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Chronic hepatitis C infection is debilitating, and investigational drugs currently in phase III clinical trials are promising. It is important that efficient antiviral medication reach market if it has the potential for inhibiting viral replication. Because of subject recruitment issues, many studies fail to meet enrollment goals and therefore cannot complete the clinical trial process and bring drugs to market. Therefore, a recruitment plan must be implemented that will ensure that enrollment goals are met.

The goal of this practicum was to test the hypothesis that educating the medical and non-medical community about the HCV clinical trials would increase subject enrollment. However, due to certain limitations, not enough data was gathered to provide clear and concise results.

**AN ANALYSIS OF SUBJECT RECRUITMENT
ISSUES FOR AN HCV INVESTIGATIONAL
DRUG CLINICAL TRIAL**

Internship Practicum Report

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For the Degree of

MASTER OF SCIENCE IN CLINICAL RESEARCH MANAGEMENT

By

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CHAPTER I

INTRODUCTION

According to the Centers for Disease Control and Prevention (CDC), “Hepatitis C virus (HCV) infection is the most common chronic blood borne infection in the United States; approximately 3.2 million persons are chronically infected.” (1) The word hepatitis means inflammation of the liver; hepatitis can be caused by a host of factors, the most common of which is usually viral. The three most common hepatitis viruses in the United States are A, B, and C, but only Hepatitis A and B have vaccines currently available. For many people living with Hepatitis C, it is only a matter of time until they develop liver cirrhosis, which may or may not lead to liver failure. Therefore, it is very important for the medical field to develop a therapeutic drug which will block the virus from replicating and proliferating.

When an antiviral drug is developed, it must go through a series of clinical trials approved by the FDA (Food and Drug Administration) before it can reach market. These clinical trials test the safety and efficacy of the drug, so the FDA and the sponsor of the drug are very stringent in their requirements regarding the conduction of these trials. This can lead to subject enrollment issues when the protocol mandates very restrictive inclusion/exclusion criteria. The problem is exacerbated when there is not a large patient pool available from which to select subjects. Thus, it becomes difficult for the principal investigator or the clinical research coordinator (CRC) to enroll a sufficient number of subjects for their clinical trials. The goal of this practicum report is to analyze the issues involved in the subject recruitment process for the Hepatitis C clinical trials at the

Transplant Institute at Baylor University Medical Center. The report will also explore and illustrate the numerous projects undertaken in order to address the problem of subject enrollment for HCV clinical trials at the Transplant Institute. Finally, a discussion will follow that will explore the results and outcome of the various approaches taken, as well as how these techniques can be implemented for non-HCV clinical trials as well.

CHAPTER II

SUBJECT RECRUITMENT ISSUES IN AN HCV CLINICAL TRIAL

Background and Literature Review

I. Hepatitis

The word hepatitis means any type of inflammation of the liver. The most common causes of hepatitis are viral, although they can also be hereditary, alcohol-related, autoimmune, or have no known cause. Usually, elevation of liver enzymes—alanine aminotransferase (ALT) and aspartate aminotransferase (AST)—is indicative of acute hepatitis (2). The medical community has identified at least six human hepatitis viruses: hepatitis A virus (HAV), hepatitis B virus (HBV), hepatitis C virus (HCV), hepatitis delta virus (HDV), hepatitis E virus (HEV), and hepatitis G virus (HGV). The three most prevalent hepatitis viruses in the U.S. will be discussed (HAV, HBV, and HCV), as well as HDV, an HBV-dependent virus.

A. Hepatitis A

The hepatitis A virus (HAV) is a non-enveloped RNA virus, a member of the Picornaviridae family of viruses whose antigenic structure is highly conserved among strains (2). It is a major cause of acute hepatitis infection and liver failure throughout the world, especially in developing countries where seroprevalence rates approach 100% (2, 3). Infection with HAV does not result in chronic disease, but remains in an acute self-limited episode of hepatitis (2). Because of improvements in socioeconomic conditions in

the west, HAV prevalence is diminishing in more industrialized countries (2). HAV is transmitted primarily through ingestion of contaminated food products (enterically), the fecal-oral route, or through person-to-person contact (4). Risk groups for HAV include those who travel to endemic countries, healthcare workers, daycare workers, military personnel, institutionalized patients, homosexuals with multiple sexual partners, and intravenous drug users (2, 4). Children between the ages of 5 and 14 years of age have the highest rate of reported disease, and this is especially true in countries where sanitary conditions are poor (2). Even so, most infections occurring in children under six are asymptomatic, whereas in adults, especially the elderly, the virus frequently takes a symptomatic course (2). Acute HAV infection is almost always followed by recovery and lifelong immunity; HAV is not known to be a cytopathic virus, and the necroinflammatory lesions observed are attributable to the normal host immune response (2). However, certain populations, like the elderly and those with chronic liver disease, have increased morbidity and a high risk of acute liver failure from HAV infection (5).

Acute hepatitis is clinically indistinguishable from other forms of viral hepatitis (2). There are currently a few FDA approved vaccines available: Havrix, Vaqta, and Twinrix. Twinrix is a special formulation in that it is a combination of hepatitis A and B vaccines and has an excellent record of safety and efficacy (6).

B. Hepatitis B and D

The hepatitis B virus (HBV) is a double-stranded circular DNA virus, a member of the Hepadnaviridae family of viruses (2); it can be transmitted through blood or body fluids. There are approximately 400 million hepatitis B carriers worldwide and 1.25

million carriers in the United States (2); over 500,000 die annually from hepatitis-B associated liver disease (7). The carrier rate for HBV ranges from 8% to 20% in highly endemic areas, which include Southeast Asia, China, and Africa (8). In highly endemic areas, spread of the virus is mostly through maternal-infant transmission (vertical), but may also be attributed to IV drug use and sexual spread, whereas in low endemic areas, such as the U.S., sexual activity and IV drug use account for most HBV cases (2). Other less common risk factors for transmission include occupational exposure, hemodialysis, acupuncture, household contact, and the receipt of infected organs or blood products (8). HBV transmission has been reduced in several countries through public education, routine infant and adolescent vaccination, screening of pregnant women, and administration of postexposure prophylaxis to infants (9).

For persons over the age of 5 years, clinical symptoms are present in 30% to 50% of cases, but most patients (95%) will clear the virus and produce lifelong immunity against the virus (2). In contrast, children under the age of 5 years have a 30% to 50% chance of developing chronic hepatitis B infection (2). Therefore, the age at which infection occurs has a significant impact on whether or not the individual will suffer from chronic infection. Even though in Western countries the rate of neonatal infection from an infected mother is less than 10%, an estimated 20,000 infants are born to infected mothers annually (10).

HBV infection is decreasing throughout the world because of a few factors: mass vaccinations for newborns, children, and adults, increased public awareness of hepatitis, educational campaigns to prevent HIV infection leading to modification of high risk sexual behavior, and reduction of syringe sharing among intravenous drug users (2).

There are currently two commercial vaccines available: Engerix-B, produced by GlaxoSmithKline, and Recombivax HB, produced by Merck.

The clinical outcome of HBV infection is dependent upon age: perinatal or childhood infection is usually associated with few or no symptoms but a high risk of chronicity whereas adult acquired infection is usually associated with symptomatic hepatitis but a low risk of chronicity (2). There are currently seven treatment options available that stop viral replication, and these include five antiviral drugs (lamivudine, adefovir, tenofovir, telbivudine, and entecavir), and two immune system modulators (interferon alpha-2a and pegylated interferon alpha-2a).

HDV is a virus that is dependent upon HBV for complete virion assembly and secretion, and because of this dependence, HDV infection always occurs in association with HBV infection (2). It is estimated that approximately 5% of HBV carriers worldwide may be infected with HDV (11). The only treatment shown to be effective against chronic hepatitis D is interferon therapy (2), which will be explained in the section on HCV therapy. The only method currently employed to prevent HDV infection is vaccination against its helper virus, HBV (2).

C. Hepatitis C

The hepatitis C virus (HCV) is a single-stranded RNA virus which is part of the Flaviviridae family of viruses (12). It is estimated that about 3% of the world's population is infected with HCV, an estimated 170 million persons worldwide (13, 14); globally, HCV accounts for 70% of chronic hepatitis cases (2). It is the most common cause of chronic liver disease in the United States (2). Because HCV is transmitted

through blood, parenteral exposure accounts for a majority of HCV infections. Routine blood screening has significantly reduced the risk of transmission of the disease through infected blood products. Up to 90% of intravenous drug users are HCV infected (15); the major risk factor for infection remains intravenous drug use (2). Other risk factors include occupational exposure, hemodialysis, medical reuse of infected needles, and tattoos, while vertical (mother-to-infant) and sexual transmission are uncommon (2).

Acute HCV infection, as well as chronic infection, is usually asymptomatic with only elevated serum aminotransferase levels, and this poses a problem as the timing of the disease onset is indeterminable. Recent studies with long follow-ups indicate that approximately 50% of acutely infected individuals progress to chronic cirrhosis, whereas in the past this number was estimated to be 80% to 90% (16,17,18). Because progression of chronic HCV infection is slow, advanced disease develops approximately 10 to 30 years later, or even longer, after infection (19,20). A liver biopsy must be done to evaluate the degree of fibrosis in order to determine the progression of cirrhosis and the development of subsequent liver complications (20,21). Risk factors which are known to increase progression to fibrosis include male gender, older age at initial infection, excess alcohol intake, coinfection with HBV or HIV, and the presence of hepatic steatosis (also known as fatty liver disease) (2).

Because the hepatitis C virus lacks proofreading ability, and has a high nucleotide substitution rate, it has a high degree of genetic diversity that has led to evolution into several viral genotypes (2). It is speculated that the virus's long incubation period and reemergence is due to this high mutation and nucleotide substitution rate, even when initially the host's immune response is able to suppress viral activity.

HCV is the leading indication for liver transplantation in the United States, accounting for approximately half of the nearly 6,000 liver transplantations performed each year (2). Unfortunately, HCV infection persists in almost all patients who undergo transplantation for chronic hepatitis C and results in severe and progressive chronic hepatitis in many, with viral levels increasing 10- to 15-fold after transplantation (22).

D. HCV Antiviral Therapy

Current antiviral therapy available to HCV infected individuals is used to prevent the development of decompensated liver disease and death. Interferons (IFN) are used extensively as antiviral agents because they inhibit the replication of many viruses through a variety of mechanisms including direct antiviral mechanisms (inhibition of virus attachment and uncoating, and induction of intracellular proteins and ribonucleases), and amplification of specific and nonspecific immune responses (23). Long-acting pegylated IFNs increase host exposure to IFN and double the response (2); pegylation involves the attachment of a large inactive molecule to a protein to reduce the rate of removal from the body (clearance). Ten years after IFN treatment was introduced, Ribavirin was added to the regimen because it was believed to induce lethal mutations in the viral genome, a mechanism known as viral error catastrophe (24). Pegylated IFNs in combination with ribavirin is currently the standard of care (SOC) for chronic hepatitis C. Overall, IFN-based therapies are reasonably tolerated (2). Ribavirin, however, causes a predictable dose-related hemolysis and has embryotoxic and teratogenic effects, so it should be used with great caution (2).

A new drug, belonging to a class of antiviral drugs known as protease inhibitors, is currently in phase III clinical trials and may soon be incorporated into the current HCV drug regimen. Protease inhibitors work by inhibiting viral proteases from cleaving necessary protein precursors into their smaller constituent parts. These smaller proteins are needed for viral replication and assembly, so by blocking proteases, these drugs essentially inhibit viral replication. Given the specificity of the target of these drugs, there is the risk of drug-resistant mutated viruses developing. To reduce this risk, it is common to use a combination of antiviral drugs that are each aimed at different targets. This is why HCV clinical trials test the efficacy of pegylated-IFN and ribavirin in conjunction with a protease inhibitor. If the protease inhibitor is shown to be effective, it will be added to the current SOC combination instead of replacing it as a monotherapy.

E. HCV and Insulin Resistance

Two of the three HCV studies enrolling at the Transplant Institute test the safety and efficacy of pegylated IFN, ribavirin, and a third investigational protease inhibitor. One of the three studies does not, however, involve a protease inhibitor. It tests the safety and efficacy of pegylated-IFN and ribavirin in combination with pioglitazone. Pioglitazone (Actos®) is an oral antidiabetic agent used in the management of type-2 diabetes mellitus that acts primarily by decreasing insulin resistance (32). The reason it has been deemed necessary to study these drug interactions is because insulin resistance and HCV infection have been found in large numbers of people. A higher incidence of insulin resistance among HCV-infected patients compared with their non-infected counterparts was observed in a cross-sectional survey of Americans over 40 years of age

(3 times more likely) (34). The same was found to be true in a prospective case-cohort study of 1084 patients 44 to 65 years of age (2 times more likely overall and 11 times more likely in patients at high risk for insulin resistance based on age and body mass index) (35). Another study found that a higher incidence of type-2 diabetes was also observed in patients with HCV infection than in patients infected with the hepatitis B virus (34). Greater insulin resistance was found in HCV-infected patients with little or no hepatic fibrosis than in healthy subjects matched for sex, body mass index, and waist-to-hip ratio (36).

It can be derived from this that HCV infection may itself induce or exacerbate insulin resistance. Although the physiological mechanisms are complex and not well understood, it is believed that impaired hepatocyte function due to insulin resistance may interfere with the anti-HCV effects of IFN therapy. Therefore, it is important to determine if antiviral therapy consisting of pegylated-IFN and ribavirin in combination will be effective on subjects who are currently taking pioglitazone for their insulin resistance.

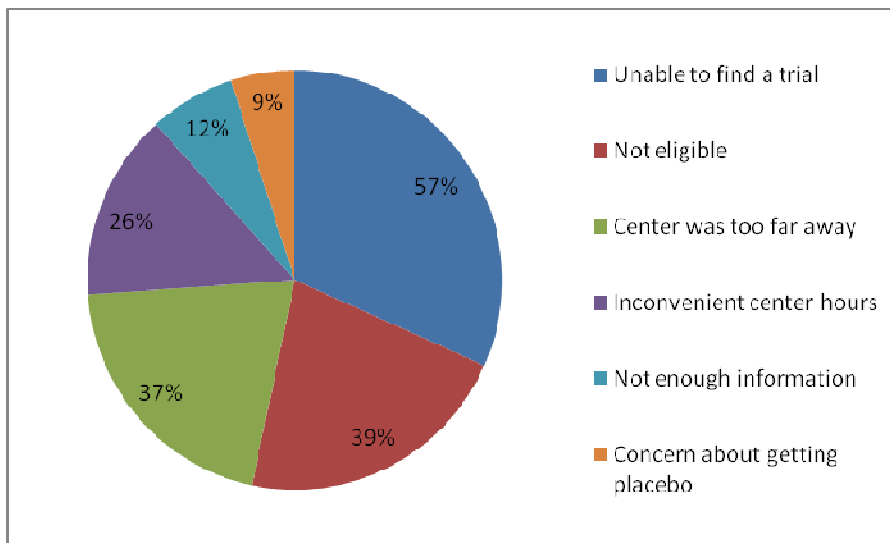
II. Subject Recruitment Issues in Clinical Trials

Subject recruitment and enrollment issues are a problem for most clinical trials: more than half of U.S. clinical trials experience enrollment delays of between one and six months (25, 29). It has been reported that subject recruiting delays 94% of clinical trials (26, 29). It is estimated that about 30% of the sites in a typical study will enroll *zero* subjects, at an average cost to the sponsor of over \$15,000 (27). Because of these statistics, numerous professional recruitment groups started to aggressively market their services, and site management organizations (SMOs) developed full-scale recruitment

programs (28, 29). Some of the more well-known patient recruitment providers include Acurian, D. Anderson & Co., Praxis, Veritas Medicine, and others.

Using the statistics provided by CenterWatch (29), the following chart (Figure 1) shows the reasons why a subject may not be able to participate in a clinical trial. This figure shows that the major reason potential subjects did not participate was because of the inability to find a suitable trial to enroll into. The second reason was being ineligible for the clinical trial, followed by the distance of the site, inconvenient center hours, inadequate information about the trial, and concern about getting placebo.

Figure 1: Reasons for Not Participating in a Clinical Trial



Source of Information: CenterWatch, 2002

It is estimated that more than sixty million people have severe, life-threatening and chronic illnesses in the U.S., but only seven million people participate in clinical trials (29). There is obviously a discrepancy in the number of actual trial subjects and the

number of people who can be eligible for clinical trials. Research conducted on this issue has shown that potential study volunteers want their physicians involved in their decisions to participate in a clinical trial. For example, in 2002, an online survey of nearly 1,000 participants showed that 73% of respondents want their physicians involved in the decision-making process (30, 29). Therefore, it is important for physicians to be involved in referring their patients to clinical trials, as well as providing information about these trials, which is another hindrance in the process of recruitment and enrollment.

Subject recruitment and enrollment can be a major problem for most clinical trials: recruitment timelines represent 22.3 percent of the entire clinical development timeline, but close to 70 percent of studies fail to recruit on time, and because of this, most U.S. clinical trials must extend enrollment by at least one month beyond the study completion period (31).

Some of the many ways clinical sites draw potential subjects is through newspaper, radio, brochures and flyers, public transit billboards, television, internet, etc. Advertising is key to subject recruitment for many clinical trials, but in order to be compliant with the sponsor and the site's IRB, guidelines must be followed. The following is a list of recommendations that will keep advertising compliant and ethical, as proposed by W. Parker Nolen, MBA, IRB administrator for St. Joseph's Hospital in Atlanta:

Include

- That the trial is *research*, not treatment
- Age restrictions or other qualifications for eligibility

- Some benefits (if any)
- Compensation (but without overemphasizing compensation)
- The time commitment expected
- The name of the center doing the research
- The name of someone affiliated with the trial who can be contacted for more information. The FDA suggests this should be someone knowledgeable about the trial rather than a general telephone operator without clinical expertise

Do not include

- Claims, whether explicit or implied, that an investigational drug or device is safe or effective for the purposes being investigated
- Representations that the product under investigation is equivalent or better than any other drug or device
- Pejorative terms that could serve as inducements to the reader to participate (e.g. in a weight-loss trial, to use a term such as “fat” to describe potential participants)

When recruiting subjects for clinical trials, it becomes necessary to have a recruitment plan developed that will target potential subjects within a given population, as well as healthcare personnel who can refer patients. This recruitment plan must lay out a strategy that targets three groups of people: physicians within the healthcare system where the clinical trials are being conducted (such as a hospital or clinic), physicians and medical personnel within the broader healthcare community, and the general public. Once a plan is developed, it must conform to the rules of the IRB and regulations in order to be ethical as well as legal. A recruitment plan can help a site reach its enrollment

goals as well as demonstrate to sponsors that this site can meet or exceed enrollment expectations.

Thus, I intend to test the hypothesis that when a recruitment plan is created and implemented for HCV clinical trials, more information is readily available to the medical and non-medical community, thereby increasing the number of participants in the clinical trials.

Specific Aims

In order to test my hypothesis, I analyzed and discussed with medical staff and personnel the patient referral process and determine the source of these patients and how these patients are recruited. I then developed a recruitment plan with Mrs. Nanette Myers, MBA, Baylor Research Institute Business Development Specialist, that targeted patient recruitment: 1) within the Baylor healthcare network through physician referrals; 2) referrals from physicians and healthcare personnel outside of this network; and 3) the general population.

Specific Aim #1:

Create pocket-sized inclusion/exclusion criteria cards for physicians that will summarize enrollment criteria in order to educate and aid physicians who will be selecting for suitable participants to refer to the clinical trials.

Specific Aim #2:

Publish detailed and informative website listings on the Baylor website of the individual clinical trials in order to educate the general public about currently enrolling trials which will facilitate enrollment.

Specific Aim #3:

Create a Research Highlight summary in the Baylor newsletter that will educate the Baylor medical community about the clinical trials in order to elicit referrals.

Significance

The HCV clinical trials at the Transplant Institute have not always met enrollment goals, and some studies have been closed due to insufficient enrollment. When inadequate recruitment becomes an issue in a clinical trial, it can reduce the ability of a trial to detect treatment differences (33). It is vital that safe and effective antiviral therapeutics are developed and reach market if they have the potential for hindering HCV replication, but insufficient subject enrollment can retard the clinical trial process and delay drug approval. The hypothesis that must be tested is: educating the medical and non-medical community about these clinical trials will help increase enrollment of subjects in clinical trials. This Internship Practicum Report will investigate the subject recruitment process for HCV clinical trials at Baylor University Medical Center's Transplant Institute and help find alternatives for the current issue of subject enrollment

in order to speed up the process of drug approval. These findings may also help with other clinical trials and subject recruitment issues they may have.

Materials and Methods

After consulting with Nanette Myers, a course of action was established involving several small projects geared towards HCV clinical trial education and advertisement (See Recruitment Plan, Appendix B). This would be not only for the clinical trial to which I was assigned, but some of the other clinical trials at the Transplant Institute as well. We needed to target the investigator's own pool of patients, referring physicians, and the public at large. I created Inclusion/Exclusion criteria cards, which were distributed to all of the hepatologists at the Transplant Institute. These cards contained a brief description of each study's inclusion and exclusion criteria, as well as a timetable for the study visits (See Appendix C for complete inclusion/exclusion criteria). These cards were pocket-sized, laminated, and placed on rings for ease of use. I then created website listings of each of the Transplant Institute's currently enrolling trials, and these listings contained trial information, including a summary of the trial and a few inclusion/exclusion criteria as well. The clinical trial listings were published on the Baylor website to be viewed by the general public. I also created a summary of the hepatitis clinical trials at the Transplant Institute to be published in the Medical Staff Newsletter which would be seen by Baylor health care personnel. All three of these activities are designed to address the hypothesis that educating the medical and non-medical community will help facilitate recruitment and enrollment. The

inclusion/exclusion cards are geared towards educating physicians, the website listings educate the general public, and the Research Highlight summary educates the general Baylor healthcare community.

Inclusion/Exclusion Criteria Cards:

My first plan of action was to create cards I could distribute to hepatologists at the Transplant Institute. In order to make these cards, I first needed to obtain the IRB approved protocols for each clinical trial that was enrolling. I then went to the section in each protocol that dealt with the selection of the study population. This section included the inclusion and exclusion criteria which each subject needed to meet in order to be enrolled into the clinical trial. The criteria list was exhaustive and included disorders and conditions which are rare. Because I wanted to create a criteria list that could fit easily onto a pocket-sized card, I summarized many of the individual criteria as well as excluding some of the less common conditions or diseases. Since these cards were designed to help physicians refer patients to the clinical trials, it was not necessary to include every inclusion and exclusion criteria. These referred patients would have their medical charts thoroughly reviewed by the Investigator and the Clinical Research Coordinator, and if they indeed had a special medical condition that excluded them from the study, they would not be allowed to enroll. Figure 2 is an example of a card I had created which contained a brief summary of the inclusion/exclusion criteria for one of the clinical trials.

Figure 2: Example of an Inclusion/Exclusion Criteria Card


Inclusion/Exclusion Cards
XXXX Hepatitis C Study

Inclusion Criteria:

- M or F >18 years old
- HCV genotype-1
- Liver biopsy w/out cirrhosis
- Insulin resistance
- Anti-HCV treatment-naïve
- Must not be pregnant, not planning to become pregnant/impregnate

Exclusion Criteria:

- Infection w/HCV other than genotype-1
- Chronic liver disease
- Decompensated liver disease
- HAV, HBV, or HIV infection
- History of HCV treatment
- Type-1 diabetes
- Receiving insulin



Exclusion Criteria:

- Pregnant or breastfeeding
- Anemia
- History of severe psych. Disease
- Poorly controlled thyroid dysfunction
- Hist of cardiac disease
- Sever seizure disorder
- Ophthalmological disorder
- Active or suspected cancer
- Antineoplastic or immunomodulatory treatment
- Hist of major organ transplant
- Immunologically mediated disease
- Chronic pulmonary disease
- Alcohol/drug abuse
- Investigational drug use

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Next, I created a study timetable that would be added to the inclusion/exclusion cards. The study timetable was a chart that outlined what medical events would occur at each study visit, from the initial screening visit until the last follow-up visit. This timetable was taken directly from the protocol, and the only deviation from the original timetable that was made was condensing multiple events that occurred at the same time in the study into one field instead of having a separate field for each event. Figure 3 is an illustration of the study timetable that was included in the set of cards.

Figure 3: Study Timetable

Schedule of Events:

Week (+pioglitazone arm)	35 days	BL(-16)	-12	-8	-4	0	4	8	12	16-20	24	28-44	48	60	72
Week (-pioglitazone arm)	35 days					BL	4	8	12	16-20	24	28-44	48	60	72
Informed Consent	X														
Medical History	X	X				X									
Physical Exam	X	X				X			X						X
Vital Signs/Preg Test	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Genotyping	X														
HCV RNA	X	X	X	X	X	X	X		X		X		X	X	X
Chest X-ray, ECG, Ophthalmologic Exam, Immunology, a-fetoprotein	X														
Hematology and Chem	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urinalysis	X	X			X	X			X		X		X		X
Thyroid Function Test	X				X				X		X		X		X
Plasma B-type Natriuretic Peptide	X			X		X			X				X		
Hemoglobin A1c	X	X		X	X	X			X		X		X		X
Blood Glucose/Insulin	X	X		X	X	X	X		X		X		X		X
Serum TNF-a and TGF-b		X		X		X	X	X	X		X		X		X
Serum adiponectin, leptin, ffa		X		X		X	X		X		X		X		X
Liver Biopsy	X														
Serum Bank	X	X				X			X				X		X
Questionnaire: BDI-FS					X		X	X	X	X	X	X	X		X
Questionnaire: BDI-II	X	X				X									
Drug Dispensing		X		X		X	X	X	X	X	X	X	X	X	
Drug Acc., AE, Concom Meds, Compliance - See Protocol		X	X	X	X	X	X	X	X	X	X	X	X		

Once these cards were printed, laminated, and placed on rings, they were distributed to the hepatologists at the Transplant Institute.

Website Listings:

My next project involved creating a website listing for the Baylor Clinical Trials website that would provide a summary for interested individuals about the HCV clinical trials at the Transplant Institute. I again needed the respective protocols of the clinical trials for this project. Figure 4 is an illustration of one of the website listings I created.

Figure 4: Website Listing

Study Title: Multicenter, randomized, open-label, controlled study of the effect of treatment with once weekly Pegasys® plus daily Copegus® with or without concomitant pioglitazone (Actos®) on early viral kinetics in treatment-naïve patients with chronic hepatitis C (genotype-1 HCV infection) and insulin resistance.

Short Title: Roche ML21301D

Study Description: To evaluate the effect of treatment with peginterferon (PEG-IFN) alfa-2a once weekly plus daily ribavirin according to body weight with and without concomitant pioglitazone on hepatitis C virus (HCV) titers during the first 12 weeks of anti-HCV therapy in treatment-naïve patients with CHC (genotype-1 HCV infection) and insulin resistance.

Some of the criteria for patients to qualify for the study include:

- Males or females 18 years or older
- Hepatitis C infection genotype I
- Liver biopsy without evidence of cirrhosis
- Insulin resistance

The following are some of the criteria which will exclude patients from the study:

- Abnormal thyroid dysfunction
- Cardiac disease
- Renal disease
- Pre-existing psychiatric condition
- Type-1 diabetes

Location:

Transplant Institute
Baylor University Medical Center at Dallas
3500 Gaston Avenue
Dallas, TX 75246

Lead Principal Investigator: Gary Davis, M.D.

For further information about this study, please contact: 1-800-4BAYLOR

The website listing contained information such as the study title, study description, a few inclusion and exclusion criteria, study location, name of the Principal Investigator, and contact information for interested individuals who wanted to learn more. The study title was easy to obtain, as it was located on the front page of the protocol, and I copied the title exactly as the sponsor had worded it. A short title was also included, as this was the title used when referring to the particular clinical trial; I used the short title the research nurses used for that study. A study description was included next,


and this was taken from the protocol as well. Because there was not an exact place in the protocol where a study description was provided, I looked under the sections labeled Trial Objectives and Purpose, and Trial Design. Looking at these different sections helped me to write a good study description which provided the necessary information about the trial. I also included a very brief inclusion and exclusion criteria list that highlighted the major conditions that would exclude someone from the study. I made sure to mention that this list only contained *some* of the criteria, not all. I ended the listing with the location of the clinical trial site, the name of the Principal Investigator, and the contact number for Baylor.

Hepatitis Newsletter Highlight:

I created a research summary for both hepatitis B and C clinical trials to be added to the Baylor Medical Staff Newsletter in the Research Highlight section. This summary provided information about the hepatitis clinical trials being conducted at the Transplant Institute in order to inform and educate healthcare employees at Baylor as well as possibly elicit a referral to one of the clinical trials. This project also required obtaining the protocol as well as researching the standard of care provided to infected patients requiring antiviral therapy. The summary needed to be worded in such a way that someone who did not know about hepatitis or antiviral therapy could still understand it. This information was found in the protocol under the section titled Background Information. Although the protocols provided a thorough description and explanation of the drugs being investigated in the study, I had to research the information online as well

in order to find simpler terms I could use in the summary. Figure 5 is an illustration of the Research Highlight that I created.

Figure 5: Research Highlight



Hepatology Research
 Currently, Baylor Research Institute (BRI) is conducting more than 800 research projects. Each month BRI highlights active research studies open to enrollment.

The following table provides an overview of studies currently being conducted related to Hepatology Research. If you have potential patients who may qualify for these research studies, please contact the research nurse(s) listed below -

Research Area	Study Summary	Contact Person
Hepatitis C	There are currently 17 active clinical trials for the treatment of Hepatitis C, with 5 studies open to enrollment. These studies have several goals, which include evaluating the safety and efficacy of combination therapies involving the use of Pegasys® and Copegus® (both are provided in standard of care) in combination with a third investigational drug. The majority of investigational combination therapy drugs are protease inhibitors. Protease inhibitors a class of direct acting antiviral drugs being developed for hepatitis C, which show great promise in inhibiting viral replication. <u>Study Population:</u> Male or female ≥ 18 years of age who are not currently pregnant or planning to become pregnant. They must be diagnosed with chronic Hepatitis C.	Karla Huang karlah@Baylorhealth.edu (214) 820-6984
Hepatitis B	There are currently 6 active clinical trials for the treatment of Hepatitis B, with 2 studies open to enrollment. These studies compare the safety and efficacy of current standard of care treatment options, as well as compare them to placebo. Two of the current FDA-approved treatment drugs are reverse transcriptase inhibitors used to block HBV viral DNA replication. Patients positive for HBV who have taken these reverse transcriptase inhibitors have shown a significant histological, biochemical, and virological improvement. <u>Study Population:</u> Male or female ≥ 18 years of age who are not currently pregnant or planning to become pregnant. They must be diagnosed with chronic Hepatitis B.	Sharon Briner sharonb@Baylorhealth.edu (214) 820-1737

Because I was assigned to a research nurse conducting clinical trials for HCV, I already knew much of the background information about the drugs provided as standard of care, as well as the investigational drug. However, the investigational drug could not

be revealed because it was proprietary information, so I researched what class it belonged to and provided information about that, namely, the class of protease inhibitors.

I did not know about the HBV investigational drugs or standard of care for HBV, so before I researched this information, I spoke with the research nurses involved in these clinical trials and asked them the necessary questions about the names of these drugs and what types of treatment options were available.

Once I obtained the necessary information, I created a brief summary of the hepatitis B and C studies, and added a general statement about the target study population. I also included the number of clinical trials that were active, and the number of studies open to enrollment. The brief summary included a short statement about the drugs that would be administered, including class information. Finally, I added a contact person, their name, e-mail address, and phone number, for interested individuals.

All of these projects were reviewed by Karla Huang, Research Nurse, Betsy Stein, Director of Clinical Research, and Nanette Myers before being submitted to the IRB for approval. The Research Highlight was also approved by Gary Davis, MD, Director of the Hepatology Department.

Results and Discussion

Results

When potential subjects are directed to Karla Huang, either by a physician or by Nanette Myers, she is given the name of the referring physician, or told if they found out about the clinical trial independently through the Baylor website. I interviewed her

regarding the success of my various projects. I was informed that I was able to help her recruit one viable patient who is now enrolled in one of her studies. This subject learned about the clinical trial through the website listing I had created, and when he contacted Nanette Myers, she directed him to Karla Huang. Because Karla's studies usually only enroll up to ten patients, as was the case with this study, I was able to help her with 10% of her total enrollment for this particular study.

I created a set of inclusion/exclusion cards for each of the three hepatitis clinical trials that were enrolling, and these cards were distributed to the hepatologists at the Transplant Institute. Unfortunately, I was not able to interview the hepatologists at Baylor about the usefulness and effectiveness of the inclusion/exclusion criteria cards due to their busy schedules and their other duties and responsibilities. Also, because of limitations on the length of my internship, I will not be able to assess the effectiveness of the cards in the future. These cards did receive good reviews from the research nurses who saw them because they were pocket-sized, easy to carry, contained on a ring, and laminated, making them durable.

The second project involved creating website listings for all of the currently enrolling clinical trials at the Transplant Institute and having them published on the Baylor website for public access. Because these website listings had already been created for other departments at Baylor University Medical Center, I felt that the Transplant Institute's clinical trials department would benefit from the exposure they received from being published on the website.

The final project was creating a summary of the hepatitis B and C clinical trials at the Transplant Institute, and having this published in the Medical Staff Newsletter. This

summary would be seen by Baylor healthcare personnel, and it helped to inform them of the hepatitis clinical trials being conducted. I was also not able to assess the effectiveness of the Research Highlight that was published in the Baylor Medical Newsletter. Again, I did not have ample time or the resources to interview medical personnel within the Baylor healthcare community.

Discussion

The intent of this practicum project was to test the hypothesis that educating the medical and non-medical community about the HCV clinical trials would increase subject enrollment. I was able to assist Karla Huang enroll one patient through my projects, which is approximately 10% of her total enrollment for that trial.

However, I do not believe that this provided sufficient information to prove or disprove my hypothesis. There were certain limitations that created challenges to my endeavor. Due to the nature of subject recruitment and enrollment, it is not possible to observe recruitment and enrollment rates over a short period of time. Because of my internship length (duration of only six months) I was not able to stay for a longer period of time and observe an increase or decrease of enrollment rates at the Transplant Institute. These projects that I developed and implemented would need to be given more time in order to assess effectiveness and viability. Also, because these clinical trials were for HCV infected individuals, which is a small target population, more time would be needed to allow these projects to reach the right audience. For instance, the inclusion/exclusion cards are great tools in helping physicians refer the right patient to a clinical trial, but more time must be given to these physicians so they can be exposed to a bigger patient

pool. Hepatitis clinical trials usually enroll about four to ten subjects per site, and this is precisely because it is difficult to find a large number of viable candidates who are HCV infected. When you target a small population, the chance of encountering someone from this population is also proportionally smaller. Therefore, my internship length did not provide sufficient time for me to observe any increase or decrease in enrollment at the Transplant Institute.

The three projects I worked on were invaluable educational tools and should be implemented at other clinical trial sites. The inclusion/exclusion criteria cards are great reference tools for physicians who cannot remember the specifics of a certain trial but need to know if a patient of theirs is eligible. The website listings are available to the public and make it easy for anyone interested in finding hepatitis clinical trials to locate a good match at Baylor. And finally, having a summary of the hepatitis trials listed in the Baylor Staff Newsletter informs everyone in the Baylor healthcare community of these trials and whom to contact if they have potential subjects they can refer.

These were the three main targets when the recruitment plan was designed: the physician's patient pool, the healthcare community, and the general public. The various projects I completed addressed these three targets. Unfortunately, because of the nature of the hepatitis clinical trials, I am not able to determine how effective my strategies were in recruiting patients versus patient enrollment before the projects were implemented. In order to make these assessments, I would need at least a year or more to observe trends in recruitment and enrollment after the completion of my projects, and compare this data with recruitment and enrollment rates from previous years. To calculate this data, I would obtain the number of patients for each study who were enrolled at the end of the

enrollment period, and compare this to the subject enrollment goal for that study. I would obtain these numbers for every clinical trial at the Transplant Institute, and create a graph visualizing these figures.

I would also create a survey or questionnaire that I would provide to hepatologists after one year had passed from when I first distributed the inclusion/exclusion criteria cards. I would ask questions such as:

- Did you find the cards helpful?
- Were the cards easy to access? Easy to read?
- How many patients were you able to refer because of the cards?
- How many patients did you exclude because of the cards?
- Is there anything you would add or take out from the cards?
- Did the timetable help you understand the clinical trial?
- Should the timetable be included?

Next, I would create a survey or questionnaire to distribute to Baylor healthcare employees which would ask questions about the Research Highlight section in the Baylor Medical Staff Newsletter. I would also ask questions specifically about the Highlight on hepatitis clinical trials. Here are some of the questions I would ask:

- Is the Highlight easy to understand?
- Does it increase your knowledge about the research topic?
- Have you ever contacted a clinical trial because of a Highlight?

- Have you ever referred a patient because of a Highlight?
- How often do you read this section?
- How often do you read the Newsletter?
- Do you want it to contain more information about the trial?

These surveys/questionnaires would be helpful in assessing the effectiveness of the inclusion/exclusion criteria cards as well as the Research Highlight, and this combined with the graph for enrollment rates after the recruitment plan implementation would provide a complete picture of the overall effectiveness of my internship projects. I would then be able to determine what can be used for future clinical trial recruitment projects and what can be improved upon.

If I were given more time during my internship, I would make a few changes. First, I would distribute the inclusion/exclusion cards to other physicians outside of the Hepatology Department. I would give them to Endocrinologists, Transplant Surgeons, General Surgeons, Gastroenterologists, and Primary Care Physicians, because I believe that these are the physicians who would most likely come across HCV infected individuals. I would also try and submit a Research Highlight Summary to newsletters at other hospitals and institutions of medicine. Finally, I would create flyers and brochures that would be placed in waiting rooms as well as exam rooms in the offices of physicians. These advertisement tools would provide information about HCV clinical trials in laymen terms, and also contain an inclusion/exclusion criteria summary which would inform interested patients if they are eligible and advise them to speak to their doctor for more information.

I would like to add a note about the enrollment efforts at the Transplant Institute. After consulting with Betsy Stein, I was informed that one of the reasons that some of the hepatology trials did not meet the enrollment goals was due to the length of time needed to get the study initiated at Baylor. Baylor is required to use a local IRB while other sites most likely use a central IRB. Processes have been changed since Michelle Acker, Manager of Transplant Research, became manager to shorten times from when a new protocol is received to get it to the IRB, prepare and negotiate the study budget, and have everything ready for study initiation (ex. prepare source documents, etc.). Since these studies are typically on a competitive enrollment model, we were definitely at a disadvantage compared to other sites who used a central IRB. I understand that the new processes in Transplant Research have provided more time to enroll on these studies which is key in meeting enrollment goals. Also, it is a big advantage for the hepatitis clinical trial site that they have one program based at two facilities (Baylor University Medical Center and Baylor All Saints). This may give them an advantage on those studies that are a fit for both campuses and allow them to enroll from two patient bases. The hepatologists are all part of one practice group and do collaborate on many projects.

Summary and Conclusion

Hepatitis is an inflammation of the liver which can be deadly if left untreated. Current antiviral therapy that is being developed is promising and can stop the disease from progressing. Clinical trials are underway and patients need to be recruited for these trials in order to test the safety and efficacy of these drugs. Unfortunately, due to the

restrictive nature of the protocols and their inclusion/exclusion criteria, as well as the lack of proper advertising of the clinical trials, an insufficient number of patients are enrolled. In some cases, a study is closed due to insufficient enrollment. My internship at the Transplant Institute at Baylor University Medical Center provided me with insight on patient recruitment and enrollment obstacles, and I was able to work on various projects that targeted this issue. I learned how to make inclusion/exclusion cards, a powerful tool in helping physicians refer patients to clinical trials. I also learned how to create website listings for clinical trials that can be seen by the public, for educational purposes and as a recruitment tool. I gained experience in the field as a Clinical Research Manager/Coordinator and learned as well as experienced all of the tasks and responsibilities that accompany the role.

Even though I was not able to fully assess the effectiveness of my three recruitment projects, I have gained much understanding of how a recruitment plan is developed and implemented. I also know now of various advertising tools that can be implemented when seeking subjects for enrollment. These learning experiences have seasoned me in the field of Clinical Research Management, and I feel that I am better equipped to conduct a clinical trial as a CRC and take on the responsibilities it entails.

CHAPTER III

INTERNSHIP EXPERIENCE

Internship Site

In fulfillment of the curriculum requirements for a Master of Science in Clinical Research Management, I interned at the Transplant Institute at Baylor University Medical Center in Dallas, Texas. My internship mentor was Betsy Stein, CCRC, of Baylor Research Institute, Director of Clinical Research. I also worked closely with Karla Huang, R.N., BSN, MBA, CCRC, at the Transplant Institute. I was fortunate in that I was able to witness two site initiations at the Transplant Institute and also take part in numerous tasks for Karla's clinical trials. I worked with doctors and nurses in the departments of Hepatology, Nephrology, and Transplant Surgery. I helped create and complete safety letters, biopsy reports, and case report forms. I also arranged and organized e-mail correspondence, regulatory binders, and patient shadow charts. I attended an IRB meeting, transplant seminars, site initiation meetings, monitor visits, a meeting with a sponsor representative, and other general clinical research coordinator meetings. Throughout my internship, I was exposed to every duty and task for which a CRC would be responsible, as well as site specific tasks within the Transplant Institute. The following staff and research personnel contributed significantly to my internship learning experience:

- Betsy Stein, CCRC, Director of Clinical Research

- Karla Huang, BSN, MSN, CCRC
- Nanette Myers, MBA, BRI Business Development Specialist
- Diane Johnson, BSN, MSN
- Sharon Bruer, RN, CCRC
- Nicole Schaben, RN, CCRC
- Jonnie Edwards, RN, BSN, CCRC
- Sonnya Coultrup, BS Biology
- Elizabeth Grayson, RN, BSN
- Dana Murdter, RN
- Kimberli Gillett, RN
- Melissa Groth, RN, BSN
- Michelle Acker, RN, BSN, CCRC, Manager of Transplant Research
- Valerie Vega
- Aaron Killian, PharmD, BCPS
- Gary Davis, MD
- Henry Randall, MD

Listed on the following pages is a summary of some of my various tasks and activities throughout my internship:

IRB Meeting

I attended Baylor's IRB meeting and was able to listen to the discussions and deliberations of the IRB members. I sat alongside Principal Investigators, Sub-

Investigators, and Clinical Research Coordinators as we listened to the IRB members go through the list of clinical trials, make arguments for or against the changes/amendments proposed, decide on letting a clinical trial proceed, and vote on the issues. Any time there was a vote on a clinical trial in which a voting member was a part of and therefore had a conflict of interest, that member would leave the room until the other members had finished voting. I learned a great deal about IRB proceedings, how protocols are approved and/or amended, and how cases are presented for or against an issue by either a voting member or an audience member.

Site Initiation Meetings

I attended two site initiation meetings: one for Karla Huang's study, another for Melissa Groth's study. In both of the meetings, the CRA (clinical research associate, aka monitor) from the sponsor would review the protocol with the Investigator, Sub-Investigator(s), and CRC, as well as make sure that the site was compliant. A powerpoint presentation was delivered in both instances, and everyone at the meeting was given a packet with the presentation's slides. Topics covered included reviewing the protocol, the informed consent process, drug delivery and accounting of drug, study visits, case report forms, and adverse events, as well as other protocol-specific topics. Also, the CRA was given a tour of the facilities, which included the pharmacy where drug was delivered and maintained, the patient room where patients were seen for their study visits, as well the Landry Center, where the monitor from the sponsor would go to meet with the CRCs.

Safety Letters

About twice a month, every month, I would organize safety letters sent from the various sponsors of Karla's studies, and create a safety letter spreadsheet to submit to the IRB. Each sponsor's safety letter report had to be submitted on separate spreadsheets to the IRB. The safety letter spreadsheet would contain information such as the date of the report, the date of the event, the case number, the type of adverse event, and how each drug in the study was related to the incident, if at all.

Biopsy Report

About twice a month, every month, a biopsy report needed to be submitted to Dr. Davis, Director of the Hepatology Department as well as the Principal Investigator for Karla's hepatitis C studies. These biopsy reports were spreadsheets that contained patient summaries for every patient who received a liver transplant, but the summary would contain information about the biopsy report of their native liver prior to the transplant. These summaries included the patient's name and identification number, diagnosis, date of biopsy, and the biopsy report of their native liver.

Clinical Trial Spreadsheet

I created a spreadsheet for the Transplant Research Manager, Michelle Acker, that contained information about every research nurse's clinical trials. This spreadsheet included information such as the study name, the principal investigator, IRB number, sponsor, enrollment status, number of subjects, anticipated completion date, subject goal,

and cash balance. Because each research nurse at the Transplant Institute had numerous clinical trials, I had to consult with each nurse to make sure I had accurate information.

Journal Summary

Contained in Appendix A is a journal of my day-to-day activities at Baylor University Medical Center. Journal entries are arranged by week, with a summary of each working day's events and activities.

APPENDIX A: INTERNSHIP JOURNAL

Weekly Journal: 08/11/08 to 08/15/08

08/11/08

I met with Betsy Stein at 7:30 AM and she introduced me to the Baylor staff in the administration office. I signed the Confidentiality Agreement and was given an Employee Handbook. We attended a manager's meeting after the introduction. I spoke with Ms. Stein about the Baylor Research Institute (BRI) and the clinical trials they're involved in, and she explained to me her roles and duties. I was then given a tour of the Landry Center, specifically the Transplant Research, where I met with the staff, including the research nurses. We then went by Dr. Hollinder's office to drop off a package, and also met with a past intern at BRI (Tory). I spoke to him about the internship and the thesis I would write. Back at Ms. Stein's office, I listened in on a phone conference she had with Gordon Hayward regarding a class they would be teaching at Dallas and Fort Worth for Baylor employees, instructing them on how to optimize use of Microsoft Outlook.

08/12/08

I read the informed consent and the protocol for the clinical trial I would be following. Ms. Stein took me to the Landry Center again for a meeting regarding payroll, and I met with Karla, the nurse in charge of the clinical trial. At the meeting, Ms. Stein spoke with Elizabeth about setting up payroll online. Ms. Stein also spoke with Sharon, another research nurse, regarding a recent job opening and a potential candidate Sharon interviewed. We ended the day by going to the Parking Office, where I had my parking assignment and I.D. Badge given to me.

08/13/08

In the morning, I worked on the BLN (Baylor Learning Network) modules that are required of all employees. I went to the Landry Center at 10:00 AM to meet with Karla. We went to the Roberts building to perform a baseline EKG for the sponsor, which we then sent to them electronically. Back at the Landry Center, I screened patients by reviewing their medical documents in order to find those who met the inclusion criteria and did not meet the exclusion criteria. Finally, I watched Karla work on the training module that the sponsor required of all nurses operating the EKG machine.

08/14/08

I worked on the BLN modules first thing in the morning. At 10:00 AM, I went to the Landry Center and continued reviewing the medical documents of potential subjects. I then had a meeting with Karla about patient screening. At 1:00 PM, I attended a training session taught by Betsy Stein for billing compliance, where I received a certificate. I went back to the Landry Center and finished my evaluation of the patients' medical records.

08/15/08

I finished all of the modules on the Baylor Learning Network first thing in the morning. I then worked on my journal entries for the week. In Betsy's office, I met and spoke briefly with a doctor who had just finished his fellowship in plastic surgery. I then attended a meeting at 2:30 PM with Betsy, Michelle Acker, the Transplant Research Manager, and a manager from Baylor All Saints in Fort Worth about staffing issues and payroll for the

islet cell research program. I attended another meeting with Betsy and JaNeene Jones, the Vice President of Transplant, about a research team being set up as part of the Baylor Regional Transplant Institute's strategic planning initiative.

Weekly Journal: 08/18/08 to 08/22/08

08/18/2008

I went to the admin building in the morning to meet up with Betsy. We talked about the internship and my Wednesday committee meeting. I then went to my desk and decided it would probably be a good idea if I looked over the CRM handbook. I found out that I had some CRM paperwork to fill out, so I did that until it was time for me to head over to the Landry Center. I got to the Landry Center and started on the patient biopsy logs Karla wanted me to type up for Dr. Davis. My job was to extract information from the patient medical documents and type it up an easy-to-read format for Dr. Davis so he would have the info in an easy to read format. At noon, I attended a site initiation meeting with Dana and Karla. We met with a sponsor and CRO concerning an autoimmune hepatitis drug they wanted to bring to market. The CRO representative went over their CRF forms and regulatory files binder. Their CRF forms were well written and very user-friendly. I finished the day by helping Karla organize her regulatory files binders and screened some more patients for her trials.

08/19/2008

I started the day looking over the CRM forms and handbook again to make sure I wasn't forgetting to do something. I filled out the required graduation documents for the CRM degree plan. At the Landry Center I finished filling out the biopsy logs for Dr. Davis. I went with Karla to 4 Roberts to see patients for their weekly visits. She told me something very interesting after we finished examining the patients: most of the patients whose viral loads disappeared after using the previous study medication had to be told months later after their follow-up visit that the virus was once again present in their blood! So some of these people would leave thinking that they were "cured", but then receive a phone call from Karla saying that the virus was back. I met two doctors that day, Drs. Henry Randall and Gary Davis, and the supervisor of the abdominal transplant ICU, Steve Kellogg.

08/20/2008

I went straight to the Landry Center first thing in the morning and started organizing Karla's lab documents. I also finally got my work computer up and running. I screened some more patients for Karla, then attended my 1:00 PM meeting with Betsy and my committee members. After the meeting, I got some delicious cheesecake from the back table, and went back to the Landry Center to finish helping Karla with paperwork.

08/21/2008

Karla and I spent the day with her sponsor's monitor, who she had no idea was coming until he showed up. He was really nice and helpful. I spent most of the day printing and organizing correspondence e-mails which needed to go into the regulatory files binder.

08/22/2008

I had an appointment with my OB in Arlington so I didn't go in to work that day.

Weekly Journal: 08/25/08 to 08/29/08

08/25/2008

I met with Betsy in the morning and we talked about my proposal. I then went to my desk and worked on my weekly journal. I spent the rest of the day at the Landry Center organizing e-mail correspondence. I also had to go back and find all the e-mails that had attachments and file those, too. I double-checked all of the e-mails and made sure I hadn't missed any attachments.

08/26/2008

I stayed in the admin building all day to work on my research proposal. I did take a couple of hours out to walk over to the Baylor library and check out some books on Hepatitis.

08/27/2008

I spent the whole day at my desk working on the research proposal. I did find an e-book on the Baylor library's website and printed out all of the chapters on hepatitis viruses.

08/28/2008

I have designated Thursdays as the day when I will work solely on my paper. I went to UNT HSC in Fort Worth and submitted my graduation documents. I also set up my RefWorks account and can now access it from anywhere, any computer.

08/29/2008

I spent the morning working on my weekly journal, which I had written down but needed to type up. I went to the Landry Center afterwards and followed Karla around as she visited with patients. At 1:00 PM, we attended a town hall meeting Janeene was doing for the transplant people. It was the best meeting I had attended so far, complete with a table full of candy and cookies, and a raffle drawing at the end. I didn't win anything, but I did eat too much chocolate. We went back to 4 Robert so Karla could finish the lab work on the blood she had collected that morning. I watched her for a little bit, then headed back to the Landry Center to finish my weekly journal.

Weekly Journal: 09/01/08 to 09/05/08

09/01/08

Labor Day.

09/02/08

I spent the day working on my paper. Well, mostly just reading up on Hepatitis. I also submitted my weekly journal from the previous week.

09/03/08

In the morning, I went to BRI and used the UNT HSC online library research engine to look up journals and articles. I didn't find a whole lot on Hepatitis subject recruitment, but I did find articles on subject enrollment and retention issues for clinical trials, in a very general sense. I then went to the Landry Center where Michelle asked if I could make a spreadsheet of all of the research nurses and their trials, color coded. I spent the rest of the day trying to read their hand-written notes on each of their clinical trials. Then, I had to go back and double-check with each nurse on the accuracy of the chart. It was a good experience for me because I found out about everyone's projects.

09/04/08

In the morning Betsy reminded me that I had lunch with her, Tory, and Lucy that day. I headed over to the Landry Center to finish the spreadsheet I had started the day before. I had to break for the lunch meet-and-greet with my fellow CRM majors and I really enjoyed myself. They were both very nice and helpful. I had Lucy show me where the class I would be attending on Friday was located. I had enough time when I got back to the Landry Center to submit the final updated spreadsheet to Michelle before I had to leave.

09/05/08

In the morning, I attended a class taught by MedTrials for clinical trial personnel about clinical trial rules and procedures. It was a good refresher course. And the food was great. I met a few nurses and generally enjoyed myself. They talked about adverse events and quizzed us on different scenarios and how we should report them. I liked that it was interactive and it was really informative at the same time. I left and went to the Landry Center to help Karla with some paperwork she needed organized and filed.

Weekly Journal: 09/08/08 to 09/12/08

09/08/08

Safiya had a pediatrician appointment in the morning. I went to the Landry Center after her appointment and spent the rest of the day with Karla printing and filling out patients' medical records and the biopsy logs she needed completed so she could have them submitted to Dr. Davis. I also screened some more patient medical records to find potential subjects for enrollment into the trials.

09/09/08

I went to the Landry Center to meet up with Sharon. We went together to 4 Roberts and visited with patients. She showed me her study equipment and gave me a tour of the back supply room. She had to draw blood from the patients and get the rest of their unused study medication so that she could give them more of the medication. We went to the lab and she performed the proper lab work on the blood and prepared it for shipping. I also saw Karla do this countless times after she drew blood from patients.

09/10/08

I followed Sharon again today, but this time I saw a double pass liver biopsy. They had to take out two pieces of liver for the study. I observed the Fellow perform this procedure. I also waited for Dr. Randall to come and give the patient a physical exam after the procedure. Sharon gave me a tour of the transplant ICU, and I met with the residents and fellows doing their rotations. I learned that residents weren't allowed to perform anything for the clinical trials because their rotations were only for six months and the nurses needed doctors who could stay for longer so the paperwork wouldn't be a nightmare for each doctor every six months.

09/11/08

I spent the day today working on my paper. I read some material on non-viral hepatitis, like alcohol or autoimmune related.

09/12/08

I followed Karla today as she visited with patients. She had three patients in the morning, two of whom had week 1 visits, and the third one was being enrolled and it was his day 1 visit. I observed her draw blood, watched her and Dr. Davis both give a brief physical exam, talk to the patients about the study and the medications, and then process the blood for shipping to the labs.

Weekly Journal: 09/15/08 to 09/19/08

09/15/08

I went to Fort Worth in the morning to meet with Dr. Oglesby and discuss the research proposal. He made some really good points, and when I left and spoke with Betsy, she made the almost exact same points about the paper. I drove back to Dallas and went to the Landry Center to see if Karla needed me to do anything. She had me type up her Safety Letters. One copy she would keep and the other copy she would send to the IRB. These letters were typed up based on IND safety reports received from other clinical trial sites. All of the adverse events had to be properly documented at each trial site, no matter where the event actually occurred. It took me a very long time to read all of the reports and extract the proper information. I also needed to find out if the Investigator thought the event was drug or study related. Surprisingly enough, in most cases the Investigator attributed the event to at least one of the drugs administered in the study.

09/16/08

In the morning I went with Betsy to a Coordinator's meeting. They went over different topics, including finance. I then went straight to 4 Roberts where Karla was seeing a patient. I observed her while she met with patients, one of whom was being enrolled into the study. I was glad to be there for the enrollment, because the subject asked very good questions that I would have liked to ask myself. They had to do with the study being blinded and if that meant he wouldn't know until later in the study if the treatment was working or not. Dr. Davis came in to speak with him, and we both ended up asking the doctor questions! At noon, I left the clinic to attend a seminar on Hepatitis B given by Dr. Perillo. It's called "Focus on Research" and I plan on attending the next one. It's more scientific than the other meetings I've attended so far, so I really enjoyed it because I could actually relate. When I left I went back to the Landry Center with Karla and worked on my weekly journals.

09/17/08

I finally had feedback from all three of my committee members, so I spent the day rewriting my research proposal.

09/18/08

I went to BRI in the morning and searched the web for journal articles for my thesis. At noon, I attended the IRB meeting and it was really eye-opening. I really enjoyed the meeting and finally understood what it is they do. They took issue with even the most minor details and any kind of wording they didn't think was appropriate. Because clinical trials involve testing on humans, it's so important for the subjects to be properly and thoroughly informed of what they're signing up for. It really is the job of the IRB to take care of the people enrolling in these trials, and Baylor's IRB does a very good job of that. When we got back to the BRI building, I continued perusing the UNT HSC online library catalog for some good articles on subject recruitment/enrollment. Unfortunately, I did not find a single article on subject recruitment/enrollment for any type of Hepatitis trial.

09/19/08

I knew that Karla saw patients on Friday, so I went to the Landry Center and waited for her. When she didn't show up, I asked the receptionist where she was, and I was told that she had her day off today. I left and went to the UNT HSC library to work on my research paper.

Weekly Journal: 09/22/08 to 09/26/08

09/22/08

I went to BRI in the morning to see what Betsy had for me. She needed to fill some vacant positions in the Transplant Institute, and she found two nurses to fill two of the three vacancies. She needed to make employee handbooks for the new hires, so she had Sherese, an administrative assistant at BRI, show me how to make them. As I made three handbooks, I saw all of the material that went into them and realized how much work it took to make them. They included documents like the ICH guidelines, Baylor rules and regulations, Ethical Code of Conduct, pamphlets, etc. I had to photocopy and organize all of the documents for the three binders, so I was able to see exactly what was needed for an employee handbook. I was also given one on my first day, so I thanked Betsy for making that one for me.

09/23/08

I spent the day working from home because Safiya was not feeling well. I read the book Schiff's Diseases of the Liver, specifically the chapters on non-viral Hepatitis.

09/24/08

While I was getting ready for work, Safiya rolled right off the bed. Needless to say, I rushed her to the ER at Medical City in Dallas and spent the whole day there.

09/25/08

I went to the Landry Center in the morning so I could spend the day with Karla. I worked on my weekly journals then attended a luncheon with the staff at the Transplant Institute on 4 Roberts. The meeting was hosted by Lisa Jennings, who is a statistician in charge of the Transplant Database. It was a teleconference, so Baylor Fort Worth also took part. At the end of the meeting I spoke briefly with Dr. Randall about observing him while he worked, and he told me to speak to his secretary to schedule a meeting. When Karla and I got back to the Landry Center, I typed up some more Safety Letters for her study and made copies for both her records and the IRB's.

09/26/08

In the morning, I met with Nanette to develop a formal recruitment plan and she gave me some books and information about subject recruitment/enrollment. She is in charge of all of that at BRI, so she had plenty of good material to give to me. She also gave me good suggestions for my thesis, and we decided to sit down with Karla and come up with a plan to help her enroll subjects for her trials opening up. I then left to go to 4 Roberts so I could watch Karla meet with patients. She told me that one of the patients told his employer he had Hep C, and that the company required a letter from Dr. Davis stating he wasn't contagious. Karla told me that not even an HIV diagnosis has to be reported to an employer, so this man didn't have to do this. He was really nice, and said that he wanted people to know that he had it and to be cautious around him. Still, he didn't have to tell anyone at work, he was under no obligation. The last patient of the day came in at 3, and Karla had to ship the bloodwork by 3:30, so she saw him and drew his blood pretty quickly in order to process it and ship it on time.

Weekly Journal: 09/29/08 to 10/03/08

09/29/08

I went to BRI in the morning to speak with Betsy about the internship and changing the time when I would come in. We decided that I would extend the internship an extra 11 days so that I could come in at 8:00 am instead of 7:30 am. I then took some files for her over to Landry. At the Landry Center, I met with Karla and we decided that it was time for September's e-mail correspondence to be filed, and she could clear her inbox. I printed out all of the e-mails she received from her sponsor, including attachments, then organized them by month in a correspondence binder. I finished filing her correspondence and then met with Nanette about recruitment ideas we came up with and that I could pursue.

09/30/08

Our religious holiday is today, so I took the day off.

10/01/08

I had a meeting with Betsy in the morning, and we went over my weekly journals, making changes where needed. She then trained me in StudyManager and taught me how the system works. It seemed pretty brilliant to me, and time efficient. When I left and went to the Landry Center, I spoke to both Karla and Sonnya about StudyManager and using it at the Transplant Institute. I spent the rest of the time making photocopies for Karla of documents that needed to be sent to the IRB, including amendments and letters from Dr. Davis.

10/02/08

Today was the day that I would meet with Nanette and Karla to discuss subject recruitment issues. I spent the whole morning making photocopies of the books and articles Nanette had given me to use for my paper. I finished half of them, then went to the meeting in the Conference Room. We talked about Karla's studies and which ones were enrolling or about to enroll. Nanette and I discussed ideas for a recruitment plan with Karla's help. We left the meeting at noon and went to a luncheon/seminar the hepatologists had started on 4Roberts. One of the Fellow's was presenting a report on a patient he was in charge of. Karla and I went back to the Landry Center and I spent the rest of the afternoon with her while she made phone calls to patients, mainly to answer questions about the study they were on. One patient wanted to enroll in a trial, so she answered questions regarding her study.

10/03/08

I spent the whole morning with Karla on 4 Roberts seeing patients for their weekly treatments. I left when she had to spin the blood she had drawn and ship it, and went to the Landry Center. There, I attended a staff interview they had for someone who was applying for a research nurse position. After the interview, I asked Sharon if I could help her with any of her studies. She had some of Elizabeth's studies, so she needed help. I spent the rest of the day filing documents for her, helping her fill out financial disclosure

forms to send to the various people on her study, organized papers for her studies, and created a binder for a new patient's shadow chart.

Weekly Journal: 10/06/08 to 10/10/08

10/06/08

Today I would learn how to use StudyManager. I spent the morning before the class at 1 to make photocopies at BRI of all of the material Nanette had provided for my thesis paper. When I finished making photocopies, I returned the documents back to her. I then went to lunch to eat and headed over to my Study Manager class. This software is really user-friendly and a great tool for any research nurse. I've had MANY discussions with Betsy about why they don't use this at Transplant Institute.

10/07/08

I went to the Landry Center in the morning, and found Sharon in distress. I spent the rest of the morning helping Sharon organize and file binders that cluttered her desk. She had picked up some of Elizabeth's studies, and she was really behind on everything, so I didn't mind helping her out. I then went to Karla's desk and filled out Safety Reports that she needed to submit to the IRB. I finished right on time for my meeting with Nanette at BRI. We discussed subject recruitment issues and possible solutions for Karla's trials, and we came up with a plan. We decided on some tasks for me to do, and I left with a copy of the plan. I spent the rest of the time looking at the attachments she had e-mailed to me that included the inclusion/exclusion cards she made for doctors/nurses and the websites where she put up information about the trials, as well as a sample newsletter she sent out to doctors.

10/08/08

I went to Fort Worth to read at the school's library. I read up on Laennec's Cirrhosis, since a lot of patients seemed to have this type of cirrhosis along with chronic hepatitis C cirrhosis. How should I put this delicately... I was not surprised at all to find that some of these hep C patients who were once I.V. drug users also had drinking problems, which will cause cirrhosis of the liver as well.

10/09/08

In the morning, Karla had patients on 4 Roberts, so we went over there first thing in the morning to see them. Again, I watched Karla draw blood, take old study medication and dispense new drugs, fill out their vital sign charts, and then spin and ship blood. We then went to the hepatology seminar and listened to a lecture given by a doctor from another hospital on fungal infections in immunosuppressed patients. When we got back to the Landry Center, I spent the rest of the afternoon organizing and filing paperwork for her various binders.

10/10/08

Karla had her usual Friday morning patients, so I went to 4 Roberts with her in the morning to go see them. We spent the morning doing that, then went back to the Landry Center to help clear the clutter off of her desk. I took some of her Vertex binders and reorganized them so that she had more room on her shelf for her other regulatory binders. She had a lot of protocols crammed into one binder, and when I asked her about why she had so many protocols, she said that she had to keep every single protocol after an

amendment was made and could not just keep a 'recent' copy. These protocols are huge documents, so I made a separate binder for just the outdated protocols.

Weekly Journal: 10/13/08 to 10/17/08

10/13/08

I went to BRI in the morning to meet with Betsy. She didn't have any assignments for me to do and it was payroll morning for her, so I headed over to the Landry Center. I found Karla filling out case report forms for one of her studies. I helped her fill the rest of them out so she could get on with her morning. When I was done, I headed over to Kim's desk to get any of my files out of the laptop that used to use. She was sick, and I was feeling a bit under the weather myself, and you know how they say misery likes company, so we ended up talking quite a bit. I told her how things usually go around the Landry Center and offered to help her with whatever she needed. I went back to Karla's desk and found out Karla needed more help organizing binders, this time for another one of her studies. I rearranged those binders for her, then updated the nurse's study trials spreadsheet for Michelle.

10/14/08

I woke up only to find I couldn't breathe. What I thought were just allergies Monday afternoon now was a full-blown cold. I called Betsy to let her know that I could not come in today. She told me a couple of people had called in sick.

10/15/08

I woke up feeling even worse than the day before. I called Betsy to let her know that I would not be coming in to work. I made the inclusion/exclusion cards for one of Karla's Vertex studies.

10/16/08

I had a meeting scheduled today with Nanette and Karla, so I showed up at BRI, much to everyone's dismay because I was still sick. Nanette said that she would reschedule our meeting. I stayed at my cubicle and found out from Karla that the one inclusion/exclusion card I had made was not going to be used because the study had stopped enrolling. Dr. Gwartz e-mailed me and said that there were some syntax errors in my research proposal, so I ended up working on my paper the rest of the time.

10/17/08

I woke up again feeling sick and miserable. This time, I could breathe but was losing my voice. I stayed at home and didn't bother driving anywhere because I was heavily medicated.

Weekly Journal: 10/20/08 to 10/24/08

10/20/08

In the morning, I went by UNT HSC's library and returned some books that were due, then drove back to the Landry Center. When I arrived, I started working on website listings that Nanette and I discussed making for Karla's hepatitis studies that were enrolling. I had to find the protocols for all four of the studies and write a description for each. These website listings would be displayed on the Baylor website for doctors and nurses to see in order to recruit subjects within the healthcare community.

10/21/08

I went to the Landry Center in the morning and started working on Safety Letters to be submitted to the IRB for Karla's study as well as patient biopsy logs that needed to be given to Dr. Davis. At 9:00 AM, I attended the monthly Coordinator's Meeting and learned about three upcoming classes I wanted to attend: two MedTrial courses, and a phlebotomy class. I returned to the Landry Center and continued to work on the Safety Letters. At noon, I attended the seminar Focus On Research, and the guest speaker was Dr. Alan Menter, a dermatologist who studies psoriasis. I returned to the Landry Center to finish the Biopsy Logs for Dr. Davis. I also met with Nicole's monitor and observed him for a little while as he went through Nicole's regulatory documents.

10/22/08

I went to the UNT HSC library to read books for my thesis. I read about hepatitis A: epidemiology, viral genome and mode of operation, and current treatment options. I also typed up my weekly journals for the past couple of weeks which were written on my notepad and e-mailed them to Betsy.

10/23/08

Karla and I had a meeting in the morning with Nanette regarding our subject recruitment plan, so I spent the time leading up to the meeting looking at the various documents Nanette had e-mailed me. After the meeting, I went with Karla and Melissa, the new hire, to 4 Roberts for a patient who needed to be seen for a weekly visit. We met with the patient and discussed some adverse events the patient experienced as well as take the patient's vitals and check his medicine diary. After we dispensed new study medication and took back any left-over medication, we went to the meeting room for the hepatology seminar. A Fellow presented his report on a patient under his charge. After the meeting, Karla showed Melissa how to spin and ship blood, as well as where all of the supplies were located. By the time we got back to the Landry Center, it was time to go.

10/24/08

I attended an all-day class held by MedTrials called Case Report Form Training. It was taught by Lynn Van Dermark, and at the end of the class, we received a certificate for attending the course.

Weekly Journal: 10/27/08-10/31/08

10/27/08

Karla had a patient to screen and enroll in the morning, and she needed the IRB approved consent form to give to the patient. We could not find the consent form behind the consent form tab in the regulatory binder, so I looked for the document behind one of the other tabs. I found it behind the tab for IRB approved documents. After screening and enrolling the patient, we came back to the Landry Center and I helped Karla file documents for two of her studies. I also condensed four regulatory file binders into three by organizing the documents behind the appropriate tabs.

10/28/08

I attended a MedTrials class at Baylor All Saints in Fort Worth. The class was for clinical trial coordinators and provided training in GCP (Good Clinical Practice).

10/29/08

I completed the fourth website listing and submitted a rough draft of the Hepatology research highlight blurb for the Baylor Medical Staff Newsletter to Nanette. I also attended a meeting in the morning with Nanette to go over our subject recruitment plan and determine the next steps I needed to take. After the meeting, I worked on my journal entries. I also spoke with both Dana and Elizabeth about their clinical trials to see if I could aid them as well with subject recruitment/enrollment.

10/30/08

I worked on the Merck inclusion/exclusion cards in the morning. I also made a timetable to add to the cards that showed how the study visits were scheduled. Karla had two patients to see, so I accompanied her and Melissa to 4 Roberts for these study visits. Between the visits, we attended the Hepatology seminar. After the seminar, I observed Karla as she centrifuged, packaged, and shipped the blood work.

10/31/08

I finished the inclusion/exclusion cards as well as the timetable and submitted these to Nanette in the morning. Karla had five patients to see today, so it was very busy. I helped her as she quickly processed the blood work between the study visits. All of the blood work needed to be completed by three for shipping, so she had to do it between patient visits.

Weekly Journal: 11/03/08 to 11/07/08

11/03/08

In the morning, I worked on the Roche inclusion/exclusion card as well as the timetable for study visits. I also edited the Merck card I had submitted to Nanette. I then looked over Karla's regulatory documents, source documents, and patient shadow charts to find anything missing or incomplete. I did this because Karla had a monitor who was going to come visit in a couple of days.

11/04/08

Interview at TCOM.

11/05/08

I worked on the inclusion/exclusion cards in the morning and finished the timetable for study visits. Karla's monitor was coming the next day, so I helped her prepare her documents for his arrival and organize the regulatory binders. One of the sponsors took us all from Hepatology research to lunch.

11/06/08

In the morning, I started organizing Karla's desk. I made folders for her different studies and tried to organize the documents. I also printed patient charts in order to create a biopsy log to submit to Dr. Davis. I went with Karla to 4 Roberts as she met with two patients for their study visits.

11/07/08

In the morning, I had a meeting with Nanette. We printed out the inclusion/exclusion cards for two of the studies, and I cut out 100 cards. There were 20 copies of each card, and there were five cards total. I then went to UNT HSC in Fort Worth to submit my intent to graduate form, as well as meet with my advisor.

Weekly Journal: 11/10/08 to 11/14/08

11/10/08

I had planned on laminating the I/E cards this morning, but I did not walk over to Barnett from the Landry Center because of the rain. Instead, I spent the morning working on my weekly journals. I also read the protocols again for both the Hep B and Hep C studies in order to revise the Research Highlight blurb for the medical staff newsletter. I submitted this to Nanette in the afternoon. I also cropped the I/E cards to make them more visually appealing and smaller.

11/11/08

I went to the Clinical Trials Office in Barnett tower to laminate the I/E cards. I was not able to use the laminating machine there, so I drove to the nearest FedEx Kinko's to use their laminating machine. I then took the laminated cards to BRI to show Nanette. There, I cut out all of the cards and hole punched them in order to put them all onto rings. I then took these to Karla to talk to her about distribution.

11/12/08

Karla had a monitor coming, so I spent the day with her going over regulatory files, source documents, binders, etc., in order to make sure that all forms were complete and accurate and that nothing was missing.

11/13/08

Doctor's appointment today.

11/14/08

I went to the Landry Center in the morning to meet with Karla before we headed to 4 Roberts to see patients. Half-way through the morning, my eyes became dry and my vision became blurry from the Lasik procedure the day before, so I went home.

Weekly Journal: 11/17/08 to 11/21/08

11/17/08

In the morning, I created patient biopsy logs to submit to Dr. Davis and then I wrote safety letters which would be submitted to the IRB. I then spent the afternoon with Karla navigating the new website one of her sponsors wanted her to use to submit CRFs. There was an online tutorial and training course that we did together.

11/18/08

Today, I attended a site initiation meeting with Karla and Melissa. This study was a continuation of a previous study, so much of the information the CRA covered was the same. We went over the protocol, drug dosing, AEs/SAEs, case report forms, and other items related to the study.

11/19/08

In the morning, Nanette asked me to add some more information to the Research Highlight blurbs concerning the study drugs, study background, and study rationale. I again consulted the respective protocols to retrieve this information. I also got IRB numbers for these studies to give to her. I created a new inclusion/exclusion card for Karla's study that had just opened and received IRB approval. I also created the timetable card for this new study.

11/20/08

I went with Karla to 4 Roberts because she had patients to see in the morning for their study visits. I attended the Hepatology seminar at noon, and spoke with Dr. Randall after the meeting about the topic they were discussing. The speaker chose to talk about the HLA system and MHC molecules, so I had a few questions. Karla then spun and shipped the blood work after the seminar.

11/21/08

Karla had patients back-to-back all day today, so I was assisting her by carrying lab equipment and paperwork, helping her keep everything organized.

Weekly Journal: 11/24/08 to 11/28/08

11/24/08

I went to the Landry Center in the morning, but it was not busy at all because of the Thanksgiving holiday that week. I spent the day looking over the protocol and packet of documents I had received at the site initiation meeting the week prior in order to familiarize myself with the new study.

11/25/08

I again went to the Landry Center in the morning, and spent most of my time looking over the pamphlets Nanette had given to me earlier over subject recruitment and enrollment. I also worked on my weekly journals and reviewed the final draft of the Research Highlight blurb.

11/26/08-11/28/08

Thanksgiving Break.

Weekly Journal: 12/01/08 to 12/05/08

12/01/08

Karla had four patients to see today at 4 Roberts, including one screening visit. In the morning, we visited with the patients who were already in a study and at noon we met with the patient who was visiting in order to be screened for a clinical trial. She asked Karla questions about the study drug and how the trials and study visits would interfere with her schedule. She also spoke with Dr. Davis about concerns she had that Karla could not address. She was enrolled into the study. After she left, we had one more patient come in for her study visit. Finally, we processed the bloodwork and shipped it out to the lab.

12/02/08

Today, Karla did not have any patients. I spent the morning typing up my weekly journal from the notepad I took notes on. After I submitted these entries to Betsy, I watched Karla as she entered information into the online CRF form for one of the sponsors. This was very cumbersome and time consuming because the website was very slow and took almost a minute to load each screen. The study drug log had to be entered on multiple pages because each page was for one log entry for one study drug for only one day. Because the sponsor's server was so slow, it took Karla a couple of hours just to enter information for one patient's study drug log. I took this time to organize and file correspondence for the month of November for one of Karla's sponsors. I also faxed documents to one of the sponsors related to a study visit.

12/03/08

Today, I attended a site initiation meeting for Melissa's first study. This was over at 4 Roberts, and Dr. Davis also attended the meeting. The sponsor's representative walked us through the study, including study drug information, the protocol, procedures, pharmacy, online CRFs, etc. We also went to the pharmacy with the representative so he could speak with the Investigational Drug Pharmacist about study drug procedures and to make sure that our pharmacy was compliant.

12/04/08

Karla only had one patient to see today, and it was the patient's week 8 study visit, so there weren't a lot of tubes of blood to fill today. After we saw the patient, we attended the Transplant seminar. They had a speaker discuss MHC molecules and compatibility when selecting for an organ donor/recipient match. When we came back to the Landry Center, I created a patient shadow chart and source document binder for one of Karla's patients that had just enrolled into a study. I also faxed documents for Karla that included shipping logs for the bloodwork, then organized and filed these documents into their appropriate binders.

12/05/08

I had a meeting in the morning with Betsy to discuss my progress and to also review the weekly journals. Betsy also printed out the inclusion/exclusion criteria cards for me so that I could make the cards to distribute to the doctors. I went to the Landry Center later

that morning. Fridays are busy days for Karla because this is when patients usually come in for their study visits. She had five patients to see today, two patients for their week 4 study visits, and two patients for their week 8 study visits. One of the patients was there for his week 16, and he was seen very quickly because less bloodwork needed to be processed for him.

Weekly Journal: 12/08/08 to 12/12/08

12/08/08

Today, Karla and I met with a patient who was there for his week 72 visit, so I had a chance to see a patient who would be finishing the study. It was a visit to draw blood in order to check his viral load. We also went by the pharmacy to drop off the extra study drug not used. We went back to the Landry Center, and I observed Karla as she entered the information into the online CRF form and made a phone call to a potential subject about one of the clinical trials they were interested in.

12/09/08

Karla had a teleconference to attend for one of her studies, so I stayed at the Landry Center and typed up Safety Letters and Biopsy Logs for the IRB and Dr. Davis, respectively. These were for the partial month of October and for the month of November.

12/10/08

Karla did not have patients to see today, so she continued working on the online CRF forms for the one study that had the really slow server. I tried helping her find keyboard shortcuts to make the process faster, but the pages took a lot of time to load and that still slowed her down. I helped her by organizing correspondence for another one of her sponsors and filing them by day and month. I also reorganized documents from two binders and condensed them into one.

12/11/08

There was only one patient to be seen today and because it was his week 4, there were not that many tubes that needed to be filled and bloodwork to be processed. After we met with the patient, we attended the Transplant seminar. I spoke with Dr. Randall after the seminar about attending one of the grand rounds he would be hosting later that month. We came back to the Landry Center and I helped Karla by filling out the CRF form for the patient.

12/12/08

Karla had three patients to see today, so we spent the day at 4 Roberts visiting with the patients for their study visit and processing/shipping the bloodwork.

Weekly Journal: 12/15/08 to 12/19/08

12/15/08

In the morning, I scheduled a meeting with Nanette for later in the week to discuss making research highlight blurbs for other studies at the Transplant Institute. I also retrieved the IRB numbers from several of the research nurses so that Nanette could use these numbers to pull the protocols and give them to me in order for me to create the study summaries. I went to Karla's desk and found safety reports a couple of the sponsors sent so I typed them up for submission to the IRB.

12/16/08

Karla spent the day catching up on paperwork because she did not have a patient visit scheduled. I helped her organize the files that were on her desk, and we went through stacks of documents in order to determine what needed to be kept and what needed to be shredded. We found documents for Melissa's new study that needed to be filed and organized into a new binder, so I created this binder and labeled the appropriate tabs, placing the documents where they needed to go. I also went through all of the sticky notes that had phone numbers and Karla's notes and organized them by writing them down onto one notepad that Karla could use.

12/17/08

Karla had patients today and another screening visit, but I decided to stay at the Landry Center and continue organizing and arranging Karla's files and documents from the day before.

12/18/08

I met with Nanette in the morning to go over the protocols for the research highlight study summaries I was creating. After the meeting, I went to 4 Roberts to meet with Karla. She had only one patient today, the same patient who liked to be seen on Thursdays, and after we met with him, we attended the Transplant seminar. When we came back to the Landry Center, I showed Karla where I had put all of the files and documents and how they were organized.

12/19/08

The Transplant Institute had a lunch party for the employees, but Karla could not attend because of patients she had to see. After eating way too much, I went to 4 Roberts to help Karla. I made copies of documents and faxed in the shipping slips to the sponsors.

Weekly Journal: 12/22/08 to 12/26/08

12/22/08

Karla had patients to see at 4 Roberts, so I stayed at the Landry Center and typed up Safety Letters for the IRB and created the biopsy logs for Dr. Davis. I also worked on my weekly journals for the past three weeks. I told Karla I would have to leave a little earlier than usual because of a doctor's appointment I had at 2:30 PM and she said it was fine.

12/23/08

Karla didn't have patients today, so we stayed at the Landry Center and I helped her file documents into the appropriate binders and helped her enter information into the online CRF form for the sponsor who had the really slow server.

12/24/08-12/26/08

Winter Break.

Weekly Journal: 12/29/08 to 01/02/09

12/29/08

Karla only had one patient in the morning, and after we spun and shipped the bloodwork, we came back to the Landry Center to fill out the CRF form. I also organized and filed correspondence that Karla had for two of her studies.

12/30/08

Karla had one patient in the morning, and this was the patient's first study visit, so a lot of blood had to be drawn for the different test tubes. These test tubes had to be processed and shipped. We came back to the Landry Center and I helped her clear away another stack of documents and files on her desk.

12/31/08

I spent the day researching for my thesis. I looked at articles that addressed recruitment issues for clinical trials and found a great deal of background material for my paper. I also read a thesis from a previous year written by a former student and got a general idea of how the paper should be constructed.

01/01/09-01/02/09

New Year's Day.

Weekly Journal: 01/05/09 to 01/09/09

01/05/09

I went to the Landry Center and spent the morning working on my weekly journals for the past few weeks. Karla did not come to work today, so I went to the Baylor library after lunch to read the book Schiff's Diseases of the Liver.

01/06/09

I had a meeting with Nanette in the morning to review my progress. We also discussed community outreach and enrolling/recruiting subjects from various centers in Dallas. When I went back to the Landry Center, I found out that Karla was over at 4 Roberts to see a patient, so I went over there to help her. After she drew, spun, processed, and shipped the bloodwork, we went back to the Landry Center so that I could help her fill out the case report form for the study visit.

01/07/09

Karla had a monitor visit today, so I helped Karla prepare her documents in the morning for the visit. We went over the regulatory files and binders in order to make sure everything was completed properly and in its place. When the monitor came to the Landry Center, I observed her and Karla as they reviewed the regulatory books.

01/08/09

I went to UNT HSC today to speak with the Graduate office about scheduling a room for my defense as well as speaking to them about the Intent to Defend form.

01/09/09

Karla had patients all day today, so I helped her by staying at the Landry Center and printing and organizing the biopsy reports, as well as entering the relevant information onto a spreadsheet to submit to Dr. Davis.

Weekly Journal: 01/12/09 to 01/16/09

01/12/09

Karla did not have a patient or monitor this morning, so I helped organize her regulatory files and file e-mail correspondence for two of her studies. I also discussed with her the Inclusion/Exclusion cards I had made for her studies and if they had helped in recruiting/enrolling patients.

01/13/09

Karla had a patient to see at 4 Roberts, so I assisted her with the study visit. We came back to the Landry Center, and I helped her organize more of the documents that we didn't get to the day before. I also made photocopies of documents that needed to be sent to the IRB as well as filed in the regulatory binders.

01/14/09

I went to Parking Services and made a new ID badge for myself. After that, I went to the Landry Center and observed Karla return phone calls to her patients who had questions about the study and study medications. She also had to complete a training module for one of her studies, so I also observed her as she completed the module.

01/15/09

Karla had patients all morning today as well as one in the afternoon. I accompanied her as she met with her patients for their study visits, and observed her spin and ship the bloodwork. We attended the Transplant Seminar as well.

01/16/09

Karla had her regular Friday study visits all day today, so I stayed at the Landry Center and worked on Safety Letters to submit to the IRB. These were reports sent from the sponsor to the PI that detailed serious adverse events that needed to be submitted to the IRB. I would create a spreadsheet with all of the relevant information in summary form and Karla would approve and sign, then send it to the IRB.

Weekly Journal: 01/19/09 to 01/23/09

01/19/09

Karla had a monitor visit planned for today, so I worked on my thesis. I read two theses from previous years and made notes on what I should incorporate into my own thesis.

01/20/09

I went to the Landry Center in the morning and filed e-mail correspondence for Karla. At noon, I drove to UNT HSC and attended the graduate defense of a fellow student. I learned a great deal about how the presentation was to be conducted and what relevant information needed to be discussed.

01/21/09

Karla had more Safety Letters to complete for two of her studies, so I did these for her while she caught up on work. She also had a monitor visit scheduled for the following Monday, so I reviewed her regulatory files and binders, and flagged items with sticky notes that needed her attention.

01/22/09

I had a meeting with Betsy this morning about my internship, my weekly journals, and my defense. Because Karla had patients all day today, I asked Betsy if I could go to school and work on my thesis. She said that it was fine, so I drove to UNT HSC and made a skeleton of my paper in order to determine the necessary elements that needed to go in as well as the order and structure.

01/23/09

Today was another busy Friday for Karla as she had patient visits all day today. I observed her as she met with patients, drew blood, spun and processed the blood, and shipped the bloodwork. Because it was a very long day, it was time for me to leave before she was able to get back to the Landry Center and fill out the case report forms, so I could not help her with the paperwork.

Weekly Journal: 01/26/09 to 01/30/09

01/26/09

Karla's monitor could not come for her visit because she had a minor accident, so the visit was conducted over the phone. I took this opportunity to help Karla by printing, organizing, and making a spreadsheet of the biopsy logs that needed to be submitted to Dr. Davis. In the afternoon, Karla received an e-mail from the manager, Michelle Acker, who said that because of the bad weather, the research nurses could leave early. And because bad weather was projected for the next two days, if there were school closings, the research nurses did not have to come in to work those days.

01/27/09

Karla did not go in to work today because of the bad weather, so I stayed at home and read the articles Nanette had given to me about clinical research recruitment/enrollment.

01/28/09

Schools were closed again today, so Karla did not go in to work and I stayed at home as well. I read more of the book Schiff's Diseases of the Liver.

01/29/09

Because of the two days off due to bad weather, there was a lot of work the research nurses had to make up. Karla had patients today, so I stayed at the Landry Center and helped with the paperwork on her desk. There were more Safety Letters that needed to be submitted to the IRB, this time for another study, so I created the spreadsheet that would be sent to the IRB. I also organized and filed paperwork that needed to be put into regulatory binders.

01/30/09

Karla had her usual Friday study visits, so I stayed at the Landry Center and finished the biopsy reports that needed to be submitted to Dr. Davis. Because Karla was not back by the time I finished, I printed them out and left them on her desk so that she could review them before submitting them to Dr. Davis. After I completed the biopsy reports, I created website listings for six of the other studies at the Transplant Institute and e-mailed them to Nanette.

APPENDIX B: RECRUITMENT PLAN

Subject Recruitment Planning Meeting - Active Studies – Open to Enrollment

Current Studies (Title)	Sponsor	Contracted to Enroll	Total Subjects Enrolled	Challenges	Recruitment Methods:
IRB#: 007-248 <i>A Multicenter, Randomized, Open-Label, Controlled Study Of The Effect Of Treatment With Once Weekly X Plus Daily Y With Or Without Concomitant Z On Early Viral Kinetics In Treatment-Naïve Patients With Chronic Hepatitis C (Genotype-1 HCV Infection) And Insulin Resistance</i>	A	6 (up to 10)	Potential: 1 Scheduled: 0 Screening: 0 Enrolled: 2	<div> <input checked="" type="checkbox"/> Patient Identification <input type="checkbox"/> Informed Consent / Patient Education Process <input type="checkbox"/> Patient Transportation <input type="checkbox"/> Budget Constraints <input type="checkbox"/> Implementing Study Procedures </div> <div> <input type="checkbox"/> Patient Screening <input type="checkbox"/> Patient Motivation <input type="checkbox"/> Eligibility Criteria <input type="checkbox"/> Time Constraints <input type="checkbox"/> Standard of Care <input type="checkbox"/> Conflict <input type="checkbox"/> Staff Resources <input type="checkbox"/> Other: </div>	<p>Implemented to Date:</p> <ul style="list-style-type: none"> PI working with private practice Hepatologists to identify potential subjects <p>Recommendations:</p> <ul style="list-style-type: none"> Within Site: 1) Physicians – Create inclusion/exclusion cards for potential referring physicians (Hepatologists and Endocrinologists) 2) Private Practice Staff – Work with scheduler/practice administrator to run ICD – 9 search and review weekly practice schedule to identify potential subjects. Let practice physicians know about potential eligibility prior to visit. 3) Potential subjects: Fliers for waiting rooms Healthcare community: 1) Posters in staff/physician areas – breakroom, etc. 2) Study reminder e-mails to physicians and staff as needed. 3) Highlight Hep B/C studies in BUMC Medical Staff Newsletter (Nanette contacted Dr. Davis re: this opportunity on 9/19/2008 – no response to date)

Current Studies (Title)	Sponsor	Contracted to Enroll	Total Subjects Enrolled	Challenges	Recruitment Methods:
					<ul style="list-style-type: none"> Community: 1) Contact community outreach organizations to let them know about Hepatology research program – Stew Pot 2) Ask BHCS marketing to do a general story on Hepatology research – Interview Dr. Davis.
Comments: Research Nurse: Karla Challenging study do to insulin resistant requirement.					

Subject Recruitment Planning Meeting - Active Studies - Open to Enrollment

Current Studies (Title)	Sponsor	Contracted to Enroll	Total Subjects Enrolled	Challenges	Recruitment Methods:
IRB # 008-068 <i>A Phase 3 Study of 2 Dose Regimens of Z in Combination with X and Y in Treatment- Naïve Subjects with Genotype 1 Chronic Hepatitis C</i>	B	8-9	Scheduled: 0 Screening: 0 Enrolled: 3	<div> <input type="checkbox"/> Patient Identification <input type="checkbox"/> Informed Consent / Patient Education Process <input type="checkbox"/> Patient Transportation <input type="checkbox"/> Budget Constraints <input type="checkbox"/> Implementing Study Procedures </div> <div> <input type="checkbox"/> Patient Screening <input type="checkbox"/> Patient Motivation <input type="checkbox"/> Eligibility Criteria <input type="checkbox"/> Time Constraints <input type="checkbox"/> Standard of Care Conflict <input type="checkbox"/> Staff Resources <input type="checkbox"/> Other: </div>	<p><u>Implemented to Date:</u></p> <ul style="list-style-type: none"> Subjects enrolled have been identified from private practice and BHCS website. <p><u>Recommendations:</u></p> <ul style="list-style-type: none"> Within Site: 1) Physicians – Create inclusion/exclusion cards for potential referring physicians 2) Potential subjects: Fliers for waiting rooms Healthcare community: 1) Posters in staff/physician areas – breakroom, etc. 2) Study reminder e-mails to physicians and staff as needed. Community: 1) Contact community outreach organizations to let them know about Hepatology research program – Stew Pot 2) Ask BHCS marketing to do a general story on Hepatology research – Interview Dr. Davis.
<u>Comments:</u> Research Nurse: Karla					

Subject Recruitment Planning Meeting - Active Studies - Open to Enrollment

Current Studies (Title)	Sponsor	Contracted to Enroll	Total Subjects Enrolled	Challenges	Recruitment Methods:
IRB#: 008-093 <i>A Phase II Randomized, Placebo-Controlled Study to Evaluate the Safety and Efficacy of X Administered Concomitantly with Y and Z for 28 Days in Treatment-Naïve Patients with Chronic Hepatitis C Infection</i>	C	2	Scheduled: 1 Screening: 0 Enrolled: 0	<input type="checkbox"/> Patient Identification <input type="checkbox"/> Informed Consent / Patient Education Process <input type="checkbox"/> Patient Transportation <input type="checkbox"/> Budget Constraints <input type="checkbox"/> Implementing Study Procedures	Implemented to Date: <ul style="list-style-type: none"> PI working with private practice Hepatologists to identify potential subjects Recommendations: <ul style="list-style-type: none"> Same as above
Comments: Research Nurse: Karla - Short enrollment timeline: Waiting on approval from Marck regulatory team to begin enrollment.					
IRB#: 008-202 <i>A Randomized Study of Stopping Treatment at 24 Weeks or Continuing Treatment to 48 Weeks in Treatment-Naïve Subjects with Genotype 1 Chronic Hepatitis C who Achieve an Extended Rapid Virological Response (eRVR) While Receiving Z, X and Y.</i>	C		Scheduled: 0 Screening: 0 Enrolled:	<input type="checkbox"/> Patient Identification <input type="checkbox"/> Informed Consent / Patient Education Process <input type="checkbox"/> Patient Transportation <input type="checkbox"/> Budget Constraints <input type="checkbox"/> Implementing Study Procedures	Recommendations: <ul style="list-style-type: none"> Same as above
Comments: Research Nurse: Karla - Pending approval.					
General Recruitment:					

Current Studies (Title)	Sponsor	Contracted to Enroll	Total Subjects Enrolled	Challenges	Recruitment Methods:
<ul style="list-style-type: none"> List all studies on BHCS website Create fliers for private practice waiting area Highlight hematology studies in BUMC Medical Staff News letter Create inclusion/exclusion cards for referring physicians and posters with study summaries for physician lounges. 					

APPENDIX C: INCLUSION/EXCLUSION CRITERIA

Selection of Study Population

Inclusion Criteria

1. May not have received any previous treatment with any approved or investigational drug or drug regimen for the treatment of hepatitis C
2. Male and female subjects, 18 to 70 years of age, inclusive
3. Genotype 1, chronic hepatitis C with detectable HCV RNA. Genotype must be confirmed during screening. Confirmation that the disease is chronic (as opposed to acute disease of less than 6 months duration) must be by at least 1 of the following criteria:
 - Diagnosis of HCV >6 months before the screening visit
 - Abnormal alanine aminotransferase (ALT) levels for >6 months before the screening period (Note: ALT does not have to be elevated to be eligible for the study, but history of elevated ALT can indicate duration of the infection)
4. Screening laboratory values within the following acceptable ranges:

Laboratory Variable:	Acceptable Range:
Hepatitis B surface antigen (HBsAg)	Seronegative
Human Immunodeficiency Virus (HIV) 1 and 2 antibodies (Ab)	Seronegative
Absolute neutrophil count	$\geq 1,500/\text{cmm}$
Platelet count	$\geq 90,000/\text{cmm}$
Hemoglobin	$\geq 12 \text{ g/dL}$ for females
OR	$\geq 13 \text{ g/dL}$ for males
Uric acid	Within normal range
TSH and T4	Within normal range, or adequately controlled thyroid function on treatment
All other hematology and clinical chemistry results	Within normal limits or showing no clinically significant abnormalities

5. Subject must have documentation of a liver biopsy within 1 year before the screening visit, or the subject must agree to have a biopsy performed within the screening period. Liver biopsy must show evidence of hepatitis (demonstrated by inflammation and/or fibrosis). If a biopsy more than 1 year prior to screening has already demonstrated histological cirrhosis, the biopsy does not need to be repeated if this biopsy report can be provided

6. Subjects (or their female partners) must be not pregnant, or planning to become pregnant with the next 72 weeks, or they must be permanently sterile or otherwise of non-childbearing potential. They must also not be breastfeeding. If of childbearing potential, subjects must agree to use 2 effective methods of contraception from screening through 6 months after the last dose of RBV. Male subjects who have a female partner of childbearing potential must agree to use 2 effective methods of contraception from Screening through 7 months after the last dose of RBV unless vasectomized. (For additional information on pregnancy and contraception requirements, please see Section 11.7)
7. Willing and able to refrain from the concomitant use of any medication, substances, or foods noted in Section 10.12, from 14 days prior to the first day of dosing through the end of treatment
8. Able to read and understand, and willing to sign the informed consent form and abide by the study restrictions

Exclusion Criteria

1. Subject has any contraindications to Peg-IFN-alpha-2a or RBV therapy, including but not limited to any of the following:
 - Hypersensitivity to Peg-IFN-alpha-2a, RBV, or to any component of these products
 - Hemoglobinopathies (including thalassemia major, sickle-cell disease)
 - History or other clinical evidence of significant or unstable cardiac disease (e.g. angina, congestive heart failure, recent myocardial infarction, significant arrhythmia) and/or clinically significant ECG abnormalities
 - Abnormal thyroid function that cannot be controlled effectively by medication
 - Poorly controlled diabetes mellitus as evidenced by HbA1C $\geq 8.5\%$ at screening
 - Creatinine clearance $\leq 50\text{mL/min}$ at screening
 - Antinuclear antibody (ANA) titer $\geq 1:640$ at screening and/or evidence of autoimmune hepatitis on liver biopsy
2. Evidence of hepatic decompensation in cirrhotic subjects: history of ascites, hepatic encephalopathy, or bleeding esophageal varices, and/or screening laboratory results of any of the following:
 - International Normalized Ratio (INR) of ≥ 1.5
 - Serum albumin $< 3.3\text{ g/dL}$
 - Serum total bilirubin > 1.8 times the upper limit of normal (ULN), unless history of Gilbert's disease
3. Any other cause of significant liver disease in addition to hepatitis C, which may include, but is not limited to malignancy with hepatic involvement, hepatitis B, drug or alcohol-related cirrhosis, autoimmune hepatitis, hemochromatosis, Wilson's disease, nonalcoholic steatohepatitis (NASH), or primary biliary cirrhosis
4. Diagnosed or suspected hepatocellular carcinoma as evidenced by screening alpha-fetoprotein (AFP) of $\geq 50\text{ ng/mL}$. If AFP is $\geq 50\text{ ng/mL}$, absence of a mass must be demonstrated by ultrasound within the screening period

5. Active malignant disease or history of malignant disease within 5 previous years (with the exception of treated basal cell carcinoma)
6. Pre-existing psychiatric condition that could interfere with the subject's participation in and completion of the study, including but not limited to:
 - Severe depression or hospitalization for depression
 - Schizophrenia, bipolar illness, severe anxiety or personality disorder
 - A period of disability or impairment due to a psychiatric disease within the past 5 years
7. History of craniocerebral trauma or active seizure disorders requiring medication
8. History of organ transplant, with the exception of corneal transplants and skin grafts
9. Medical condition that requires frequent or prolonged use of systemic corticosteroids (e.g. severe asthma, severe arthritis or autoimmune conditions, organ transplantation, adrenal insufficiency, etc.)
10. Autoimmune-mediated disease (e.g. Crohn's disease, ulcerative colitis, idiopathic thrombocytopenic purpura, systemic lupus erythematosus, autoimmune hemolytic anemia, scleroderma, severe psoriasis)
11. History of acute pancreatitis within 5 years prior to the screening visit
12. History or other evidence of severe retinopathy or clinically significant ophthalmological disorder due to diabetes mellitus or hypertension. For subjects with a history of hypertension or diabetes, written clearance from an ophthalmologist has to be obtained before the start of treatment
13. History or other clinical evidence of chronic pulmonary disease associated with functional impairment
14. History of hemophilia
15. Evidence of serious or severe bacterial or fungal infection(s), including active tuberculosis
16. Currently abusing illicit drugs (narcotics or other controlled substances) or alcohol, or has a history of illicit substance or alcohol abuse within 2 years prior to the screening visit. Subjects who have a history of abuse of illicit drugs or alcohol should have had no incidents of abuse within the 2 years prior to the screening visit
17. Participation in any investigational drug study within 90 days before study drug dosing, or participation in more than 2 drug studies in the 12 months before study drug dosing, or participation in any concurrent research study including non-drug studies from screening until the end of the subject's participation in this study
18. Hypersensitivity to tartrazine (yellow dye #5)

APPENDIX D: INCLUSION/EXCLUSION CRITERIA CARDS

Inclusion/Exclusion Cards XXXX Hepatitis C Study

Inclusion Criteria:

- M or F > 18 years old
- HCV genotype-1
- Liver biopsy w/out cirrhosis
- Insulin resistance
- Anti-HCV treatment-naïve
- Must not be pregnant, not planning to become pregnant/impregnate

Exclusion Criteria:

- Infection w/HCV other than genotype-1
- Chronic liver disease
- Decompensated liver disease
- HAV, HBV, or HIV infection
- History of HCV treatment
- Type-1 diabetes
- Receiving insulin

Exclusion Criteria:

- Pregnant or breastfeeding
- Anemia
- History of severe psych. Disease
- Poorly controlled thyroid dysfunction
- Hist of cardiac disease
- Severe seizure disorder
- Ophthalmological disorder
- Active or suspected cancer
- Antineoplastic or immunomodulatory treatment
- Hist of major organ transplant
- Immunologically mediated disease
- Chronic pulmonary disease
- Alcohol/drug abuse
- Investigational drug use

Schedule of Events:

Week (+pioglitazone arm)	35 days	BL(-16)	-12	-8	-4	0	4	8	12	16-20	24	28-44	48	60	72
Week (-pioglitazone arm)	35 days					BL	4	8	12	16-20	24	28-44	48	60	72
Informed Consent	X														
Medical History	X	X				X									
Physical Exam	X	X				X			X						X
Vital Signs/Preg Test	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Genotyping	X														
HCV RNA	X	X	X	X	X	X	X		X		X		X	X	X
Chest X-ray, ECG, Ophthalmologic Exam, Immunology, a-fetoprotein	X														
Hematology and Chem	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urinalysis	X	X			X	X			X		X		X		X
Thyroid Function Test	X				X				X		X		X		X
Plasma B-type Natriuretic Peptide	X			X		X			X				X		
Hemoglobin A1c	X	X		X	X	X			X		X		X		X
Blood Glucose/Insulin	X	X		X	X	X	X	X	X		X		X		X
Serum TNF-a and TGF-b		X		X		X	X	X	X		X		X		X
Serum adiponectin, leptin, ffa		X		X		X	X	X	X		X		X		X
Liver Biopsy	X														
Serum Bank	X	X				X			X				X		X
Questionnaire: BDI-FS					X		X	X	X	X	X	X	X		X
Questionnaire: BDI-II	X	X				X									
Drug Dispensing		X		X		X	X	X	X	X	X	X	X	X	
Drug Acc., AE, Concom Meds, Compliance - See Protocol		X	X	X	X	X	X	X	X	X	X	X	X		

Inclusion/Exclusion Cards XXXXX Hepatitis C Study



Inclusion Criteria:

- M or F, 18≤65 years of age
- Chronic Hep C genotype I
- Normal lab values
- Liver biopsy w/o cirrhosis
- Must use two forms of birth control
- Eye exam prior to study drug dosing

Exclusion Criteria:

- History of psychiatric disorder
- Underage; mentally, emotionally, or legally incapacitated.
- Pregnant or planning to become pregnant/impregnate.
- Patient has had 3 or more doses of IFN, peg-IFN, or ribavirin.
- Received other antiviral therapy or vaccine for HCV.

Exclusion Criteria:

- Unlikely to tolerate 4 weeks of therapy: peg-IFN and ribavirin.
- Chronic hepatitis not caused by HCV.
- Coinfection with HIV.
- Evidence of active Hep B infection.
- Disorder that interferes w/ absorption of study medication (ex: gastric bypass surgery)
- Stroke, seizures, major neurological disorder.
- Clinically sig. uncontrolled endocrine, gastrointestinal, cardiovascular, hematological, immunological, renal, respiratory, or genitourinary abnormalities or diseases.

Exclusion Criteria:

- Any condition contraindicated for peg-IFN or ribavirin.
- Alcohol/drug abuse
- W/in 30 days prior to start: had surgery, donated 500 mL of blood, or received another investigational therapy.
- Clinically significant abnormality on ECG.

Please feel free to contact Karla Huang at 214-820-6984 or
KarlaH@BaylorHealth.edu, if you have questions.



Schedule of Study Events:

Visit	1	2	3	4 & 5	6	7	8	9	10	11 to 21	22	23
Day	-75 to -8 (screen)	-7 to - 2	1	3 & 7	14	21	28	35	42	Wk 8 to 48*	Wk 60	Wk 72
Study Procedures				+1 day	+1 day	+1 day	+1 day	+1 day	+1 day	+/- 1 wk	+/- 1 wk	+2 wks
Study IC, Med. His & I/E Criteria Rev.	X											
Clinical Safety Evaluations												
Physical Exam	X		X		X		X		X			
Weight	X		X				X		X	X		
Height	X											
12-lead ECG	X		X				X		X			
Vital Signs	X		X	X	X	X	X		X			
Review Study Med Diary				X	X	X	X	X	X	X		
Review AE/SAE		X	X	X	X	X	X	X	X	X	X	X
Lab Safety Eval	X	X	X	X	X		X		X	X		
PK Eval (XX-7009 PK (plasma))			X	X	X	X	X	X	X			
HCV Eval												
Serology	X											
Genotype Determination	X											
Viral RNA Levels	X	X	X	X	X	X	X	X	X	X	X	X
Viral Resistance Test		X	X	X	X	X	X	X	X	X		X

Monthly Visits: Every 4 wks (wk 8 to 48)

Inclusion/Exclusion Cards

XXX Hepatitis C Study



Inclusion Criteria:

- M or F between 18 to 70, inclusive
- HCV genotype-1
- Liver biopsy
- Normal lab value ranges
- Anti-HCV treatment-naïve
- Must not be pregnant, not planning to become pregnant/impregnate

Exclusion Criteria:

- Contraindication to Peg-IFN or RBV
- Evidence of hepatic decompensation
- Non-Hep C related significant liver disease
- Hepatocellular carcinoma
- History of or active malignant disease
- Psychiatric condition
- Craniocerebral trauma/seizure disorder

Exclusion Criteria:

- Organ transplant
- Use of systemic corticosteroids
- Autoimmune-mediated disease
- Acute pancreatitis
- Severe retinopathy or ophthalmological disorder
- Chronic pulmonary disease
- Hemophilia
- Bacterial or fungal infection
- Abusing illicit drugs or alcohol

Schedule of Study Events:

	S	1	2	3	4	6	8	10	12	16	20	22	24	28	36	48	Dis- conti- nuati on	4 wks	12 wks	24 wks
Evaluation	Screening																			
IC, review I/E, medical hist	X																			
PE, ECG	X																X			
AFP, ANA, HbsAg, HIV-1, HIV-2 Ab, HCV genotyping, HbA1C, urinalysis	X																			
Paxgene DNA	X																			
Liver biopsy	X																			
Vital Signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Pregnancy Test	X	X			X		X		X	X	X		X		(Wks 28, 32, 36, 40, 44, 48)		X	X	X	X
Hematology, Serum Chem, LFTs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
HCV RNA	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
HCV viral sequencing	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Symptom-directed PE	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
Subject Randomization												X								
Study Drug Accountability		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X				
Study Drug Dosing																				
Current Meds	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
AE/SAE	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
FSS, EQ-5D, Productivity	X				X				X								X			X
Pharmacokinetic Assessments	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X				

Continues based on viral response assessment and treatment assignment.

APPENDIX E: WEBSITE LISTINGS AND RESEARCH HIGHLIGHT

Website Listing #1:

Study Title: A Phase 2, Randomized, Open-Label, Parallel Group, Multi-Center Study To Assess the Safety and Efficacy of X in De Novo Kidney Transplant Recipients

Short Title: X

Study Description: This is a randomized, open-label, parallel group, multi-center study to assess the safety and efficacy of X in de novo kidney transplant recipients who are at least 18 years of age. The study will include a 6 month treatment period with a 6 month follow-up period. All subjects who meet the entry criteria for the study will be randomized to one of four treatment arms.

Some of the criteria for patients to qualify for the study include:

- Recipient of a kidney from a non-HLA identical donor
- Recipient of de novo kidney transplant
- 18 years of age or older

The following are some of the criteria which will exclude patients from the study:

- Previously received or is receiving an organ transplant other than a kidney
- Sensitivity to iodine
- Pregnant or lactating
- Significant liver disease

Location:

Transplant Institute
Baylor University Medical Center at Dallas
3500 Gaston Avenue
Dallas, TX 75246

Lead Principal Investigator: Larry Melton, M.D.

For further information about this study, please contact: 1-800-4BAYLOR

Website Listing #2:

Study Title: Evaluation of X as First-line Immunosuppression in De Novo Liver Transplant Recipients

Short Title: X

Study Description: This is a phase 2 study to explore several X-based regimens and find at least one regimen with a favorable risk-benefit profile in liver transplant recipients. This is a randomized, partially blinded, active controlled, parallel-group, multi-center clinical trial.

Some of the criteria for patients to qualify for the study include:

- First time recipient of a deceased donor liver transplant
- Ages 18 to 70 years, inclusive

The following are *some* of the criteria which will exclude patients from the study:

- Pregnant or breastfeeding
- Fulminant hepatic failure
- Received a split liver
- History of hypercoagulable state

Location:

Transplant Institute
Baylor University Medical Center at Dallas
3500 Gaston Avenue
Dallas, TX 75246

Lead Principal Investigator: Goran Klintmalm, M.D.

For further information about this study, please contact: 1-800-4BAYLOR

Website Listing #3:

Study Title: Pancreatic Islet Transplantation- A Novel Approach to Improve Islet Quality and Engraftment

Short Title: Pancreatic Islet Cell Transplantation

Study Description: This open-label, prospective single-center study is designed to assess the safety and efficacy of pancreatic islet-cell transplantation in patients with type 1 diabetes mellitus.

Some of the criteria for patients to qualify for the study include:

- Type 1 diabetes mellitus of more than 5 years duration
- Age between 18 and 65

The following are *some* of the criteria which will exclude patients from the study:

- Received or is receiving an organ or bone marrow transplant
- Pregnant or lactating
- Smoking in the last 6 months

Location:

Transplant Institute
Baylor University Medical Center at Dallas
3500 Gaston Avenue
Dallas, TX 75246

Lead Principal Investigator: Marlon Levy, M.D.

For further information about this study, please contact: 1-800-4BAYLOR

Website Listing #4:

Study Title: Tele HF: A Study of Telemonitoring to Improve Outcomes in Patients with Congestive Heart Failure

Short Title: Tele-HF Monitoring for CHF

Study Description: The Tele-HF study is a 40year, randomized controlled trial of 1,640 participants that will compare outcomes in HF patients who participate in daily technology-based telemonitoring and education with the Pharos Tel-Assurance™ system with those who receive usual care.

Some of the criteria for patients to qualify for the study include:

- 18 years or older
- Heart failure hospital admission within the last 14 days
- Access to a telephone line

The following are *some* of the criteria which will exclude patients from the study:

- Severe valvular disease
- Currently a prisoner
- Resident of a nursing facility

Location:

Transplant Institute
Baylor University Medical Center at Dallas
3500 Gaston Avenue
Dallas, TX 75246

Lead Principal Investigator: Clyde Yancy, M.D.

For further information about this study, please contact: 1-800-4BAYLOR

Website Listing #5:

Study Title: Comparison of two protocols for optimization of gastrointestinal tolerability using Y in liver transplant recipients with gastrointestinal side effects from X

Short Title: Novartis Y Liver Conversion

Study Description: The study involves randomized conversion of de novo (less than 3 months post-transplant) liver transplant recipients that are on X® for a period of more than 7 days and have gastrointestinal side effects (greater than 5 days duration) as decided by the study investigator or sub-investigators. Therefore, liver transplant recipients more than 7 days and less than 3 months after transplant will be eligible to participate in this study.

Some of the criteria for patients to qualify for the study include:

- 18 years of age or older
- Medically eligible to convert to Myfortic
- Experiencing dyspepsia, anorexia, nausea, vomiting, or another condition not listed

The following are some of the criteria which will exclude patients from the study:

- Previous history of diarrhea not related to CellCept®
- Document psychiatric illness
- Known sensitivity to Myfortic® or CellCept®

Location:

Transplant Institute
Baylor University Medical Center at Dallas
3500 Gaston Avenue
Dallas, TX 75246

Lead Principal Investigator: Edmund Sanchez, MD FACS

For further information about this study, please contact: 1-800-4BAYLOR

Website Listing #6:

Study Title: A 24 month, multi-center, open-label, randomized, controlled study to evaluate the efficacy and safety of concentration-controlled X to eliminate or to reduce Y compared to Y in de novo liver transplant recipients

Short Title: Novartis Z Liver

Study Description: This study is a 24 month, multicenter, open-label, randomized, controlled study that will consist of a screening period, a baseline period (3 to 7 days post-transplantation) followed by a run-in period that ends on the day of randomization at 30 days (± 5 days) post-transplantation.

Some of the criteria for patients to qualify for the study include:

- Age 18 to 70 years
- Received primary liver transplant from a deceased donor

The following are some of the criteria which will exclude patients from the study:

- Combined liver-kidney transplant
- Antibody induction therapy
- Recipients of ABO incompatible transplant grafts

Location:

Transplant Institute
Baylor University Medical Center at Dallas
3500 Gaston Avenue
Dallas, TX 75246

Lead Principal Investigator: Goran Klintmalm, MD

For further information about this study, please contact: 1-800-4BAYLOR

Website Listing #7:

Study Title: Multicenter, randomized, open-label, controlled study of the effect of treatment with once weekly X® plus daily Y® with or without concomitant pioglitazone (Actos®) on early viral kinetics in treatment-naïve patients with chronic hepatitis C (genotype-1 HCV infection) and insulin resistance.

Short Title: Y

Study Description: To evaluate the effect of treatment with Y once weekly plus daily X according to body weight with and without concomitant pioglitazone on hepatitis C virus (HCV) titers during the first 12 weeks of anti-HCV therapy in treatment-naïve patients with CHC (genotype-1 HCV infection) and insulin resistance.

Some of the criteria for patients to qualify for the study include:

- Males or females 18 years or older
- Hepatitis C infection genotype I
- Liver biopsy without evidence of cirrhosis
- Insulin resistance

The following are some of the criteria which will exclude patients from the study:

- Abnormal thyroid dysfunction
- Cardiac disease
- Renal disease
- Pre-existing psychiatric condition
- Type-1 diabetes

Location:

Transplant Institute
Baylor University Medical Center at Dallas
3500 Gaston Avenue
Dallas, TX 75246

Lead Principal Investigator: Gary Davis, M.D.

For further information about this study, please contact: 1-800-4BAYLOR

Website Listing #8:

Study Title: A Phase II randomized, placebo-controlled study to evaluate the safety and efficacy of MK-7009 administered concomitantly with X and Y for 28 days in treatment-naïve patients with chronic hepatitis C infection.

Short Title: Z

Study Description: This is a multicenter, double-blind (with in-house blinding), randomized, placebo-controlled, dose-ranging study to assess the safety, tolerability, and efficacy of MK-7009 administered concomitantly with peg-IFN and ribavirin to HCV-infected patients for 28 days. Patients will continue in the study to receive a complete course of treatment with peg-IFN and ribavirin at standard doses per standard-of-care (SOC) guidelines.

Some of the criteria for patients to qualify for the study include:

- Between 18 to 65 years of age
- Chronic, compensated, hepatitis C infection genotype I
- Liver biopsy without evidence of cirrhosis
- Eye examination performed prior to study drug dosing

The following are some of the criteria which will exclude patients from the study:

- Coinfection with human immunodeficiency virus (HIV)
- HCV genotype I exhibiting more than one subtype or another genotype
- Unlikely to tolerate at least 4 weeks of continuous therapy with peg-IFN and ribavirin
- Pre-existing psychiatric condition
- History of stroke, chronic seizures, or major neurological disorder

Location:

Transplant Institute
Baylor University Medical Center at Dallas
3500 Gaston Avenue
Dallas, TX 75246

Lead Principal Investigator: Gary Davis, M.D.

For further information about this study, please contact: 1-800-4BAYLOR

Website Listing #9:

Study Title: A randomized, double-blind, placebo-controlled, Phase III trial of 2 regimens of X (with and without delayed start) combined with Y and Z in subjects with chronic genotype 1 hepatitis C infection who failed prior X plus Y treatment.

Short Title: Realize

Study Description: The trial is designed to compare the efficacy, safety, and tolerability of 2 regimens of Z (with and without delayed start) combined with X and Y versus standard treatment. Y will be administered at a dose of 750 mg every 8 hours and X and Z at standard doses.

Some of the criteria for patients to qualify for the study include:

- Between 18 to 70 years of age
- Chronic hepatitis C infection genotype I
- Failed at least 1 prior course of Peg-IFN/RBV therapy
- Subject is judged to be in good health (besides HCV infection)

The following are some of the criteria which will exclude patients from the study:

- Previous non-responder that is classified as a viral breakthrough case
- HCV genotype I exhibiting more than one subtype or another genotype
- Intolerant to Peg-IFN/RBV therapy
- Pre-existing psychiatric condition

Location:

Transplant Institute
Baylor University Medical Center at Dallas
3500 Gaston Avenue
Dallas, TX 75246

Lead Principal Investigator: Gary Davis, M.D.

For further information about this study, please contact: 1-800-4BAYLOR

Website Listing #10:

Study Title: A randomized study of stopping treatment at 24 weeks or continuing treatment to 48 weeks in treatment-naïve subjects with genotype I chronic hepatitis C who achieve an extended rapid viral response (eRVR) while receiving X, Y, and Z.

Short Title: 950-111

Study Description: This is a randomized, open-label, multicenter study to be conducted in treatment-naïve subjects with genotype I, chronic hepatitis C infection. The study is designed to evaluate and describe the sustained viral response (SVR) rates in subjects who achieve an eRVR with X, Y, and Z after stopping treatment at Week 24 or continuing X and Y to Week 48.

Some of the criteria for patients to qualify for the study include:

- Between 18 to 70 years of age
- Chronic hepatitis C infection genotype I
- Liver biopsy with evidence of hepatitis
- Subjects (or their female partners) must not be pregnant, or planning to become pregnant

The following are some of the criteria which will exclude patients from the study:

- Any other cause of significant liver disease in addition to hepatitis C
- Currently abusing illicit drugs
- History of organ transplant, with the exception of corneal transplants and skin grafts
- Pre-existing psychiatric condition
- History of hemophilia

Location:

Transplant Institute
Baylor University Medical Center at Dallas
3500 Gaston Avenue
Dallas, TX 75246

Lead Principal Investigator: Gary Davis, M.D.

For further information about this study, please contact: 1-800-4BAYLOR



Hepatology Research

Currently, Baylor Research Institute (BRI) is conducting more than 800 research projects. Each month BRI highlights active research studies open to enrollment.

The following table provides an overview of studies currently being conducted related to Hepatology Research. If you have potential patients who may qualify for these research studies, please contact the research nurse(s) listed below -

Research Area	Study Summary	Contact Person
Hepatitis C	<p>There are currently 17 active clinical trials for the treatment of Hepatitis C, with 5 studies open to enrollment. These studies have several goals, which include evaluating the safety and efficacy of combination therapies involving the use of Pegasys® and Copegus® (both are provided in standard of care) in combination with a third investigational drug. The majority of investigational combination therapy drugs are protease inhibitors. Protease inhibitors a class of direct acting antiviral drugs being developed for hepatitis C, which show great promise in inhibiting viral replication.</p> <p><u>Study Population:</u> Male or female ≥ 18 years of age who are not currently pregnant or planning to become pregnant. They must be diagnosed with chronic Hepatitis C.</p>	<p>Karla Huang karlah@Baylorhealth.edu (214) 820-6984</p>
Hepatitis B	<p>There are currently 6 active clinical trials for the treatment of Hepatitis B, with 2 studies open to enrollment. These studies compare the safety and efficacy of current standard of care treatment options, as well as compare them to placebo. Two of the current FDA-approved treatment drugs are reverse transcriptase inhibitors used to block HBV viral DNA replication. Patients positive for HBV who have taken these reverse transcriptase inhibitors have shown a significant histological, biochemical, and virological improvement.</p> <p><u>Study Population:</u> Male or female ≥ 18 years of age who are not currently pregnant or planning to become pregnant. They must be diagnosed with chronic Hepatitis B.</p>	<p>Sharon Bruer sharonb@Baylorhealth.edu (214) 820-1737</p>

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