

A COMPARATIVE REVIEW OF SCREENING, CONSENT, AND TRIAL VISITS AND
FOLLOW-UP PRACTICES IN CARDIOVASCULAR DUAL ANTIPLATELET THERAPY
DRUG, DEVICE, AND REGISTRY STUDIES AT LEGACY HEART CENTER AND THE
HEART HOSPITAL BAYLOR PLANO

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I. INTRODUCTION

The main purpose of this internship practicum report is to delineate the differences between three types of clinical research trials: drug trials, device trials, and registry trials. This sort of descriptive review will take place within the context of dual antiplatelet therapy (DAPT).

Drug trials are those in which a substance is used “in the diagnosis, cure, mitigation, or prevention of disease...which achieves its primary intended purpose through chemical action within or on the body.” [2]. A device functions similarly, but “is not dependent on metabolism for the achievement of its primary intended purpose.” [2]. This kind of research is incredibly thorough in nature, because specific interventions are conducted on patients; thus, safety and efficacy are of significant importance. There are differences in how drug and device trials approach safety and efficacy. Typically, drug trials are put through four phases of research. Phase I trials are done on small groups of people in order to test an intervention’s safety [3]. Phase II trials expand on the number of patients and also test for safety. Phase III trials are those that provide a drug or treatment to a large number of people, tracking effectiveness, side effects, and seek to make judgments on a treatment when compared to standard of care. Phase IV trials are post-market trials that track a treatment’s impact on populations and long-term risks [3]. The drug study under review for this practicum report is the Prevention of Thrombotic Events with Ticagrelor Compared to Placebo on a Background of Acetyl Salicylic Acid (ASA) Therapy in Patients with History of Myocardial Infarction (PEGASUS-TIMI 54). The aim of the

PEGASUS-TIMI 54 study is to determine the safety and efficacy of ticagrelor and aspirin in the reduction of cardiovascular events when compared to placebo and aspirin.

Research on an investigational device is more staged than conducted in phases, with feasibility, application development, and pivotal stages being the necessary steps determining safety and efficacy [2]. Though these terms are not exclusive to investigational devices, they are more reflective in describing the true nature of device studies than phase models. Feasibility in device trials is used to estimate parameters that will be of critical importance in the development of a research design, such as standard deviation of an outcome measure, willingness of participants to be randomized, and specific characteristics of outcomes measures [4]. These studies serve as the foundational piece for which investigational device trials build upon. Application development is centered on risk assessment and classification [2]. Pivotal studies are analogous to Phase IIB or Phase III trials, and are designed to get statistically significant evidence of efficacy and safety [5]. The device study being reviewed in this practicum report is the COBRA PzFTM Coronary Stent System in Native Coronary Arteries for Early Healing, Thrombus Inhibition, Endothelialization and Avoiding Long-term Dual Antiplatelet Therapy (PzFTM SHIELD) trial. The primary purpose of this study is to determine whether or not the novel technology in the COBRA PzFTM Coronary Stent System is safe and effective at reducing the incidence of stent thrombosis in patients long-term. Patients will on DAPT regimens for a shorter period of time than that which is current standard of care.

Registry studies track the practices and outcomes of a certain disease condition while a subject to standard of care. Registry studies are non-interventional in nature, and seek to give researchers an idea of the “real world” application of treatment patterns [1]. The key component of registry studies is observational; they do not tied to an investigational product or device. The

data collected from these studies can be used to determine costs or specific treatment patterns that might vary across different regions. The Long-Term Risk, Clinical Management and Healthcare Resource Utilization of Stable Coronary Artery Disease in Post-Myocardial Infarction Patients (TIGRIS) study is the registry study being analyzed for this practicum report. TIGRIS arises as an extension of the PEGASUS-TIMI 54 study, and seeks to delineate how patients with stable coronary artery disease are treated across the world. Surprisingly, comprehensive worldwide information on the healthcare resource utilization and event rates for patients with a history of myocardial infarction is not readily available.

II. SPECIFIC AIMS

Ultimately, this practicum report intends to highlight the differences between three categories of clinical research: drug, device, and registry trials under the umbrella of dual antiplatelet therapy (DAPT) at Legacy Heart Center and The Heart Hospital Baylor Plano. The following specific aims are pertinent to this sort of descriptive review:

1. Review the salient literature regarding cardiovascular DAPT in the context of :
 - a. How DAPT functions in the body
 - b. Aspirin and its effect on reducing stent thrombosis
 - c. Other antiplatelet therapeutic agents, describing
 - i. P2Y₁₂ receptor structure and function
 - ii. Thienopyridines (Clopidogrel and Prasugrel)
 - iii. Novel antiplatelet agents (Ticagrelor and Cangrelor)
 - d. Cardiovascular stenting and the development and evolution of stent options, including:
 - i. Bare metal stents (BMS) versus drug eluting stents (DES)
 - ii. Current research being conducted on novel stenting strategies
 - e. Research studies aimed at determining the optimal time for which DAPT should be used in at-risk patients.
2. Compare the differences among DAPT drug, device, and registry studies at Legacy Heart Center and the Heart Hospital Baylor Plano, specifically the PEGASUS-TIMI 54 trial,

the PzF SHIELD trial, and the TIGRIS clinical research study. These studies will be compared based on the following criteria:

- a. Screening Practices
 - b. The Informed Consent Process
 - c. Trial visits and Follow-up Practices
3. Elucidate the limitations of this descriptive study.
4. Discuss the internship experience, highlighting the significant aspects of clinical research that are necessary to manage a clinical research trial.

III. SIGNIFICANCE

Ischemic coronary artery disease and cerebrovascular disease represent two of the three most frequent causes of death in the United States [6]. Dual antiplatelet therapy (DAPT) is considered standard of care in the practice of preventing future ischemic events, and studies have shown their effectiveness in inhibiting the thrombus formation and improving long-term outcomes. DAPT studies are relevant in the scope of cardiology because there are many unanswered questions regarding the best treatment strategy. Physicians are presented with a host of DAPT drugs and stent options to use on patients, and it is not yet clear how long patients should be on DAPT when weighing out risks vs. benefits. These questions have spurred the research studies presented. The PEGASUS-TIMI 54 drug study aims to answer the safety and efficacy of using DAPT beyond the window that is standard of care. The PzF SHIELD study, the device trial relevant to this report, is designed to determine if DAPT therapy is even necessary beyond a month. Finally, the TIGRIS registry study intends to give researchers an idea of how cardiovascular disease is treated across the world.

A descriptive review of clinical research studying DAPT is significant in its ability to outline the differences among the types of drug, device, and registry studies being done. Baylor Research Institute (BRI), which is one of the top research institutions in the nation, manages dozens of clinical research trials. Cardiovascular research comprises a significant portion of the studies being conducted. One of the potential benefits of this practicum report is describing how the BRI's policies on organizing and implementing clinical trials make them so successful. A

discussion on the differences between drug, device, and registry studies can provide insight into how groundbreaking research can be applied to patient populations. Comparing these studies in how patients are screened, consented, treated during trial visits and followed up, will demonstrate how studies with seemingly different principles can have the same aim to answer some of the same fundamental questions.

IV. LITERATURE REVIEW

In order to thoroughly investigate the intricacies of drug, device, and registry studies within the context of dual antiplatelet therapy (DAPT), a fundamental understanding of DAPT is necessary. In cardiology, DAPT is used to prevent stent thrombosis in patients that have recently undergone a percutaneous coronary intervention (PCI) with a coronary stent [7]. It has other uses in the treatment of stroke and vascular diseases, and is now being tested as a means of preventing cardiovascular events, pre-PCI [7]. Stent thrombosis is best prevented by the inhibition of platelet aggregation, and thus the pathways upregulating platelet formation and aggregation are of specific interest. DAPT is combination therapy of acetylsalicylic acid—more commonly called aspirin—and a Purinergic receptor G Protein-Coupled Receptor 12 (P2Y₁₂ receptor) antagonist.

Aspirin is a non-steroidal anti-inflammatory drug (NSAID) with a variety of functions in the body, but its antiplatelet characteristics are of beneficial use in the realm of cardiovascular disease. Aspirin works on cyclooxygenase-1 (COX-1), an enzyme intimately tied to prostaglandin synthesis. COX-1 converts arachidonic acid to prostaglandin H₂ (PGH₂), which becomes thromboxane-A₂ (TXA₂). TXA₂ functions by stimulating the activation of new platelets, as well as increasing platelet aggregation. Therefore, inhibition of TXA₂ would be instrumental in the prevention of stent thrombosis and coronary artery restenosis. Aspirin acts in inhibiting COX-1 by acetylating its serine 529 residue [8]. This blockage prevents binding of

arachidonic acid to the tyrosine 385 residue (the active site of COX-1), thereby irreversibly inhibiting platelet-dependent thromboxane formation [8].

While the effects of aspirin in secondary prevention of cardiovascular events—mainly stent thrombosis—are clear, its effects in primary prevention are still unclear. In a meta-analysis of randomized clinical trials, Baigent et al. indicated that the use of aspirin in primary prevention of any serious vascular event—defined as myocardial infarction (MI), stroke, or vascular death—was not significant enough to introduce it into treatment regimens of patients that have not yet shown pre-existing signs of a cardiovascular disease condition [9]. The trials under review by Baigent et al. did not include patients who were on statin therapy, which is known to reduce the incidence of MI and stroke [10]. Given the current widespread availability of generic statins, the potential risks of the use of aspirin alone in the primary prevention of major adverse cardiovascular events (MACEs) may outweigh any potential benefit [9].

The biggest risk posed by aspirin, through the inhibition of platelet aggregation and formation, is bleeding. These risks of aspirin are further magnified in patient populations above the age of 70 years [11]. Unfortunately, many patients experiencing MACEs and suffering from cardiovascular disease are older. Thus, the risk-benefit ratio of the use of aspirin (and other antiplatelet therapy) must be weighed on a patient-to-patient basis. PGH_2 , the precursor to TXA_2 , is also converted to a variety of other prostaglandins (PGs) that function in enhancing mucosal blood flow in the GI tract, largely thought to be caused by their vasodilating properties [12]. Inhibition of COX-1 carries the risk of GI bleeding and damage. For this reason, NSAIDs focused on specifically targeting COX-2, which plays a more significant role in the inflammatory response while minimizing the GI bleeding risk, are often preferred as options to combat pain and inflammation.

Despite the risks aspirin poses, it remains a potent ally in the fight against stent thrombosis and the prevention of future MACEs. While there are differences among the P2Y₁₂ antagonists that cause physicians to recommend one over another, aspirin is always prescribed as part of a DAPT regimen. Randomized, blinded studies investigating DAPT therapy mostly center on P2Y₁₂ receptor antagonists, and use aspirin in both the experimental and control cohorts. Thus, any conclusions formulated from these trials hope to highlight the specific effects of the P2Y₁₂ antagonists and not aspirin.

The other component of DAPT—the P2Y₁₂ antagonist—serves as the main focus of clinical research on the subject. The P2Y₁₂ receptor, a G-protein coupled receptor (GPCR) found mainly on blood platelets, plays a significant role in platelet activation and aggregation [13]. Mutations in the gene encoding for the P2Y₁₂ receptor can cause severe congenital bleeding disorders. Further, knockout experiments in mice have indicated increased bleed time and impaired platelet activation [13]. These experiments can manifest themselves in multiple ways: first, mutations in the receptor can affect its ability to adequately and effectively bind ADP. Other mutations, namely a mutation changing the arginine 256 residue to tryptophan, do not affect ADP binding but cause a loss-of-function mutation in G protein activation [13].

Structurally, the P2Y₁₂ receptor follows the motif of most GPCRs, with seven transmembrane α -helices and a C-terminus on helix VII that lies parallel to the cell membrane. Using the experimental drug AZD1283, an investigational antiplatelet, Zhang et al. elucidated the binding pocket of P2Y₁₂ to extend between helices IV and VII, while interacting with helices III through VI [14]. The binding orientation of AZD1283 is significant when compared to other class A GPCRs. Zhang et al. determined that the orientation of AZD1283 is slightly orthogonal when compared to the binding of other analogous ligands to other class A GPCRs. This

discrepancy in binding is caused by a unique property of the P2Y₁₂ receptor: it is structurally different in multiple areas from known class A GPCRs. Nearly all class A GPCRs have a characteristic bend in helix V; however, the P2Y₁₂ receptor lacks this kink, and instead holds a straight confirmation throughout helix V [14, See Figure 1].

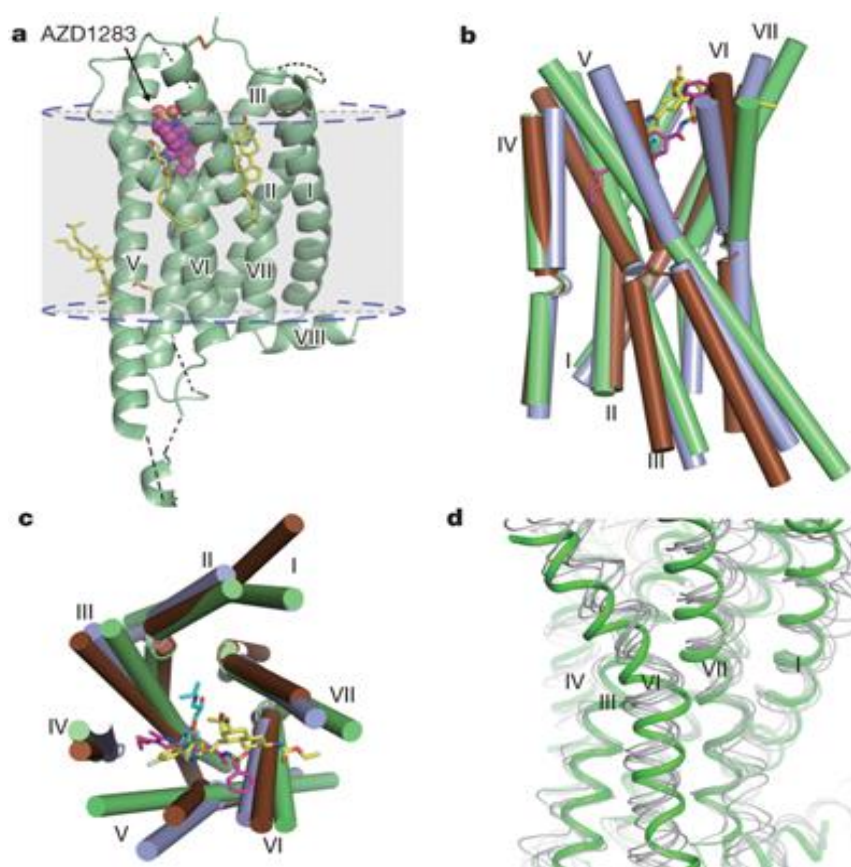


Figure 1: **a**, Cartoon representation of P2Y₁₂R. P2Y₁₂R is colored green. AZD1283 is shown as magenta spheres. **b**, **c**, Side (**b**) and top (**c**) views of P2Y₁₂R (green cylinders) compared with β_2 AR (PDB accession 2RH1, brown) and PAR1 (PDB accession 3VW7, blue). The ligands AZD1283, carazolol and vorapaxar are shown as sticks with magenta, cyan and yellow carbons, respectively. **d**, Comparison of P2Y₁₂R, shown in green, and the other GPCRs, in grey. Reprinted by permission from Macmillan Publishers Ltd: NATURE (Zhang K, et al. Structure of the human P2Y₁₂ receptor in complex with an antithrombotic drug. 509:115-118), Copyright (2014).

A second shift from the canonical class A GPCR is seen in helices VI and VII, where the intracellular portion of helix VI is angled more closely towards the intracellular surface. This has implications for the ionic bonding of helix VI to a conserved portion of class A GPCRs [14]. It is thought that these differences in the intermolecular properties of the receptor lend itself to more sensitive activation, evidenced by high levels of basal activity [15, See Figure 2]. The structure of the P2Y₁₂ receptor exhibits a high level of malleability given the ligand it binds, and opens the door to multiple binding pockets for the receptor [14]. Armed with such knowledge, there is potential to tailor a medication to target specific regions on the receptor—thereby affecting it in different and potentially less harmful ways—while achieving the same desired physiological response. The flexibility in the receptor’s structure has allowed a number of treatment options to emerge as potential candidates for the other arm of dual antiplatelet therapy.

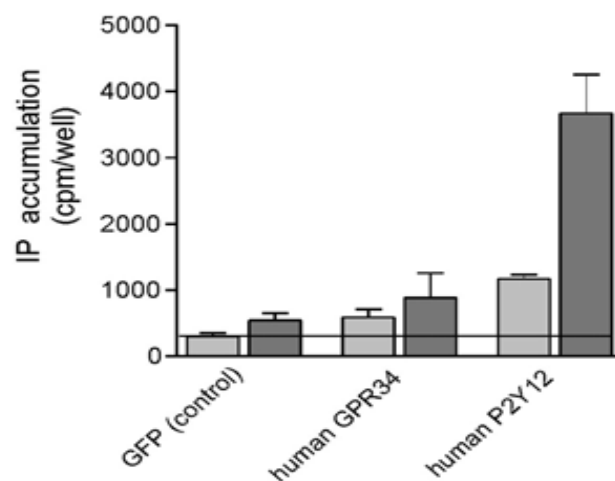


Figure 2: Plasmids encoding GFP (control), the human GPR34, and the human ADP receptor were co-transfected with $G\alpha_{q14}$. IP formation under basal conditions (light gray bars) and in the presence of 10 μ M ADP (dark gray bars) was determined. This research was originally published in *The Journal of Biological Chemistry*. Schulz A, Schönberg. The Structural Evolution of a P2Y-like G-protein-coupled Receptor. *The Journal of Biological Chemistry*. 2003; 278:35531-35541. © the American Society for Biochemistry and Molecular Biology.

Activation of the P2Y₁₂ receptor by ADP causes a chain of reactions that stimulate platelet activation and aggregation. Platelet activation is done through ADP-mediated generation of TXA₂, while aggregation is caused through intracellular messengers through the activity of G_i. Beyond the traditional function of G_i to inhibit adenylyl cyclase—and by extension cAMP—other messengers are at play in causing fibrinogen receptor activation. These messengers include: PI3K, Rap1b, and Akt (Protein Kinase B). Studies have shown Rap1b function is necessary for normal platelet function [16]. Akt/PKB has a variety of intracellular functions, and abnormalities in its function have been implicated in a number of disease states. Further, activation of the P2Y₁₂ receptor causes the activation of potassium channels—whose specific function remains unclear—that are tied to platelet activation [13, See Figure 3]. The complexity of the P2Y₁₂ receptor in both its structure and its recruitment of secondary messengers allows for it to be manipulated in the context of dual antiplatelet therapy through multiple mechanisms. Research has been geared towards finding the “perfect” P2Y₁₂ inhibitor that is reversible, potent, and fast-acting, all while minimizing bleeding risks. For the purposes of this discussion, four drugs: clopidogrel (Plavix[®]), prasugrel (Effient[®]), ticagrelor (Brilinta[®]), and cangrelor will be discussed. Clopidogrel and prasugrel are considered thienopyridines, ticagrelor is a cyclopentyltriazolopyrimidine, and cangrelor is an adenosine triphosphate analog [17][18]. The differences among these drugs are significant in how they act on the P2Y₁₂ receptor, despite all seeking to achieve the same desired effect.

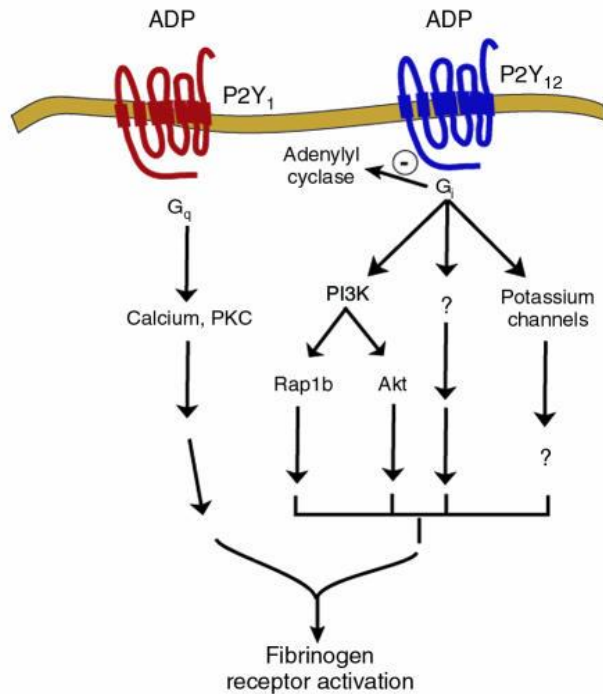


Figure 3: Intracellular signaling events downstream of the P2Y₁ and P2Y₁₂ receptors. ADP binds to the P2Y₁₂ receptor and causes a number of intracellular signaling events downstream of the G_i pathway that contribute to fibrinogen receptor activation and platelet aggregation. The P2Y₁₂ receptor-mediated inhibition of adenylyl cyclase is not directly responsible for fibrinogen receptor activation. Potassium channels and PI3K are also activated by the P2Y₁₂ receptor. Both Rap1b and Akt are signaling mediators that contribute to platelet aggregation and are activated in a PI3K-dependent manner. Other mediators of P2Y₁₂ signaling remain to be elucidated. Reproduced with permission from Journal of Clinical Investigation (Dorsam RT, Kunapuli SP. Central role of the P2Y₁₂ receptor in platelet activation, 3:340-345), Copyright (2004).

Clopidogrel acts as a P2Y₁₂ receptor antagonist through its selective activity on the receptor's ADP binding site. This inhibits the ADP-mediated G-protein (specifically G_i) pathways that lead to platelet aggregation [17]. A regimen of clopidogrel and aspirin as a treatment option to combat MACEs emerged in the early 2000s, beginning with the Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) trial. This study examined the effects of clopidogrel in combination with aspirin in patients hospitalized within 24 hours of suffering

from acute coronary syndrome (ACS) but had not yet demonstrated any ST-segment elevation on their electrocardiograms. Patients were randomized to one of two groups: a 300 mg clopidogrel loading dose (LD) followed by a 75 mg maintenance dose (MD) plus a physician-recommended dose of aspirin, or corresponding dosages of placebo with aspirin, and were followed for three to 12 months. The study tracked two primary outcomes. The first primary outcome was death from cardiovascular disease, nonfatal myocardial infarction, or stroke; and the second was the first primary outcome with the addition of refractory ischemia. On the basis of both of these outcomes, clopidogrel significantly outperformed placebo in the reduction of both primary outcomes. As one might expect based on the characteristics of inhibiting platelet activation and aggregation, the bleeding risk associated with clopidogrel was markedly higher than that of placebo. The study does note, however, that the increased risk in bleeding was not associated with any increased risk of stroke, surgical intervention or ionotropic agents, or that caused permanent disability [18].

Clopidogrel is not without limitations, however. Beyond the obvious bleeding risks associated with all P2Y₁₂ inhibitors, clopidogrel presents some specific challenges in its activation and mechanism of action. As an oral medication, clopidogrel is subject to intestinal absorption, where some 85% of the drug is subject to degradation by esterases, leaving only 15% available for hepatic metabolism. As a prodrug, clopidogrel is subject to hepatic activation, and undergoes two transformations via cytochrome P450 pathways [19]. Another limitation of clopidogrel is its irreversibility, which is significant in that its effects on platelet activation and aggregation are present throughout the lifetime of a given platelet—anywhere from seven to 10 days [17]. This irreversibility provides a challenge to patients that may require surgery while taking the drug. The CURE study presented that a five-day period of clopidogrel treatment

cessation had limited harmful effects on surgery [18]. However, that cessation period would be impossible to implement with patients undergoing emergency surgery, which does occur in post-PCI patients. The most troubling limitation of clopidogrel-driven DAPT is high residual platelet reactivity (HRPR) or high on-treatment platelet reactivity (HTPR). This condition causes a poor platelet response to clopidogrel in patients that have developed clopidogrel resistance. Resistance is tied to loss-of-function variants of the cytochrome 2C19 enzyme; these variants alter the metabolism of clopidogrel during the two-step hepatic activation, thereby rendering it useless in combatting potential stent thrombosis. As one might expect, HRPR and HTPR are strongly linked to future ischemic events [20]. The two-step metabolic activation of clopidogrel, especially when coupled with its irreversibility, poses significant questions about its efficacy.

Prasugrel, another thienopyridine, works similarly to clopidogrel in its mechanism of action, but has subtle differences that make it a more suitable option for DAPT regimens. Like clopidogrel, prasugrel is an oral drug and undergoes intestinal absorption. However, prasugrel only undergoes one step of hepatic metabolic activation, thereby increasing its bioavailability and its time of onset [19]. The Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel-Thrombolysis in Myocardial Infarction 38 (TRITON-TIMI 38) compared prasugrel (60 mg LD followed by 10 mg MD) with clopidogrel (300 mg LD with a 75 mg MD) in over 13,000 patients exhibiting moderate to high risk ACS undergoing a planned PCI. Patients were followed for six to 15 months. Like the CURE trial, the primary endpoints for the TRITON-TIMI 38 study were cardiovascular death, MI, and stroke. Prasugrel saw favorable results when compared to clopidogrel, with 9.9% of patients reaching the primary endpoint (compared to 12.1% for clopidogrel), making prasugrel a more suitable option for patients that had undergone a PCI. There was an increased bleeding risk with

prasugrel when compared to clopidogrel, thought to be because of its increased efficacy and bioavailability [21].

Another study, the Targeted Platelet Inhibition to Clarify the Optimal Strategy to Medically Manage Acute Coronary Syndromes (TRILOGY ACS), compared prasugrel to clopidogrel in patients who were not undergoing revascularization [22]. Study treatment was administered for six to 30 months. The primary endpoint was exactly the same as that of the TRITON-TIMI 38 study. However, in this study, prasugrel was not proven to decrease the frequency of the primary end point, and the bleeding risks were the same. Despite this, prasugrel was shown to have been more effective at inhibiting platelet activation and aggregation [22]. When compared to the TRITON-TIMI 38 study, TRILOGY ACS highlights the importance in investigating how P2Y₁₂ receptor antagonists differ when implemented in patients that have undergone revascularization versus patients whose MACEs are medically managed.

Unlike the thienopyridines, ticagrelor—the drug being studied in the PEGASUS-TIMI 54 trial—does not bind directly to the P2Y₁₂ receptor's ADP binding site. Rather, it binds to a different site on the receptor, allowing it to act both allosterically and reversibly [19]. This provides a significant advantage in the treatment of patients, as ticagrelor's effects do not last throughout a platelet's lifetime. Though ticagrelor is an oral medication and goes through intestinal absorption, it does not require hepatic activation. However, it is metabolized in the liver to an equipotent active metabolite [23]. Such qualities would make ticagrelor a viable option for patients that experience clopidogrel resistance. The Platelet Inhibition and Patient Outcomes (PLATO) trial compared ticagrelor (180 mg LD with 90 mg MD twice daily) to clopidogrel (300 or 600 mg LD with 75 mg MD) against MACE indications in over 18,000 patients over the course of 12 months. Patients also were put on a regimen of aspirin (75 to 100

mg at their physician's discretion). Ticagrelor was concluded to significantly reduce primary endpoints (death from vascular causes, MI, or stroke) when compared with clopidogrel. Ticagrelor was shown to have a greater degree of inhibition of platelet activation (IPA) while also reaching peak activity faster. Probable stent thrombosis was also reduced, and overall study-defined bleeding events were the same across both study arms [24].

A much smaller study (n=44) sought to directly compare the pharmacodynamics properties of ticagrelor when compared with prasugrel. The study design followed patients with HTPR suffering from ACS post-PCI (within 24 hours). Patients were in one of two arms: ticagrelor (90 mg twice daily) with aspirin, or prasugrel (10 mg daily) with aspirin and were followed for a 15 day period. Then each arm was switched over to the alternative treatment and was followed for a subsequent 15 days. While the study found that both treatment options were superior to clopidogrel, ticagrelor was more effective at inhibiting platelet activity than prasugrel [25]. Another study focused on DAPT regimens in diabetic patients concluded that ticagrelor was more effective than prasugrel in inhibiting platelet activation in diabetic populations [26]. Interestingly, a meta-analysis of prasugrel and ticagrelor concluded that prasugrel is more effective at preventing stent thrombosis, while ticagrelor prevents bleeding events more effectively [27]. Ultimately, it appears as though the data directly comparing ticagrelor and prasugrel does not make a definitive conclusion as to which treatment option is better for the vast majority of patients.

Cangrelor acts differently than both the thienopyridines and ticagrelor in that it is an adenosine triphosphate analog. Like ticagrelor, cangrelor is reversible and does not require biotransformation into an active form [19, See Figure 4]. Unlike the drugs mentioned previously, cangrelor is taken intravenously, and has the fastest time of action of any mainstream P2Y₁₂

inhibitor. While ticagrelor and prasugrel have half-lives of around eight hours, cangrelor's half-life is far less at three to six minutes [19]. The Clinical Trial Comparing Cangrelor to Clopidogrel Standard Therapy in Subjects Who Require Percutaneous Coronary Intervention (CHAMPION PHOENIX) compared cangrelor with clopidogrel and found that it was superior in all outcomes with fewer bleeding risks. While all of these qualities indicate that cangrelor is a superior treatment option to other P2Y₁₂ inhibitors, the Food and Drug Administration's Cardiovascular and Renal Drugs Advisory Committee voted against approving cangrelor for post-PCI patients and patients whose DAPT therapy is interrupted with surgery. The committee cited concerns with the study's design and risk/benefit profile [28]. Currently, there are a number of phase II clinical trials studying cangrelor in comparison with clopidogrel, ticagrelor, and prasugrel.

If the CHAMPION PHOENIX trial can be improved, then the development of cangrelor as a viable, FDA-approved drug has incredible potential in the treatment of ACS and the prevention of stent thrombosis. There is not a conclusive answer to which P2Y₁₂ inhibitor is most effective. Though prasugrel and ticagrelor have been shown to be superior to clopidogrel, there are a number of considerations that still must be considered. A large-scale randomized trial studying ticagrelor and prasugrel head-to-head has not yet been conducted. Clopidogrel, given its profile and long-standing history as a P2Y₁₂ inhibitor, remains the go-to option for many physicians. Because of its longevity in the market, generic clopidogrel is available, while generic versions of ticagrelor and prasugrel are not [28]. Ultimately, decisions based on which drug should be coupled with aspirin in DAPT therapy is one a physician makes based on specific patient profiles.

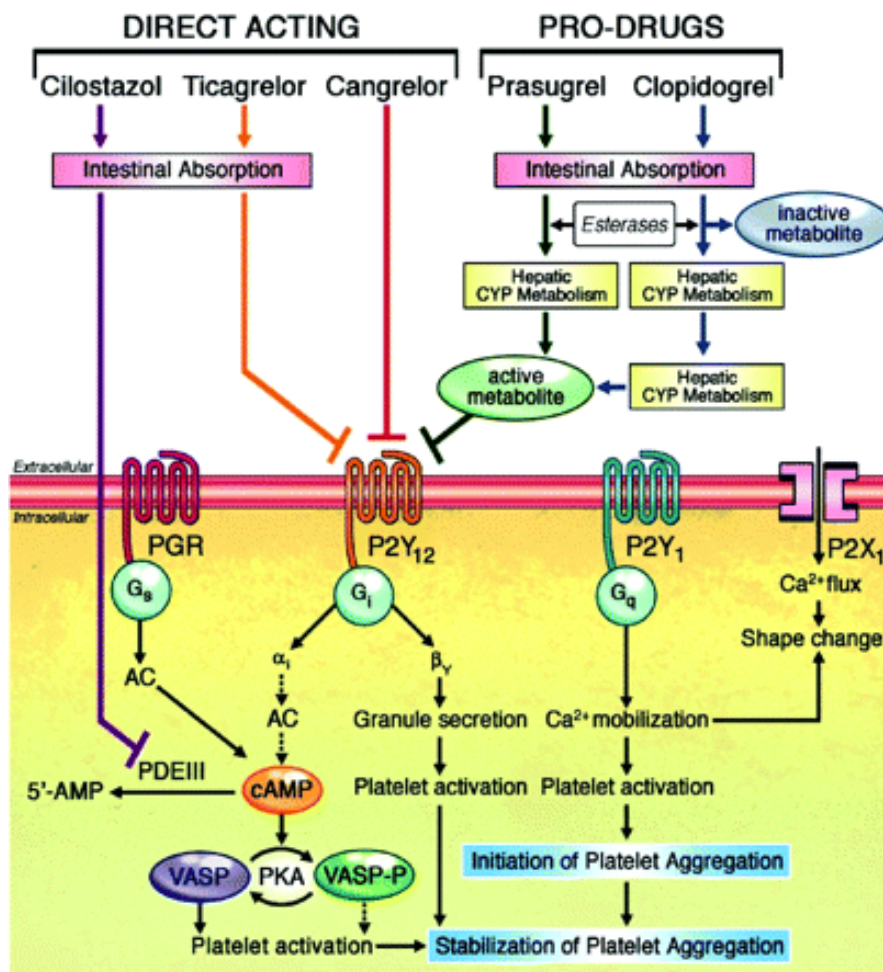


Figure 4: Schematic of different therapeutic options for inhibition of platelet P2Y₁₂receptor. Reprinted from J Am Coll Cardiol Inv., Vol. 4, Angiolillo DJ, Ueno M. Optimizing platelet inhibition in clopidogrel poor metabolizers: therapeutic options and practical considerations, 411-414 Copyright (2011), with permission from Elsevier.

The device arm of this practicum report is tied to the use of coronary stents in patients suffering from coronary artery disease. The first coronary stent—the Wallstent—was implanted in 1986 in France as an elective procedure in the treatment of coronary artery restenosis [29]. While the initial idea of stenting procedures was to use them in emergency situations where angioplasty was not sufficient, they have become the hallmark of interventional cardiology over the past 30 years. While coronary artery bypass grafts (CABG) are still used in more serious

cases, especially those involving multivessel blockages, stent procedures are widely used in an interventional capacity. The CABG versus stent debate is one that has played out for decades in the cardiology community, and both options have their benefits. Studies such as the American College of Cardiology (ACC) Foundation/STS Collaboration on the Effectiveness of Revascularization Strategies (ASCERT) trial indicate that CABG procedures have better long-term outcomes than stenting procedures [30]. Nonetheless, stents are a mainstay in the treatment of coronary artery disease, and have the advantage of being minimally invasive, useful in interventional strategies, all while showing improved patient outcomes compared to procedures involving angioplasty and balloon catheters.

The first generation of stents involved bare metal stents (BMS). The advent of the bare metal stent proved to be revolutionary in cardiovascular health. Studies comparing bare metal stenting with balloon angioplasty indicated the vast superiority of stenting [30]. Procedures were deemed to be more successful, the lumen of the occluded vessel was larger immediately and after the procedure, the frequency of death related to cardiovascular events or ischemia was less, and revascularization was less frequent [31]. As stenting was investigated more thoroughly, it was discovered that the healing process that follows the implantation of a BMS is similar to that of wound healing. Over the course of 12 months post-procedure, smooth muscle cells, re-endothelialize the affected region, causing hyperplasia and potentially the need for revascularization. If the hyperplasia is excessive, as is the case in 30-40% of patients, revascularization becomes a serious possibility [32][33, See Figure 5].

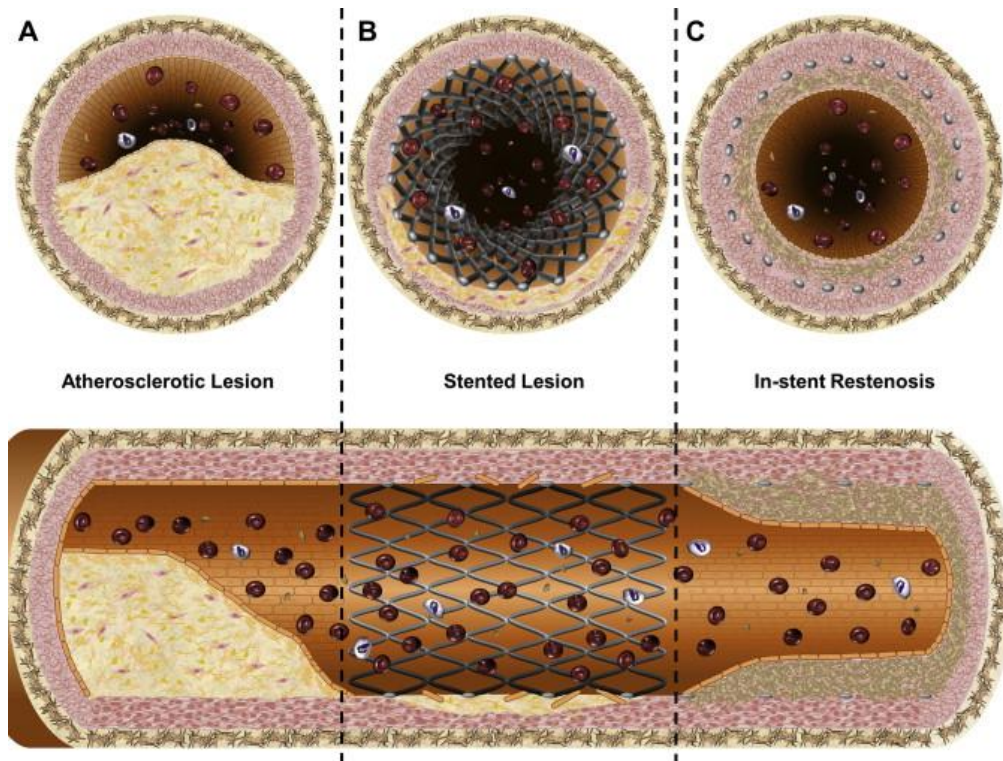


Figure 5: **a**, Atherosclerotic lesion that requires stent treatment. **b**, Opening of coronary artery post-stent procedures. **c**, Restenosis following stent placement. Reprinted from Canadian Journal of Cardiology, Vol 30, Simard T et al., The Evolution of Coronary Stents: A Brief Review, 35-45, Copyright (2014), with permission from Elsevier.

It was within this context that drug eluting stents (DES) were developed. DES options differ from BMS in that they are coated with a polymer that releases an anti-inflammatory or antiproliferative agent [33]. The first therapeutic agent that was used was sirolimus, which functions to arrest the cell cycle before DNA replication begins, thereby inhibiting replication. Paclitaxel was the next agent introduced to DES, and functions later in the cell cycle—during mitosis—to arrest cell division. In head-to-head studies, sirolimus eluting stents were shown to be superior in reducing MACEs and restenosis, both in short and long-term follow-ups [33]. In order to facilitate the release of anti-inflammatory agents, DES structures were thinner and had an increased risk of erosions or fissures forming within the stent matrix. Those risks came to

fruition, as studies began to show that DES had a greater risk of late and very late stent thrombosis. Further, the paclitaxel eluting stents were shown to have nonhomogenous hyperplasia that required stenosis [29]. As second and third generation DES have been developed, the risks of late thrombosis have decreased, and a vast amount of literature suggests that DES are now the better, safer, option in preventing MACEs, stent thrombosis, and revascularization.

A novel stent option is found with the COBRA PzFTM Coronary Stent System, the device being used for the PzF SHIELD trial, which is the device study being compared in this report. The PzF SHIELD study is a prospective, multi-center, non-randomized, single arm clinical trial, planning to enroll nearly 300 patients. The primary endpoint of this study is target vessel failure, defined to be cardiac death, target vessel MI, or revascularization of the target vessel over the course of 270 days. Though considered a BMS, the COBRA PzFTM stent is coated with a Polyzene FTM surface modification that is thromboresistant while providing a quick onset of stent endothelialization to the surface of the occluded artery. Patients enrolled in this study will receive the COBRA PzFTM stent, and will undergo DAPT for 30 days [37]. The COBRA PzFTM stent was used in a single-center study featuring 100 patients receiving the stent and a 30-day DAPT regimen of aspirin and clopidogrel. The study showed 100% angiographic success, with no reports of stent thrombosis, myocardial infarction. There was one reported death, with 3% of patients requiring revascularization [38]. This is a significant shift from other reports in the literature regarding how long DAPT therapy should be administered post-PCI. A 30-day treatment period, as opposed to a 12-month period, is advantageous when factoring in costs, patient compliance, and the bleeding risks associated with long-term DAPT therapy.

The next step in investigating DAPT regimens post-PCI is to determine how long DAPT should be administered to a patient. In an analysis by Park et al. in 2010, data from two studies,

Correlation of Clopidogrel Therapy Discontinuation in Real-World Patients Treated with Drug-Eluting Stent Implantation and Late Coronary Arterial Thrombotic Events (REAL-LATE) and the Evaluation of the Long-Term Safety after Zotarolimus-Eluting Stent, Sirolimus-Eluting Stent, or Paclitaxel-Eluting Stent Implantation for Coronary Lesions – Late Coronary Arterial Thrombotic Events (ZEST-LATE), was collected in order to determine the efficacy of using clopidogrel beyond the recommended 12-month window (a median 19.2 month follow-up). Patients were either given clopidogrel (75 mg) and aspirin (100 or 200 mg) or aspirin alone (100 or 200 mg)[34]. These studies concluded that aspirin monotherapy was just as effective in combatting stent thrombosis and preventing MACEs as the DAPT therapy of clopidogrel and low-dose aspirin [34]. Another multi-center study in Korea in 2014 conducted by Lee et al. examined DAPT outcomes for two years after the recommended 12-month treatment period [35]. They came to the same conclusion as the REAL-LATE and ZEST-LATE studies: that DAPT therapy consisting of clopidogrel and aspirin was not superior in reducing the risk of MACEs when compared to aspirin alone [35]. While such reports may seem definitive against the use of DAPT past 12 months, they have only used clopidogrel as the P2Y₁₂ receptor antagonist.

The PEGASUS-TIMI 54 study, is designed to test the same hypothesis as the REAL-LATE and ZEST-LATE trials, but with ticagrelor as the receptor antagonist [36]. The PEGASUS-TIMI 54 study is an event-driven, randomized, double blind, placebo controlled, parallel group, multi-site study, and hopes to enroll 21,000 patients. Patients will be randomized to one of three arms: Ticagrelor (90 mg) with aspirin (75 to 150 mg), Ticagrelor (60 mg) with aspirin (75 to 150 mg), or Placebo, and will be followed over the course of 44 months. The primary endpoint of this study is that of any cardiovascular death, non-fatal MI, or non-fatal stroke [36]. Ticagrelor has already been proven to be a superior antiplatelet therapy than

clopidogrel based on the results of the PLATO trial. Therefore, it may be a better treatment option for sustained, long-term DAPT in patients suffering from ACS.

Given the many options that are available to physicians to stent and medicate patients with coronary artery disease, it is important to develop an idea of the general treatment practices and how healthcare resources are utilized across the world. It is from this question that the TIGRIS study, a multinational, multi-center, observational, prospective, longitudinal study, was developed [39]. As a non-interventional study, the 10,000 patients that are expected to enroll in the study will not see any change in their medication, nor will have any study-related procedures performed on them. Primary endpoints track event rates—MI, need for revascularization, stroke, or death for any cause—and health care resource utilization associated with these events over a three year period.

All of the clinical studies reviewed answer fundamental questions about improving patient outcomes, and try finding the best drug, stent, or treatment strategy to achieve that effect. The PEGASUS-TIMI 54 study, the drug study being analyzed in this practicum report, was born out of decades of research investigating P2Y₁₂ antagonists and how long treatment should last. The device study being compared, the PzF SHIELD trial, was developed as a novel stent option that hopes to minimize how long patients are on DAPT, in the hopes of minimizing bleeding risks. Physicians treating patients at high risk for MACEs must weigh out the risk/benefit profiles for every drug and stent option in the context of what is best for their patients. The TIGRIS registry study seeks to answer what the standard practices are of physicians treating stable coronary artery disease, and how patients utilize healthcare resources in the prevention of future adverse events.

V. METHODOLOGY AND RESULTS

Methodology

Primarily, the information necessary to adequately compare the PEGASUS-TIMI 54, PzF SHIELD, and TIGRIS studies was taken from observations made over the course of the six month internship. The day-to-day work tied to screening, interacting with patients, carrying out study-related activities, and working through regulatory requirements through Baylor Research Institute's Institutional Review Board proved to be a valuable resource. These daily experiences gave insight into how clinical research is actually conducted and how it requires a concerted effort from research coordinators, administrators, physicians, and healthcare staff.

Secondly, the thoughts and considerations of coordinators throughout the internship have been invaluable, and their experience working on these research trials provides another layer of perspective when comparing the studies. The PEGASUS-TIMI 54 drug trial and PzF SHIELD device trial were actively enrolling before the internship began. In trying to compare these studies, it is necessary to look at them through a coordinator's perspective. To help in this endeavor, I created a questionnaire for the PEGASUS-TIMI 54 and PzF SHIELD trials in order to utilize the insights of the coordinators working on them (APPENDIX C). The TIGRIS registry study is the study I am most heavily involved with, because I have screened and provided consent to the majority of enrolled patients. Therefore, it was not necessary for me to use the

questionnaire in order to adequately compare screening, consent, and trial visits and follow-up practices.

Finally, the protocols for all three studies were referenced, but special considerations were taken to corroborate the information found within the confidential protocols with information that is readily available to the public—such as that which is available on ClinicalTrials.gov, design and rationale research articles, and press releases. Because of these considerations, specific information on the schedules of visits and specific procedures done during those visits was purposefully not included in the practicum report. The overall intention is to paint a picture of the general practices that occur in each kind of study, without violating any confidentiality agreements. The details of each study are not necessary to gain a comprehensive idea of how drug, device, and registry studies differ on the basis of screening, consent, and trial visits and follow-up practices.

Results

a. Screening

Unlike most clinical research sites, which use databases to identify potential patients, Legacy Heart Center only enrolls patients that see physicians in the practice. Patients have an established rapport with the practice and the physicians who are investigators in the research trials. Therefore, the PEGASUS-TIMI 54 study and the TIGRIS study, which took place at Legacy Heart Center, are composed of patients that are established patients of the practice. The PzF SHIELD trial only screened for patients that were being treated at The Heart Hospital Baylor Plano (THHBP) where the trial is conducted.

Screening procedures for the PEGASUS-TIMI 54 study took a multifaceted approach. First, the physician's office schedule was reviewed. This schedule included the patient's name, date of birth, and problem list/reason for the office visit. The primary indicator that a patient might fit the research study was any indication of an old myocardial infarction, or coronary artery disease. Any potential candidates for the PEGASUS-TIMI 54 study were screened further, via two systems that contain electronic medical records, to see if they fit within the inclusion and exclusion criteria. Another, approach in identifying candidates was for a physician to identify potential candidates. Physicians had the added advantage of introducing patients to a study during an office visit, allowing for a constructive conversation of how a clinical research study could positively affect the patient's health. A number of the physicians at Legacy Heart Center, where the PEGASUS-TIMI 54 study was conducted, hold an active interest in clinical research. Their efforts were instrumental in successfully identifying patients who might enroll in the study. The TIGRIS study follows the same screening procedures as the PEGASUS-TIMI 54 study, especially considering the main inclusion criteria—MI in the past one to three years—is the same for both studies. Screening for the main inclusion criteria could be difficult at times, given the limited timeframe for an MI. Physicians did not recommend patients to be in the TIGRIS trial as much as they did for PEGASUS, because unlike drug studies, a registry study often does not have any tangible health benefits for a patient to take part. Besides the main inclusion criteria, the TIGRIS study does not have very strict inclusion and exclusion criteria, meaning that screening identified many potential enrollees in the last six months (Table 1).

After a patient was successfully screened as a candidate for the study, the coordinator would speak with the patient's physician regarding their potential inclusion in the study. This conversation is an incredibly important one, as the PEGASUS-TIMI 54 trial required changing a patient's medication. More importantly, as a randomized, placebo-controlled trial, there was a possibility that a patient enrolled would be on aspirin monotherapy because they were receiving the placebo. Physicians had to weigh the risks of enrolling a patient in the study, as well as determine whether or not a patient would be compliant in following through with the study. In weighing out the risk/benefit ratio to their specific patients, and in taking into account the overall study, physicians often declined to allow consenting of a patient. Physicians are far more amenable to consenting patients for the TIGRIS study, because it is non-interventional and requires no procedures or new medications.

The PzF SHIELD device trial was screened differently than the PEGASUS-TIMI 54 and TIGRIS trials. The drug and device trials screened for patients that were medically managing their coronary artery disease. The PzF SHIELD study, because it requires stenting of a patient, looks at a patient population at a much higher risk of experiencing MACEs. The differences in patient population required for each study is the main reason why there were differences in how screening was conducted. Screening for the PzF SHIELD study requires looking at the Catheterization Laboratory Schedule for the following day, specifically looking for left heart catheterization, as that is a massive indication of coronary artery disease and the need for stenting. If the interventional cardiologist performing the procedure is either in the Principal Investigator or Sub-Investigator of the study, the patient is screened further, specifically looking at their

History and Physical Examination (H&P) profiles to see if the patient could enroll based on inclusion and exclusion criteria.

After a potential patient was identified, coordinators speak with the physician scheduled to perform the intervention to see if the patient would be a good fit for the PzF SHIELD trial, based on the physician's medical opinion. Like the PEGASUS-TIMI 54 drug study, physicians have to weigh out the pros and cons of a patient enrolling in the study. But because the patient is going to receive a stent regardless of their inclusion in the study, physicians have given the coordinators the green light to consent in all of my observed cases.

While these screening descriptions represent what theoretically should happen, there are exceptions. I was fortunate enough to be able to observe these exceptions, and how they are managed in a clinical trial. First, physicians decline patients for certain reasons, such as age, compliance, and health factors that are not part of the exclusion criteria. This happens with some regularity, because the primary focus of the physicians is to treat the patient responsibly. Also, their judgment is essential in enrolling patients that are going to meet the study obligations and be compliant. Interestingly, there are instances when a physician disagreed with the medical record that indicates a patient has had a myocardial infarction based on the patient's history and relevant labs. This was due to the generality of ICD-9 codes, where a patient was on the verge of having a myocardial infarction—if an intervention was not performed—but when coded, the patient was said to have had an MI. In these situations, the opinion of the practice physician is always taken, and patients are not consented. Screen failing, is another element to the real world application of screening, and is especially relevant to the device

study. The PzF SHIELD trial has inclusion and exclusion parameters not seen in the drug and registry studies that took place in the Cath Lab. The patient had to fit specific parameters, dealing with the location of the blockage, if the occluded artery had been stented before, and the number of blockages that were present. These angiographic criteria are the most common reasons a patient screen fails (Table 1).

b. The Informed Consent Process

After a patient is successfully screened and a coordinator has the physician's permission to speak with the patient, informed consent must be provided before a patient can enroll in the study. The informed consent process is one of the most critical aspects of clinical research, as it is the method through which a patient understands the purpose of a trial, what the benefits and risks are of partaking, and what their roles and responsibilities are as a participant. A coordinator must stay impartial and objective in presenting a study, and patients are encouraged to ask questions and internalize the intricacies of a study before agreeing to take part. It is always made clear that a patient's participation is 100% voluntary and that they may opt out at any point. They also may be removed from the study, if their physician feels it is a detriment to their health. As per the procedures of Baylor Research Institute, an Informed Consent Note is filled out and filed for every patient that enrolls in a study (APPENDIX E). Overall, the consenting procedure was the same for each study. The main difference between consent with each study was the information presented; the risks and benefits were specific to each trial.

The PEGASUS-TIMI 54 study held many advantages for potential enrollees. The PLATO study concluded that ticagrelor was a more effective than clopidogrel in the

prevention of thrombosis and other cardiovascular events. Patients saw the potential advantage of being randomized to one of the two ticagrelor arms as a benefit—given that their risk for coronary events would decrease. Second, study-related drug (ticagrelor) was provided without any cost to the patient. Study procedures were also done without any cost to the patient, and the idea of having one’s laboratory work closely analyzed—albeit by a third party as labs were blinded—and overall health consistently monitored was an advantage to participating in the study [39]. The PEGASUS-TIMI 54 study enrolled 15 patients, but some patients did withdraw consent from the study (Table 1). Reasons for withdrawal were: unhappiness with the known side effects of the drug, a medical event that required a patient to be treated with a different drug, two patients had adverse events near the end of the study that caused them to be taken off the study drug, and lastly one patient moved and did not want to continue being a part of the study at a different site. One patient was transitioned to different therapy, because they had an MI during the study. Another patient transferred to a different site to finish treatment.

The PzF SHIELD trial presents different advantages to potential patients. Unlike a drug study, where the standard of care that would be given to a patient might be no treatment at all, or a device study, where standard of care is no action whatsoever, potential PzF SHIELD patients are absolutely going to be stented. A massive advantage the PzF SHIELD trial is the potential of being off DAPT in 30 days. This greatly differs from the 12 month window that is typical of standard of care. For patients with a high bleeding risk, or ones that may require surgery in the near future, being off of DAPT therapy in a month has significant implications for their health. One patient, upon hearing the 30-day DAPT requirement, was incredibly eager to enroll in the study, because of the

bruising that clopidogrel had caused. Physician input and approval is helpful at the consenting stage, because to many patients the differences between bare metal stents and drug eluting stents were unclear. Many patients opt for what their physician recommends, knowing it is in their best health interest. So far, 19 patients have consented to take part in the PzF SHIELD trial, with 3 enrolling. One patient declined because they preferred to be stented with a DES (Table 1).

The TIGRIS study is distinct in that it did not present any tangible benefit to the participating patient. Patients are told that their involvement may help the medical community better understand how stable coronary artery disease is managed in patient populations worldwide. Altruism is a huge motivator for people to enroll in the study, with many people citing their desire to “pay it forward,” or help the community at large. Because it is a non-interventional study, patients are more amenable to enrolling. In total, 26 patients have enrolled in the TIGRIS study (Table 1). The biggest issue with consenting patients for the TIGRIS study was the right to privacy. The idea of “tracking healthcare resource utilization” often spurred questions about who had access to a patient’s information. As is the case with the vast majority of clinical research studies, all relevant information was de-identified. The overwhelming majority of patients enrolled so far saw the benefits of clinical research on society, and were eager to participate. Only a handful of patients declined consent, with one citing concerns with privacy.

It is interesting to note when consent was performed for each study. Coordinators on the PEGASUS-TIMI 54 study would often call patients to schedule a consenting appointment. Randomization had to occur within 2 weeks after a patient was enrolled. This approach was taken because the PEGASUS-TIMI 54 study is not dependent on a

procedure for a patient to enroll. Instead, inclusion is based off of a widespread medical history. The decision to pursue consent was only made after a physician weighed out whether or not the physician wanted to place a patient on an investigational product that has significant risks, or a placebo that might be ineffective at treating a known problem.

The PzF SHIELD study allowed for consent to take place within one week to the procedure. A potential patient in the PzF SHIELD trial was going to receive a stent, regardless of whether or not they enrolled. The risks of the COBRA PzFTM stent and other stent options were very similar, and in most cases it was advantageous for a patient to receive the COBRA PzFTM stent. Typically, consent was performed hours before the stent procedure. This allowed ample time for a coordinator to go through the study and its requirements, as well as time for a physician to answer any questions a patient might have had. However, it must be made clear that the practice of performing consent hours before the procedure does not apply to all investigational device trials. There are many trials in which a patient can opt in to having a device implanted—such as an implantable cardiac monitor—where a consenting visit would be scheduled days, not hours, before the procedure, similar to the PEGASUS –TIMI 54 study.

The TIGRIS study was similar in that the informed consent process only took minutes to complete, and was done before or after a patient's regular office visit. Patients were encouraged to take the consent form home and think about their participation, but every patient enrolled so far has opted into the study the same day as their office visit. This is primarily because the TIGRIS registry study is non-interventional, and has no risks associated with it.

| Name of Study | Patients Enrolled | # of Patients Screen Failed | # of Patients off IP | Site Enrollment Start Date | # of Patients Screened | Still Enrolling? |
|----------------------|--------------------------|------------------------------------|-----------------------------|-----------------------------------|-------------------------------|-------------------------|
| PEGASUS-TIMI 54 | 15 | N/A | 7 (1) | 01/2011 | > 200 | No |
| PzF SHIELD | 3 | 14 | N/A | 07/2014 | > 211 | Yes |
| TIGRIS | 26 | N/A | N/A | 06/2014 | 1,089 | Yes |
| | | | | | | |

Table 1: Enrollment Data for DAPT Studies at Legacy Heart Center and THHBP

c. Trial Visits and Follow-up Practices

Trial visits and follow-up practices are where clinical research trial study practices are conducted. They consist of all of the relevant study interactions that occur between a patient and coordinator. It is important to note that the verbiage among the studies use the terms differently. In the PEGASUS-TIMI 54 study, “trial visits” are the interactions between a patient and the coordinator up until the investigational product is discontinued. At that point, there is one “follow-up visit.” [36]. The PzF SHIELD trial follows secondary outcomes for five years post-procedure. The TIGRIS study follows its primary endpoints for three years post-enrollment.

The practices and procedures of drug and device study are similar: the patient’s health in direct relation to the investigational product or device is of primary importance. These differ slightly in what practices are conducted, but their overall intention is the

same. For the PEGASUS-TIMI 54 study, the most significant procedure done during trial visits was the blood and urine sampling done. These labs are typical of most drug studies, and are processed by a third party central laboratory. Though the results of the blood draws are blinded to both the Principal Investigator and coordinator, they are closely watched by a third party, ensuring that a patient's health is always closely monitored. One component of the PEGASUS-TIMI 54 study's trial visits that was not seen in either of the other two studies was the dispensing of study medication. As discussed during the consent process, an enrolled patient has a responsibility to be compliant in taking correct number of pills and returning the unused pills, per the study. Two weeks after the patient was taken off of the investigational product, they either came to the clinic for their follow-up visit, or were called over the phone [39]. Visits in the PzF SHIELD trial have the same purpose as the PEGASUS-TIMI 54 study: to ensure that study patients were in good health and not experiencing any adverse events that could be related to the device. Clinical assessments and a physical exam are the major components of trial visits. In order to test the safety of the device, an angiography will be performed—signaling the end of the study's tracking of the primary endpoint. Compliance with the PzF SHIELD study, as is the case with all device studies, is related to a patient showing up for their clinical assessments and participating in the phone visits [40]. .

The priorities of the TIGRIS study make it different than that of the PEGASUS-TIMI 54 and PzF SHIELD trials. As it is observational in nature, the TIGRIS study collects data from patients regarding any adverse events, new medications, or healthcare resource utilization. TIGRIS study's patient visits will be done by a third-party. This is a particular quality about TIGRIS that is common in clinical research studies, and is

completely unheard of in drug or device studies—where a third-party phone call is not an adequate means of measuring any outcome. Many registry studies track data through an in-trial visit or through a coordinator calling a patient, but a physical exam and clinical assessment are not necessary to get the data required. The study is still interested in adverse events, but they are not tied to any study-related drug or device. The self-reported nature of the data also distinguishes a registry study from drug and device trials. This means that the patient's word is the main method of tracking data and outcomes. The study sponsor will only investigate a patient's medical records thoroughly if they have experienced a serious adverse event related to their cardiovascular health.

d. Methodology and Results Conclusions

The methodology and results yielded a number of conclusions regarding the differences among the PEGASUS-TIMI 54 drug study, the PzF SHIELD device study, and the TIGRIS registry study. First, with respect to screening, the PEGASUS-TIMI 54 study and the TIGRIS study follow the same procedures. This was due to the fact that they had much of the same inclusion criteria, and that they involved patient populations who are managing their CAD. The PzF SHIELD study, given that it examines high-risk, in-patient populations, is screened in a distinct manner. Also, there were factors that influence screening, such as physician input and screen failing, which cannot be ignored. Second, the informed consent process was different between all three studies in the benefits each study presented. Potential patients weighed these benefits versus the potential risks differently, and that could explain how enrollment differed. The general practice for the PEGASUS-TIMI 54 study was to schedule a consenting appointment. The patient was then randomized within two weeks. The PzF SHIELD study consents

patients hours before their stent procedure, which is possible because a patient was going to receive a stent even if they decided not to enroll in the study. In the TIGRIS study, because it does not carry any risks and has little responsibility relative to the other studies, consent is done on the same day as a patient's normal office visit. Trial visits were similar for both the PEGASUS-TIMI 54 study and the PzF SHIELD study. The main focus of visits is to assess patient health based on the investigational product or device given. The TIGRIS study differed with trial visits, because data was self-reported and not focused on any study-related intervention. One distinct feature about TIGRIS, even compared to most registry studies, was that data was collected by a third party.

VI. LIMITATIONS

A number of limitations must be addressed when attempting to discuss the different forms of clinical research trials. The first and most significant is the limitation of time. This internship practicum report spans some six months of work. While that was ample time to develop significant knowledge of DAPT and the current research studies being conducted related to it, clinical research trials span a number of years. Looking at these studies retrospectively may have provided a different, and perhaps more thorough, understanding of the differences among these trials. Time was not a limiting factor in the TIGRIS registry study, as the study design meant that follow-up practices were conducted by an outside entity. But for the PEGASUS-TIMI 54 trial, which began in 2010, and the PzF SHIELD trial, which will measure primary outcomes until June 2015, a six month study only represents a portion of the large amount of work being done.

The inability to use proprietary information in this discussion was another limitation. Clinical research protocols are an incredible resource in understanding clinical trials, as they map out the study design in significant detail. Trial visits are broken down into the exact samples that will be collected with specific parameters that must be met. Unfortunately, clinical research protocols are considered confidential throughout, and many times beyond, the entirety of the trial. These measures are protected under confidential disclosure agreements (CDAs).

The descriptive nature of this internship practicum report, along with the nature of self-reported data is a final limitation. This does open the door to further research that is focused on quantitatively describing the differences between clinical research trials. Coordinating clinical research is a complex process, and all elements of conducting a trial vary from study to study. Sponsors often have specific requirements for screening and consent that must be adhered to. One DAPT drug study may see greater numbers of recruitment and retention than other DAPT drug study, solely based on the requirements of each study's sponsor. A large amount of clinical research is centered on patient interaction, and coordinators have different styles of performing informed consent, seeing patients during trial visits, and following up with patients. It is possible that many of the differences seen across DAPT drug, device, and registry studies are related to a coordinator's style in interacting with patients.

VII. DISCUSSION OF INTERNSHIP EXPERIENCE

The overall internship experience has been a fantastic way to learn of the intricacies of clinical research. Learning clinical research through observation and practice is entirely different than learning about it through the classroom. Baylor Research Institute has an incredible framework set up to maximize the success of their clinical trials. Cardiovascular research represents a massive portion of BRI's research, in large part due to the structure and dedication of administrators and coordinators. There is a significant amount of administrative legwork that goes into ensuring a clinical research study's success. Contract negotiations, study budgeting, and coordinating with the BRI legal department are all necessary elements of clinical research not discussed in this internship practicum report. I was fortunate enough to be able to get some insight into some of these processes, as BRI expands into other regions—such as McKinney—or takes on more studies. Potential studies are rigorously considered, with administrators, coordinators, and physicians constantly interacting to determine whether or not a study is feasible given the resources available and is interest among physicians.

Physician involvement throughout the clinical research process is instrumental in smoothly running a trial. Through the design of clinical research, FDA regulations, and ethical considerations, Principal Investigators are ultimately responsible for a clinical research trial they are conducting. There is a significant burden of protocol deviations, revisions, safety reporting, and IRB approvals that a physician responsible. Legacy Heart Center and the Heart Hospital Baylor Plano are set up to efficiently and responsibly tackle these parts of clinical research.

Coordinators are partners in clinical research with physicians and administrators, ensuring that all parties are updated and informed on a study's progress. My day-to-day work meant that I was in close contact with coordinators, and though the focus of this internship practicum report was on three studies, I was involved the work of multiple other studies. My responsibilities ranged from processing and shipping laboratory samples, submitting reports to the Institutional Review Board, consenting patients, to creating of source documents and developing Informed Consent Forms. Through this work, I was able to witness firsthand the support system in place to facilitate clinical research responsibly and ethically. Physicians were always available to answer questions, sign documents, or discuss studies. Coordinators were thoroughly informed on each other's studies, meaning that there was always a backup coordinator or helping hand around if necessary.

The Baylor Research Institute's Institutional Review Board (BRI IRB) played a large part in my clinical research internship. The IRB works towards ensuring that all research is done ethically, with the patient's best interest always at the forefront of research. Having a local IRB has distinct advantages in that the process of approval in clinical research is standardized across nearly all studies. The practice of safety reporting, study revisions, protocol deviations, and applying for new studies was incredibly similar for every study I worked on, and appears to be a massive advantage over using multiple IRBs for multiple studies. As part of the internship practicum guidelines, I kept a daily journal of my activities and responsibilities as a clinical research intern. This information can be found under APPENDIX A: Daily Journals.

APPENDIX A

DAILY JOURNALS

Monday, June 9th, 2014

AM: Ms. Kathy Rodkey

Study: PEGASUS

- Closing soon, have to schedule End of Study visits for patients enrolled
- Does Ticagelor (60 or 90mg) + aspirin help prevent number of cardiovascular events (death, MI, stroke) when compared to placebo + aspirin?
- Met with pt., observed lab procedures (drawing blood, centrifugation, collecting of samples)
- Necessary paper work
 - o Confirmed drugs received and drugs dispensed
 - o Worked on the source documentation and then called in the verification

PM:

- Read informed consent form for an ongoing study on hyperlipidemia drugs coupled with a statin and the protocol for a future study (subject to IRB approval in mid-June)

Tuesday, June 10th, 2014

AM: Ms. Kathy Rodkey and Ms. Angela Germany

Study: Hyperlipidemia treatment with statin therapy (drug names are proprietary information)

- Met with pt. participating in hyperlipidemia treatment/statin therapy for their day one/randomization visit
- Observed lab procedures (drawing blood)
- Helped with collecting and packing of samples (centrifugation and pipetting techniques)
- Met with Ms. Angela Germany to go over orientation procedures

PM: Ms. Kathy Rodkey, Ms. Robin , Ms. Angela Germany, and Dr. Marcus McKenzie to go over thesis proposal

- Went over thesis proposal and discussed the progress of several studies (including PEGASUS, hyperlipidemia treatment/statin, and two other studies)
- Completed Baylor Research Institute's specific CITI training

Wednesday, June 11th, 2014

AM:

- Worked on Baylor Learning Network Modules for training purposes
- Began reading Baylor Research Institute's Policies and Procedures for Clinical Research
- Read up further on the PEGASUS-TIMI 54 study

PM:

- Downloaded PEGASUS-TIMI 54 Safety Reports

Thursday, June 12th, 2014

AM: Ms. Angela Germany

- 7:00AM: Attending meeting at the Baylor Heart Hospital where a study was presented on Resilience and its effect on outcomes post-surgery
- 9:00AM: Began screening patients for the hyperlipidemia study
- 10:00AM: Met with a physician at the Baylor McKinney campus to discuss bringing research and clinical studies to the hospital

PM: Ms. Kathleen Rodkey

- Met with Dr. Shalek at the other Legacy Heart Center office to discuss a patient's eligibility to participate in a clinical trial

Friday, June 13th, 2014

AM:

- Screened patients
- Attended a meeting with Dr. Peter McCoullough, three physicians at the clinic, and the Clinical Research team regarding a new study that may be worth pursuing. The study is in the earliest stages and would require significant work from the team at Legacy Heart Center to get it started

PM:

- Kathy's birthday lunch
- Screened patients for all three studies

Monday, June 16th, 2014

AM:

- Screened patients throughout the entire morning for two different studies: the hyperlipidemia/statin study and a registry study
- Left after lunch to finalize apartment details

Tuesday, June 17th, 2014

AM:

- Visited with a patient to discuss their first visit as a participant in the hyperlipidemia/statin study
- Centrifuged, collected, and shipped samples that were taken from the patient
- Attempted to process the EKGs from the patient
- Took inventory of their returned medications and calculated compliance
- Helped report an SAE for the same study, but regarding a different patient

PM:

- Begun paperwork for the patient seen in the morning, verifying which drugs were dispensed, updating the source documentation and the IXRS files
- Attended a Baylor Research Institute Employee Meeting at BUMC with Ms. Angela Germany

Wednesday, June 18th, 2014

AM:

- Filed sponsor correspondence, IRB forms, and other documents (informed consent, etc.), in regulatory binders.
- Visited with a patient with Ms. Robin Buckner in order to give informed consent regarding a survey trial
- Visited with another patient with Ms. Kathleen Rodkey for their Week 9 visit as a part of the PEGASUS-TIMI 54 study
- Verified drugs dispensed

PM:

- Screened patients for the hyperlipidemia study and the survey with little success

Thursday, June 19th, 2014

AM:

- Patient missed meeting, will reschedule for tomorrow
- Filled in the EDC (via RAVE) for a patient on the hyperlipidemia study for their Week 12 and Week 4 visit

- Filled in the EDC (via InForm) for a patient in the PEGASUS-TIMI 54 study
- Went to IRB Meeting at BUMC

PM:

- IRB Meeting regarding atrial fibrillation study at BUMC
- Answered Queries regarding the PEGASUS-TIMI 54 Study

Friday, June 20th, 2014

AM:

- Visited with patient for Day 1 visit of the hyperlipidemia study
- Centrifuged and collected samples
- Shipped ambient and refrigerated samples
- Processed EKGs

PM:

- Left early for Friday prayer

Monday, June 23rd, 2014

AM:

- Met with patient for registry study, performed informed consent
- Met with patient for hyperlipidemia study
- Centrifuged, collected, and shipped samples
- Completed EDC for patient

PM:

- Called patients to reveal results of a closed study (Stability)
- Met with patient, sat in on informed consent, for implantable cardiac monitor
- Centrifuged, collected, and shipped patient samples

Tuesday, June 24th, 2014

AM:

- Went to Plano Heart Hospital and participated in a pig heart dissection in the Bioskills Laboratory
- Called patients to reveal results of a closed study (Stability)
- Received and recorded drug shipment for hyperlipidemia study

PM:

- Researched different clinical trials that may be worth pursuing

Wednesday, June 25th, 2014

AM and PM:

- Screened patients for three different studies:
 - o The hyperlipidemia/statin trial
 - o The registry trial
 - o The implantable cardiac monitor trial
- Saw varying success in my ability to screen
 - o It is a pretty time-intensive activity, each patient takes about 30-35 minutes to go through fully to be convinced they might be a good fit
 - That process then gets approved by one of the Clinical Research Coordinators
- Of the three studies, I really only saw success in the hyperlipidemia/statin study, which was weird because its inclusion criteria is the most specific
 - o There were about 5 patients I was able to screen successfully, only 2 or 3 will end up being a good fit for the study

Thursday, June 26th, 2014

AM:

- Completed and scanned in Safety Reports to be submitted to the IRB
- Screened patients for three different studies

PM:

- Screened patients for the registry study, was not successful
 - o Inclusion criteria is not terribly complex, but one portion of it is specific enough to make it difficult

Friday, June 27th, 2014

AM:

- Read over the protocol for a new study that will begin enrolling in the next couple of weeks
 - o Weight loss pill that is being tested for cardiovascular safety and efficacy in preventing type 2 diabetes

Monday, June 30th, 2014

AM:

- Went to Baylor University Medical Center in downtown Dallas to participate in Good Clinical Practice training from 7:30am to 12:30pm
- The presenters (former CRM professors in Med Sci), discussed how to approach different situations as a coordinator, and how technology is changing clinical research.

PM:

- Screened patients for the registry study, found three patients that went through the full extent of screening and thus qualify for the study

Tuesday, July 1st, 2014

AM:

- Had my advisory committee meeting with Dr. Gwartz, Dr. Reeves, Claudia Mattil, Natalie Settele, Angela Germany, Robin Buckner, and Kathy Rodkey. Discussed the extent of my internship so far and developed an idea for what my thesis could be
- Screened patients into the afternoon for the registry study, had far less luck this time around than the previous day

PM:

- Continued to screen for patients
- Reviewed some of the patient charts of previously screened patients in order to determine if they qualify for the hyperlipidemia study
- Filed documents for the open and closed studies

Wednesday, July 2nd, 2014

AM:

- Met with a patient at 8:30am in order to discuss the registry trial. He consented to being a part of the study
- Individually met with another patient at 9:00 to gauge their interest in being a part of the study. They declined
- 10:15am: met with the last patient I screened (from Monday), who agreed to take part in the study

PM:

- Left early with a stomach ache

Thursday, July 3rd, 2014

AM:

- Reviewed screenshots of source documentation for one of the studies
 - o I'll be creating new source documents for the study starting next week
 - o The screenshots were really basic documents that stated what information will be needed at each visit
- Filled out stipend forms for patients for three different studies
- Prepared lab kits for the next week
- Everyone left the Clinic early in anticipation for Independence Day

Friday, July 4th, 2014

- Off for Independence Day

Monday, July 7th, 2014

AM and PM:

- Worked on formatting new source documents for two studies
 - o The process was slow and a bit tedious because it requires going through protocols to see what information is necessary for each visit
- Made 5 or 6 forms individually, had them looked over, but now need to condense them into forms per visit

Tuesday, July 8th, 2014

AM:

- Continued to work on making source documents
- Visited with a patient, centrifuged, collected, and shipped samples for his labs as well as another patient's labs that was seen earlier in the morning

PM:

- Completed forms required for advertising studies on Baylor's website and through other media
- Completed the EDC forms in Biomedical for the patient we saw earlier in the morning

Wednesday, July 9th, 2014

AM:

- Met with patient for hyperlipidemia study, centrifuged, collected, and shipped samples
- Tried to meet with a patient to see if they would enroll in our registry study, but they turned us down citing a potential invasion of privacy

PM:

- Worked on source documentation for the new study we are soon to begin
- Screened for the hyperlipidemia and registry study
- Filled out the EDC queries for the ticagrelor study

Thursday, July 10th, 2014

AM:

- Filled out stipend forms for the ticagrelor study
- Scanned and filed safety reports
- Edited physician CVs to match the BRI template, as these will be sent to sponsors

PM:

- Submitted documents to be approved by the IRB to the online BRI IRB system for two studies
 - o These forms are signed by physicians, and normally have to do with small updates to the study (advertising, translated forms, etc.)

Friday, July 11th, 2014

AM:

- Screened for patients for the registry study, found a couple of patients that we might be able to talk to next week
 - o The screening process is getting easier as I become more comfortable with the EMRs

Monday, July 14th, 2014

AM and PM: Was not at work because of stomach virus

Tuesday, July 15th, 2014

AM and PM:

- Worked under Dr. Marcus McKenzie reading stress echocardiograms, stress nuclear tests, and electrocardiograms
- Learned how to read stress nuclear tests, and gained some insight into EKG reading
- Visited with some patients briefly to discuss the results of their tests

Wednesday, July 16th, 2014

AM and PM: Was not at work because of stomach virus

Thursday, July 17th, 2014

AM:

- Went to THHBP for a research meeting, discussing the possibility of introducing two new clinical trials to the hospital
- Went back to the hospital to see a procedure installing an implantable cardiac monitor (ICM)
 - o The procedure was done in the patient's exam room
 - o It took only a couple of minutes, but the preparation time dragged along the entire process
 - Potential room for improvement here—collecting the necessary items for a procedure could be done more efficiently

PM

- Screened for patients for the registry study
- Found one patient, however upon closer inspection they were taking one of the drugs that is a part of the exclusion criteria

Friday, July 18th, 2014

AM:

- Worked a little bit on editing my thesis proposal to be presented to Ms. Angela Germany and potentially one of the physicians
- Screened patients for our registry study, found 3 patients. Will follow-up with them next week.

PM:

- Went to lunch for one of the volunteers' last day at the clinic
- Left the clinic early for Friday prayer/to drive to Houston after lunch

Monday, July 21st, 2014

AM:

- Downloaded, filed, and submitted IND Safety Reports for an ongoing study (Ticagrelor/PEGASUS)
- Screened for patients for the registry study

PM:

- Worked on a BRI-specific informed consent form for a substudy for the hyperlipidemia clinical trial.
- Most of the work was editing, copying and pasting, and rewording some of the consent form that the sponsor provided us with. However, there is some Baylor-specific language that is required.

Tuesday, July 22nd, 2014

AM:

- Compiled and submitted IND Safety Reports for an ongoing study (Ticagrelor/PEGASUS)
- Made minor edits to internship practicum proposal

PM:

- Reviewed edits and made corrections to the BRI-specific informed consent form for the substudy in the hyperlipidemia clinical trial
- Edited the resumes of certain physicians to include Baylor Research Institute Affiliation

Wednesday, July 23rd, 2014

AM:

- Had Research meeting with members of the Heart Hospital Baylor Plano's research team
 - o Discussed billing compliance, audits, back-ups to study's and how best to approach study's that are taken over by a different coordinator, and other administrative issues
- Re-edited internship practicum proposal
- Re-edited CVs of two physicians
 - o Did this the other day, but needed to reformat some things and clean up some parts of it
- Received and called in drug shipment
 - o Also did some housekeeping with the drug bottles to make them easier to read and access

PM:

- Reviewed and learned how to read parts of an EKG with Kathy
- Screened patients for registry study
- Practiced performing an EKG on Kathy's son

Thursday, July 24th, 2014

AM:

- Went to research meeting at THHBP
- Discussed potential for new clinical trial, as well as updates on old investigator-led trials

PM:

- Collected and shipped patient samples for the hyperlipidemia trial
- Screened for patients for the registry trial

Monday, July 28th, 2014

Out for Eid-ul-Fitr

Tuesday, July 29th, 2014

AM:

- Both of my successful screenings last week ended up joining the registry study!
- Worked on safety reports for two studies: the hyperlipidemia trial and the antiplatelet therapy (PEGASUS)
 - o I knew how to do the PEGASUS-TIMI 54 safety report reporting from previous experience, but had to learn for the other study
 - I made a bunch of errors in reporting that I did not catch until I was almost finished, but I was able to fix all of the mistakes
- Reported a receipt of shipment for drugs that we received

PM:

- Legacy Heart Center Staff Meeting
 - o Discussed PI Meeting Updates, Screening Process Review, Communication Flow, as well as regular study updates
- Tried to figure out shared research calendar issues

Wednesday, July 30th, 2014

AM:

- Tried to figure out calendar issue, was not able to find a solution. Luckily Angela did
- Worked on safety reports, made the spreadsheet, downloaded them, and submitted the reports

PM:

- Collected, centrifuged, packaged, and shipped patient samples for the hyperlipidemia study
- Made new spreadsheet for safety reports, downloaded and submitted two new ones

Thursday, July 31st 2014

AM:

- Attended BRI North meeting discussing upcoming clinical trials and proposals... meeting started late and ran a little long
- Filed Safety Reports
- Read CV research articles relevant to the clinical trials we are doing. These may be used as really helpful background information for my research practicum

PM:

- Screened for the registry and hyperlipidemia study, found one patient for the registry study. We will be visiting with them tomorrow afternoon

Monday, August 4th, 2014

AM:

- Worked on editing thesis proposal
 - o Researched new study I will be referencing/screening (COBRA-PZF)
- Filed safety reports

PM:

- Screened patients for the registry study. Found two patients. We will meet and discuss the study with them tomorrow
- Screened patients for the hyperlipidemia study. Found one candidate, however they barely fit the criteria and the physician in charge may not want to change their drug regimen (which is required).
 - o Kathy may discuss it with the physician if she thinks it is worth pursuing

Tuesday, August 5th, 2014

AM:

- Attended a Site Initiation Visit for a new study that we are about to begin enrolling
 - o There are many issues to iron out with this new study, it is already complex in its design—but the sponsor has some unrealistic expectations it seems for physician involvement

- Some of this goes against the established protocol at the clinic, but the representative from the sponsor said they would follow-up with the coordinators to see if Legacy Heart Center could follow their established methods

PM:

- Drove to Fort Worth to turn in Intent to Graduate form and my thesis evaluation form
- Returned to the clinic at 3:00pm, briefly filed/counted safety reports

Wednesday, August 6th, 2014

AM:

- Collected and shipped patient samples for hyperlipidemia study
- Filed source documentation for a variety of studies the clinic was working on

PM:

- Caught up with filing and reporting for registry study
 - Required to report every patient that was pre-screened to see why or why not they did not progress into the screening process
- Worked on a project assigned to me by Angela looking at study timetables

Thursday, August 7th, 2014

AM:

- Screened patients for the registry study. No patients were found.
- Received a new batch of safety reports that I filed and reported for statin clinical trial

PM:

- Went through the protocol for two of the studies I will be citing in my thesis to find relevant background information
- Continued to work on a project Angela gave me that creates a timetable for studies. The project is tricky, however, because it requires going through the regulatory binders to find correspondence linking trial benchmarks with specific dates. For some studies, this is easier to find. I have made little progress on this despite working on it for a couple of hours

Friday, August 8th, 2014

AM:

- Screened patients for both studies, found a number of patients for the registry study (three total), and one potential patient for the hyperlipidemia study
 - o This patient's labs showed that his drug regimen was not effective, and from his charts, he seemed like a person that was keeping up with his medication
 - The hyperlipidemia study might help significantly in lowering his LDL
- Continued catching up with the filing/reporting of pre-screening for the registry study

Monday, August 11th, 2014

AM:

- Screened for patients for the registry study
- Enrolled another patient for the registry study (Screened on Friday)!
- Have to meet with another patient later in the afternoon
- Had physicians sign documents for a variety of studies
- Filed safety reports for statin study

PM:

- Screened patients for the registry study
 - o Found two patients
 - o One of them was already enrolled in our study
 - o We will meet with the second patient tomorrow
- Second patient screened on Friday declined to be a part of the study
- Signed and sent (back to hospital) Form 35 for the closing of one of the hospital studies

Tuesday, August 12th, 2014

AM:

- Filled out pre-screening log for the registry study
 - o I am now fully up-to-date with the amount of patients I have screened (500+ have made it to the pre-screening process, which means thousands have been pre-pre-screened)
- Worked on study timetable for a new study. I was able to find some of the information relevant to the research side of things. A lot of the administrative timelines are things I'll need to look more closely for. I am a little uncertain of where I should find that information, and will follow-up with Angela once I have done my part to the best of my ability

PM:

- Met with a patient I screened for the hyperlipidemia study!
 - o Overall it was a neat process, because I had looked through his charts and we were able to follow-up with him
 - o It was just an introductory visit, no informed consent was delivered. Kathy suggested the patient take home the relevant information and discuss it with his family before proceeding
 - o My inkling is that he will commit to the study, he seemed excited by its potential
- Continued working on source documents for one of the studies. I have made a couple of them already, but there is work left to be done
- Screened patients for the registry study

Wednesday, August 13th, 2014

AM:

- Screened for patients for the registry study
- Filled out pre-screening log

PM:

- Went to hospital for an orientation on a new study I will be working on
- Met with the staff, saw where I will be working
- Reviewed the ICF, protocol, and inclusion/exclusion criteria
- Screened for patients for this device study

Thursday, August 14th, 2014

AM:

- Screened for patients in the morning for Friday at the Clinic
- Went to the hospital to meet with patient we screened yesterday
 - o she did not speak English
 - o we need to get a Spanish ICF

PM:

- Saw multiple procedures in the Cath Lab, met some of the Interventionalists that perform them

Friday, August 15th, 2014

AM:

- Screened for patients for Monday and Tuesday for the registry study

- Filled out pre-screening logs for the study
- Filed relevant source documents for multiple studies

Monday, August 18th, 2014

AM:

- Finished screening Tuesday's patients and began screening for Wednesday
- Went to lunch for Robin's birthday

PM:

- Screened for Wednesday's patients
- Read protocol for a new study (the study I helped develop source documents for)

Tuesday, August 19th, 2014

AM:

- Finished screening for Wednesday's patients, there are 3 that we will speak to tomorrow

PM:

- Worked on reconciled budget for the hyperlipidemia study
 - o There were instances where the clinic was not paid enough for what we billed, and instances where the Sponsor paid too much
 - o Ended up figuring out almost all of the discrepancies
- BRI LHC Staff meeting
 - o Reviewed studies and protocol review
 - o Discussed my role in the future

Wednesday, August 21st, 2014

AM:

- Read device study protocol, worked on background section (outlining) of thesis
- Caught up on prescreening logs that I neglected to do for the past couple of days

PM:

- Screened for patients for Thursday, found one patient
 - o Found a more specific way to screen for registry study, but it would not work for the hyperlipidemia study
 - o Will speak to patient tomorrow morning

Thursday, August 22nd, 2014

AM:

- Went to hospital, reviewed protocol for device study
- Screened patients for left heart catheterizations tomorrow
- Found one patient that we will try consenting tomorrow morning

PM:

- Screened for patients at LHC for Friday
 - o Did not find a single patient
- Finished catching up on pre-screening log, and am now fully up to date
- Filed documents for two studies

Friday, August 23rd, 2014

AM:

- Consented patient at the hospital for the device study, she agreed to take part
- Was at the hospital for most of the day, but was not able to see if the patient fit the angiographic criteria to take part in the study

Monday, August 25th, 2014

AM:

- Filled out pre-screening log for Friday's patients
- Screened for Tuesday's patients, did not find one to talk to tomorrow
- Completed the Continuing Review Form for Baylor's IRB for the hyperlipidemia study

PM:

- Filed and submitted safety reports for the ticagrelor study
- Met with one patient who was screened Friday
 - o The second patient may be a no-show per the physician

Tuesday, August 26th, 2014

AM:

- Made copies of the ICF for the hyperlipidemia study
- Brought documents to the physicians that needed to be signed ASAP for hospital studies

PM:

- Went to the hospital to screen for patients for the device study
 - o did not find any patients
- kept going through the protocol for the device study
 - o Julie says to go through it with a “fine toothed comb” to have a solid understanding of it
 - It’s a lot of information and a lot to remember

Wednesday, August 27th, 2014

AM:

- Processed and shipped lab samples for the hyperlipidemia study
 - o I almost made a mistake in the labs that would have required the patient to come back, luckily I caught myself before I made the mistake
 - It was a good reminder to pay attention to detail!

PM:

- Made flyers to be posted in the Cath Lab for studies that we are enrolling for that would have patients at the hospital
- Screened for patients for the registry and hyperlipidemia studies
 - o Found a patient for the hyperlipidemia study, but the physician who oversees the patient might not be agreeable to letting them enroll

Thursday, August 28th, 2014

AM:

- Filed and submitted safety reports for a couple of studies that I do not work on
 - o The process is a little different, because there are so few of them, it’s a bit easier to manage
 - Physicians for these studies sign off on individual reports, even though I make and submit a spreadsheet

PM:

- Answered queries for the registry study, most of them were data entry errors and were pretty simple to fix
 - o This took a good amount of time, though, because it required going through source documentation to make sure I had the right information, and to figure out where I made a mistake

Friday, August 29th, 2014

AM:

- Screened for patients for the registry study, did not find any
- Filled our prescreening logs for the registry study
- Filed and reported safety reports

Monday, September 1st, 2014

Labor Day

Tuesday, September 2nd, 2014

AM:

- Screened patients for registry and hyperlipidemia study
 - o Found a patient for each study
 - Registry study we will consent tomorrow
 - Hyperlipidemia study, the patient may not work out based on liver function
- Filed, downloaded, and reported safety reports for PEGASUS-TIMI 54 and one other study
- Read over informed consent form for the registry study, I will consent my first patient this afternoon
 - o Would have this morning, but she was feeling ill and wanted us to speak with her later

PM:

- Spoke to physician about the patient I will be consenting
 - o Second patient is not a good fit per the physician
 - o Initially, it seemed as though the patient would be, but after visiting with her the physician decided it was not worth our efforts

Wednesday, September 3rd, 2014

AM:

- Consented my first patient and he agreed to be a part of the study!
 - o Went through the process of filling out the source documents
 - o Filled out the EDC

PM:

- Screened for patients for all studies. Did not find any matches
- Worked on spreadsheet for budget discrepancies for a closed study

Thursday, September 4th, 2014

AM:

- Finished budget discrepancy spreadsheet, tried to make it match the data we had and another spreadsheet that Angela had
- Filled out prescreening logs from previous days

PM:

- Filed and submitted safety reports
- Reported patient from yesterday to the IRB
 - o Similar process to EDC, but more tailored to BRI interests
- Screened for patients for all of the studies

Friday, September 5th, 2014

AM:

- Consented patient for registry study at the other clinic location
- He agreed to take part in the study
- Learned how to fill out the EDC for this study as well as report the new enrollee to the IRB

Monday, September 8th, 2014

AM:

- Was late to consent a patient, we did not realize that the patient was going to be at the clinic's other location
 - o Missed the patient for consenting, but there was another patient later in the day (10:30 AM)
- The second patient did not show up for his appointment and was rescheduled to later in the day
- Screened for Tuesday's patients

PM:

- Filled out prescreening logs for the registry study
- Robin and I split up the two patients we could consent today, I went to consent the patient at the clinic's other location
- He agreed to take part in the study

Tuesday, September 9th, 2014

AM:

- Finished the EDC and source documentation for the patient that was consented the day before
- Helped Kathy process labs, made copies of ICFs, and other minor things while she met with patients
- Robin tried consenting a patient that I was going to consent (while I was processing labs), but he did not show up for his appointment

PM:

- Filed and reported safety reports
- Screened for patients for the next day

Wednesday, September 10th, 2014

AM:

- Filled out prescreening logs that I have been behind on
- Found out I could consent a patient at the other clinic location, so I rushed over there
- That patient agreed to be a part of the study

PM:

- Filled out the source documentation for this new patient
- Continued filling out prescreening logs
- Screened patients for Thursday

Thursday, September 11th, 2014

AM:

- Filled out prescreening logs for the registry study
- Continued filling out the EDC for the newly enrolled patient
 - o Made sure this time to not to fill in the EDC properly, so as to not have queries this time
- Filed safety reports

PM:

- Processed labs for the hyperlipidemia study, and then shipped them
- Screened for patients for the registry study

Friday, September 12th, 2014

AM:

- Screened for patients for the registry study

Monday, September 15th, 2014

AM:

- Attempted to meet with patient, but physician declined (did not meet criteria)
- Filed safety reports for the hyperlipidemia study
- Screened patients for Tuesday, did not find any

PM:

- Filled out pre-screening logs for registry study
- Completed continuing review for a closing study
- Physician was running behind schedule, so I waited a while to speak with patient
- Patient consented to the registry study
- Filled out source documentation and reported the patient to IRB

Tuesday, September 16th, 2014

AM:

- Fixed mistakes in safety report submission
- Completed a continuing review for a closing study
- Filled in EDC for enrolled patient
- Filed safety reports

PM:

- Screened for patients for two studies

Wednesday, September 17th, 2014

AM:

- Screened for patients for the registry study
- Filed, reported, and submitted safety reports for hyperlipidemia study
- Met with patient at the other clinic location regarding the registry study

PM:

- Patient consented to being in the trial—the 25th patient recruited
- Filled out EDC and updated the patient log for the IRB

Thursday, September 18th, 2014

AM:

- Helped Kathy process labs for the hyperlipidemia study
- Completed safety reports for the hyperlipidemia study

PM:

- Filed and submitted safety reports for an enrolling study
 - o This study has not been one that I have been involved with, and the safety reports are few and far between

Friday, September 19th, 2014

AM:

- Screened for hyperlipidemia study and the Belviq study
 - o Found a potential patient for the Belviq study, however the patient barely qualifies
 - o Kathy will review the charts in order to determine if they were a good fit
 - I don't think they'll end up panning out—seems a little unnecessary to put a patient on an experimental drug that might not need it

Monday, September 22nd, 2014

AM:

- Filed documents, faxed necessary forms for a variety of studies
- Looked at patients that physician's suggested for the Belviq study
 - o The three patients I looked at all qualified

PM:

- Submitted application to update the informed consent form for the registry study

Tuesday, September 23rd, 2014

AM:

- Met with and consented a patient for the registry study
- Patient agreed to be a part of the study
 - o Went through the EDC and reported the patient to the IRB

PM:

- Found out the informed consent was not entirely valid (it required a stamp of approval from BRI)
- This constituted protocol deviation and had to be reported
 - o Begun the process of reporting the deviation

Wednesday, September 24th, 2014

AM:

- Filed safety reports for the hyperlipidemia study
- Continued the process of reporting the protocol deviation—attempted to contact the patient to re-consent

PM:

- Did not consent screened patients for the registry study until we can get the deviation and other contractual issues sorted
- Had a meeting to go over goal-setting at the Heart Hospital

Thursday, September 25th, 2014

AM:

- Begun working on presentation for nurse's meeting that will introduce some of the research studies that are being conducted at the clinic
- Had a research staff meeting to go over study updates, recruiting, and the goal setting meeting from the day before

PM:

- Finished the presentation for the nurse's meeting
- Listened into a web conference for a study we have not yet begun enrolling for
 - o There are some issues in the protocol that will be amended so that we can begin enrolling

Friday, September 26th, 2014

AM:

- Spoke to Dr. McKenzie about the protocol deviation, and had him sign the necessary paperwork (as well as other paperwork)
- Submitted some reports and documents to the IRB and other entities (finance, etc.)
- Filed a couple of documents for the hyperlipidemia study
- Had a meeting with some of the Echocardiogram Technicians regarding a study that will require echocardiograms

- The basic protocol, scheduling, and rundown of the study was reviewed

Monday, September 29th, 2014

AM:

- Copied and faxed lab reports to PCPs for a number of patients
- Worked on background section of thesis
- Filed and reported safety reports
- Attempted to contact patient from last week regarding the protocol deviation

PM:

- Screened for patients for the registry study
- Scanned and submitted closeout letter for one of the studies

Tuesday, September 30th, 2014

AM:

- Screened for patients
- Got ready for the nurse's meeting that we were going to have during lunch
 - Made copies of the handouts we would be using
 - Had some issues with the projector but was able to figure it out

PM:

- Conducted the nurse's meeting
- Went to physicians to fill out forms necessary for the studies
- Scanned and submitted documents to the IRB

Wednesday, October 1st, 2014

AM:

- Screened for patients for the BELVIQ study
 - Did not find any patients that were definite fits for the study

PM:

- Screened for patients for the registry study
- Prepared a letter for the protocol deviation and kept a log of the activities in order for the IRB to be up to date on what has happened
 - I have been in contact with the sponsor regarding the issue, they suggested that we mail a consent form to the patient

Thursday, October 2nd, 2014

AM:

- Filled in prescreening logs for the registry study
 - o I have fallen pretty far behind for this, need to continue filling them out to catch up
-

PM:

- Everyone left after lunch, the office got a bit humid and everyone started to feel kind of sick

Friday, October 3rd, 2014

- Was not at work due to illness

Monday, October 6th, 2014

AM:

- Had Dr. Bakshi and Dr. Rawitscher fill out paperwork for a new study at THHBP
- Delivered the documents to the hospital as they were needed that day

PM:

- Returned to the clinic after lunch and screened for patients

Tuesday, October 7th, 2014

AM:

- Found articles for the literature review aspect of my internship practicum report
 - o These all dealt with stenting procedures and how it has developed over the course of the last 20 years
 - o Read through the articles and tried to find the important aspects to incorporate into my report

PM:

- Screened for patients for the registry study, found two patients that would fit
- Will consent them tomorrow

Wednesday, October 8th, 2014

AM:

- Both patients for the registry did not enroll
 - o One patient canceled (at the other clinic location, found out after I went to the clinic)
 - o The second patient the physician felt would not be a good fit, they may not have had a heart attack

PM:

- Received the signed consent from the patient with which the protocol deviation happened
- Reported this to the IRB and the sponsor
 - o Was able to fill out the deviation information on the EDC

Thursday, October 9th, 2014

AM:

- Went to the office and hospital to get my internship practicum forms signed
- Went to campus to get forms signed and to briefly meet with my advisory committee regarding how my internship practicum was going

PM:

- Came back to the office at around 2:45 PM, and screened for patients for the registry study, did not find any patients

Friday, October 10th, 2014

AM:

- Worked on background section for my internship practicum report
 - o Found the figures I want to use, but need to apply for licenses
 - Emailed one of the physicians that works in histology with regards to using his stent slides

Monday, October 13th, 2014

AM:

- Filed IRB correspondence
- Compiled, printed, submitted safety reports for the ticagrelor study
- Worked on internship practicum report

PM:

- Screened for patients for the registry study

- Found one patient to speak to tomorrow
- Filled out prescreening logs for the registry study

Tuesday, October 14th, 2014

AM:

- Set up room and binders for monitor visit
 - Filed correspondence, organized binders, made sure the monitor had everything required to complete work
- Edited a physician's CV with the current BRI template
- Printed and filed documents for new studies being considered
- Had meeting at the Heart Hospital Baylor Plano regarding changes to BRI

PM:

- Made orientation binder for new coordinator
- Potential research patient screened yesterday rescheduled for November 6th
- Filed and reported safety reports for a closing study
- Completed Billing Forms for patients in the ticagrelor study
- Screened for patients for the registry study

Wednesday, October 15th, 2014

AM:

- Trained new coordinator on tasks necessary for BRI and Legacy Heart Center, such as:
 - Screening procedures
 - EMR access
 - Inclusion and exclusion criteria for some of the studies
- Had a lunch baby shower for Amy

PM:

- Filled out prescreening logs for registry study
- Went to the Heart Hospital to get forms signed by Dr. McKenzie
- Looked at ECGs with Dr. McKenzie for some of the patients he was seeing
- Screened for patients for the registry study

Thursday, October 16th, 2014

AM:

- Answered queries for the registry study per the request of the data management team

- Helped set up Diana's printer, and scanned documents for the hyperlipidemia study
- Filled out prescreening logs for the registry study

PM:

- Screened for patients for the registry study
- Briefly met with patient getting an echocardiogram for the BELVIQ study
- Made copies and faxed lab results to PCPs for patients
- Filed safety reports for the hyperlipidemia study

Friday, October 17th, 2014

AM:

- Filed safety reports for the ticagrelor study
- Filled out prescreening logs for the registry study
- Cleared out some space and reorganized filing shelves to fit in some of the new studies

Monday, October 20th, 2014 – Friday, October 24th, 2014

AM & PM:

- Worked on internship practicum report throughout the week, as the final draft is due early next week
- Screened for patients for the registry study
- Filed and submitted safety reports

APPENDIX B

GLOSSARY OF ABBREVIATIONS

Table 2: Glossary of Abbreviations

| Abbreviation | Definition |
|---------------------|---|
| ACS | Acute Coronary Syndrome |
| BMS | Bare Metal Stent |
| BRI | Baylor Research Institute |
| CABG | Coronary Artery Bypass Graph |
| CDA | Confidential Disclosure Agreement |
| COX-1 | Cyclooxygenase-1 |
| DAPT | Dual Antiplatelet Therapy |
| DES | Drug Eluting Stent |
| GPCR | G Protein Coupled Receptor |
| HRPR/HTPR | High Residual Platelet Reactivity/High On-Treatment Platelet Reactivity |
| IPA | Inhibition of Platelet Activity |
| LAD | Left Anterior Descending Artery |
| LCX | Left Circumflex Artery |
| LD | Loading Dose |
| MACE | Major Adverse Cardiac Event |
| MD | Maintenance Dose |
| MI | Myocardial Infarction |
| NSAID | Non-Steroidal Anti-Inflammatory Drug |
| P2Y ₁₂ | Purinergic G Protein-Coupled Receptor 12 |
| PCI | Percutaneous Coronary Intervention |
| PTCA | Percutaneous Transluminal Coronary Angioplasty |
| THHBP | The Heart Hospital Baylor Plano |
| TXA2 | Thromboxane A2 |

APPENDIX C

SUMMARY TABLE OF DAPT CLINICAL RESEARCH STUDIES

Table 3: Summary of Referenced DAPT Clinical Research Studies (in reference order)

| Study Name | Summary | Conclusions |
|---|---|--|
| Aspirin Meta-Analysis | Use of aspirin in primary MACEs | Risks may outweigh benefit |
| CURE | Clopidogrel vs. aspirin in MACE prevention | Clopidogrel > aspirin |
| TRITON-TIMI 38 | Prasugrel vs. clopidogrel in MACE prevention with PCI | Prasugrel > clopidogrel |
| TRILOGY ACS | Prasugrel vs. clopidogrel in MACE prevention without PCI | Prasugrel = clopidogrel in the frequency of primary endpoints |
| PLATO | Ticagrelor vs. clopidogrel in MACE prevention | Ticagrelor > clopidogrel |
| Ticagrelor Versus Prasugrel in Acute Coronary Syndrome Patients With HTPR Post-PCI | Small study comparing ticagrelor vs. prasugrel in inhibition of platelet activity | Ticagrelor > prasugrel in the inhibition of platelet activity |
| Randomized Assessment of Ticagrelor versus Prasugrel Antiplatelet effects in Patients with Diabetes | Ticagrelor vs. prasugrel in inhibition of platelet activity | Ticagrelor > prasugrel in the inhibition of platelet activity in DM patients |
| Ticagrelor vs. prasugrel Meta-Analysis | Ticagrelor vs. prasugrel in thrombosis and bleeding | Ticagrelor < prasugrel in prevention of stent thrombosis Ticagrelor > prasugrel in minimizing bleeding events |
| CHAMPION PHOENIX | Cangrelor vs. clopidogrel | Cangrelor > clopidogrel, but FDA rejected use of cangrelor |
| ASCERT | CABG vs. stenting in long-term revascularization outcomes | CABG > stenting |
| ABSORB | Use of bioresorbable stents in prevention of MACEs and thrombosis | Bioresorbable stents are effective at minimizing MACEs and preventing thrombosis |

| | | |
|---|---|--|
| REAL-LATE & ZEST-LATE | Efficacy of using clopidogrel beyond recommended 12-month window, compared to aspirin | Aspirin monotherapy = clopidogrel at preventing MACEs and stent thrombosis |
| Optimal Duration of DAPT after DES Implantation | Clopidogrel vs. aspirin in MACE prevention over 36 months | Aspirin = clopidogrel in MACE and stent thrombosis prevention |
| PEGASUS-TIMI 54 | Ticagrelor vs. placebo in MACE prevention and stent thrombosis over 44 months | TBD |
| PzF SHIELD | Use of COBRA PzF™ stent system in prevention of MACEs and in reduction of DAPT usage | TBD |
| TIGRIS | Healthcare resource utilization for patients with stable CAD | TBD |

APPENDIX D

CLINICAL RESEARCH STUDY COORDINATOR QUESTIONNAIRE

Legacy Heart Center and The Heart Hospital Baylor Plano Dual Antiplatelet Therapy Clinical Research Study Coordinator Questionnaire

The purpose of this document is to review the various components (Screening, Consent, and Trial Visits and Follow-up Practices) of clinical research relevant to DAPT. Through this questionnaire, it is hoped that some of the strategies clinical research coordinators use to manage a clinical trial will become clear. This will aid in the development of a descriptive review seeking to compare the differences among DAPT drug, device, and registry trials at Legacy Heart Center and The Heart Hospital Baylor Plano.

Screening

1. What were the methods with which you screened for this study?
 - a. What were the advantages/disadvantages of using this method
 - b. Would you have preferred another method (use of databases, etc.) to screen for patients?
2. How important was physician-involvement in the screening process?
3. When a patient would screen fail, what part of the inclusion/exclusion criteria was generally the reason?

The Informed Consent Process

1. What were the biggest advantages to taking part in the study?
2. Was the use of an investigational drug/device a big draw to the study, in the eyes of patient (not applicable to TIGRIS)?
3. Were physicians involved in the recruitment and consent process?
4. Was the idea of being closely monitored at a facility like LHC or THHBP a big draw for patients?

Trial Visits and Follow-up Practices

1. What were the general practices done during trial visits (please be vague enough as to not breach CDAs)?
2. Did patients see a physician during the trial visit?
 - a. What specific practices did you implement personally during patient visits?
3. Was there anything different about the follow-up visits for your specific study than what you have seen normally for drug/device studies?

APPENDIX E

BRI INFORMED CONSENT NOTE

Informed Consent Note

On _____ at _____ o'clock, IRB Number # _____ entitled: _____ was presented to _____ by _____.

☐ Initial Consent

☐ Re-consent

The informed consent document was read by the subject and was followed by verbal discussion. The verbal discussion covered but was not limited to: the purpose of the study, length of study, the study procedures and required follow-up, possible and potential side effects (risks), potential benefits, notification of new findings, other treatment options, study cost, and privacy issues. It was explained that his/her participation is voluntary and he/she can withdraw at any time without penalty or loss of benefit. The possible reason(s) for the study doctor or sponsor to remove him/her from the study was explained. Additionally, information on how to contact the study doctor or study coordinator was provided, as well as contact information to the IRB covering this protocol. The entities that may have access to the subject's research records were disclosed. The subject was given ample time to review the document and was offered the opportunity to review at home, if applicable. Patient exhibited understanding of the Informed Consent document.

Once he/she stated there were no additional questions regarding this study and/or procedures, he/she signed and dated the informed consent document. A copy of the informed consent document was given to him/her.

Study screening procedures began after the informed consent document was signed.

Comments: (ie, other people present, MD discussion, special circumstances)

____ Patient was re-consented on the current IRB approved consent (Version: _____)

Name of Person Obtaining Consent

Date

Time

APPENDIX F

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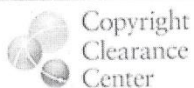
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REFERENCES

1. "Is My Study Observational or Interventional?" *NHLBI*. National Institute of Health, Feb. 2011. Web. 14 Sept. 2014.
2. Van Dermark, Lynn. "Product Development – From Discovery to Market: Medical Devices and Combination Products." Clinical Research Management. University of North Texas Health Science Center, Fort Worth. 13 Feb. 2014. Lecture.
3. "FAQ: ClinicalTrials.gov - Clinical Trial Phases." *National Institute of Health*. U.S. National Library of Medicine, 18 Apr. 2008. Web. 15 Sept. 2014.
4. Arain, Mubashir, Michael J. Campbell, Cindy L. Cooper, and Gillian A. Lancaster. "What Is a Pilot or Feasibility Study? A Review of Current Practice and Editorial Policy." *BMC Medical Research Methodology* 10.67 (2010): n. pag. *BMC Medical Research Methodology*. BioMed Central, 16 Jan. 2010. Web. 21 Sept. 2014.
5. Bahadur, Namrata. "Overview of Drug Development." Emerging Growth Markets. Bangkok. 17 Mar. 2008. *International Conference of Harmonisation*. Web. 15 Sept. 2014.
6. Nappi, J., and R. Talbert. "Dual Antiplatelet Therapy for Prevention of Recurrent Ischemic Events." *American Journal of Health Systems Pharmacy* 59.18 (2002): 1723-735. *U.S. National Library of Medicine*. American Journal of Health Systems Pharmacy, 1 Sept. 2002. Web. 13 Sept. 2014.
7. Kirtane, A. J., and G. W. Stone. "How to Minimize Stent Thrombosis." *Circulation* 124.11 (2011): 1283-287. Web.
8. Schrör, Karsten. "Aspirin and Platelets: The Antiplatelet Action of Aspirin and Its Role in Thrombosis Treatment and Prophylaxis." *Seminars in Thrombosis and Hemostasis* 23.04 (1997): 349-56. Web. 3 Sept. 2014.
9. Antithrombotic Trialists', Collaboration. "Aspirin in the Primary and Secondary Prevention of Vascular Disease: Collaborative Meta-analysis of Individual Participant Data from Randomised Trials." *The Lancet* 373.9678 (2009): 1849-860. Web. 12 Sept. 2014.

10. Cholesterol Treatment Trialists' "Efficacy and Safety of Cholesterol-lowering Treatment: Prospective Meta-analysis of Data from 90 056 Participants in 14 Randomised Trials of Statins." *The Lancet* 366.9493 (2005): 1267-278. Web. 3 Sept. 2014.
11. Lanas, Angel, and James Scheiman. "Low-dose Aspirin and Upper Gastrointestinal Damage:epidemiology, Prevention and Treatment." *Current Medical Research and Opinion* 23.1 (2007): 163-73. Web. 13 Sept. 2014.
12. Vane, J. R., S. Bakhle, and R. M. Botting. "Cyclooxygenases 1 and 2." *Annual Review Pharmacology and Toxicology* 38 (1998): 97-120. Web. 11 Sept. 2014.
13. Dorsam, R. T. "Central Role of the P2Y₁₂ Receptor in Platelet Activation." *Journal of Clinical Investigation* 113.3 (2004): 340-45. Web. 17 Sept. 2014.
14. Zhang, Kaihua, Jin Zhang, Zhan-Guo Gao, Dandan Zhang, Lan Zhu, Gye Won Han, Steven M. Moss, Silvia Paoletta, Evgeny Kiselev, Weizhen Lu, Gustavo Fenalti, Wenru Zhang, Christa E. Müller, Huaiyu Yang, Hualiang Jiang, Vadim Cherezov, Vsevolod Katritch, Kenneth A. Jacobson, Raymond C. Stevens, Beili Wu, and Qiang Zhao. "Structure of the Human P2Y₁₂ Receptor in Complex with an Antithrombotic Drug." *Nature* 509 (2014): 115-18. Web. 13 Sept. 2014.
15. Schulz, A., and T. Schöneberg. "The Structural Evolution of a P2Y-like G-protein-coupled Receptor." *Journal of Biological Chemistry* 278.37 (2003): 35531-5541. Web. 17 Sept. 2014.
16. Chrzanowska-Wodnicka, Magdalena, Susan S. Smyth, Simone M. Schoenwaelder, Thomas H. Fischer, and Gilbert C. White. "Rap1b Is Required for Normal Platelet Function and Hemostasis in Mice." *Journal of Clinical Investigation* 115.3 (2005): 680-87. Web. 13 Sept. 2014.
17. "Plavix (Clopidogrel Bisulfate)." *RxList*. RxList, 30 Dec. 2013. Web. 28 Oct. 2014.
18. "Effects of Clopidogrel in Addition to Aspirin in Patients with Acute Coronary Syndromes without ST-Segment Elevation." *New England Journal of Medicine* 345.7 (2001): 494-502. Web. 17 Sept. 2014.
19. Ferreiro, J. L., and D. J. Angiolillo. "New Directions in Antiplatelet Therapy." *Circulation: Cardiovascular Interventions* 5.3 (2012): 433-45. Web. 18 Sept. 2014.

20. Garabedian, T., and S. Alam. "High Residual Platelet Reactivity on Clopidogrel: Its Significance and Therapeutic Challenges Overcoming Clopidogrel Resistance." *Cardiovascular Diagnosis and Therapy* 3.1 (2013): 23-37. Web. 16 Sept. 2014.
21. Pride, Yuri B., Stephen D. Wiviott, Jacqueline L. Buros, Cafer Zorkun, M. Umer Tariq, Elliott M. Antman, Eugene Braunwald, and C. Michael Gibson. "Effect of Prasugrel versus Clopidogrel on Outcomes among Patients with Acute Coronary Syndrome Undergoing Percutaneous Coronary Intervention without Stent Implantation: A TRIal to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel (TRITON)–Thrombolysis in Myocardial Infarction (TIMI) 38 Substudy." *American Heart Journal* 158.3 (2009): E21-26. Web. 22 Sept. 2014.
22. Roe, Matthew T., Paul W. Armstrong, Keith A.a. Fox, Harvey D. White, Dorairaj Prabhakaran, Shaun G. Goodman, Jan H. Cornel, Deepak L. Bhatt, Peter Clemmensen, Felipe Martinez, Diego Ardissino, Jose C. Nicolau, William E. Boden, Paul A. Gurbel, Witold Ruzyllo, Anthony J. Dalby, Darren K. McGuire, Jose L. Leiva-Pons, Alexander Parkhomenko, Shmuel Gottlieb, Gracita O. Topacio, Christian Hamm, Gregory Pavlides, Assen R. Goudev, Ali Oto, Chuen-Den Tseng, Bela Merkely, Vladimir Gasparovic, Ramon Corbalan, Mircea Cinteza, R. Craig McLendon, Kenneth J. Winters, Eileen B. Brown, Yuliya Lokhnygina, Philip E. Aylward, Kurt Huber, Judith S. Hochman, and E. Magnus Ohman. "Prasugrel versus Clopidogrel for Acute Coronary Syndromes without Revascularization." *New England Journal of Medicine* 367.14 (2012): 1297-309. Web. 26 Sept. 2014.
23. James, Stefan, Axel Åkerblom, Christopher P. Cannon, Håkan Emanuelsson, Steen Husted, Hugo Katus, Allan Skene, Philippe Gabriel Steg, Robert F. Storey, Robert Harrington, Richard Becker, and Lars Wallentin. "Comparison of Ticagrelor, the First Reversible Oral P2Y₁₂ Receptor Antagonist, with Clopidogrel in Patients with Acute Coronary Syndromes: Rationale, Design, and Baseline Characteristics of the PLATelet Inhibition and Patient Outcomes (PLATO) Trial." *American Heart Journal* 157.4 (2009): 599-605. Web. 22 Sept. 2014.
24. Wallentin, Lars, Richard C. Becker, Andrzej Budaj, Christopher P. Cannon, Håkan Emanuelsson, Claes Held, Jay Horrow, Steen Husted, Stefan James, Hugo Katus, Kenneth W. Mahaffey, Benjamin M. Scirica, Allan Skene, Philippe Gabriel Steg, Robert F. Storey, and Robert A. Harrington. "Ticagrelor versus Clopidogrel in

Patients with Acute Coronary Syndromes." *New England Journal of Medicine* 361.11 (2009): 1045-057. Web. 20 Sept. 2014.

25. Alexopoulos, Dimitrios, Anastasia Galati, Ioanna Xanthopoulou, Eleni Mavronasiou, George Kassimis, Konstantinos C. Theodoropoulos, George Makris, Anastasia Damelou, Grigorios Tsigkas, George Hahalis, and Periklis Davlourous. "Ticagrelor Versus Prasugrel in Acute Coronary Syndrome Patients With High On-Clopidogrel Platelet Reactivity Following Percutaneous Coronary Intervention." *Journal of the American College of Cardiology* 60.3 (2012): 193-99. Web. 18 Sept. 2014.
26. Alexopoulos, D., I. Xanthopoulou, E. Mavronasiou, K. Stavrou, A. Siapika, E. Tsoni, and P. Davlourous. "Randomized Assessment of Ticagrelor Versus Prasugrel Antiplatelet Effects in Patients With Diabetes." *Diabetes Care* 36.8 (2013): 2211-216. *Diabetes Care*, 2013. Web. 16 Sept. 2014.
27. Biondi-Zoccai, Giuseppe, Marzia Lotrionte, Pierfrancesco Agostoni, Antonio Abbate, Enrico Romagnoli, Giuseppe Sangiorgi, Dominick J. Angiolillo, Marco Valgimigli, Luca Testa, Fiorenzo Gaita, and Imad Sheiban. "Adjusted Indirect Comparison Meta-analysis of Prasugrel versus Ticagrelor for Patients with Acute Coronary Syndromes." *International Journal of Cardiology* 150.3 (2011): 325-31. Web. 3 Oct. 2014.
28. Stone, Gregg, Gilles Montalescot, Petr Kala, and George Dangas. "The Antiplatelet Debate: Pretreatment and Its Role in Clinical Practice." *Rev. of Cardiology Today's Intervention. Cardiology Today's Intervention* July-Aug. 2014: n. pag. July 2014. Web. 11 Aug. 2014.
29. Meher, Benhard. "The Infamous Coronary Stent Saga." *Cardiovascular Medicine* 2014: 239-44. Web. 18 Sept. 2014.
30. Society of Thoracic Surgeons. "Long-Term Outcomes Favor Heart Surgery Over Stents and Angioplasty." *ScienceDaily*. ScienceDaily, 29 Jan. 2013. Web. 1 Oct. 2014.
31. Fischman, David L., Martin B. Leon, Donald S. Baim, Richard A. Schatz, Michael P. Savage, Ian Penn, Katherine Detre, Lisa Veltri, Donald Ricci, Masakiyo Nobuyoshi, Michael Cleman, Richard Heuser, David Almond, Paul S. Teirstein, R. David Fish, Antonio Colombo, Jeffrey Brinker, Jeffrey Moses, Alex Shaknovich, John Hirshfeld, Stephen Bailey, Stephen Ellis, Randal Rake, and Sheldon Goldberg. "A Randomized Comparison of Coronary-Stent Placement and

Balloon Angioplasty in the Treatment of Coronary Artery Disease." *New England Journal of Medicine* 331.8 (1994): 496-501. Web. 3 Oct. 2014.

32. Foerst, Jason, Marc Vorpahl, Michael Engelhardt, Till Koehler, Klaus Tiroch, and Rainer Wessely. "Evolution of Coronary Stents: From Bare-Metal Stents to Fully Biodegradable, Drug-Eluting Stents." *Combination Products in Therapy* 3.1-2 (2013): 9-24. Web. 2 Oct. 2014.
33. Simard, Trevor, Benjamin Hibbert, F. Daniel Ramirez, Michael Froeschl, Yong-Xiang Chen, and Edward R. O'brien. "The Evolution of Coronary Stents: A Brief Review." *Canadian Journal of Cardiology* 30.1 (2014): 35-45. Web. 5 Oct. 2014.
34. Park, Seung-Jung, Duk-Woo Park, Young-Hak Kim, Soo-Jin Kang, Seung-Whan Lee, Cheol Whan Lee, Ki-Hoon Han, Seong-Wook Park, Sung-Cheol Yun, Sang-Gon Lee, Seung-Woon Rha, In-Whan Seong, Myung-Ho Jeong, Seung-Ho Hur, Nae-Hee Lee, Junghan Yoon, Joo-Young Yang, Bong-Ki Lee, Young-Jin Choi, Wook-Sung Chung, Do-Sun Lim, Sang-Sig Cheong, Kee-Sik Kim, Jei Keon Chae, Deuk-Young Nah, Doo-Soo Jeon, Ki Bae Seung, Jae-Sik Jang, Hun Sik Park, and Keun Lee. "Duration of Dual Antiplatelet Therapy after Implantation of Drug-Eluting Stents." *New England Journal of Medicine* 362.15 (2010): 1374-382. Web. 4 Oct. 2014.
35. Lee, C. W., J.-M. Ahn, D.-W. Park, S.-J. Kang, S.-W. Lee, Y.-H. Kim, S.-W. Park, S. Han, S.-G. Lee, I.-W. Seong, S.-W. Rha, M.-H. Jeong, D.-S. Lim, J.-H. Yoon, S.-H. Hur, Y.-S. Choi, J.-Y. Yang, N.-H. Lee, H.-S. Kim, B.-K. Lee, K.-S. Kim, S.-U. Lee, J.-K. Chae, S.-S. Cheong, I.-W. Suh, H.-S. Park, D.-Y. Nah, D.-S. Jeon, K.-B. Seung, K. Lee, J.-S. Jang, and S.-J. Park. "Optimal Duration of Dual Antiplatelet Therapy After Drug-Eluting Stent Implantation: A Randomized, Controlled Trial." *Circulation* 129.3 (2014): 304-12. Web. 3 Oct. 2014.
36. Bonaca, Marc P., Deepak L. Bhatt, Eugene Braunwald, Marc Cohen, Philippe Gabriel Steg, Robert F. Storey, Peter Held, Eva C. Jensen, and Marc S. Sabatine. "Design and Rationale for the Prevention of Cardiovascular Events in Patients With Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin—Thrombolysis in Myocardial Infarction 54 (PEGASUS-TIMI 54) Trial." *American Heart Journal* 167.4 (2014): 437-44.e5. Web. 4 Oct. 2014.
37. "POLYZENE®-F (PZF) SURFACE TECHNOLOGY." *CeleNova Biosciences*. CeleNova Biosciences, n.d. Web. 11 Oct. 2014.

38. CeleNova Biosciences. *First-In-Man Study of the COBRA PzF™ Coronary Stent Shows Promising Results Highlighted by Short, 30-Day Dual-Antiplatelet Therapy and Low, 3% TLR Rate*. CeleNova Biosciences. CeleNova Biosciences, 16 Sept. 2014. Web. 9 Oct. 2014.
39. Rodkey, Kathleen. "Legacy Heart Center and The Heart Hospital Baylor Plano Dual Antiplatelet Therapy Clinical Research Study Coordinator Questionnaire." Personal interview. 19 Oct. 2014.
40. McCracken, Julie. "Legacy Heart Center and The Heart Hospital Baylor Plano Dual Antiplatelet Therapy Clinical Research Study Coordinator Questionnaire." Personal interview. 23 Oct. 2014.