb Ceron at IRB office about Novartis advertisement: changes made to advertisement of study, therefore, I called to put a hold on advertisement release until approval received from Novartis on new changes
- Documentation of SAEs for Merck 066 & 076
- Filing lab reports in patient charts for Merck and Centocor
- Genentech contract signature retrieval and delivery (hand-delivered) to IRB office.
- Research Proposal corrections received from major professor: correspondence with major professor and began corrections

Tuesday, September 21, 2004

- Library: research on research proposal
- Called Merck 076 subject to remind of visit
- Reminded PI, sub-PI, nurse about subject visit via email and/or phone call

- Readiness for Merck 076 patient visit and reviewed schedule study protocol for visit
- Copy, filed, and delivered signed SAEs to IRB office

Wednesday, September 22, 2004

- Room readiness for subject Merck 076 visit
- Conducted subject visit : Merck 076
    - Performed vital sign
    - Dispensed study medication
    - Drug accountability: counted returned study medication and documented
    - Performed blood draw lab collection with Michelle, RN
    - Observed physical examination by PI
- Lab specimen: centrifuged blood samples and collected serum, prepared hematology slides, packaged lab and delivered to Quest Diagnostics
- Correspondence with Rheumatologist and Physician Assistant about Centocor subject 109003 concomitant methotrexate medication dosage increase.
- Called Centocor subject 109003 and informed of the decision made by Rheumatologist

Thursday, September 23, 2004

- Reseach: research on proposal and copy of final draft given to committee member for review and major professor
- Documentation of SAEs for Merck 066 & 076, and Pfizer
- Faxd enrollment logs for Pfizer and Centocor to monitors
- Assisted and created spreadsheet for Susan Bitner for DXA scan Amgen study

Friday, September 24, 2004

- Research – library

Monday, September 27, 2004

- Assembly of faxed lab reports for Centocor and Merck 076 documents
- Subject visit reminder calls to Centocor patients and assembly of appropriate forms in subject binders (source documents)
- Sent reminder emails and phone calls to PI, sub-PI, pharmacist, RN, and infusion RN to remind of Centocor subject visits.
- Documentation of SAEs for Merck and Astrazeneca
- Audited patient chart for Novartis study
- Correspondence with coordinator/mentor about Centocor subject 109003 concomitant medication increase decision and 109005 subject study continued participation in clinical trial

- Called Centocor monitor to inquire about subjects 109003 and 109005 continued participation in study as per protocol
- Telephone log documentation of correspondence between monitor at Centocor and myself on Centocor subject determination of 109003 concomitant medication increase and 109005 missed study injection on previous subject visit and if allowed continuation in study.
- Reviewed research proposal critiques with committee member, Dr. Rubin, via phone

Tuesday, September 28, 2004

- Centocor subject visit (x 4) 7am-11am: performed vital signs, faxed correspondence of subject visit to pharmacist
- Lab specimen assembly and dry ice packaging: centrifuged and collected serum
- Received subject screenin visit laboratory report on subject 051600001 ELH for Novartis CZOL446H4315 and reviewed novartis inclusion/exclusion criteria to ensure patient qualified for baseline visit (randomization).
- Review of Gout subject lab report and delivery to sub-PI
- Faxed Aventis subject enrollment log to monitor
- Signed and listed functions I perform for Centocor site signature and responsibilities log C0524T02
- Checked case report form binder for Astrazeneca subject previous visit to ensure appropriate forms available

Wednesday, September 29, 2004

- Faxed correspondence of subject 109003 start date of concomitant medication increase (MTX) to Centocor monitor
- Discussed novartis subject screening lab results with mentor and set-up randomization date for new patient with coordinator/mentor and primary investigator, Dr. Rubin
- SAE documentation, filing, and mailing interoffice to IRB for acknowledgement
- Subject visit reminder call for new novartis subject randomization visit
    - Reminded subject to be fasting and to collect 2nd void urine between 8-11am
- Email communication with Dr. Gwirtz and Dr. Rubin on final corrections for research proposal
- Readiness of study binders for Merck 076 for Monitor visit tomorrow
- Created note to file for protocol/ regulatory binders Merck 076 and Novartis to update location of safety reports

Thursday, September 30, 2004

- Discussed with Rheumatologist national media announcement of Merck pulling Vioxx off market
    - Pulled all study subject charts and made sure if on Vioxx as concomitant medication, then subjects would be instructed to stop usage and discontinue. Alternative NSAIDS were called into pharmacy and subject chart was updated with Vioxx stop date and new start date recorded for new prescribed NSAID.
- Faxed weekly correspondence of subject enrollment log to monitor at Centocor and Pfizer
- Filed returned SAEs for Pfizer study in regulatory binder
- Filed lab specimen verification forms for Centocor subjects
- Research: Final corrections on proposal

Friday, October 1, 2004

- Subject visit reminder call for Novartis baseline (randomization) visit
- Called Merck 076 subjects to inform of Vioxx
- Documentation of SAEs for Astrazeneca
- Delivered Lilly study materials to IRB office for approval
- Readiness of subject visit for Novartis baseline visit
    - Assembly of source documents and binder
    - Assembly of study lab kit
    - Checked study drug readiness

Monday, October 4, 2004

- Rheumatology Meeting 8:30-9:30 am
- Novartis subject baseline visit: performed vital signs, informed family member (husband) of progression/ status of visit
- Dry ice assembly and lab specimen packaging
- Documentation of SAEs for Merck and Astrazeneca studies
- Assemblied Centocor subject 109003 source document binder for sstudy continuation post week 20 visit.

Tuesday, October 5, 2004

- Documentation of SAEs for Merck 066 & 076
- Filing signed & updated financial disclosures for Aventis and delivery of form to IRB
- Received Investigator Brochure for Merck 066 & 076 and copied and filed in regulatory binders.

Wednesday, October 6, 2004

- Subject visit Merck 066: performed vital signs, documented and performed drug accountability, counted returned study medication,

redispensed drug and allocation of new study therapy bottles, reviewed subject previous lab report with sub-PI and subject.

- Tap/Gout monitor visit: assisted monitor when applicable
- Documentation of SAE for Merck 066 & 076
- Filing and faxing correspondence of study materials to monitors
- Began review of regulatory binder with mentor for Lilly study and fully discussed contents of regulatory binder.
    - Discussed why each section is assembled the way it is, what belongs in each section, and what each section means and must have in it for FDA, IRB, and sponsor regulations to be met.

Thursday, October 7, 2004

- Documentation of SAEs for Astrazeneca, Merck 066 & 076
- Faxed Pfizer & Centocor Subject Enrollment logs to monitors
- Assembly of regulatory binder for Lilly Generation Study
    - Reviewed each section of binder, how to assemble each section, and corresponded with on-site IRB for any missing information/submission required in binder.
    - Faxed updated CV's and licenses to monitor and any correspondence.
    - Reviewed correspondence from sponsor and at site to compare information. Filed all correspondence by chronological order
    - Updated CV's of PI and sub-PI's and licensure for participation in study
    - Reviewed & assembled contact details, study communication, and subject information sections
    - Assembly of Protocol section: checked dates of most recently submitted protocol and checked IRB approval and signatures
    - Assembly of Safety Information: copied investigator brochure from IRB and added to regulatory binder
    - Assembly of IRB section: reviewed each IRB submission; checked informed consent, protocol dates, and all other dates listed on submission for verification.
    - Assembly of Investigator Agreement section: reviewed the 1572 of PI and verified financial disclosures for PI and all sub-PI's.
    - Assembly of site staff details: checked CV for PI and all sub-PI's, checked expiration dates on all licenses
    - Reviewed & assembled Investigational product section and CRF section
    - Laboratory section assembly: checked license expiration dates on all contracts between study site and laboratories used. Checked CAP & CLIA license and accreditation expiration dates.

- Organized entire binder ensuring most recent chronological dates in front and all information present.
- Copied any missing material & called Propath laboratories for updated CAP license information and received via fax.

Friday, October 8, 2004

- Subject visit Merck 066: performed vital signs, drug accountability of returned study medication, witnessed informed consent, witnessed discussion of Vioxx between subject and sub-PI and importance of clinical trials due to recent recall of Vioxx, addressed any concerns of subject and ensured subject that study therapy currently on is not Vioxx.
- Obtained signatures from sub-PI's in Lilly study for financial disclosure forms
  - Worked with IRB (on-site) to created appropriate financial disclosure forms for sub-PI's.
- Obtained signatures for site personnel responsibility log for lilly study: required form in regulatory binder
- Documentation of SAEs for Merck 066 & 076

Monday, October 11, 2004

- Obtained signature for Astrazeneca safety report form Dr. Clearfield
- Obtained remaining sub-PI's and PI signatures for site personnel signature form for Lilly study
- Filing of lab reports for Merck 066 subject visit in patient chart
- Copied, sorted, and delivered signed SAE reports for Merck 066, 076, and Astrazeneca to on site IRB office
- Novartis subject visit: performed vital signs, dry ice shipment assembly and packaging of lab specimens
- Subject visit reminder calls for Centocor subjects: called subjects and reminded of visit time, fasting (if applicable), and which medications to avoid day of visit.
- Readiness of subject visit for Centocor C0524T02 by assembly of source document forms and lab kits

Tuesday, October 12, 2004

- Subject visits (x 6) for Centocor and Merck 076: performed vital signs, faxed correspondence of patient/subject visit to pharmacist for injection, room readiness for subjects
- Listened and gave constructive criticism to PA, Linda Davis, on journal presentation "Model for Early (RA) Rheumatoid Arthritis Clinic".
- Dry ice packaging and lab specimen shipment: hematology slides, centrifuged and collected serum from samples
- Filed returned SAEs from IRB office
- Dinner meeting with Quintiles monitor, Lisa Buffington and mentor, Cynthia.

Wednesday, October 13,2004

- Documentation of SAE Merck 066 & 076
- Reviewed protocols for lilly and novartis studies
- Telephone screening/auditing of potential subjects for novartis and lilly studies
    - Called potential subjects whom had responded to osteoporosis advertisement in paper
    - Described protocol information to potential subjects, discussed study therapy, and reviewed study visits
    - Audited patient medical history over phone or retrieved chart (if applicable) and reviewed inclusion/exclusion criteria for novartis and lilly studies to see if patient qualified for study.
- Faxed Pfizer and Centocor subject enrollment log to monitors
- Made copies of required forms from novartis regulatory binder for subject source document binder

Thursday, October 14, 2004

- Subject visit Merck 066: performed vital signs
- Lab specimen packaging
- Continued to call and screen potential novartis and/or lilly subjects over the phone: reviewed inclusion/exclusion of protocol information, described study protocols to ensure subject interest, obtained subject medical history over the phone or audited chart to see if qualify fro study, reviewed study visit schedule and procedures
- Correspondence to Lilly and Novartis monitors about subject medical history of gastric bypass and esophageal dilations and if these procedures were exclusionary criteria.
- Documentation of SAEs for Merck 066 &076
- Attended meeting with business manager in internal medicine regarding clinic room utilization for all departments in internal medicine.

Friday, October 15, 2004

- Subject visit for Centocor: lab drawn only by RN
- Lab specimen packaging and dry ice shipment assembly
- Filing and Copying for Astrazeneca, Tap, Merck, and Centocor studies and faxing correspondence to monitors.
- Telephone documentation of correspondence between Lilly monitor, Fazeli, and myself about gastric bypass surgery and esophageal dilations, and whether considered exclusionary or not.
- Correspondence, via email, with Charity Bishop at Novartis to discuss whether gastric bypass considered exclusionary.

Monday, October 18, 2004

- Novartis subject visit: performed vital signs and observed study therapy allocation.
- Dry ice assembly & lab specimen packaging
- Library: search for osteoporosis books/ resources
- Filing correspondence from sponsor and IRB for studies: Novartis and Tap/Gout
- Faxed W-9 Form to Karen Callahoun of Novartis
- Filing in regulatory binders and organization of:
  - Protocol synopsis & IRB acknowlegment of synopsis
  - CV's
  - 1572
  - Financial disclosures for Lilly, Novartis, Tap, and Merck 066 & 076 due to submission of additional sub-PI to studies.
- Teleconference for Novartis study

Tuesday, October 19, 2004

- Subject visit for Centocor study: blood drawn only by RN/coordinator
- Reviewed with mentor & assisted in assembly of IRB renewal forms for continuation of Centocor C0524T02 study IRB submission
- Reviewed medical history and inclusion/exclusion criteria for potential Lilly study subject over phone (pre-screen)
- Filing, copying, and delivery of signed SAEs to IRB
- Input of Merck 076 SAEs reports into computer log spreadsheet
- Documentation of SAEs for Merck 066 & 076

Wednesday, October 20, 2004

- Correspondence to IRB office for assembly of interoffice IRB financial disclosure forms for addition of new sub-PI to ongoing studies
- Documentation of SAEs for Merck 066 & 076
- Subject visit Merck 076: performed vital signs, drug accountability by counting returned study therapy and allocation of new study therapy
- Faxed Pfizer and Centocor enrollment log to monitors

Thursday, October 21, 2004

- Documentation of SAEs for Merck 066 & 076
- Discussed room utilization for internal medicine dept. with mentor and business manager, Chris:
  - Reorganization of consult room by addition of cabinets (2)
- Assembly of CV, 1572, IRB acknowledgment of protocol synopsis for IRB submission and Fed-ex delivery to sponsor
- Obtained signature for financial disclosure from new sub-PI

- Telephone screening calls to potential subjects for lilly and novartis studies
- Discussed appropriate procedure to follow when research subject is potentially lost/unreachable for subject follow-up:
  - Call subject 3 consecutive days
  - If no response, send certified letter with signed receipt upon delivery

Friday, October 22, 2004

- Documentation of SAEs for Merck 066 & 076
- Obtained signatures for Genenteck study 1572 and financial disclosures from PI and sub-PI's
- Assembly of Lilly source documents (x3)
- Filing investigator brochure and correspondence for lilly, merck 066 & 076.
- Assembly of investigator brochures for IRB submission
- Discussed potential novartis subject with mentor and called subject to schedule screening visit.
- Delivery of study material, signatures, and regulatory required forms to IRB office
- Mailed copy of informed consent for Novartis CZOL446H2315 study to subject scheduled for screening visit on Wednesday.

Monday, October 25, 2004

- Documentation of SAEs for Merck 066 & 076 and Centocor (30 total)
- Posted Advertisements for Osteoporosis Studies, Lilly and Novartis, throughout Internal Medicine clinic, patient rooms, and doctor dictation areas on 3rd and 4th floor of patient care center.

Tuesday, October 26, 2004

- Subject visit for Centocor C0524T02 (x4): performed vital signs and faxed subject visit week to pharmacist for study therapy preparation
- Added protective plastic cover to posted advertisements for osteoporosis studies lilly and novartis in accordance to JACHO regulations
- Dry ice assembly and lab specimen shipment and packaging
- Readiness for Aventis study close-out visit: copied & updated CV's and checked regulatory binder
- Filing correspondence for Tap & Merck 066 studies
- Faxed Pfizer enrollment log to monitor
- Observed and participated in electronic data capture for Centocor C0524T02 study subjects
- Readiness for Novartis subject screening visit on tomorrow

Wednesday October 27, 2004

- Subject visit for Novartis study: screening visit
  - Witnessed informed consent

    - Patient screen failure due to DXA numbers at hip & spine
- Subject visit for Merck 066: performed vital signs and study therapy allocation (called in subject numbers on IVRS system and received new study therapy dispersement numbers)
- Aventis monitor study close-out visit: assisted monitor when needed
- Copied, filed, and delivered signed SAE reports to IRB office
- Audited patient chart for potential novartis subject study participation
    - Phone patient and completed medical hx
    - Reviewed inclusion/exclusion criteria with patient

Thursday, October 28, 2004

- Assemblied new Genentech study shipment and lab supplies: separated and cleared-out Aventis & Pfizer study lab kit materials and broke-down kits.
- Delivery to IRB correspondence of Aventis continuing review and final report form
- Phoned potential lilly & novartis subjects to acquire medical hx and review incl./excl. criteria for studies to determine if qualify
- Filing lab reports in patient charts for merck 066

Friday, October 29, 2004

- Subject visit for Centocor: blood draw only by RN\
- Lab specimen packaging and dry ice assembly and shipment
- Financial disclosure forms: obtained signatures from new sub-PI for all study protocols that list him
- Re-order of supplies (lab kits) from Covance for novartis study visits
- Re-order of lab shippers from Quintiles for Centocor study
- Subject visit reminder call to novartis subject for Monday visit
- Called potential lilly patient to inform of exclusionary deep venous thrombosis (DVT)
- Participated in Halloween costume contest along with mentor and won Grand Prize and honorable mention for costume. (Cruella DaVille-mentor & Dalmation-me)
- Helped set-up for Halloween lunch party

Monday, November 1, 2004

- Rheumatology meeting: discussed clinic problems and study enrollment suggestions for increased enrollment in ongoing osteoporosis trials.
- Subject visit for novartis study: drug allocation of study medication, performed vital signs, dry ice assembly and lab specimen packaging
- Phoned and scheduled Novartis screening visit for new patient
- Pre-screening via phone of potential lilly and novartis subjects

- Filing of returned IRB acknowledged SAE reports in appropriate binders for Merck 066 & 076 and Centocor studies

Tuesday, November 02, 2004

- Performed Serious Adverse Event (SAE) documentation for Centocor (x2), Pfizer (x6), and Merck (x4).
- Centocor subject visit wk. 17 (blood drawn only)
- Lab Specimen Packaging and Dry Ice Assembly: centrifuge, collect serum from sample and packaged
- Phoned potential Lilly & Novartis osteoporosis study subjects: reviewed study protocols with subjects to determine interest, reviewed/performed medical history of subjects over phone (pulled patient chart if applicable), reviewed inclusion/exclusion criteria of study to determine participation status.
- Gave Susan Bitner potential names of patients she had previously DXA scanned and informed her of which study or studies each qualified for.
- Interviewed potential subjects working in patient care center for osteoporosis studies Novartis & Lilly. (Note: patients interviewed had shown interest by responding to email advertisement of studies) Performed medical history and reviewed inclusion/exclusion criteria to determine participation status. Reviewed previously performed DXA scans of interested patients with Susan to determine if DXA numbers are inclusionary.

Wednesday, November 3, 2004

- Phoned potential subjects whom responed to campus-wide osteoporosis email advertisement for Novartis & Lilly studies: patient interviewing and obtaining medical history, chart auditing, and discussion of study protocols and inclusion/exclusion criteria for study participation.
- Faxed subject enrollment log for Centocor C0524T02 and Pfizer/ Bextra studies
- Faxed periodic project review and re-approved consent to Centocor monitor after IRB approval received: discussed why periodic project review performed and how proper forms are assemblied.
- Readiness of regulatory binder and subject source binders for Centocor C0524T02 monitor visit
- Advertisement dispersal to Psychologist on information concerning osteoporosis studies: Novartis & Lilly
- Copied, filed, and delivered to IRB Centocor SAE reports
- Filed financial disclosures for Tap, Merck 076, Genentech, Lilly, and Novartis studies
- Conversed with Novartis monitor, Charity Bishop, over phone about subject enrollment progression at site and recent advertisement tactics in local papers and email.

Thursday, November 4, 2004

- Subject Visit Tap/Gout Study (7am): Performed vital signs, preparation of lab specimen (centrifuge chemistry and collected serum) and packaged for shipment
- Pfizer/Bextra Safety Reports (X6) documented, coped and filed into regulatory binder in preparation for study close-out
- Greeted Centocor monitor and assisted when applicable
- Phoned and interviewed patients/potential subjects interested in osteoporosis studies: discussed protocol, reviewed and obtained medical history, and reviewed incl./excl. criteria to determine if eligible to participate in study
- Merck 066 & 076 documentation/write-up of SAEs
- Chart auditing for potential osteoporosis subjects

Friday, November 5, 2004

- Documentation/ write-up of Merck SAEs
- Scheduling of Novartis subject screening visit:
  a) called subject to remind of visit time, DXA scan appt., and reminded subject to bring all current prescription and non-prescription therapy and to be fasting
  b) assembled screening visit kit and source binder
  c) Reminded PI, Dr. Pertusi, and sub-PI, Linda Davis, PA-C, of 8 am consenting of subject. Reminded Susan of 8:30 am DXA scan
- Filing lab reports in patient/subject chart for Merck 066 study
- Chart auditing for Novartis osteoporosis study: complete medical history with chart and phoned subject to review history and review incl./excl. criteria for study
- Rearranged and reorganized study binders from storage room to new storage cabinets
- Conversation with Charity Bishop about incl./excl. criteria for Novartis study
  a) Asked if progesterone topiqul cream considered exclusionary criteria and documented conversation in Novartis correspondence under telephone log section.

Monday, November 8, 2004

- Subject Screening visit (8 am) for Novartis CZOL446H2315 study: subject = no show
- Drug accountability for Aventis study: delivered study therapy (3 bottles of Oscal) to Pharmacist to discard appropriately, faxed drug accountability form to Aventis monitor, Bea, and filed form in regulatory binder
- Documentation of SAE reports for Centocor study
- Chart auditing for osteoporosis Novartis & Lilly studies

- Phoned potential patients/subjects interested in osteoporosis studies: obtained complete medical history and audit chart (if available), discussed protocol and visit schedule with patients, reviewed incl./excl. criteria to determine patient's participation status

Tuesday, November 9, 2004

- Centocor subject visit (x 6), Merck 076 subject visit (x 1), and Tap/Gout subject visit (x 1): performed vital signs, faxed pharmacist visit date for centocor subject therapy infusion, drug accountability for Merck 076 returned study therapy and dispense new study therapy, lab specimen assembly and dry ice packaging (centrifuge and collect serum from blood samples and made hematology slides)
- Filing IRB approved Protocol amendments for Lilly, IRB approved consent, and correspondence for Lilly study
- Discussed potential Lilly subject with mentor: reviewed DXA scan T-score and reviewed medical history including current prescription and non-prescription therapy

Wednesday, November 10, 2004

- Subject visit for Astrazeneca (final visit): performed vital signs and ECG
- Chart auditing for potential Novartis patient/subject
- Scheduling for DXA/BMD scan with technician, Susan Bitner, and consenting for screen visit with Dr. Pertusi's availability
- Initial patient introduction meeting to discuss potential participation in future clinical trial: Retrieve patient contact information and gave brief overview of future Tap/Gout study with physician, Dr. Pertusi and Linda Davis, PA-C.
- Patient interviewing for osteoporosis studies over phone & review of medical history

Thursday, November 11, 2004

- Subject visit 8 am for Tap/Gout: performed vitals and lab specimen packaging
- Greeted monitor for Novartis, Charity Bishop, and discussed enrollment progress and exclusionary criteria with monitor and mentor.
- Obtained financial disclosure signature from Dr. Patel for Merck 066 & 076 studies
- Mailed consent forms to MLS subject for Novartis screen visit
- Documentation of SAE reports for Merck 076 & 066
- Microsoft word spreadsheet update of Merck 076 adverse events log
- Scheduled screening visit for Novartis subject DLR: obtained home address, scheduled DXA scan, assemblied & delivered consents to office at UNTHSC for review prior to screen visit and reminded subject to fast & bring all current medications (including vitamins)

- Subject visit reminder calls to SRM & LGT for Centocor wk 16 day 3 visit on tomorrow: Assembly and readiness of subject source document binder and lab kits for visit

Friday, November 12, 2004

- Subject visit for Centocor (SRM & LGT Blood draw)
- Dry ice pick-up & lab specimen assembly & packaging
- Documentation of SAE reports Merck 066 & 076
- Chart review of Novartis subject MLS for screen visit Monday with mentor: complete review of subject medical history and medication (prescription & non-prescription)
- Assembly & readiness for Tuesday Centocor subject visits
- Attended Endnotes class at Library 12 p.m. - 1 p.m.
- Correspondence with potential Lilly subject on closure of Stratum B group, therefore, excluding subject from participation.
- Retrieval of waiver from Novartis accepting subject MLS DXA scan number at femoral neck for inclusion into study

Monday, November 15, 2004

- Subject visit reminder calls to LGT & SRM for Centocor visits: informed subjects of time of visit and which meds. to avoid morning of visit
- Subject MLS documentation of decision to decline participation in Novartis Study: emailed Dr. Pertusi, PI, to inform of subject's decision
- Research at library: Worked on thesis

Tuesday, November 16, 2004

- Centocor subject visits LGT 7am & SRM 9 am: blood drawn by RN, performed blood pressure on LGT
- Documentation of SAE reports for Merck 066 & 076
- Lab specimen assembly & dry ice packaging (centrifuge & collected serum)
- Correspondence via phone with Babek Fazeli on enrollment progression status of Lilly study at site
- Readiness for Pfizer/Bextra monitor for Close-out visit

Wednesday, November 17, 2004

- Assembly of advertisements for osteoporosis studies Novartis and Lilly : prepared advertisement for posting and added contact phone number to advertisements
- Subject visit for Merck 066 study
- Assembly & packaging of ambient lab specimen and delivered to Quest Laboratory
- Copied Genentech Protocol for preparation and readiness for site initiation visit on tomorrow: reviewed and studied protocol

- Documentation of SAE reports for Merck 066 & 076 and Pfizer/Bextra (x 2)
- Attended and participated in teleconference for Genentech study
- Pfizer/Bextra close-out visit: greeted monitor and assisted monitor whenever applicable
- Faxed subject enrollment log for Centocor to monitor
- Readiness for Genentech initiation visit: checked received regulatory documents, manuals, and lab kits
- Copied, filed, and delivered SAE reports for Pfizer/Bextra and Merck 066 &076 to IRB office for IRB acknowledgement

Thursday, November 18, 2004

- Genentech initiation visit 8-2 p.m.: observed & participated in entire review process of protocol and objectives of study with Genentech monitor and key personnel in study.
- Gave monitor tour of infusion room, lab supply storage room, -20 freezer, and consult room for monitor visits with coordinator.
- Coordinator & I showed Genentech monitor, Lisa Buffington, crash box/emergency crash cart and verified all dates were updated. Showed monitor laboratory where lab samples and packaging occurs. Checked dates on centrifuge machine.

Friday, November 19, 2004

- Unscheduled/ emergency subject visit for AMG in Merck 066 study: performed vital signs and observed joint shoulder injection of depomedrol 40 mg by Dr. Rubin in patient's left shoulder due to subacromial bursitis.
- Organization of Case Report Form (CRF) binder and regulatory binder for Genentech study: rearrangement of office study binders to make room/ space available for new study
- Boxed –up Aventis CRF, source, and regulatory binders to place in storage now that study is closed and is post-study close-out visit
- Correspondence sent/ mailed to Pfizer/ Bextra monitor of requested SAE reports with IRB acknowledgements
- Correspondence w/ Pharmacist, Dan Hooper, regarding Clinphone manual, investigational product worksheets, and Clinphone account set-up for Genentech study
- Retrieval of Clinphone signatures for account set-up and site personnel signatures for Genentech study

Monday, November 22, 2004

- Documentation of SAE reports for Merck 066 & 076 and Novartis & Astrazeneca
- Phoned possible Novartis & Lilly osteoporosis subjects and conducted patient interviews via phone: obtained potential subjects complete medical history via

phone (audit chart if applicable), reviewed and described study protocol, study visit schedule, and study drug, and reviewed incl./excl. criteria
- Phoned Charity Bishop, Novartis monitor, to inquire about exclusionary criteria for potential subject. Documented telephone conversation in correspondence section of regulatory binder

Tuesday, November 23, 2004
- Subject visit FMC wk 20 for Centocor: performed vital signs and witnessed amended consent signing
- Mailed correspondence of informed consents of osteoporosis studies to potential subject
- Copy and filed Novartis and Astrazeneca safety reports and sent signed original to IRB office.
- Scheduled screening visit with required DXA scans for two subjects: reviewed subjects medical hx with mentor, consulted PI on questions concerning subject's past history of kidney stones and GERD, mailed consent information to subject for review prior to screen visit, called subjects and reviewed materials needed for screen visit (bring medication & vitamins) and reminded subject to fast. Confirmed DXA schedule time with technician.
- Filing of fax correspondence and IRB correspondence in appropriate study regulatory binders

November 24 –28, 2004
- Thanksgiving Holiday

Monday, November 29, 2004
- Subject screen visit for Novartis CZOL446H2315 Study: consent witness, performed vital signs
- Subject ELH visit 6 for Novartis: performed vital signs
- Lab specimen assembly and dry ice packaging and shipment
- Filing of IRB acknowledged SAE reports for Centocor, Merck, and Genentech
- Readiness/ assembly for subject screening visits (x 2): assembly of source binder and appropiate consent forms and lab kits; called subjects to remind of visit time and materials to bring
- Faxed Centocor subject enrollment log

Tuesday, November 30, 2004
- Documentation of SAEs for Merck 066 & 076
- Creation of source binders for subjects FMC & VDD for Centocor continuation post wk. 20
- Unscheduled subject visit (FMC) for Centocor study: performed vital signs, urine dipstick analysis, assembly of lab specimen and hematology slides. Ambient packaging of lab & shipment

- Filing in Novartis correspondence for upcoming teleconference

Wednesday, December 1, 2004

- Study supplies inventory for Centocor study lab kits and Merck 066 & 076 lab kits: brokedown expired lab kits and documented remaining viable kits, ordered study lab supplies (lab kits, shippers, and labels for shippers) for Centocor, Merck 066 & 076
- Documentation of SAE for Centocor (x1), Merck 066 (x3), and Merck 076 (x 3)
- Subject visit forms mailed interoffice to IRB
- Faxed correspondence to Pfizer monitor

Thursday, December 2, 2004

- Faxed subject enrollment log for Genentech & Centocor studies
- Documentation of SAE reports for Genentech, Lilly, Merck 066 & 076
- Copied and filed signed SAEs for Merck 066 & 076 and sent interoffice mail to IRB for acknowledgement
- Creation of safety report binder for Lilly study

Friday, December 3, 2004

- Filing correspondence for Lilly, Novartis, & Astrazeneca studies
- Reviewed subject RBP screening visit lab results for Novartis study: checked incl./excl. criteria to ensure lab numbers met inclusion criteria
- Documentation of SAE reports
- Library: Research and worked on thesis paper and presentation

Monday, December 6, 2004

- Novartis randomization visit: performed vital signs
- Centrifuged lab specimen and collected serum and packaged with dry ice for shipment
- Monitor for Merck 076 study: assisted monitor with SAE report accountability and documentation, escorted monitor to meeting with PI, Dr. Rubin, study coordinator, and myself
- Phoned (pre-screened) potential Novartis subjects: reviewed study objectives, visit schedule, and protocol, obtained subject medical hx., and reviewed study incl./excl. criteria to determine subject participation
- Obtained sub-PI, Dr. Patel, signature for internal IRB conflict of Interest form for Genentech study

Tuesday, December 7, 2004

- Centocor subject visits (x 5) 7 am – Noon: performed vital signs, assisted with questionnaires, faxed correspondence of subject visit to pharmacist for study drug assembly/preparation, observed postural drainage performed by PA, Linda Davis, witnessed consent signing of revised consents

- Lab specimen assembly and dry ice packaging and shipment
- Preparation for assembly of source document binders for Genentech study: copied all necessary forms
- Performed inventory of study lab kits for Tap/Gout & Novartis studies: ordered necessary lab kits, shippers, and any other supplies needed for upcoming visits.

Wednesday, December 8, 2004

- Creation of source binders (x 5) for Genentech study
- Copied & filed signed SAE reports (x 21) and mailed interoffice to IRB for acknowledgement
- Input of documented SAE reports for Merck 076 into Microsoft word spreadsheet log
- Updated and faxed enrollment log for Novartis, Genentech, and Centocor studies
- Discussed with mentor potential screen visit and randomization dates for Genentech subject visit.
- Worked on thesis in library

Thursday, December 9, 2004

- Filing IRB correspondence for Merck 066 & 076 pertaining to distribution letter providing info. On withdrawal of Vioxx: faxed & copied correspondence to monitor of Merck 066 & 076
- Documentation of SAEs
- Brokedown expired lab kits for Tap/Gout study and stored newly received lab kits for Merck 076
- Phoned potential Novartis subject: obtained permission to audit chart, obtained brief medical hx via phone, explained study protocol, and reviewed incl./excl. criteria of study to determine eligibility
- Informed PI of all SAE malignancies reported to site as of 12-9-04 and relation of reports to study drug for Novartis study: Documented conversation with PI and action taken regarding informed consent
- Informed PI of Novartis study of potential subject past medical history of heart condition and current medication usage: documented conversation and action taken with regards to screening subject into study

Friday, December 10, 2004

- Library: worked on thesis and met with Major Professor to discuss progress.

Monday, December 13, 2004

- Novartis subject visit: lab specimen and hematology slides, dry ice shipment
- Filing IRB acknowledged SAE reports for Merck 066, 076, Genentech, Lilly, Centocor, and Novartis
- Copy & file signed SAE reports and sent interoffice mail to IRB for acknowledgement

- Filing and faxing correspondence and IRB approvals for Centocor, Astrazeneca, and Merck 076.
- Centocor revised informed consent delivered to on-site IRB for acknowledgement and approval
- Filing copy of Vioxx letter (explanation of withdrawal) in subject binder for Merck 076 and then mailed letter to subjects in study

Tuesday, December 14, 2004

- Centocor subject visit (x 2) wk. 20: unblinding of subjects, performed vital signs, assisted with PAQ questionnaires and preparation of joint assessment.
- Lab specimen assembly and dry ice packaging
- Copy and filed signed SAE and sent interoffice mail to IRB for acknowledgement
- Filing correspondence for Merck 066 & 076
- Readiness for Tap/Gout monitor visit
- Alertness to infusion nurse, sub-PI, RN joint assessor of possible Centocor visit during Christmas holiday

Wednesday, December 15, 2004

- Discussion with Dr. Weiss, cardiologist, about potential Novartis subject participation
- Documentation of SAEs for Novartis, Merck 066 & 076
- Faxed subject enrollment log for Genentech, Centocor, and Novartis studies
- Storage of drug/ study supplies: shippers and lab kits

Thursday, December 16, 2004

- Documentation of SAEs for Merck 066 & 076
- Data Clarification Form (DCF) for Aventis study
- Creation of post wk. 20 source binder for Centocor study for subject SRM & LGT
- Filing of DCF/ Query in correspondence regulatory binder
- SAEs: copy and filed and mailed interoffice to IRB for acknowledgement
- Readiness of subject visit for next week: assembled source binders and lab kits
- Subject visit reminder call for Novartis & Centocor

Friday, December 17, 2004

- Meeting with major professor
- Worked on thesis

December 18 – January 2, 2005

- Christmas holiday

Monday, January 3, 2005

- Novartis subject visit: performed vital signs and dry ice packaging and shipment of lab specimen
- Filing of IRB acknowledged SAE reports for Tap, Novartis, Merck 066 & 076, and Centocor
- Documentation of SAEs for Novartis, Astrazeneca, and Centocor

Tuesday, January 4, 2005

- Centocor subject visit (x 4) and Genentech screen visit: performed vitals, assisted with questionnaires and readiness for joint assessment; correspondence with pharmacist on subject visit wk for preparation of study drug; discussed Bextra & Celebrex with subjects (observed & listened)
- Lab specimen collection and packaging both ambient and frozen
- Ordered supplies for Centocor study
- Worked on thesis

Wednesday, January 5, 2005

- Merck 066 visits (x 3): study drug count for accountability and dispensed new study therapy, performed vitals
- Faxed subject enrollment for Centocor, Novartis, & Genentech studies
- Filing lab reports in patient's charts
- Readiness for Centocor monitor visit: checked CV liscense expiration dates & replaced with updated liscense if needed. Faxed updated liscense to monitor
- Consent correspondence for Centocor: copied new revised informed consent and made ready to mail to subjects for review prior to next visit
- Reviewed deviations in protocol with mentor: observed and participated in writing deviations in regulatory binder according to provided codes

Thursday, January 6, 2005

- Faxing correspondence to Centocor monitor
- Greeted & assisted Centocor monitor when needed during monitoring visit
- Tap/Gout subject visit: lab specimen assembly and dry ice packaging & shipment
- Filing Centocor forms in source binders
- Documentation of SAEs
- Called potential Novartis patients and informed of study enrollment closure

Friday, January 7, 2005

- Documentation of SAEs
- Worked on thesis/ practicum report

Monday, January 10, 2005

- Filing correspondence in storage of Aventis and Centocor studies currently closed

- Data Clarification Form (DCF) for Aventis study: corrected data and faxed to monitor
- Rheumatology meeting 8:30-9:30 am: discussed areas of improvement in rheumatology clinic and need for doctors to pre-screen for Genentech subject enrollment
- Documentation of SAEs: Merck 076
- Drug accountability/ organization of study supplies: brokedown expired Tap/Gout lab kits

Tuesday, January 11, 2005
- Documentation of SAEs: Merck 066 & 076
- Updated spreadsheet AE log for Merck 076

Wednesday, January 12, 2005
- Tap/ Gout subject visit (8 am)
- Faxed site enrollment log to monitors of Genentech, Novartis, and Centocor
- Made copies of protocol and investigator brochure for Genentech study
- Made copies of signed SAEs and sent to IRB for acknowledgement
- Filing of lab reports in Centocor study patient charts

January 13 – 14, 2005
- Library: research for practicum repor and assembly of rough draft

Monday, January 17, 2005
- MLK holiday

Tuesday, January 18, 2005
- Room readiness for Merck 076 subject PAB visit and Centocor subject visits (8-11 am): assisted subject with questionnaires, joint assessment readiness of patient room, performed vital signs, lab specimen packaging, witnessed informed consent signing, and correspondence between pharmacist and myself on subject visit wk for study injection preparation
- Broke-down expired Merck 076 & 066 lab kits
- Filing of IRB acknowledged SAE reports
- Readiness of lab kits and source binders for subject visits on tomorrow
- Aventis DCF/Query addressed and corrected

Wednesday, January 19, 2005
- Tap/ Gout subject visit & Merck 066 subject visit: performed vital signs, ECG; counted drug for accountability, and lab specimen packaging and assembly
- SAE documentation
- Inventor of supplies and ordering of lab kits and shipment supplies for Genentech and Tap/Gout

- IRB: discussed approvals needed for study advertisements and proper documentation and correspondence
- IRB: discussed amendment changes to consent language when subject enrollment number has been altered or the exact number of subject enrollment is known.

Thursday, January 20, 2005
- Documentation of SAEs
- IRB consultation on Genentech approval correspondence for advertisements

Friday, January 21, 2005
- Worked on thesis/ practicum report and submitted 1st draft to committee for review

Monday, January 24, 2005
- Phoned Esoterix for lab results & fax of lab results from screen visit of subject SAM
- Obtained signatures for Confidentiality to Genentech monitors on IRB approvals of advertisement
- Faxed IRB approval of informed consent, protocol amendment, and protocol synopsis
- Copied IRB approved protocol amendment for sub-PI's

Tuesday, January 25, 2005
- SAE documentation Novartis, Merck 066 & 076
- Delivery of Confidentiality Agreement to IRB for submission
- Copied signed SAEs and sent to IRB for acknowledgement
- IRB: review of submitted documents in IRB sectionof regulatory binders and confirmed received approvals in Centocor and Merck 066 study binders
- Input of SAEs into AE log for Merck 076 study

Wednesday, January 26, 2005
- Safety documentation
- Copied and sent signed SAEs to IRB for acknowledgement
- Readiness of regulatory binder for Merck 076 study close-out & annual continuing review completion

Thursday, January 27, 2005
- Audit charts for Genentech study
- Filing of IRB acknowledged SAEs
- Correspondence with PI on practicum report section of appendix items

Friday, January 28, 2005

- Obtained Novartis informed consent and outlined principles of informed consent. Reviewed principles of informed consenting process with mentor and discussed design and conditions of consent.
- Ensured that consent had every aspect of FDA required Title 21 CFR 50.25 regulations
- Discussed importance of individual rights of research subject and ensuring subject completely understands information in consent.
- Discussed case examples of situations for obtaining informed consent when patient is unable to communicate, has a life-threatening condition, or no alternative treatment is available that offers equal or greater value to saving life of patient, and physician's judgment on administration. (IRB must approve any deviation to consenting process and be notified of any exceptions to normal consenting process)
- Audited potential subject chart and reviewed incl./excl/ material for Genentech study with subject medical history
- Faxed enrollment logs to monitors
- Met with major professor to discuss practicum report corrections to first draft
- Readiness of lab kit and source binder for Novartis subject visit on Monday
- Ordered lab kit supplies for Novartis study

Monday, January 31, 2005

- Subject visit for Novartis study: performed vital signs and blood draw (taught technique of drawing blood by mentor and performed it)
- Broke-down expired lab kits and performed new inventory
- Packaged and assembled lab draw with dry ice and shipped
- Merck 076 monitor: Close-out visit
- Worked on power point for defense

Tuesday, February 1, 2005

- Centocor subject visits (x 3) 7 am- 9 am
- Assembly of lab specimen and dry ice packaging and shipment
- Documentation of SAEs
- Ordered lab kit supplies and lab shippers for Centocor and Genentech study
- Copied and filed signed SAEs and sent interoffice to IRB for acknowledgement

Wednesday, February 2, 2005

- Genentech subject screen visit : performed vital signs
- Meeting with major professor 11-1:30 pm
- Filing correspondence in regulatory binder for Merck 066, 076, and Centocor studies
- Distribution of final draft of practicum report to committee members

Thursday, February 3, 2005

- Documentation of SAEs
- Called potential Genentech subjects who showed interest in study and documented time and date of call
- Attended meeting about merger of UNTHSC with physician aassociation
- Filing correspondence in regulatory binders
- Assembled binders, labeled, and prepted for making extended source for Merck 066 study
- Practiced powerpoint defense 3:30-5:00 pm

Friday, February 4, 2005

- Created extended source binders for visits 9-14 for Merck 066 study (x 11)
- Merck 066 subject visit: lab specimen assembly and packaging
- Safeties: Copied and filed signed SAEs and delivered interoffice to IRB for acknowledgement

Monday, February 7, 2005

- Rheumatology meeting
- Merck 066 subject visit : performed vital signs and witnessed consent signing
- Copied IRB approved consents for Centocor, IRB approved continuing review acknowledgement and consent. Filed copy in regulatory binder and faxed to sponsor.
- Filing correspondence in regulatory binders
- Supplies accountability and re-arrangement of lab kits and shippers in storage room: ordered needed lab kit supplies

Tuesday, February 8, 2005

- Updated licenses of sub-PI and PI in regulatory binders, as needed
- Faxed updated licenses to sponsors of corresponding studies
- Filing in patient charts
- Copied updated/ amended protocol and infusion notecards for Dorothy, infusion nurse.
- Defense practice 3:30- 5:00 pm

Wednesday, February 9, 2005

- Filing signed and IRB acknowledged SAEs
- Documentation of deviation from protocol Centocor study: reviewed and documented subject KKD concomitant medication deviation
- Reviewed and received critiques on powerpoint presentation with mentor
- Documentation of Merck 066 SAEs
- Filing correspondence and lab reports in patient charts
- Practice for defense, 1:30- 5:00 pm with major professor

Thursday, February 10, 2004

- Created (4) source binders for Genentech study
- Greeted Astrazeneca monitor for close-out of study and assisted when needed
- Faxed enrollment logs for Novartis, Centocor, and Genentech studies
- Re-faxed updated license to sponsors, as needed
- Filed signed, IRB acknowledged Tap/Gout safety report
- Broke-down expired lab kits

Friday, February 11, 2005

- Copied, filed, and sent interoffice signed SAEs to IRB for acknowledgement
- DCF: Data Clarification Forms corrected for Aventis
- Packaged and stored Lilly study binders
- Defense 2-4 pm!!!

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