

STATINS AND PCSK9 INHIBITORS:  
HOW THEY HAVE SHAPED MEDICINE,  
A COMPARATIVE REVIEW

INTERNSHIP PRACTICUM REPORT

Presented to the Graduate Council of the  
Graduate School of Biomedical Sciences  
University of North Texas  
Health Science Center at Fort Worth  
in Partial Fulfillment of the Requirements

For the Degree of

MASTER OF SCIENCE

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December 2016

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## ACKNOWLEDGEMENTS

I would first like to thank my major professor, Dr. Rustin Reeves at the University of North Texas Health Science Center. He was always available for questions or comments on my research and report. I would also like to thank Dr. Patricia Gwirtz for being in my committee and being available to give helpful comments on my drafts.

At Legacy Heart Center in Plano, I'd like to thank my research manager, Angela Germany, for giving me the opportunity to have my internship here at this site. I'd also like to thank the research coordinators here, Kathy Rodkey, Precillia Vasquez, and Liana Von Bose for helping me learn about the process behind clinical research and teaching me the different processes for each study.

I would also like to thank my parents and close friends who have supported me in my academic journey so far through several years of studying. This accomplishment would not have been possible without them. Thank you.

## PREFACE

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## TABLE OF CONTENTS

CHAPTER 1 INTRODUCTION .....	1
CHAPTER 2 CLINICAL TRIALS.....	3
CHAPTER 3 LIPID BIOCHEMISTRY .....	5
CHAPTER 4 STATINS.....	7
CHAPTER 5 PCSK9 INHIBITORS.....	11
CHAPTER 6 LIPID MANAGEMENT .....	16
CHAPTER 7 DISCUSSION.....	21
CHAPTER 8 LIMITATIONS.....	22
APPENDIX A PERMISSIONS.....	23
APPENDIX B INTERNSHIP JOURNAL .....	25
APPENDIX C ABBREVIATIONS.....	61
BIBLIOGRAPHY.....	62

## LIST OF TABLES

TABLE 1 STATIN DRUGS.....	9
TABLE 2 PCSK9 INHIBITORS.....	13
TABLE 3 OUTCOMES TRIALS AND FURTHER INFORMATION.....	20

## LIST OF ILLUSTRATIONS

FIGURE 1 LDL AND HDL IN ARTERIES .....	6
FIGURE 2 STATIN MECHANISM OF ACTION .....	7
FIGURE 3 TIMELINE OF ADVANCES IN PCSK9 RESEARCH .....	12
FIGURE 4 PCSK9 INHIBITORS MECHANISM OF ACTION.....	14

## CHAPTER 1

### INTROUDCTION

Cardiovascular disease, which includes the various disorders of the heart and blood vessels, killed about 17.5 million in 2012, which was about 31% of all deaths worldwide according to the World Health Organization [1]. The main risk factors for cardiovascular disease (CVD) are the following: plasma cholesterol levels, diabetes, diet, family history, hypertension, obesity, physical inactivity, stress, tobacco, age, and male gender. Some of these, such as family history and age must be considered but cannot be treated such as lifestyle changes for obesity, diet, tobacco, and physical activity. Others, such as hypertension and plasma lipid levels, can be treated with medications to reduce overall cardiovascular risk for a patient. Statins have long been the drug of choice to lower lipid levels since they were discovered in the 1970s and have held that position since [2]. However, a promising new drug class has arrived on the field comparatively recently and has been a hot topic for physicians and researchers.

PCSK9 (proprotein convertase subtilisin/kexin type 9) inhibitors are a new therapy aimed at lowering LDL levels. Patients who cannot tolerate statins due to drug reactions or patients who cannot keep their LDL levels within the recommended range [3] with statin therapy are prime candidates for PCSK9 therapy. Furthermore, patients with heterozygous or homozygous familial hypercholesterolemia are also candidates for PCSK9 therapy.

There have been several completed clinical drug trials examining PCSK9 inhibitors, and as mentioned previously, there are currently five phase 3 clinical drug studies conducted here at Legacy Heart Center. The two clinical trials from Pfizer that are underway at Legacy Heart Center are titled the following: “The Evaluation of Bococizumab in Reducing the Occurrence of Major Cardiovascular Events in High Risk Subjects (SPIRE 1)” and “The Evaluation of



Bococizumab in Reducing the Occurrence of Major Cardiovascular Events in High Risk Subjects (SPIRE 2).” The two trials aim to evaluate cardiovascular outcomes in patients when taking bococizumab, a PCSK9 inhibitor developed by the drug company Pfizer, compared to a placebo while concurrently taking a background statin medication [4, 5]. Amgen, another pharmaceutical company, also has developed PCSK9 inhibitor called evolocumab. Currently, they are studying the long term effects in two studies called “Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk (FOURIER)” and “Extension Study to Assess Safety and Efficacy of Evolocumab (OLE)” [6, 7]. Furthermore, there is a sub study being conducted under FOURIER which is called “Evaluating PCSK9 Binding Antibody Influence on Cognitive Health in High Cardiovascular Risk Subjects (EBBINGHAUS),” which will evaluate the effect of PCSK9 on cognitive function [8]. These studies will be compared and will ensure further discussion about the advancement of PCSK9 inhibitors in the field of lipid therapy.

## CHAPTER 2

### CLINICAL TRIALS

Clinical trials are designed to advance medical knowledge by discovering new treatments of diseases by conducting studies in human subjects. The main branches of clinical trials are interventional studies and observational studies. Interventional studies are used to test the effect of a treatment or preventative measure on a patient or population. The studies discussed in this practicum report are interventional studies because the subjects would be given a drug to affect a change in the subject and the subject is followed to test the hypothesis. The purpose of observational studies, on the other hand, are to observe a group to find information about risks or the effects of lifestyle on health [9].

An Investigational New Drug (IND) must be approved by the Food and Drug Administration (FDA) and then by the Institutional Review Board (IRB) to start the clinical trial, and then must be finally approved by the FDA to be marketed to the public. This process was developed after several attempts were made at developing ethical guidelines for human research after several shocking events, such as the Doctors' Trial after World War II, when the world discovered that the Nazi doctors had been experimenting on humans, and other atrocities of the 20<sup>th</sup> century, such as the Tuskegee syphilis study [10]. In 1974, the National Research Act was established, which identified basic ethical principles that are used today and also declared that research needed to be reviewed by an IRB [11]. Shortly after, the Belmont Report was published in 1979 and focused on three main points for ethical research: Respect for Persons, Benevolence, and Justice [12]. Today, the IRB is able to approve, review, and monitor clinical studies and can even halt studies if the board deems that it is being performed unethically or to the harm of the patients.

Clinical trials are split into four phases. Phase I is generally used to determine a drug candidate's side effects, pharmacokinetics (how the human body absorbs and distributes the drug), and pharmacodynamics (the effects of the drugs on the physiology of the body). This initial phase is usually done in a small population of healthy humans. If the drug is a good candidate, phase II trials will start. The focus of phase II trials is to examine the effectiveness of the drug, i.e., which is to test if the drug works on people with the disease or condition that the drug will be treating. The drug will be tested against a placebo or, if a placebo is deemed unethical due to better treatments available, the drug will be tested against current medications on the market. Phase II trials usually have a population up to about 300 subjects who have the disease, and the surrogate markers and biomarkers of that disease are monitored throughout the trial through lab testing, imaging studies, and other reports. Promising drugs will progress to phase III trials. These trials are large scale studies designed to examine the effectiveness and safety in many different populations and several dosages and also for drug interactions. There can be hundreds to thousands of subjects in phase III trials. If the results go well, the company that owns the drug would then file for a New Drug Application (NDA), which is used to get FDA approval for the new drug to be marketed in the U.S [13]. This process of clinical trials can take up to a decade. After approval to be sold to the public, the drug company will continue to monitor for side effects in the general population in what is called phase IV.

## CHAPTER 3

### LIPID BIOCHEMISTRY

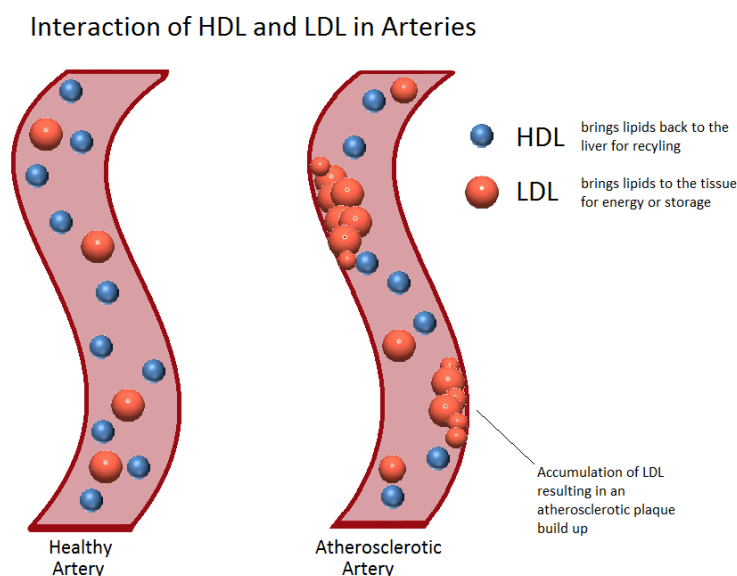
In order to understand the main studies that will be discussed later on in this report, a short introduction into the science of the affected systems in the body will have to be discussed. There will be a brief overview of the biochemistry behind lipoproteins and cholesterol, followed by the medications that can be used to control the levels of lipoproteins.

As mentioned previously, cardiovascular disease (CVD) is a group of diseases that affect the heart and blood vessels. This can be due to narrowed or blocked vessels, which can increase risk of heart attack or stroke from atherosclerotic plaque rupture and thrombosis, or be due to affected muscles or valves causing the heart to work less efficiently due to weakness in the muscle or blockage of an artery feeding that muscle with oxygenated blood. One condition in particular that increases risk of CVD is hyperlipidemia, which refers to increased lipid levels in the blood. It does not necessarily have symptoms but greatly increases a patient's risk of CVD, both coronary and peripheral types of disease [14]. Therefore, lowering lipids, and therefore their CVD risk, through diet or medication is very beneficial to patients.

Lipoproteins are a structure of proteins and lipids which help transport lipids through the blood to tissues in the body [15]. Single lipids are nonpolar, meaning they are not soluble in water, but lipids are special in that they are amphipathic, which means that they have one polar end and one nonpolar end. This allows them to form a bundle of molecules, called lipoproteins, in which the polar end (or hydrophilic end) faces outwards and the nonpolar end (or hydrophobic end) faces the inside. Because of this characteristic, they become soluble in fluid. On the outside of a lipoprotein, several proteins called apolipoproteins surround and stabilize the structure, and the inside is filled with varying levels of triacylglycerol, cholesterol, phospholipids, and proteins

[15]. There are several types of lipoproteins, which have an inverse relationship between density and diameter. They are listed as follows starting with the most dense to the least dense: High Density Lipoprotein (HDL), Low Density Lipoprotein (LDL), Intermediate Density Lipoprotein (IDL), Very Low Density Lipoprotein (VLDL), and chylomicrons [16].

LDL is commonly called the “bad” cholesterol, and HDL is generally thought of being the “good” cholesterol. This is due to the way they interact within the cardiovascular system. LDL is produced by the liver to bring lipids to the tissues which require lipids for energy for storage or for using them as a precursor to build new molecules. This LDL can accumulate on the blood vessel walls and build up plaques, which can internally cause a condition called atherosclerosis. If left uncontrolled, atherosclerosis can lead to increased risks of heart attack, stroke, and other cardiovascular events. HDL, however, can regulate plaque that has built up by taking up fatty acids and cholesterol not metabolized by the tissues and transporting them back to the liver where the fatty acids or cholesterol will be transferred into VLDL and LDL. HDL will also transfer its excess cholesterol to the liver in order to convert it into bile which will eventually make its way into the duodenum to aid in digestion [17]. The following is a simplified explanation of the LDL-HDL interaction and is shown in a diagram.

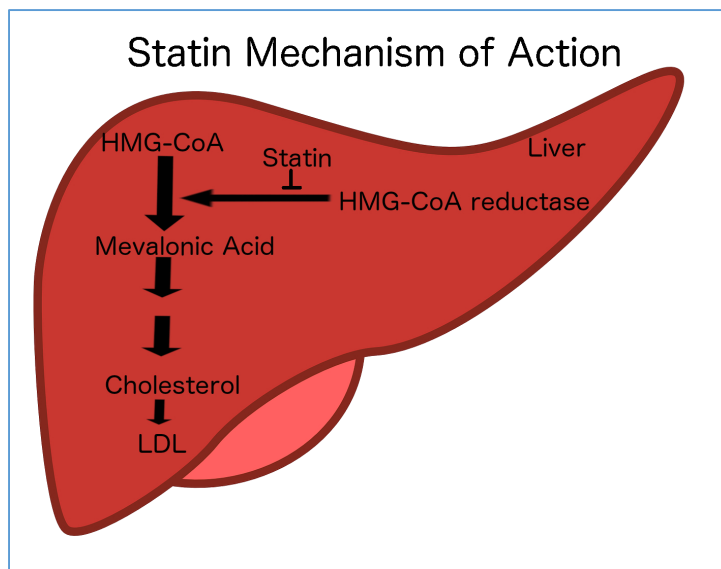


*Figure 1 LDL and HDL in Arteries. Excess LDL can form plaques on the artery wall causing building and narrowing (stenosis) of the artery. HDL can interact with LDL in the blood stream to bring lipids back to the liver and other parts of the body. These lipids can be converted into bile for digestion or be packaged into other LDL and IDL particles. Figure created by author from information in Berne and Levy, Physiology [15].*

## CHAPTER 4

### STATINS

The cholesterol and lipids in lipoproteins are produced by the body in a complex process. One of the rate limiting steps in this process uses a molecule called HMG-CoA. HMG-CoA is acted on by HMG-CoA reductase to form mevalonate which can proceed on to form many end products, one of which is cholesterol [18]. HMG-CoA reductase, in particular, is quite notable because it is a target for statins, the current major drug class for lowering lipid plasma levels [19]. Statins are HMG-CoA reductase inhibitors, which means they stop HMG-CoA reductase from functioning properly. This inhibition of HMG-CoA reductase limits cholesterol biosynthesis and also increases expression of LDL receptors on the liver because the body is tricked into thinking it needs more LDL, which in turn clears a greater amount of LDL from the blood [20, 21]. Both these effects work to lower cholesterol and triglyceride levels in the blood.



**Figure 2** Simplified cholesterol pathway and statin mechanism of action. (Left) In the liver, HMG-CoA is an enzyme that is acted upon by HMG-CoA reductase to make mevalonic acid, which can go on to produce cholesterol and LDL, among other products. Statins inhibit this first step of cholesterol synthesis by inhibiting HMG-CoA reductase, blocking the pathway at one of the first steps. Figure created by author from data in "Introduction of Cholesterol Metabolism"[18]

Several advances were made in the 19<sup>th</sup> century connecting atherosclerosis with atherosclerotic plaques and later on with heart attacks in 1939. By the 1960s, it was understood that high blood cholesterol levels had a genetic component which led to a higher rate of

premature heart attacks in several families that were studied. Epidemiologic studies in the United States in the 1960s further demonstrated a connection between LDL, HDL, and coronary atherosclerosis and heart attacks. There began an effort to determine the pathway that synthesized cholesterol in the body [22]. Two biochemists, Konrad E. Bloch and Feodor Lynen were awarded the Nobel Prize in 1964 "for their discoveries concerning the mechanism and regulation of the cholesterol and fatty acid metabolism." [23]

Following that discovery, regulation of the cholesterol biosynthetic pathway was studied in depth by scientists in several countries. They found that cholesterol cannot only be synthesized in the body, but is usually absorbed from the diet. The body synthesizes cholesterol if the dietary cholesterol is not enough, and there is genetic programming determining the baseline rate of cholesterol biosynthesis. There are several feedback mechanisms to ensure that this level of cholesterol is kept within a certain range [24]. In the late 1960s, many pharmaceutical companies began searching for molecules that could block one of the thirty steps in the cholesterol synthesis pathway. There were many molecules that were analyzed for the potential to interact with the cholesterol pathway, and some were viable in animal models but either were not effective or had side effects at the clinical (human) level [22, 25, 26]. In 1959, a promising drug called Triparanol (MER/29) became available for clinical use in the U.S and was the first drug available that inhibited cholesterol synthesis. However, it was withdrawn from the market a few years later in the early 1960s due to the discovery of several serious side effects, including cataracts [27]. This was due to inhibition of the final stage of the cholesterol synthesis pathway leading to a buildup of other sterols in the body [28].

Scientists soon discovered that HMG-CoA reductase was the rate limiting step in the cholesterol biosynthetic pathway. This proved to be an attractive target to inhibit. Many

companies focused research on finding a molecule that inhibited HMG-CoA reductase. Two molecules, named compactin and citrinin, were isolated from fungi but were never marketed after clinical trials. In 1978, Merck Research Laboratory found a molecule which later became the first FDA approved commercial statin available in 1987 when it debuted as Lovastatin. Several other statins were soon released by other pharmaceutical companies, and today, atorvastatin is the most popular statin on the market [22].

*Table 1 Statin drugs. Table created by author from information in FDA and pharmaceutical product labels [29-35].*

<b>Drug Name</b>	<b>Trade Name</b>	<b>Company</b>	<b>FDA Approval</b>
Lovastatin	Mevacor	Merck	1987
Pravastatin	Pravachol	Bristol-Myers Squibb	1991
Simvastatin	Zocor	Merck	1991
Fluvastatin	Lescol	Novartis	1993
Atorvastatin	Lipitor	Pfizer	1996
Rosuvastatin	Crestor	AstraZeneca	2003
Pitavastatin	Livalo	Kowa Pharmaceuticals	2009

Statin are categorized into generations, which generally categorized by the time they are developed. The first generation of statins – Lovastatin, Pravastatin, and Fluvastatin – were the first statins to be developed and achieve FDA approval [36]. These generally require a 40 mg or 80 mg dose to achieve a 30% reduction in serum LDL levels. The next generation of statins – Atorvastatin and Simvastatin – have a greater efficacy and only require 10 mg and 20 mg, respectively, to achieve the same 30% reduction in serum LDL levels [36]. Rosuvastatin and Pitavastatin, the third generation of statins, are different from the other two generations in that they have a unique chemical structure which allows them to have a comparatively low chance of drug interactions and also have a different metabolizing pathway allowing them to be used in patients who are otherwise are statin intolerant [37].



There are a few side effects to using statins, such as an increased risk of diabetes, chance of myalgias (muscle aches) [38], and very rare risk of hepatotoxicity. These effects, however, are rare, and according to UT Southwestern, muscle aches occur in 10% of people who take statins and “actual muscle damage occurs in only 1 in 10,000 patients” and that “liver damage from taking statins is extremely uncommon.”[39] According to one study done in 2010, statins actually increased liver function when comparing a statin group with a placebo group [40]. Reported myalgias are often reversible by either switching medications or taking a lower dose. Some patients cannot tolerate statins at all, and they are switched to a different type of medication or another treatment plan [39].

There are some patients who cannot take statins, either due to experiencing some side effects to them or perhaps due to issues with compliance. There are also some patients who cannot lower their LDL sufficiently through statins, particularly those with familial hypercholesterolemia. These patients may benefit from the newer drug class of PCSK9 inhibitors.

## CHAPTER 5

### PCSK9 INHIBITORS

The new drug class, called PCSK9 inhibitors, is one of the latest topics in the medical field. In 2003, it was first noted by French researchers that a mutation in the gene called proprotein convertase subtilisin/kexin type 9 (PCSK9) caused autosomal dominant hypercholesterolemia [41], which caused very high levels of cholesterol in the blood. The year after, in 2004, it was found that mice with overexpression of PCSK9 interferes with LDL-receptor mediated LDL uptake causing an increase of LDL-C [42]. Then in 2005, different mutations in PCSK9 were found to be linked to low LDL in humans [43] and in mice [44]. In these two years, scientists have defined two different PCSK9 mutations which result in a gain of function mutation and a loss of function mutation in both humans and mice.

Cohen et al. found that certain sequence variations in the *PCSK9* gene were statistically associated with lower plasma LDL levels and that this was able to lower cardiovascular risk in patients [45]. The Dallas Heart Study, in 2006, was used to prove that loss of function mutations in PCSK9 did lower LDL. They were able to take a small subset of African Americans who were found to have very low LDL-C. They sequenced the PCSK9 gene and found that there were two main mutations which caused the gene to lose its function [46]. Scientists were still unsure of whether lowering LDL-C to extremely low levels would be safe and how it would affect the other organ systems so they started a study to search for individuals with extremely low LDL-C. They were able to find several patients living normal healthy lives with no PCSK9 protein and with very low LDL-C in their blood serum [47]. Linsel-Nitschke et al. identified a variant of PCSK9 which lowered LDL-C levels which correlated with lower risk of coronary heart disease. This risk reduction was similar to that of statins [48]. These years, from 2003-2006 were the

period for target validation for PCSK9 [49]. These discoveries proceeded to generate interest from the medical field and from pharmaceutical companies who started looking into drugs that would affect PCSK9.

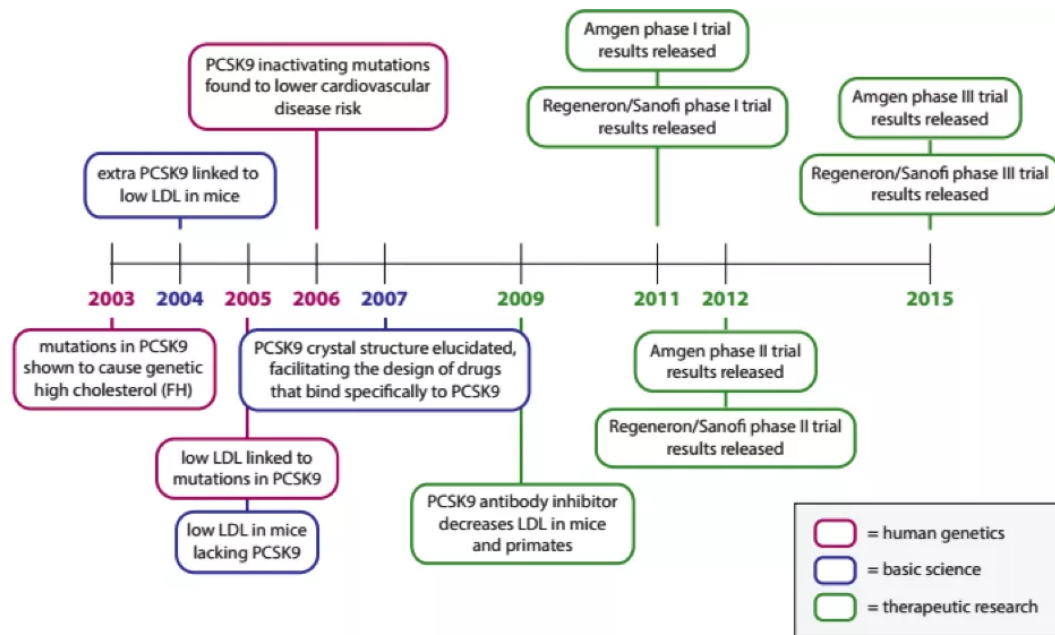


Figure 3 Timeline of Advances in PCSK9 Research. Retrieved from Science in the News article "A potential new weapon against heart disease: PCSK9 inhibitors" [50]. Copyright 2015 by Mary Gearing and Kristen Seim. Reprinted with permission from Science in the News (Appendix A).

In 2007, several studies proved to be a turning point for researchers as they were able to discern the crystal structure of PCSK9, allowing drugs to be designed specifically to bind to PCSK9 [51]. Several animal studies were published in 2007-2009, proving efficacy of PCSK9 inhibition to lower LDL in mice and primates using various methods of inhibiting PCSK9 [52-54]. Soon after, phase I clinical trials were started up by Amgen [55], Regeneron Pharmaceuticals [56], and Pfizer [57] to test out their PCSK9 inhibitors. The results for the phase I trials were released in 2011, and the results for phase II trials, which were started after the initial phase of the phase I trials did not show safety issues, were released the year after in 2012.

By 2015, several phase III results were released, and there are still studies ongoing about effects of PCSK9 on different organ systems and for the long term effects of PCSK9 inhibitors.

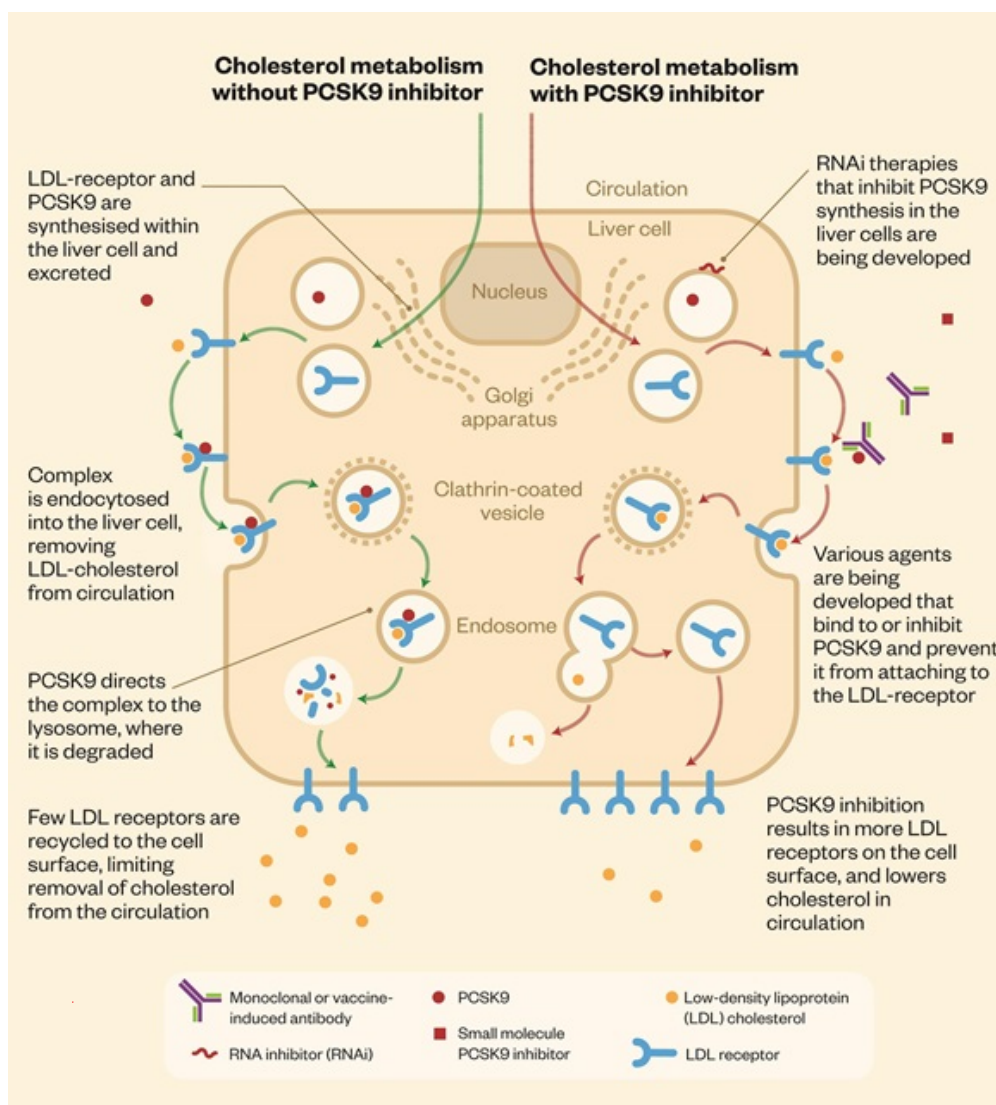
*Table 2 Current PCSK9 inhibitors. Table created by author using information from FDA and pharmaceutical websites. [4, 58, 59]*

<b>Drug Name</b>	<b>Trade Name</b>	<b>Company</b>	<b>FDA Approval</b>
Alirocumab	Praluent	Sanofi Regeneron	2015
Evolucumab	Repatha	Amgen	2015
Bococizumab	-	Pfizer	-

PCSK9 is a protein that binds to LDL receptors on the liver. This causes the LDL receptor to be brought from the cell surface to inside a lysosome where it would be degraded with the LDL that has attached to it [60]. This results in the liver cells having less LDL receptors and, therefore, not being able to breakdown the LDL that is circulating in the blood as well. PCSK9 inhibitors, however, inhibit PCSK9 from staying bound to the LDL receptor after being brought to the lysosome inside the cell. When LDL binds to the LDL receptor, the receptor internalizes into the cell, the LDL receptor and LDL uncouple and the receptor is sent back to the cell surface while the LDL is broken down in the lysosome. This results in an increased number of LDL receptors on the cell surface allowing more LDL to be taken from the blood and broken down in the cells [61].

Current method of inhibiting PCSK9 is through monoclonal antibodies. Antibodies are molecules produced by B-lymphocytes of the immune system to help fight against antigens (foreign agents that may cause infection). In a laboratory, a highly specific single antibody can be cloned on a mass scale, which would be called a monoclonal antibody. These monoclonal antibodies can detect a highly specific chain of molecules, called an epitope [62]. In the case of PCSK9 inhibitors, the monoclonal antibodies are modeled to bind to the PCSK9 molecule. After the monoclonal antibody binds to a PCSK9 molecule, the PCSK9 molecule cannot interact

further with the LDL receptor on the surface of the liver cell. The LDL receptor can go on to bind to LDL and bring it into the cell for degradation [16].



**Figure 4** Mechanism of action for PCSK9 inhibitors. In normal cholesterol metabolism (without PCSK9 inhibitor), LDL receptors and PCSK9 are synthesized within liver cells. The LDL receptor is excreted to the cell surface and binds LDL in the blood stream. When PCSK9 binds to this complex, it does not allow the LDL receptor to release the LDL particle. The receptor complex that is endocytosed is then broken up and degraded by the lysosome. When a PCSK9 inhibitor is used, the PCSK9 cannot bind to the LDL-receptor. When the LDL receptor binds to LDL and endocytosed, the LDL receptor can dissociate and is able to return to the surface, but the LDL particle is degraded in the lysosome. This recycling of the LDL receptor increases the amount of LDL receptors on the liver cell surface allowing more LDL to be degraded and a new lower LDL level to be achieved in the blood. Figure retrieved from "Cholesterol-busting PCSK9 drugs"[60]. Copyright 2015 by The Pharmaceutical Journal. Reprinted with permission (Appendix A).

One thing to note though, is how the mechanism for PCSK9 inhibitors and the mechanism for statins are separate. PCSK9 inhibitors work on the process whereby the liver cells break down LDL and allow them to continually break down the LDL particles. On the other hand, statins work by blocking the pathway whereby cholesterol and LDL products are synthesized in the body. These two types of medications therefore have synergistic action. Current clinical trials have patients taking statins and PCSK9 inhibitors concurrently [4-8].

## CHAPTER 6

### LIPID MANAGEMENT

In 2013, the American College of Cardiology (ACC) and the American Heart Association (AHA) came together and published a report on practice guidelines on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults. This report was produced by an expert panel, initially appointed by the National Heart, Lung, and Blood Institute (NHLBI), that included primary care physicians, cardiologists, and experts in clinical lipidology, clinical trials, nutrition, and other fields [63].

This report, titled “2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines,” was generated by the panel looking at data from clinical studies and developing recommendations from these studies. The recommendations were then mapped into a chart which categorizes the recommendation along two axes. One axis describes the size of treatment effect, and the other axis estimates how certain a treatment would affect the patient. For the size of the treatment effect, there are three classes or levels which define how beneficial a treatment would be versus how risky it would be. In “Class I,” the benefit is exceedingly useful or effective and there have been numerous studies or evidence on the treatments effects. “Class II” has two subdivisions. “Class IIa” is a category in which the benefits strongly outweigh the risks but there may have been conflicting evidence in some studies concerning the treatment, and “Class IIb” is the category where benefits are greater than the risk and treatment can be plausible under certain situations. Finally, “Class III” includes those where no benefit or harm would come to the patient if such a treatment were given [64].

The chart also gives three levels of how certain a treatment would be beneficial to a population. In “Level A,” multiple populations have been extensively studied by multiple randomized clinical trials. In “Level B,” a smaller number of populations have been studied and there may only be a few or one clinical trial from which the data has been derived from. “Level C” consists of very limited populations or when the data available is from case studies or opinion based articles [63].

One of the primary results of this review was the development of new health management guidelines. The baseline recommendation they give is that healthy lifestyle and habits are the best way to avoid atherosclerotic cardiovascular disease (ASCVD). The panel then outline the use of statins in an algorithm to recommend high intensity statin (a dose that lowers LDL-C by more than 50%) and moderate intensity statin (a dose that lowers LDL-C by 30% to 50% of baseline). If a patient has clinical ASCVD (coronary syndromes, history of myocardial infarction, stable or instable angina, arterial revascularization, stroke, or peripheral arterial disease [63]) and is over 21, it is recommended they are put on a high intensity statin unless they are over 75 years old. If the patient’s LDL-C is over 190 mg/dL, then it is recommended they are put on a high intensity statin regardless of their risk factors for cardiovascular disease. If they are diabetic, it is recommended to prescribe them at least a moderate intensity statin. There are also several other recommendations on statin prescribing based on primary prevention depending on several risks or risk scores. The final decision on prescribing statins is, of course, the patient, and it is up to the physician to talk to them on about the risks and benefits of taking a statin and what sort of lifestyle modifications that are to follow [65]. The main rationale for these recommendations from the expert panel include the following:



- “1. Cholesterol-lowering medications, particularly statins, are efficacious and effective for reducing risk of initial cardiovascular events.
2. Statins are associated with similar relative risk reductions for cardiovascular events across the majority of primary-prevention patient groups studied.
3. The extent of relative risk reduction for ASCVD is proportional to the degree of LDL-C lowering observed on statin therapy. Therefore, more intensive statin therapy could reduce risk more than moderate- or lower-intensity statin therapy.”[63]

Although statins are the main method used to lower blood serum cholesterol, they are not without any risks. On a whole, statins are generally safe, but there is a percentage of the population that either cannot take statins due to side effects or which statins do not control their lipid serum levels well enough.

Currently, the FDA only recommends PCSK9 inhibitors for patients with either heterozygous familial hypercholesterolemia, homozygous familial hypercholesterolemia not controlled by a statin, or statin intolerance [66]. Evolocumab (Repatha) has been studied in homozygous familial hypercholesterolemia and found to be well tolerated and significantly reducing LDL compared to placebo [67]. Having been approved by the FDA, Repatha and Praluent are two PCSK9 inhibitors currently on the market and are being used by patients. Pfizer’s PCSK9 inhibitor, bococizumab, is awaiting results from a cardiovascular outcomes trial before obtaining FDA approval, hoping that these results will compensate for being the third PCSK9 inhibitor to be approved [68]. Table 3 lists the current ongoing outcomes trials for PCSK9 inhibitors and details such as length of the study and what the study is measuring. At Legacy Heart Center, the PCSK9 inhibitor related clinical drug studies – FOURIER, OLE,

SPIRE I, and SPIRE II – are ongoing, but as a reminder, only information that can be obtained publically will be discussed. The studies listed have generally similar outcome measures, which is to measure the time to a cardiovascular event such as myocardial infarction or hospitalization. These studies are long term and are expected to last about five years. There are also other studies concerning PCSK9 inhibitors not listed or discussed here that examine other long term effects.

Trial name	Official Title	ClinicalTrials #			
FOURIER	Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects With Elevated Risk	NCT01764633			
OLE	Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk Open-label Extension	NCT02304484			
ODYSSEY	A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Effect of Alirocumab (SAR236553/REGN727) on the Occurrence of Cardiovascular Events in Patients Who Have Recently Experienced an Acute Coronary Syndrome	NCT01663402			
SPIRE-1	Phase 3 Multi-center, Double-blind, Randomized, Placebo-controlled, Parallel Group Evaluation Of The Efficacy, Safety, And Tolerability Of Bococizumab (Pf-04950615) In Reducing The Occurrence Of Major Cardiovascular Events In High Risk Subjects	NCT01975376			
SPIRE-2	The Evaluation of Bococizumab (PF-04950615; RN316) in Reducing the Occurrence of Major Cardiovascular Events in High Risk Subjects	NCT01975389			
Trial name	Study drug	Company	Patient population	Primary outcome measure	Follow-up
FOURIER	Evolocumab	Amgen	<i>n</i> = 27,564	Time to time to cardiovascular death, myocardial infarction, hospitalization for unstable angina, stroke, or coronary revascularization whichever occurs first.	5 years
OLE	Evolocumab	Amgen	<i>n</i> = 5,000	Number of participants with adverse events as a measure of safety and tolerability	
ODYSSEY	Alirocumab	Sanofi/Regeneron	<i>n</i> = 18,600	Time to CHD death, any non-fatal MI, fatal and non-fatal ischemic stroke, unstable angina requiring hospitalization	64 months
SPIRE-1	Bococizumab	Pfizer	<i>n</i> = 17,000	Time to major cardiovascular (CV) event, a composite endpoint of CV death, non-fatal MI, non-fatal stroke, and hospitalization for unstable angina needing urgent revascularization	60 months
SPIRE-2	Bococizumab	Pfizer	<i>n</i> = 11,000	Time to major cardiovascular (CV) event, a composite endpoint of CV death, non-fatal MI, non-fatal stroke, and hospitalization for unstable angina needing urgent revascularization	60 months

Table 3 Ongoing PCSK9 clinical trials. These are long term studies to study the long term effects of PCSK9 against various measures. FOURIER, OLE, SPIRE I, and SPIRE II are currently ongoing trials at Legacy Heart Center. ODYSSEY included for completeness of all pharmaceutical companies developing PCSK9 inhibitors. Table created by author using information from ClinicalTrials.gov [4-7, 69].

## CHAPTER 7

### DISCUSSION

PCSK9 inhibitors have the possibility to reduce cardiovascular care costs by \$29 billion over 5 years and also prevent 4.3 million major adverse cardiovascular events when adding PCSK9 inhibitors to statin therapy. Researchers found that, in the U.S., the PCSK9 inhibitor annual cost needs to be reduced to \$4,536 or less per patient to be cost effective [70]. The current issue with PCSK9 inhibitors is that, because they are the latest drug on the market, they are expensive and not very cost effective currently. The current annual cost for a PCSK9 inhibitor is about \$14,350 [71]. Comparatively, the average annual cost of a statin for one patient ranges from \$4 per month (\$48 per year) for generics to about \$500 per month (\$6,000 per year) for brand name statins [72, 73]. In 2011, one study found that the low cost of statins was cost-effective for people with moderate risk factors and even cost saving for certain categories of people [74].

The price of statins has dropped since they were discovered in the 1970s, and because of that, statins have remained as the primary method of lowering LDL levels and therefore lowering their risk of cardiovascular disease. With concurrent statin use, PCSK9 inhibitors likely will play a key role in the future of medicine, largely dependent on the current and future studies that will be examining the long term effects of PCSK9 inhibitors.

## CHAPTER 8

### LIMITATIONS

Research on PCSK9 is still in progress, and although there have been numerous publications on previous research concerning PCSK9 inhibitors, the currently running clinical trials have yet to be published. The majority of research on statins occurred soon after they were discovered in 1970s, but there are still studies on certain aspects of statins that need clarification such as in highly specific situations such as risk of statin use prior to heart surgery. This practicum report only references data available to the public and information that is published in the public domain.

## APPENDIX A

### COPYRIGHT PERMISSIONS

From: **Phillip Escarsega** [Phillip.Escarsega@my.unthsc.edu](mailto:Phillip.Escarsega@my.unthsc.edu)  
Subject: Re: Permission to use figure for thesis  
Date: August 8, 2016 at 11:06 AM  
To: Dawn Connelly [dawn.connelly@pharmj.org.uk](mailto:dawn.connelly@pharmj.org.uk)

EP

I can get a big enough photo from the website. Thank you!

*Phillip Escarsega*

----- Original message-----

**From:** Dawn Connelly  
**Date:** Mon, Aug 8, 2016 10:53  
**To:** Phillip Escarsega;  
**Cc:** Maria Gonzalez;  
**Subject:** RE: Permission to use figure for thesis

Dear Phillip,

Sorry for the delay in getting back to you, I've been away on holiday. It is fine for you to use the figure as long as you credit *The Pharmaceutical Journal*. Do you need us to send you the figure or can lift a version from the website?

Many thanks,  
Dawn

=====

Dawn Connelly  
Features editor  
The Pharmaceutical Journal

Direct line: 020 75722427  
Email: [dawn.connelly@pharmj.org.uk](mailto:dawn.connelly@pharmj.org.uk)  
[www.pharmaceutical-journal.com](http://www.pharmaceutical-journal.com)

---

**From:** Phillip Escarsega [<mailto:Phillip.Escarsega@my.unthsc.edu>]  
**Sent:** 25 July 2016 17:17  
**To:** PJ Letters <[correspondence@pharmaceutical-journal.com](mailto:correspondence@pharmaceutical-journal.com)>  
**Subject:** Permission to use figure for thesis

Hello,

I am a student working on my Master of Science in Clinical Research Management at the University of North Texas Health Science Center, and I am working on my thesis which is titled "Statins and PCSK9 Inhibitors, How They Have Shaped Medicine, a Comparative Review."

I saw the article on [your website titled](#), "Cholesterol-busting PCSK9 drugs," and I wanted to ask permission to use the figure labeled "Cholesterol metabolism and PCSK9 inhibitors," which details the pathway for PCSK9 inhibitors. If possible, please let me know what the process is if you are able to do so.

Thank you,  
Phillip Escarsega

**From:** Phillip Escarsega <Phillip.Escarsega@my.unthsc.edu>  
**Subject:** Re: Permission to use figure for thesis?  
**Date:** September 14, 2016 at 11:23 AM  
**To:** SITN Boston <sitnbostonblog@gmail.com>



Alright, Thank you!

Phillip Escarsega  
UNT Health Science Center 2016  
UT Dallas 2013

On Sep 14, 2016, at 11:14 AM, SITN Boston <[sitnbostonblog@gmail.com](mailto:sitnbostonblog@gmail.com)> wrote:

Hi Phillip,

It's fine to use the figure--we're glad you like it! When giving credit, please include the names of both the author and the graphics designer.

Thanks!  
Kelsey

On Tue, Sep 13, 2016 at 12:01 PM, Phillip Escarsega <[Phillip.Escarsega@my.unthsc.edu](mailto:Phillip.Escarsega@my.unthsc.edu)> wrote:

Hello,  
I'm a Master's student at UNT Health Science Center working on a thesis report about PCSK9 inhibitors. In an article on Science in the News called "[A potential new weapon against heart disease: PCSK9 inhibitors](#)," I had some interest in the timeline presented in the article. I want to ask permission to use it in my thesis (with citation of course) which will eventually be published in the UNT HSC Scholarly Repository.

Regards,  
Phillip Escarsega  
UNT Health Science Center 2016  
UT Dallas 2013

APPENDIX B  
INTERNSHIP JOURNAL

**Week 1**

May 31, 2016

AM:

- Today was my first day at my internship site, Legacy Heart Center. I met with my site mentor, Ms. Angela Germany, in the morning and she introduced me to her team.
- Ms. Kathy Rodkey gave me a tour around the facility and introduced me to Dr. McKenzie, one of the doctors they work with frequently. She also explained the different studies that we are currently recruiting or following.
- When we got back, I worked on getting my workstation organized.

PM:

- Had my committee meeting here at the office. Dr. Gwartz and Dr. Reeves met with my team and we discussed my internship and timeline.
- Afterwards, I did some preliminary research on PCSK9 inhibitors, which I am told that one of our studies concerned with a drug in this category and that these inhibitors are a hot topic in medicine.
  - o There are LDL receptors on the liver which remove LDL cholesterol from the blood. PCSK9 is an enzyme that binds to LDL receptors, which starts the process to break them down. If PCSK9 is inhibited, it cannot bind to LDL receptors and break them down, and the LDL receptors will continue to remove LDL from blood.



June 1, 2016

AM:

- Read through the following forms to better understand the clinical trial process:
  - o Spire 1 Study
    - Prescreening Informed Consent Form (11 pages)
    - Informed Consent Form and HIPAA Authorization (25 pages)
  - o Spire 2 Study
    - Amendment 2

PM

- Kathy taught me how to package biological samples (ambient, refrigerated, and frozen samples).
- Assisted in preparing for a Baylor internal monitor visit tomorrow by preparing the monitor room.
- Kathy showed me how to enter information for a subject visit into the electronic data capture (EDC) system.
- Researched possible topics for my practicum report.

June 2, 2016

AM

- Went offsite with Kathy to Legacy Heart Center in Medical Village to see if a physician was interested in possible upcoming study.
- Assisted with patient paperwork.

- Learned about a different EDC system, this time, and how to enter investigational product that has been dispensed.

PM

- Completed several CITI modules completed:
  - o Research Misconduct
  - o Conflicts of Interest
  - o Basic: Refresher modules

June 3, 2016

AM

- Angela gave me a laptop to use and I set it up at my workstation and worked on getting access to various systems.
- Completed another CITI module:
  - o CITI Health Information Privacy and Security (HIPS) for Clinicians

PM

- Left early for meeting at UNTHSC.

## **Week 2**

June 6, 2016

AM

- Finished the rest of the CITI Modules:
  - o GCP Course for Clinical Trials Involving Investigational Drugs
  - o GCP Course for Clinical Trials Involving Investigational Medical Devices

PM

- Worked on getting proper full access to EMR with IT support.
- Kathy showed me how to use Centricity EMR and showed me how she would screen for a patient for the SPIRE study.

June 7, 2016

AM

- Was on phone with IT support. Still having issues with Centricity EMR. I can log in but it says I do not have access to do anything else. Need access to be able to screen patients for studies.
- Spent some time researching about different classes of lipid lowering drugs.

PM

- Went to Baylor Regional Medical Center at Plano to get my badge, however, found a note on the door saying they were closed on Tuesday and Friday.

June 8, 2016

AM

- Arrived at Baylor Regional Medical Center at Plano in order to get my badge ID.
- Researched on the history of PCSK9.
- Settled my thesis topic on the background, history, current research on PCSK9 and comparing it to current use of statins. Will figure out title at a later time.

PM

- Helped Kathy prepare for another monitor visit for tomorrow and the day after by moving records, making copies, and preparing the monitor room.
- Disposed of expired product from several studies. Organized the boxes, the tubes, the needles, and disposed of each properly.

June 9, 2016

AM

- Kathy taught me how to screen patients and what to look for and how to prepare for presenting patients to the physician concerning the study.
- Screened patients for study all morning and was able to find 3 possible subjects.

PM

- Screened for patients for the rest of the day.

June 10, 2016

AM

- Kathy taught me how to process the biological samples for one of the studies. I then processed, packed, and sent them for shipment.

PM

- Worked on thesis proposal and developing a title for the rest of the day.
- Helped report an adverse event (AE).

### **Week 3**

June 13, 2016

AM

- One of the studies was closed per sponsor before enrollment. Liana showed me what was needed to close out the study and how to report it through the IRIS system.
- Screened for patients for SPIRE study.

PM

- Was able to screen more patients for bococizumab study.
- Reviewed some cardiovascular anatomy because I will be following Dr. McKenzie on Wednesday.

June 14, 2016

AM

- Screened patients for study, was able to find 1 more potential candidate.
- Reviewed EKG book for following Dr. McKenzie tomorrow.

PM

- Found that two of the patients I had screened for a patient were excluded from study.  
Liana found one line in each medical chart that would eventually exclude them.
- Reviewed cardiovascular basics in anatomy and physiology.

June 15, 2016

AM

- Started day off with following Dr. McKenzie in the reading room because he is the doctor of the day.
- Dr. McKenzie showed me how to read stress echocardiograms and the basics of how ultrasounds work. He also taught me more about the issues that they look for and how to spot non-normal findings in the test results.

PM

- After lunch, I stayed with Dr. McKenzie. He had more quick patient visits after the patients' stress tests, which were all normal when I was there. He also reviewed EKGs with me and also taught me about positron emission tomography (PET) scans.

June 16, 2016

AM

- Screened patients for one of our studies.
- Worked on proposal and read several studies concerning PCSK9 inhibitors.

PM

- Went with Liana to talk to a physician about the patient he is about to see who is in one of our studies.
- A sponsor representative visited to talk to Dr. McKenzie and us about a genetic study they were proposing. Dr. McKenzie seems to have a positive opinion about it so far. We will wait on informed consent documents to be sent so we can check on them.

June 17, 2016

AM

- Had a staff meeting with the coordinators where we updated each other on the studies they are in charge of and current status of each study. Also talked about upcoming meetings or workshops that are available to us.
- Kathy showed me how to receive investigational product, record the receipt, store it in the fridge, and document that it was received so that the sponsor can confirm delivery.
- Read through articles in journals (American Journal of Cardiology, JAMA) which relate to cardiology and possible studies that will be started here in the near future.

PM

- Precillia showed me how to prepare for an unscheduled patient visit. Patient had some symptoms and was asked to come in on Monday morning, and the PI will evaluate the patient.
- Reviewed the different blood tube colors and the tests that each can be used for when I help process labs on Monday.



## **Week 4**

June 20, 2016

AM

- Precillia showed me how to process samples for one of her studies.
- I talked to the Amgen pharmacy representative about Amgen's PCSK9 inhibitor called Repatha (evolocumab).
- Kathy showed me how to order dry ice for the frozen samples.
- I processed another set of samples for a study.
- Kathy showed me how to handle and package dry ice for the frozen samples.

PM

- Researched the development and method of action for statins.
- Worked on the organization and formatting of my thesis proposal.

June 21, 2016

AM

- Processed some samples in the clinic.
- Was able to screen three patients when going through several of the physician schedules for the next week.
- Helped Precillia go through patients for two studies and check their informed consent version, serious adverse events log, and unscheduled visit dates.

PM

- Worked on screening patients.
- Left early for car maintenance appointment.

June 22, 2016

AM

- Entered in received product in binders and labeled and stored product properly.
- Kathy showed me how to enter in a patient phone call visit on the REDUCT-IT study.
- Precillia had me help organize documents into proper sections in binders for the study.

PM

- Helped Kathy prepare patient binders for upcoming visits by looking up any new visits the patients have had since the last time they had a research visit.
- Documented all the informed consents and revisions of informed consent that were done for all the subjects for the SPIRE I, SPIRE II, and FOURIER studies.
- Completed several lessons on the Baylor Learning Network:
  - o BRI: Definitions and Examples of Research
  - o BRI: Examples and Expedited Review
  - o BRI: Introduction to the IRB Process
  - o BRI: Principal Investigator Reporting Responsibilities
  - o BRI: Recruiting, Screening, Consenting and Retaining Research Subjects
  - o BRI: Risk Assessment
  - o BRI: Special Considerations for Vulnerable Subjects
  - o BRI: Shipping Diagnostic Specimens

June 23, 2016

AM

- Prepared documents and lab kits for upcoming regular scheduled patient visits.
- Helped Precillia document patients that she has screened for one of the studies she is working on.
- Reformatted informed consent data I collected yesterday for a AMG.

PM

- Worked on organizing citations for proposal and general outline and formatting of the document.

June 24, 2016

AM

- Checked screening for about a dozen patients who had previously qualified for the SPIRE study but for some reason had to wait and be rechecked at a later time.
- Worked on thesis.

PM

- Worked on thesis for the rest of the day.

## **Week 5**

June 27, 2016

AM

- Processed and shipped blood specimens for a study.
- Read several studies which are related to a clinical trial which we may take. It has a genetic basis on how patients metabolize drugs and would look at data on how useful such a test would be and if a patient's medications would be changed based on the information in the test.

PM

- Completed BRI Human Research Protection Lessons (7 lessons).

June 28, 2016

AM

- Developed a database to look up prescreened patients to make sure they have not been talked to about the study previously.
- Entered in the patients that have failed prescreening in the last year and a half into this database. Found that there were several patients who have been screened previously and been talked to about the same study multiple times.

PM

- Went to Baylor McKinney with Liana to visit a patient in the ICU who qualified for a study. This was the first patient we were able to screen successfully for the study.

June 29, 2016

AM

- Worked on editing my thesis proposal with the changes suggested by my committee.
- Went with Precillia for a patient visit for the SPIRE study in which they were randomized for either the drug or the placebo. Saw the cognitive testing that was done for this study.

PM

- Received shipment of drug, confirmed all the product that was listed was received and labeled all the bottles for easy identification.

June 30, 2016

AM

- Used online resources to teach myself how to use EndNote X7 more efficiently.

PM

- Reformatted my citations in my thesis proposal using EndNote.

July 1, 2016

AM

- Worked on editing thesis proposal.
- Everyone left at noon to have an early start to the 4<sup>th</sup> of July weekend.

## **Week 6**

### July 4, 2016

- Fourth of July – Day off.

### July 5, 2016

- Worked on finalizing the edits to my thesis proposal from the comments of my three committee members.
- Talked with Angela about my proposal progress and she signed my proposal approval form.

### July 6, 2016

- Drove to UNT Health Science Center and met Dr. Reeves to talk about my practicum proposal progress and he signed the approval form. Dropped off the form at Dr. Gwartz's office so she can sign it when she gets back into the office.

### July 7, 2016

#### **AM**

- Read several Journal of the American Medical Association articles in the July 5, 2016 edition.
- Processed some samples for the REDUCE-IT study.

#### **PM**

- Ordered dry ice and shipped samples when the dry ice arrived because some of the tubes needed to be shipped on the same day as collection and also needed to be shipped frozen.

July 8, 2016

AM

- Processed several samples. Sent them out to the medical laboratory associated with that study.

PM

- Helped prepare for next week's patient visits.

## **Week 7**

July 11, 2016

- Processed a set of samples for a patient visit, put the frozen samples into the freezer for later shipment.

July 12, 2016

AM

- Screened for patients for our open studies.
- Processed blood samples from a patient then prepared them for shipment.
- Entered data into the EDC system for this clinical trial.

PM

- Read journal articles from the Journal of the American Medical Association related to cardiovascular events.

July 13, 2016

AM

- Processed labs for two different studies today: prepared them and boxed them up for shipment.
- Worked on adding screened patients into data base.



July 14, 2016

AM

- Centrifuged blood tubes, transferred them into proper tubes, then prepared them for shipment.
- Gift cards are given to patients for some of the studies when they come in for a visit. A new bundle of gift cards came in, and I went through each one to confirm the last four digits with the list we had received to make sure everything is in order.

July 15, 2016

- Learned that one of our studies will be ending soon, and the patients will be rolled over into this new study for the purpose of following long term effects of the drug. We had a discussion on the work that would need to be done and Kathy mentioned I would be able to help with the labs for each visit.

## **Week 8**

July 18, 2016

AM

- Started reading through the Protocol / Investigator's Brochure for one of our studies. This is what is given to an interested Principle Investigator to give them all the information and science behind it so that they may evaluate for themselves whether they are interested or not in the clinical trial.

July 19, 2016

AM

- Processed several labs for two patient visits and then shipped the ambient samples.
- Read cardiovascular articles in the New England Journal of Medicine.

July 20, 2016

AM

- Worked on creating a database of safety reports for one of the studies we were working on. Confirmed that older reports were in the older files then imported them into the new file. Added new entries into the database and organized the documents into a binder.

July 21, 2016

AM

- Attended a meeting with the coordinators to be updated on what clinical studies were available in cardiovascular and diabetes research topics.

- Ordered dry ice to arrive in the afternoon so that we can sent out the frozen specimens.

PM

- Had a meeting with a physician and the coordinators to discuss the difficulties we were having enrolling subjects for one of the studies. We were able to figure out the issue and proceed with screening patients.
- Dry ice arrived and I was able to package and send the frozen specimens to the lab for that study.
- Screened patients for previously mentioned study for the rest of the day.

July 22, 2016

AM

- Went to IRB study staff meeting that was at the downtown Dallas Baylor University Medical Center's IRB building. I learned about the iRIS system and how the IRB processes incoming studies and what sort of language needed to be in the Baylor IRB informed consent document.

PM

- After getting back, was able to distribute the current Baylor Research Institute Research Regulatory Affairs current contact list to the other coordinators.
- I screened patients for the rest of the day on one of our newer studies.

## **Week 9**

July 25, 2016

- Finished screening patients that I had not finished from last week's list for ISCHEMIA study.
- Learned about copyright policy because I want to use a figure from an article for my thesis. Sent out email to see if they could grant me permission to use the image for my thesis.
- Looked through nuclear stress tests to check for criteria for a study.

July 26, 2016

- Traveled with Liana to Baylor McKinney to visit a patient who qualified for the ARTEMIS study. I talked to the patient to see if they were interested but patient declined after telling them about the study.
- Sat in on a patient visit for a device download (interrogation) for a device trial we are running.
- Met with MedTronic's representative of their research department. Observed as they downloaded data from a patient's implanted device. Patient has a second device at home which uploads data through the cellular network, but must come in for in person download every few months.

July 27, 2016

- Prepared a set of lab specimens to be sent to the lab, put the frozen samples in the freezer, and then prepared the ambient samples for shipment.

- We had a meeting with Amarin representatives about the REDUCE-IT study and they addressed how we were doing a great job with the patient retention and how we compared to other sites around the world and in the United States. They also told us what we should expect for the rest of the study.
- Received shipment of supplies for one of the studies. Unboxed them, took note of what was received, and put them in our supply room.

#### July 28, 2016

- Our department had a round table meeting for the research team. Angela updated us on the current lookout for future studies, and the coordinators updated her on how the meeting with Amarin went yesterday. We discussed recruitment about one of our studies and possible ways to screen more patients before they were ineligible.
- Received a shipment of investigational product from sponsor. Verified product received with requisition form listing what was included. Wrote box numbers on side of box for ease of finding when looking for a certain box number. Put product in the fridge and logged received product into the binders.

#### July 29, 2016

- Processed lab samples and shipped the ambient samples to the lab.
- Drive to UNT Health Science Center to make sure my graduation forms are in order. I updated Dr. Gwartz and Dr. Reeves on my work here at my internship.

## **Week 10**

### August 1, 2016

- Liana was able to screen a patient for the ARTEMIS study. We drove over to the hospital to speak to the patient about the study to see if he would be interested in joining it. I read up on the informed consent document because I would try to introduce the study to the patient. We got there, had to wait for a nurse to finish with the patient. I was able to give a short description of the study, but unfortunately the patient was not interested in the study.

### August 2, 2016

- Today, I screened for patients in the ARTEMIS study. Still having trouble finding patients. We are each looking at a different part of the schedule, but there have been very few patients that qualify and the few that do are caught too late and would not qualify anymore.

### August 3, 2016

- Received product. Learned how to complete the temperature probe that comes in these coolers. They are there to ensure that the product temperature stays within a specified range. I stopped the recording, then plugged it into the computer to print out a temperature log for our records.
- Confirmed and recorded product in our records and then labeled and organized them in the refrigerator.

#### August 4, 2016

- Processed samples in the morning and sent them for shipment to the proper laboratory for that study.
- Another patient was screened for the ARTEMIS study, and I went with Liana to see if the patient would participate in the study. When we got there, we had to wait quite a while because the patient was having a short procedure done in their room. We were able to successfully talk the patient into joining the study and complete the informed consent.

#### August 5, 2016

- Took this day off to get my graduation forms signed at UNT Health Science Center.
- Did some research for my thesis while at the school library.

## **Week 11**

### August 8, 2016

- Meeting with Angela and coordinators about goals in employment in the research department.
- Processed two sets of samples from patient visits today. Sent the ambient samples in.
- Ordered dry ice for the frozen samples that we have been keeping in the freezer.
- Packed and shipped frozen samples to the labs.

### August 9, 2016

- Processed, packaged, and sent the ambient samples from today's visit for the SPIRE study.
- Received new shipment of drug. Unpacked it, confirmed shipment, and set it up in the refrigerator.

### August 10, 2016

- Processed samples in the morning, then packed them for shipment and set them in the pick-up area.
- Re-edited my figure for my thesis that I drew up a few days ago.
- Screened for patients in the ISCHEMIA study, but I was not able to find any today.

### August 11, 2016

- Processed and packaged samples in the lab from today's study visit.



- Assisted with checking for drug compliance by counting the amount of doses returned from the previous drug that was issued in previous visits. I then calculated how many doses were taken versus how many doses were not taken.

#### August 12, 2016

- I learned about one of the device trials that is ongoing at this site. I was able to look at demo units of version one and version two of the device. This device was used to monitor for atrial fibrillation and is implanted subcutaneously between two ribs.

## **Week 12**

### August 15, 2016

- I worked on updating a database for patients that have been screened for the past month. I had to go through list of patients that were screened and fill out information on them and save it to our research drive.
- We received new Aegis Security Key flash drives which are now required for transferring files from computer to computer. I had to figure out how to use it and then show the others how to access and unlock it for their computer.
- I attended a goals meeting with Angela and our coordinators.

### August 16, 2016

- Processed specimens from several subjects. Processed and packaged them for shipment.
- Ordered dry ice to send in the frozen samples we have collected.
- Received dry ice, packed the frozen shipment boxes with dry ice and packed them for shipment. Ordered pick up by the shipping carrier.

### August 17, 2016

- Processed samples in the lab and prepared the ambient shipments for the day.
- Received a box with study drug. Accounted for them, stopped the temperature probe and printed out the report, and stored them in the research fridge. Recorded values in the binder.

#### August 18, 2016

- Spent time looking for a figure for the LDL mechanism online. Could not find a simplified one, so I made my own. This took some time to get it to where I wanted it.
- Listened in to the tele-conference with Baylor IRB board for continuing review on one of our studies.

#### August 19, 2016

- Spent time writing out the Acknowledgements and Abstract to my thesis.
- Adjusted formatting and had to figure out how to get the page numbers to work correctly on my document.
- There is a training for the electronic medical record (EMR) change over next month, but Angela is not sure if I can attend because my name is not on the attendance list. She will be checking on this to see if I can attend.

## **Week 13**

### August 22, 2016

- We had a site initiation visit (SIV) meeting here in office. This is when a company wants to see if our site is a good candidate for one of the clinical trials they have. A representative visits and looks at our facilities and talks to the team and principle investigator (PI) about the clinical trial. They discuss the objective, the inclusion and exclusion criteria, and get information on the team and PIs and sub-PIs. The representative then took a tour around our facility to see if it meets their company's standards.
- We also had a physician meeting during lunch where we update the physicians here about the research going on and any news. Another pharmaceutical representative also wanted to stop by this week and so she sponsored the lunch and had a quick presentation for the physicians before the main physician research meeting.

### August 23, 2016

- Took the day off to get some dental work done.
- Worked on thesis.

### August 24, 2016

- Processed labs in the morning for several patients then packaged them to go to each individual lab.
- Assisted in packing bags for volunteer program for people in Louisiana.
- Had meeting with study coordinators about the current progress on the ISCHEMIA study.

- Attended a web conference with Dr. McKenzie and the study coordinators about an upcoming study that another company wants us to host. This is similar to the SIV meeting the other day except as an online conference. Looks promising so far, but will see if it works out.
- Left early for optometrist appointment.

#### August 25, 2016

- Office cooler had a leak so helped bring it outside. Apparently it cannot hold water anymore due to some issue in the piping.
- Updated internship journal for this week.
- Prepared the articles I have printed out for citations and notes.
- Helped bring back the binders from the monitor visit the other day.

#### August 26, 2016

- Received gift card stipends given for patient visits for some clinical studies. Confirmed that all listed cards were included. Distributed them to the coordinators after each envelope for ease of finding.
- I had organized a lunch for us today which we brought some ingredients for queso and chips.
- Worked on thesis first draft more.

## **Week 14**

### August 29, 2016

- New drug has arrived for a study that is rolling over into a follow up study. Received, confirmed, and labeled all the drug boxes, and then put them into the refrigerator for storage. The box that the drug came in had to be returned so organized a return and set it out for pick up.
- Processed specimens that were collected this morning. Centrifuged them in the lab and then packed them for shipment after verifying proper labelling.

### August 30, 2016

- Worked on thesis draft in the morning.
- Organized patient chart and double checked product log.

### August 31, 2016

- Our whole team had an all-day training at another facility in Dallas to familiarize us with the new electronic medical record (EMR), called Epic, that our whole facility will be using in the near future.

### September 1, 2016

- Received three very large boxes that had investigational product (IP) for our SPIRE studies. Had to open each, stop the temperature reading sensor, print out the report from that sensor, and confirm and label all the small boxes that were included. These were

stored in the research fridge, and next I had to enter all the product into the investigational binder for record keeping.

- While I was doing that, a patient had come in wanting to opt out of the study unexpectedly. The patient was scheduled for his final visit next week, but since he came in early, it would be labeled as “early termination.” I helped organize his end of study kit and one of the other coordinators went to talk to the patient and get the paperwork written up.
- Had the weekly meeting with the coordinators about our findings for the ISCHEMIA study. Today, I had found a patient that qualified and two others who had an exclusionary criterion when I looked into them a little closer. The lead coordinator for this study took the information to the PI to see if he wants to talk to the patient about the study.
- Labeled lab kits for other end of study visits happening next week.

#### September 2, 2016

- Processed labs for two end of study trial visits. This had more than a dozen transfer tubes from about nine blood specimens and also two urine transfer tubes. Had to wait for centrifuge to spin because we have more tubes than spaces in the centrifuge.
- Processed labs for a different study but this was a standard visit.
- Left early for noon dental appointment.

## **Week 15**

September 5, 2016

- Labor Day! Day off.

September 6, 2016

- Processed two sets of labs for end of study visits for our FOURIER study.
- Labeled and prepared kits for visits tomorrow.
- Packaged and shipped the ambient and refrigerated samples that needed to be sent today.
- Reviewed several articles for my thesis and took notes on parts that I was interested in referencing.

September 7, 2016

- Prepared more lab kits for end of study visits tomorrow.
- Processed samples in the lab for the end of study visit we had today.
- Received new product and supplies for one of the studies we have.
- Saw that new medical journals issues had a few articles on PCSK9 inhibitors so I reviewed them.

September 8, 2016

- Took the day off for appointments today. Had dental issue recently and had to get it seen.
- Worked on editing thesis and journal.



September 9, 2016

- Had to figure out an issue with my access with our EMR called Centricity. Somehow my access had expired, and I had to resolve with the IT department.
- Received stipend cards that are given in some clinical study visits to the patients.  
Confirmed that all were received and labeled them for future use.
- Prepared more kits for end of study visits this next week.
- Listened in to conference call for one of our studies. Updated on how enrollment will be wrapping up very soon and we will just follow patients for the next year.

## **Week 16**

### September 12, 2016

- Took day off because family member got in an accident this morning.
- Worked on thesis when I had time waiting.

### September 13, 2016

- Received new product for the new study we are rolling over patients into. Labeled the boxes, and put them in the fridge. Then for this study, we have to ship back the container they came back. Packed that up and organized a pickup from UPS.
- Prepared another end of study visit testing kit for tomorrow.
- Worked on the history part of PCSK9 in my thesis.

### September 14, 2016

- Helped prepare the monitor room for the monitor visit we will have tomorrow. Pulled all the binders and paper records that the monitor would need and put them in the room.
- Working on getting permission to use another figure that would pair well with a section of my thesis.
- Had another EPIC training session at another facility. This training was for “Clinical Research Coordinators” and would be incredibly helpful and give us the ability to do much more work without having to contact scheduling or billing for clarification.

#### September 15, 2016

- Processed a shipment that was received, labeled and sorted all the drug, and then put everything in the refrigerator.
- Had our coordinator meeting for one of the studies to talk about what we were able to screen since we have divided up the schedules. Gave results to Precillia since she is the lead for this study.

#### September 16, 2016

- Went to get a signature from one of our physicians but had to find him at the hospital where he was doing rounds on his hospitalized patients.
- The monitor for one of our studies was done with the drug accountability. Next we had to break down and dispose of the empty boxes that the patients have returned.
- Angela bought us all lunch because yesterday was my birthday.
- When we got back, I worked on the history section of my thesis.

## **Week 17**

### September 19, 2016

- Worked on thesis in the morning.
- Prepped samples in the lab and then prepared them for shipment.
- Listened in on conference call about one of the studies and the progress in it so far.
- Received faxed labs for patients in a study and put them in the patient binders.
- Helped prepare another end of study testing kit by filling out paperwork and labelling and preparing the blood specimen tubes and transfer tubes.

### September 20, 2016

- Fixed citation issue I had on my thesis leading to wrong citations being referenced.
- Helped prepare monitor room for one of the studies by bringing the patient binders and other documents to the room.
- Received shipment of IP, confirmed the box numbers, labeled for ease of retrieval, and then put them in the fridge.
- Had a phone conference for a site initiation visit. The sponsor asked questions about what we were able to do and spoke about what the aims of the study were. Dr. McKenzie attended the first part of this as there were questions that he specifically had to answer.
- Screened for patients for one of our studies.

### September 21, 2016

- Received a list of stipend cards. Checked them against the list of cards dispersed, labeled the envelope to find them faster when needed, and then gave them to Kathy.

- An order of dry ice was put in this morning. Received it after noon and packaged the frozen samples with the dry ice for shipment.
- Had our weekly meeting for the ISCHEMIA study with the coordinators here. I was able to find one candidate this last week that had not already been scheduled for a procedure.

#### September 22, 2016

- I was given a list of documents for the primary investigator and each sub-investigator that was going to participate in an upcoming study. I had to track each physician down and make sure that they signed in the proper sections and that they wrote the date in a very specific manner. I had to reprint any pages with mistakes. It took some time, but I was able to get all the physician signatures before lunch.
- Worked further on my thesis. Created a table of statins and referenced the FDA labels for the date of FDA approval.

#### September 23, 2016

- Processed labs from a patient's visit. Had to repeat the blood smears a few times to ensure they were done right. Shipped the two best ones with the ambient samples.
- Received a list of screened patients for one of our studies. Updated the screened patient log with the proper data to send to the sponsor to confirm that we are screening patients.

## **Week 18**

### September 26, 2016

- Was still sick from this last weekend so I took the day off to fully recover.

### September 27, 2016

- Worked on thesis. Finished another chapter and proof read the previous section of my thesis. Updated citations that did not save from last time I worked on my thesis.
- Received a shipment of IP. Confirmed that the boxes were as listed in the requisition. Labeled and then put them in the fridge. Shipped back the container they came in as per protocol.
- Had to leave early for an appointment.

### September 28, 2016

- Received the Baylor Research t-shirt for tomorrow's company picnic
- Screened for patients in the ISCHEMIA study.
- Worked further on my thesis and researched more about the different clinical studies being done on PCSK9 inhibitors and how they could relate to my thesis.

### September 29, 2016

- Today we had the company picnic for Baylor Scott and White Research Institute. People who worked in both North Texas and Central Texas came together (although it was mandatory) to meet up and have a picnic in Waxahachie. Buses were provided for large groups. Since we only have five people, the closest bus to us was at downtown Baylor.

We elected to carpool and had to arrive earlier. We drove down, and when we got there it was a large camp ground which was part of a church. Everyone was wearing the shirt provided for us, and we signed in. Breakfast was provided, and we had speakers from different aspects of Baylor's research. Then we had a keynote speaker who spoke about leadership and how to communicate with different styles of people and when they will be receptive to criticism that may be needed to be said. Then we had a break for lunch which was grilled hotdogs and burgers. We were able to take a walk around the area and it was very nice. There were cabins, a lake, a small skate park, a volleyball court with an inflated floor for bounciness, archery activities, and basketball courts. We went back in for some quick presentation and then they let us out to do whatever we would like to do. Some people played basketball, some people tried the archery activity, and some people walked around and soaked up the sunny scenery. Afterwards, we drove back and our day was done because we arrived about the time for the end of the day.

#### September 30, 2016

- Completed labs for patient visits and shipping them out to the lab.
- Cleaned out supply closet from any expired needles, tubes, and other medical supplies.
- Broke down boxes for research visits that we were allowed to dispose of.
- Had our weekly coordinator meeting for the ISCHEMIA study. I had found 4 candidates and was able to put those in for consideration.

## **Week 19**

### October 3, 2016

- I could not contact the publishing author for one of the figures I wanted to use so I decided to design my own figure. Took longer than I anticipated.
- Received comments from Dr. Gwartz about my current thesis draft. Worked on incorporating those changes and editing some things based on her comments.
- Had to relabel all my figures and tables to properly show citations.

### October 4, 2016

- Worked further on my thesis in the morning for better flow of ideas.
- Processed a sample for a patient that had come in late in the day. Worked with Kathy to get it shipped out as soon as possible so that it will arrive on time.
- Our weekly meeting for ISCHEMIA study was conducted today. Gave the patients I screened to Precillia so that she can contact them if the physician approves.

### October 5, 2016

- Helped process samples for several visits this morning. Shipped them out for Precillia because she is busy today with paperwork and a monitoring visit.
- Worked on re-editing my thesis and added in my journal to Appendix B.

### October 6, 2016

- Helped with the patient study visits by working in the lab for the study visits we were having today. Prepared the samples in the lab and then got them ready for shipment.



- We had ordered some dry ice for shipments. When it arrived, I shipped out the frozen samples that had accumulated from the previous patient study visits since the last frozen shipment batch.

#### October 7, 2016

- We kept receiving faxes of the same report over and over. I had to sort through the stack of papers we received and throw out any doubles. Eventually, we turned off the fax machine and called the lab to see what was happening.
- Spent time updating my internship journal and editing it.

## **Week 20**

### October 10, 2016

- Processed several samples for the patient visit that was done today.
- Received the protocol for a study that our site has been approved for so that I can read through it.
- Worked on my thesis on the final draft to be sent out to my committee members.

### October 11, 2016

- Worked on editing my thesis further and having better flow between some topics.
- Asked Dr. McKenzie to read through my draft and tell me his opinion. Surprisingly, he returned it barely two hours later and had some good comments.

### October 12, 2016

- Screened for patients for our ISCHEMIA study.
- Had our coordinator meeting to see what patients each of us were able to screen. This time, I was not able to screen any qualifying patients.
- I performed a final read and adjustments to my thesis before sending it out to my committee members.
- Worked on figuring out how to run reports on the EMR we had recently transition to – Epic. I am able to run the template reports and get results, but if I try to change them to work for what we need, I cannot get any results back.

#### October 13, 2016

- Updated the screened patients log for our AUGUSTUS trial.
- Had another attempt at trying to figure out how reports work on Epic. Have not been successful so far. Heard from another coordinator that the physicians might have taken the training class to run reports so I might need to get with one of them.

#### October 14, 2016

- Screened for patients at the start of the day.
- Did a quick search on the clinical trials website to see if there were any new upcoming trials that might be done at our site.

## **Week 21**

### October 17, 2016

- Prepared and shipped some specimens from one of our research studies.
- Screened for patients.
- Worked on the PDF for my presentation.

### October 18, 2016

- Drew up an invitation page to post up outside my station that lists my thesis defense time, room, and address.
- Worked on my presentation defense.
- Finished the general layout of my slides.

### October 19, 2016

- Screened for patients.
- Had the coordinator weekly meeting for one of our studies.
- Worked on various slides and how to better present them.
- Finished the history of statins section

### October 20, 2016

- Processed specimens for one of the research studies, and then shipped them.
- Went to school to get laptop checked out for a crack in the screen.
- Worked further on my presentation. Finished the history of PCSK9 section.

October 21, 2016

- Worked on my defense.
- Went to school to get laptop fixed.
- Version 2 of my defense finished.

## **Week 22**

### October 24, 2016

- Screened for patients on the ARTEMIS study.
- Went to UNT HSC to rehearse defense presentation with Dr. Reeves. He gave me some good points to work on.

### October 25, 2016

- Spent the day preparing for my defense tomorrow.
- Made adjustments to make my presentation flow better.

### October 26, 2016

- Defense date!
- Overall, a good experience.

### October 27, 2016

- Learned about some news concerning PCSK9 inhibitors. One of the trials has unexpectedly received notice to end early.
- Performed the patient screening so I can get the data for our weekly coordinator meeting for one of our studies.

### October 28, 2016

- Prepared specimens for shipment
- Screened for patients. Quiet day otherwise.

## **Week 23**

October 31, 2016

- Received product for one of our studies.
- Helped one of the coordinators with checking the binders for one of the studies.
- Looked for different cardiology journals which may be available for me to publish a review article in.

November 1, 2016

- Screened for patients.
- Through reading about pharmaceutical news, I found a study that we are looking into to see if the sponsor is still looking for sites. Possible.

November 2, 2016

- Brought cupcakes for the research team.
- Cleaned my station and took home any of my belongings.
- We went out to lunch for my final day.

## APPENDIX C ABBREVIATIONS

<b>Abbreviation</b>	<b>Definition</b>
ACC	American College of Cardiology
AHA	American Heart Association
ASCVD	Atherosclerotic cardiovascular disease
BRI	Baylor Research Institute
CHD	Coronary heart disease
CVD	Cardiovascular disease
EDC	Electronic Data Capture
EMR	Electronic medical record
FDA	Food and Drug Administration
HDL	High density lipoprotein
HeFH	Heterozygous familial hypercholesterolemia
HMG-CoA	3-hydroxy-3-methyl-glutaryl-coenzyme A
HoFH	Homozygous familial hypercholesterolemia
IDL	Intermediate density lipoprotein
IND	Investigational new drug
IRB	Institutional Review Board
LDL	Low density lipoprotein
MACE	Major adverse cardiovascular events
MI	Myocardial infarction
NHLBI	National Heart, Lung, and Blood Institute
PCSK9	Proprotein convertase subtilisin/kexin type 9 An enzyme that binds to LDL receptors enabling breakdown of receptors
RCT	Randomized controlled trial
VLDL	Very low density lipoprotein



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