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The history of stent development with regard to the use of coating materials and eluting drugs, with special emphasis on mechanism of release and duration of action of drugs used in drug-eluting stents, was summarized. The general safety profile of currently used adjunctive pharmacotherapy to coronary stenting, with special emphasis on the clinical trials providing the scientific assessments of the effectiveness and safety of the regimens, was reviewed. The enrollment process and the critical role of the Clinical Research Coordinator (CRC) in the process of the implementation of a clinical study with a new drug-eluting stent were described.

REVIEW OF THE HISTORY OF CORONARY STENTING,

ROLE AND EVOLUTION OF ADJUNCTIVE PHARMACOTHERAPY AND

EXPERIENCE WITH AN ONGOING DRUG-ELUTING STENT TRIAL

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REVIEW OF THE HISTORY OF CORONARY STENTING, ROLE AND EVOLUTION OF ADJUNCTIVE PHARMACOTHERAPY AND EXPERIENCE WITH AN ONGOING DRUG-ELUTING STENT TRIAL

INTERNSHIP PRACTICUM REPORT

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By

Mi Jung Kang, B.S.

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TABLE OF CONTENTS

LIST OF TABLES

Page

LIST OF FIGURES

Page

CHAPTER I

INTRODUCTION

My internship took place at the Baylor Research Institute (BRI) Clinical Trials Office for six months. The BRI Clinical Trials Office provides investigators at Baylor Health Care System with research support services from study coordination, budget development and financial management to Institutional Review Board (IRB) study submission. The office also benefits clinical investigators and research coordinators through a comprehensive education program on research compliance and procedures, thereby improving their knowledge on the issues related to the conduct of clinical trials. Interning at the BRI Clinical Trials Office has provided me with a great chance to take a closer look into the field of clinical research. Under the supervision of the Director of the Clinical Trials Office, I could oversee different aspects of clinical research management.

The main goal of this internship was to gain a better understanding of the clinical trial of a coronary stent system as well as the clinical research coordinator's (CRC) role in the process of the implementation of this clinical trial. The particular clinical trial that I was involved in was a prospective, multi-center, randomized, single-blind, controlled clinical trial of a drug-eluting coronary stent system versus a Food and Drug Administration (FDA) approved drug-eluting coronary stent system in *de novo* native coronary artery lesions. This ongoing study was designed to assess the equivalence in safety and efficacy of the experimental drug-eluting stent system as compared to the

FDA-approved drug-eluting stent system. There have been significant efforts to improve the treatment outcomes of coronary artery disease (CAD). With the development of the stent and adjunctive therapy, the coronary stenting is now the most commonly used technique in the treatment of CAD. Currently, two types of drug-eluting stents (DES) are predominantly used with the appropriate adjunctive pharmacotherapy. Nevertheless, the search for safer and better stents and treatments remains ongoing as long as the desire for better outcomes exists. Many clinical trials are still underway to find more effective stent designs and medication therapies, and I had the opportunity to participate in one of these new clinical trials.

A new clinical trial is designed based on what researchers learned from laboratory studies and previous clinical studies. Background information from the previous studies or review articles helps to understand a new idea to be tested through a clinical trial. While observing and assisting a clinical research coordinator to manage this clinical trial of a new drug-eluting stent, I reviewed the history of stent development with regard to the use of coating materials and drug coatings and identified changes in outcomes related to the modification in the stent design. A review of the general safety profile of currently used adjunctive pharmacotherapy to coronary stenting was also conducted. This review of the stent evolution and adjunctive pharmacotherapy has enhanced my understanding of how the results of related studies were incorporated into the protocol design of this ongoing clinical trial. Involvement in the ongoing study provided me valuable practical knowledge of the implementation of a clinical study with a new drug-eluting stent.

CHAPTER II

HISTORY OF CORONARY STENT DEVELOPMENT AND CLINICAL TRIAL EXPERIENCE

Background

The gradual deposition of lipid and cholesterol plaque on the inner layer of the arteries leads to the narrowing and hardening of the arteries, or atherosclerosis. Coronary artery disease (CAD) is due to atherosclerosis of the coronary arteries, the blood vessels that supply oxygen and other nutrients to the heart muscle. From mild chest pains (angina pectoris) to the most serious heart attack (myocardial infarction, MI), approximately 12 million Americans suffer from CAD.[1] The past decades have seen the evolution of an exciting technology that has changed the treatment of CAD.

Percutaneous transluminal coronary angioplasty (PTCA) using the balloon catheter was first performed by Andreas Gruenzig in 1977 to compress the plaque deposit inside the arteries and increase the diameter of the arteries.[2] The introduction of PTCA represented the first revolution in interventional cardiology [3] and millions of people have been successfully treated by PTCA.[4] However, the balloon-related restenosis was an important problem (Figure 1). The weakened artery wall sometimes collapsed after balloon dilation (lesion elastic recoil) requiring emergency coronary artery bypass graft (CABG) surgery.[5] Approximately 30-50% of cases began to close up again due to negative remodeling (a general shrinkage of the entire wall of the vessel at the site of

treatment) and neointimal proliferation (the development of scar tissue in healing response to balloon induced-injury) necessitating repeated revascularization.[6]

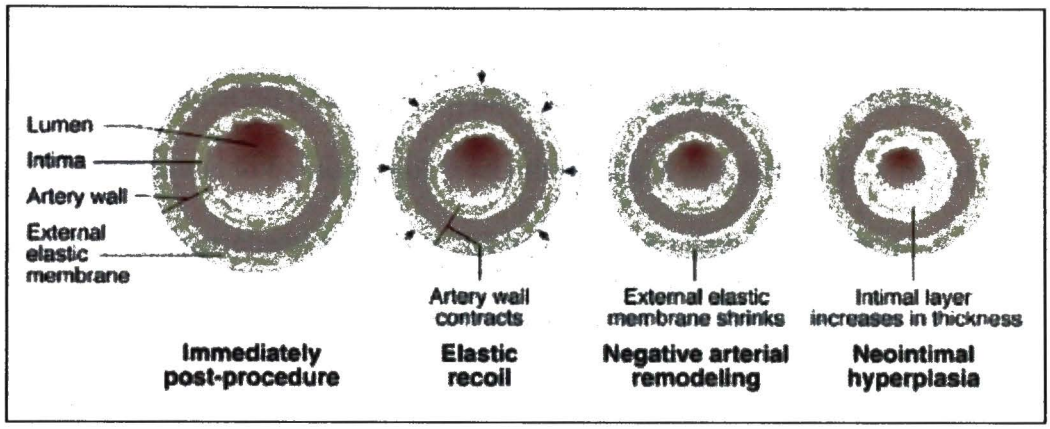

Figure 1. Cross-Section of Coronary Artery.
Original image taken from Cath Lab Digest Volume 11 Issue 4 April 2003

Many efforts had been initiated testing newer techniques to find some new devices that would supplant PTCA in the late 1980s and early 1990s. Directional atherectomy (DCA), rotational atherectomy (rotablator), and excimer laser devices were invented and used directly to remove atherosclerotic plaque at the site of stenosis. However, with higher rates of complication and no better result in the incidence of restenosis compared with balloon angioplasty, these devices were not widely adopted in the percutaneous coronary intervention (PCI).[5] The major step toward overcoming limitations of PTCA was started with the development of the coronary artery stents. Coronary stents, tiny tubes made of a mesh of metal, were developed to prevent elastic recoil of the vessel and a series of randomized clinical trials demonstrated better acute angiographic results and reduced recurrence rates (restenosis) compared to the use of balloon coronary angioplasty

alone.[7] In a few years, coronary stenting became a routine treatment for coronary artery disease and was widely utilized in interventional cardiology.

However, the clinical benefit of coronary stenting was limited by stent-associated complications such as acute or subacute thrombosis and the late in-stent restenosis.[8] Intensive anticoagulation treatment recommended for the first few weeks after the procedure was found to be associated with other clinical problems consisting of hemorrhagic and peripheral vascular complications.[9] A number of different approaches were tested to find solutions to prevent or reduce these problems. With better understanding of the thrombosis and in-stent restenosis mechanisms, the most promising approach has been through the development of new stent designs in combination with pharmacological therapy.[10] In the past decade there have been significant efforts by device manufactures to prevent these unfavorable outcomes through the development of different stent designs using different carrier stents, different kinds of coatings, and different eluting drugs. The application of the drug-eluting stents (DES) is one of the outcomes of the technological development. Along with the stent evolution, adjunctive drug regimens have been developed concomitantly to provide various standards of drug management during and after coronary stenting.

At the present time, intracoronary stenting is used in more than 90% of patients undergoing PCI (1.2 million annually in the United States) either as a primary or an adjunctive procedure. This is made possible by the conjunction of drug-eluting stents (DES) and concomitant use of antithrombotic regimens consisting of anticoagulants and antiplatelet agents.[11] Research is still ongoing to find the ideal combination of stent,

eluting drug, and adjunctive medication. Understanding the history of coronary artery stents and adjunctive pharmacotherapy is necessary to optimize the design and enhance interpretation of current and future clinical trial.

Specific Aim

Given the growing body of evidence regarding the benefits of the stent design and adjunctive pharmacotherapy on the stent-associated complications, it is important to review the history of coronary artery stents and adjunctive pharmacotherapy to understand the design of current and future clinical trial. The objectives of this report are (1) to review the history of stent development with regard to the use of coating materials and drugs, with special emphasis on mechanism of release and duration of action of drugs used in drug-eluting stents; (2) to identify changes in outcomes related to the modification in the stent design, with special emphasis on the stent-associated complications; (3) to review the general safety profile of currently used adjunctive pharmacotherapy to coronary stenting, with special emphasis on the clinical trials providing the scientific assessments of the effectiveness and safety of the regimens; and (4) to gain practical knowledge on implementation of a clinical study with a new drug-eluting stent.

Significance

The medical community is divided when it comes to selecting an appropriate combination of coronary stent and adjunctive pharmacotherapy. This report provides a comprehensive synthesis of the literature on the development of coronary stent design and adjunctive pharmacotherapy with emphasis on outcome parameter. Personal involvement in a real-world clinical trial comparing two drug-eluting stents enhances the knowledge about the implementation of a new clinical trial of an unapproved drug-eluting stent.

Materials and Methods

Data sources: Peer-reviewed articles and publications relevant to this project, documenting the evolution of technological variations of the stent design and their relationship to the stent-associated complications and the adjunctive pharmacotherapy were retrieved and studied through comprehensive searches of the MEDLINE database (PubMed), US Food and Drug Administration web site, and the Cochrane Controlled Trials Registry. I also conducted a manual search of the relevant journals that cover the fields of coronary artery disease (CAD) and clinical trials. The keywords used were the combination of "bare metal stent (BMS)", "drug-eluting stent (DES)", "acute thrombosis", "sub-acute thrombosis", "late in-stent restenosis", "anti-proliferative", and "adjunctive pharmacotherapy".

Data extraction: A review and evaluation of the published articles lead to data extraction and summarization of the following; stent coating materials and drugs used for coating of the stent, stent-associated complications (acute or sub-acute thrombosis and late restenosis), and adjunctive pharmacotherapy (aspirin, ticlopidine, clopidogrel, heparin, and glycoprotein IIb/IIIa inhibitors).

I was involved in the implementation of a new clinical trial comparing the safety and effectiveness of a drug-eluting coronary stent system versus an FDA-approved drug-eluting coronary stent system in *de novo* native coronary artery lesions at Baylor Heart and Vascular Hospital (BHVH) and Baylor University Medical Center (BUMC).

Protocol synopsis: This clinical trial was a prospective, multi-center, randomized, two-arm, single-blind trial enrolling a total of 1,548 patients (up to 70 active study sites in the

United States and up to 10 active study sites in Canada) with symptomatic ischemic heart disease attributable to the stenosis of native coronary arteries. This trial was designed to assess the equivalence in safety and efficacy of a new drug-eluting coronary stent system versus the FDA-approved drug-eluting coronary stent system in *de novo* native coronary artery lesions. Patients were randomized to receive either the study stent or the control stent in a 1:1 ratio and were blinded to their assignment throughout the 12 months follow-up period. The primary endpoint was target vessel failure (TVF) rate at 9 months post-procedure. TVF is defined as the composite of cardiac death, recurrent myocardial infarction, or clinically-driven target vessel revascularization (TVR) rate of the treated vessel. Follow-up clinic visits were scheduled at 30 days and at 8 and 9 months, and follow-up assessment (phone contact) at 6, 12 months, 2, 3, 4, 5 years.

A list of commonly used Acronyms and a Glossary with definitions related to the area of cardiac intervention are attached in Appendix A and B.

Results

Stent evolution

Bare Metal Stents (BMS)

Intracoronary bare metal stents were developed to provide metal scaffolding for vessel closure after PTCA.[12]

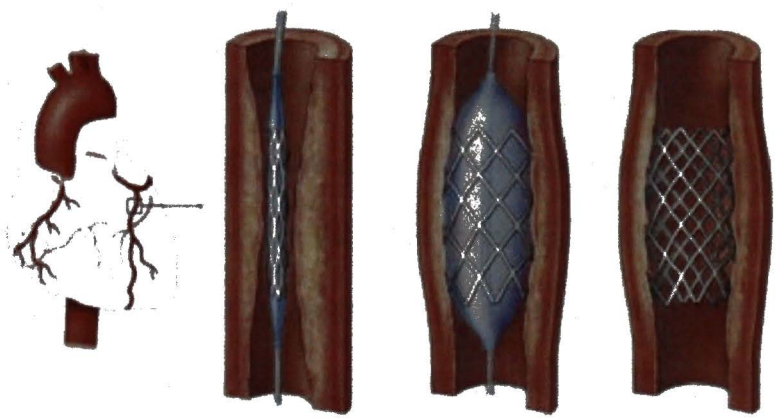

Figure 2. Coronary stenting procedure
Original image taken from www.nucleusinc.com

The first human implant using self-expanding tubular mesh stent (Wallstent®, Boston Scientific) was performed and the successful result in preventing abrupt vessel closure was reported by Sigwart et al. in 1987.[13] About a decade ago, the first stent was approved by the Food and Drug Administration (FDA) in 1993. This balloon expandable Gianturco-Roubin® stent (Cook) was successful in reducing the incidence of emergent CABG surgery associated with PTCA.[14] The second stent was the Palmaz-Schatz® stent

(Cordis, a Johnson & Johnson Company) approved in 1994. After two landmark studies (BENESTENT and STRESS study) confirmed the efficacy of the Palmaz-Schatz stent in the reduction of restenosis rates,[15,16] the Palmaz-Schatz stent served as the standard stent in the treatment of CAD. The Belgium Netherlands Stent Trial (BENESTENT study) showed restenosis rates of 22% for stents and 32% for PTCA.[15] In the Stent Restenosis Trial (STRESS study), the angiographic restenosis rate was 31.6% for stents and 42.1% for PTCA.[16]

Despite the fact that stent placement resulted in a larger lumen and prevented the elastic recoil of the vessel,[17] stent-associated complications emerged as another concern. The stent-associated complications have been demonstrated by Hashiguchi et al. as (1) acute vessel occlusion/closure due to thrombus formation occurring from immediately following to within 24 hours of the procedure; (2) sub-acute thrombosis occurring between 1 and 30 days after stenting; and (3) late coronary restenosis caused by intimal hyperplasia or proliferation of smooth muscle cells secondary to growth factors released from platelets, occurring between 3 weeks and 6 months after stent placement.[8]

In order to reduce the incidence of thrombosis and in-stent restenosis, a pharmacological approach with systemic antithrombotic treatment was employed. However, this strategy was ineffective in preventing stent thrombosis and resulted in prolonged hospital stays to achieve therapeutic anticoagulation and in excessive bleeding complications.[10] Based on the ideas that the inherent thrombogenicity of stents might be better overcome by changing stent designs and coating materials,[18] various designs and materials were incorporated into the construction of stents. The efforts on the design

adjustments resulted in greater durability and flexibility of stents. Stents can be classified according to the following characteristics: nature of expansion – self-expanding or balloon-expandable; stent design – coil, tubular mesh, and slotted tube; and stent material – 316L stainless steel, cobalt alloy, tantalum, or platinum.[11,19] (Table 1)

Table 1. Classification of currently marketed stents not including DES

	Stent name	Nature of expansion	Stent design	Stent material
1	Wallstent®	Self expanding	Tubular mesh	Platinum + Cobalt alloy
2	Driver®	Balloon expandable	Tubular mesh	Cobalt alloy
3	Gianturco-Roubin II®	Balloon expandable	Coil	316 L stainless steel
4	Wiktor®	Balloon expandable	Coil	Tantalum
5	beStent® / beStent2®	Balloon expandable	Slotted tube	316 L stainless steel
6	BiodivYsio® OV/SV/AS	Balloon expandable	Slotted tube	316 L stainless steel
7	Bx VELOCITY®	Balloon expandable	Slotted tube	316 L stainless steel
8	Express®	Balloon expandable	Slotted tube	316 L stainless steel
9	JOSTENT Flex®	Balloon expandable	Slotted tube	316 L stainless steel
10	Multi-Link PENTA® / RX® / Vision®	Balloon expandable	Slotted tube	316 L stainless steel
11	NIR® / NIRFLEX®	Balloon expandable	Slotted tube	316 L stainless steel
12	Palmaz-Schatz® 153/ 154 / Crown	Balloon expandable	Slotted tube	316 L stainless steel

Butany J at el. Coronary artery stents: identification and evaluation. J Clin Pathol. 2005 Aug; 58(8):795-804.[19]

Coated Stents

The efforts to decrease the incidence of thrombosis and in-stent restenosis after stent implantation were more focused on investigating coating materials. The first attempt was done by using inorganic compounds mainly to provide a biologically inert barrier between the stent surface and the circulating blood. Numerous coating materials such as gold, carbon, iridium-oxide, and silicon-carbide were tested and commercialized, but these coatings did not show significant influence on the thrombotic events.[10] Based on promising results from subsequent studies using synthetic polymers and human polymers,[20,21] the phosphorylcholine-coated BiodivYsio® stent (Biocompatibles, an Abbott Laboratories company) was approved by the FDA and clinically used. Phosphorylcholine is the main component of the cell membrane and when coated on the stent, has the possibility of behaving as intact tissue elements. The most extensively tested technique was the coating with immobilized drugs (heparin, paclitaxel, and abciximab) that were known to interrupt the biological processes that caused restenosis. Heparin was most widely used as an immobilized drug on the stent surface. Different chemical binding techniques were used to keep the activity of the heparin intact.[22]

The heparin-coated Palmaz-Schatz stent (Cordis, a Johnson & Johnson Company) was first clinically tried in the BENESTENT II pilot trial. In 202 patients treated with heparin-coated stents, stent thrombosis did not occur and the overall restenosis and reintervention rates were 13% and 8.9%, respectively.[23] In the subsequent BENESTENT II randomized trial and PAMI (Primary stenting in Acute Myocardial Infarction) pilot/ randomized trials, less than 1 % of sub-acute thrombosis was demonstrated at 6

months.[24,25] Clinically available heparin-coated stents are Palmaz-Schatz® Carmeda-coated stent (Cordis, a Johnson & Johnson Company), BX Velocity® Hepamed-coated stent (Cordis, a Johnson & Johnson Company), Wiktor-GX® Hepamed-coated stent (Medtronic), and JOSTENT Flex® Corline-coated stent (JOMED, an Abbott Laboratories company).[18,19,22]

However, with respect to an antiproliferative effect of heparin, data of preclinical and clinical studies suggested no reduction of neointimal hyperplasia in stented segments compared to uncoated stents.[26] Neointimal hyperplasia, the cause of in-stent restenosis, is a natural healing response to arterial injury and involves the migration of vascular smooth muscle cells from the media to the intima, their subsequent proliferation, and later accumulation of extracellular matrix.[27] The implanted stent acts as a foreign body and can cause a long-lasting injury to the vessel wall, leading to this prolonged healing response.[26] In an effort to overcome the double problem of a healing response and a foreign body that was believed to cause 10 % to 30 % of in-stent restenosis rate,[28] the concept of prolonged local drug administration to the site of injured vessel using drug eluting stents has explored.

Drug-Eluting Stents (DES)

Several preclinical trials using the drug-eluting stents that consist of polymer mixtures with incorporated antithrombotic and platelet-inhibiting drugs such as hirudin, prostacyclin analogue iloprost, and glycoprotein IIb/IIIa antibody, demonstrated significant improvement in patency rates, but no impact on neointimal thickness.[29,30] Inspired by the mechanisms of neointimal hyperplasia, research has focused on drugs that have antiproliferative, antimigratory, and antiinflammatory properties. While a variety of drug classes such as anti-neoplastics, immunosupressives, migration inhibitors, and enhanced healing factors have been considered for the drug-eluting stent, sirolimus (immunosuppressive) and paclitaxel (anti-neoplastic) were found to have dramatic inhibitory effects on neointimal proliferation through many laboratory and animal tests.[31,32]

SIROLIMUS - The first drug-eluting stent approved by the FDA in 2003 was the sirolimus-eluting balloon-expandable CYPHER® stent (Cordis, a Johnson & Johnson company). Sirolimus, formerly known as rapamycin (Rapamune®), is a macrolide antibiotic derived from a fungus (Figure 3). With immunosuppressive properties, sirolimus was originally developed by Wyeth-Ayerst Laborotories and approved by the FDA for the use in renal transplant rejection in 1999. Sirolimus binds to an intracellular receptor protein and elevates p27 levels. This action finally inhibits the cell division cycle and thus cellular proliferation by arresting the G_1 phase of cell replication just prior to the

S phase.[33] This anti-proliferative property was also found when applied on to stents and led to the exciting results of inhibiting in-stent restenosis.

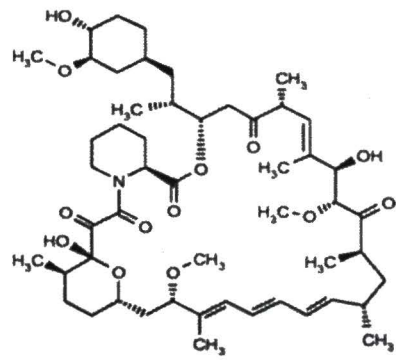

Figure 3. The chemical structure of Sirolimus [35]

Sirolimus was blended in a mixture of polymers (PEVA/PBMA) and a layer of drug-polymer matrix was applied to the surface of the Bx Velocity stent platform. An outer layer of drug-free polymer was applied on top of the drug-polymer matrix as a diffusion barrier to prolong the release of the drug. Initial drug concentration of 1.4 microgram per square millimeter, a maximum amount of 314 microgram, was loaded onto the CYPHER stent designed to release 53% of the drug within the first ten days and up to 80% of the drug within 30 days of implantation (Figure 5).[34] The pharmacokinetics of sirolimus as delivered by the CYPHER stent have been determined in patients with coronary artery disease after implantation of CYPHER stent. The peak blood concentration of less than 1 nanogram per milliliter (mean 0.57 ng/ml) is negligible compared to the mean blood level of 9~17 ng/ml following oral rapamycin dosing (2~5 mg/day). The peak concentration occurs at mean 3.9 hours.[35]

To date, three supportive and pivotal clinical studies have demonstrated the sirolimus-eluting coronary stent to be associated with less in-stent restenosis than uncoated stents and these trials were the basis for the FDA approval of the sirolimus-eluting CYPHER stent.[36] The FIM (First In Man) study demonstrated a sustained suppression of neointimal proliferation by sirolimus-eluting stent 1 year after implantation (Figure 4).[37]

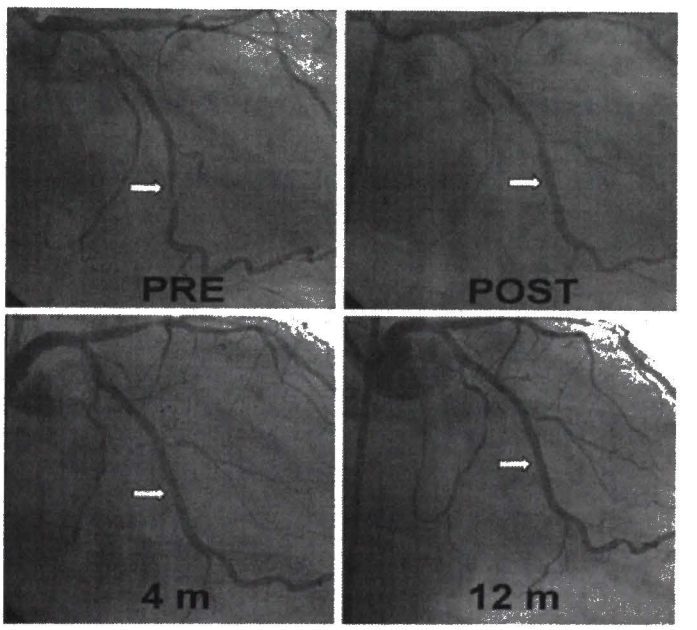

Figure 4. Sustained suppression of neointimal proliferation by sirolimus-eluting stent : one-year follow-up
Angiogram shows a lesion in the mid portion of the left circumflex marginal branch (white arrow), which was treated with the implantation of a sirolimus-eluting stent (top right). Lumen dimensions remained unchanged at 4- and 12- month follow-up (bottom).[37]
(Sousa JE at el. Circulation. 2001 Oct 23; 104(17):2007-11)

The RAVEL (RAndomized study with the sirolimus-eluting Bx VEocity balloon-expandable stent in the treatment of patients with de novo native coronary artery Lesions) study demonstrated that the use of the sirolimus stent decreases the need for repeat revascularization for up to two years with exciting results of 0% in-stent restenosis, 0% target vessel revascularization, and 94% survival rate without major cardiac event.[38] The SIRIUS (SIRolImUS-eluting Bx Velocity balloon-expandable stent trial) study is the largest trial that determined the safety and effectiveness of the sirolimus-eluting stent. Target vessel failure was significantly lowered at 8.6%, compared to 21% of control. MACE (Major Adverse Cardiac Event: Death, MI, and Revascularization) free rate was 91.1%, compared to 78.6% for the control (Table 2).[39,40]

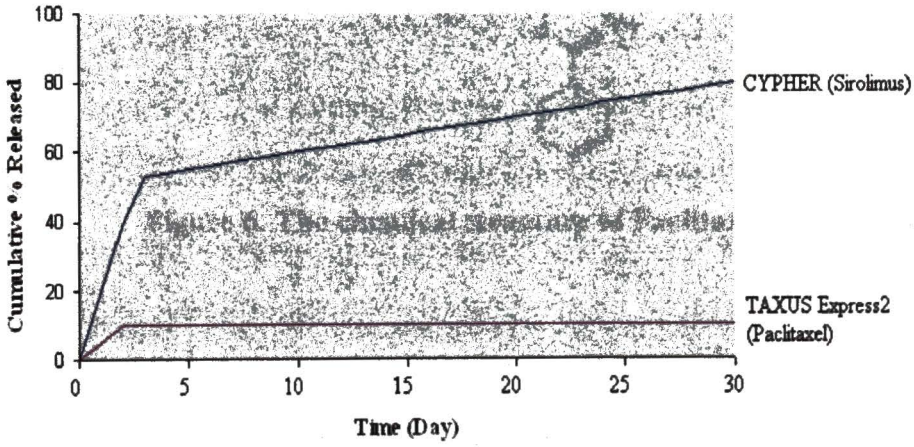

Figure 5. Comparison of cumulative % release of drug over time for Cypher (Sirolimus) and TAXUS Express2 (Paclitaxel)
(Data extracted from Vishnevetsky D et al. Am J Health Syst Pharm. 2004 Mar 1; 61(5):449-56.[34] and Waugh J et al. Am J Cardiovasc Drugs. 2004; 4(4):257-68.[41])

PACLITAXEL - The second drug-eluting stent, the paclitaxel-eluting balloon-expandable TAXUS Express^2 Stent (Boston Scientific), was FDA approved in 2004. Paclitaxel, a member of class of Taxanes (Taxol®), was isolated from the yew tree and used as cancer chemotherapeutic agent for breast and ovarian cancer (Figure 6). The mechanism of action of this anti-neoplastic drug is through inhibition of microtubule disassembly in dividing cells. Investigators have found that this inhibition of the mitotic process prevents vascular smooth muscle cell proliferation and migration at the site of the injury.[33]

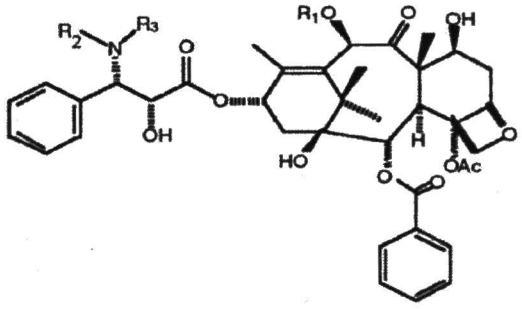

Figure 6. The chemical structure of Paclitaxel [42]

The TAXUS Express^2 stent comprises a stainless steel Express^2 stent coated with a SIBS polymer matrix containing an initial paclitaxel concentration of 1.0 microgram per square millimeter (a maximum amount of 209 microgram). Paclitaxel is released in a controlled manner with the higher release rate in the first 2 days slowing over the next 10 days. Approximately 90% remains sequestered within polymer formulation without further release after 30 days of implantation (Figure 5).[41] The amount of paclitaxel loaded onto the stent is at a minimum 1000 times lower than that used in oncological regimen

(175 mg/m^2) and systemic levels of paclitaxel have not been detected post-stent placement in clinical trials.[42]

The efficacy of the paclitaxel-eluting stent was compared with that of a bare-metal stent (BMS) in four randomized, double-blind, multicenter trials in patients with de novo coronary artery lesions. The TAXUS (pacliTAXel-elUting Stent trail) I and II trials used the NIR stent, while the pivotal TAXUS IV trial used the Express^2 stent. With no meaningful result, the TAXUS III trial was not considered. The TAXUS I trial showed no restenosis compared to 10% in the control group.[43] The well designed TAXUS II and IV trials indicated superiority for the paclitaxel-eluting stent over the BMS. The in-stent neointimal volume in the DES was only one-third of that in the BMS. The incidence of cumulative major adverse cardiac events was also significantly lower in DES than BMS (Table 2).[44-46]

The major studies[38-40, 43-46] performed with the stents eluting sirolimus or paclitaxel have shown reductions in restenosis, target vessel revascularization, and major adverse cardiac events. Therefore, these two FDA-approved DESs are currently taking up about 70 % of the stent market.[47] In addition to these stents, many other drug eluting stents are currently in development. Rapamycin derivatives such as everolimus and ABT578 have been employed in eluting stent designs and are being tested in clinical trials.[33]

Table 2. Summary of Major Clinical Trials on the Safety and Efficacy of Drug-eluting Stents

Study	Type of Drug	Follow-up (Mo)	Sample size (DES/BMS)	Late loss (mm) Restenosis (DES/BMS)	Thrombosis (DES/BMS)	Event free Survival (DES/BMS)	MACE (DES/BMS)			
							Death	MI	TVR	CABG
RAVEL (2002)	Sirolimus	12	120/118	-0.01 / 0.08 mm 0.0 / 26.6%	0.0 / 0.0%	94.1 / 70.9%	2/2	4/5	0/27	0/1
SIRIUS (2003)	Sirolimus	9	533/525	0.24 / 0.81 mm 3.2 / 35.4%	0.4 / 0.8%	91.1 / 78.6%	5/3	15/17	20/83	3/8
SIRIUS (2004)	Sirolimus	12	533/525	0.24 / 0.81 mm 3.2 / 35.4%	0.4 / 0.8%	91.7 / 77.4%	7/4	16/18	26/105	5/9
TAXUS I (2003)	Paclitaxel	12	30/30	0.36 / 0.71 mm 0.0 / 10.0%	0.0 / 0.0%	97.0 / 90.0%	0/0	0/0	0/1	1/3
TAXUS II (2003)	Paclitaxel	12	129/132	0.31 / 0.79 mm 2.3 / 17.9 %	1.1% / NA	89.2 / 78.7%	0/2	3/7	13/21	4/1
TAXUS IV (2004)	Paclitaxel	9	662/652	0.39 / 0.92 mm 7.9 / 26.6%	0.6 / 0.8%	91.5 / 84.9%	9/7	23/24	24/59	7/22
TAXUS IV (2004)	Paclitaxel	12	639/633	0.39 / 0.92 mm 7.9 / 26.6%	0.6 / 0.8%	89.2 / 80.0%	9/8	25/30	35/88	11/25

RAVEL (RAndomized study with the sirolimus-eluting Bx VEocity balloon-expandable stent in the treatment of patients with de novo native coronary artery Lesions) study,[38]
SIRIUS (SIRolImUS-eluting Bx Velocity balloon-expandable stent trial) studies,[39,40]
TAXUS (pacliTAXel-elUting Stent trail) I II III IV studies.[43-46]
Mo=Month; DES=Drug-Eluting Stent; BMS=Bare Metal Stent; MACE=Major Adverse Cardiac Event;
MI= Myocardial Infarction; TVR=Target Vessel Revascularization; CABG=Coronary Artery Bypass Graft

Adjunctive Pharmacotherapy

Since the adoption of stent implantation, adjunctive pharmacotherapy has been considerably modified and has proven to improve clinical outcomes making the PCI with stenting more effective and safe. Pharmacological classes of drugs that have the potential to be used adjunctively during coronary stenting are first reviewed. Subsequently the evolution of the use of these compounds in connection with development of safer stenting procedures is highlighted. Coronary stenting usually causes plaque disruption and endothelium exposure stimulating coagulation processes and platelet aggregation. Thus, the adjunctive pharmacotherapy to coronary stenting mainly consists of antithrombotic agents (anticoagulants and antiplatelet agents).

Anticoagulants

Anticoagulants are used to prevent the formation of clots or extension of existing clots within the blood by inhibiting the thrombin activity directly or indirectly. Thrombin plays a central role in the thrombotic process acting to convert circulating fibrinogen to fibrin and to trigger a shape change in platelets stimulating aggregation and granule release. Warfarin (Coumadin®), unfractionated heparin (UFH), low molecular weight heparin (LMWH, enoxaparin), and direct thrombin inhibitor (DTI, bivalirudin) are the major agents. Warfarin (Coumadin®) is the oral anticoagulant and antagonizes the effects of vitamin K which is necessary for the synthesis of many coagulant factors (II, VII, IX, and X). UFH and LMWH are the intravenously administered anticoagulants and work by

activating antithrombin, which blocks thrombin (II) from clotting blood. Bivalirudin is a specific and reversible direct thrombin (II) inhibitor and is administered intravenously (Figure 7).[47]

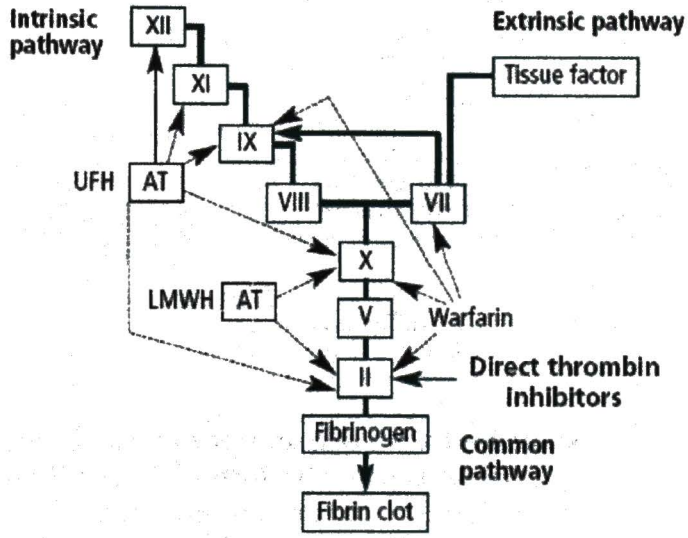

Figure 7. Schematic diagram of the coagulation cascade showing the effects of anticoagulants. (Nutescu EA et al. Cleveland Clin J Med. 2005 Apr; Vol 72 • Supp 1) [48]
AT = antithrombin; UFH = unfractionated heparin;
LMWH = low-molecular-weight heparin;
Roman numerals represent clotting factors (II=Thrombin)

Antiplatelet agents

Antiplatelet agents are used to prevent the formation of a platelet-rich thrombus at the site of a disrupted atherosclerotic plaque, targeting one or more of the pathways that mediate platelet aggregation (Figure 8).

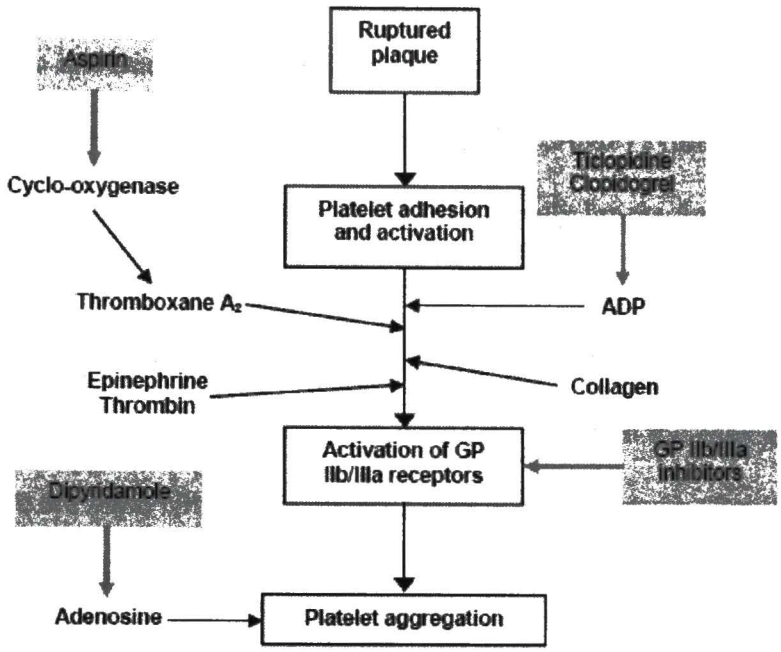

Figure 8. Flow diagram showing platelet adhesion, activation, and aggregation and the site of antiplatelet drugs action.
(The National Institute for Clinical Excellence (NICE), 2004) [49]
ADP=Adenosine diphosphate;
GP IIb/IIIa inhibitors=Glycoprotein IIb/IIIa inhibitors

Aspirin (acetylsalicylic acid), administered orally, inactivates the enzyme cyclo-oxygenase, which in turn blocks the formation of thromboxane A_2. The inhibition of thromboxane A_2 synthesis gives rise to the antiplatelet effect of aspirin. On the basis of studies that demonstrated lower adverse event rates in patients who received pretreatment aspirin than in those who did not, aspirin has been standard medication for the PCI. The oral thienopyridines, ticlopidine (Ticlid®, Roche Pharmaceuticals) and clopidogrel (Plavix®, Bristrol-Myers Products) selectively inhibit the binding of adenosine diphosphate (ADP) to its platelet receptor and prevent platelet aggregation. Dipyridamole

inhibits the enzyme adenosine deaminase which normally breaks down adenosine. This inhibition leads to increased levels of adenosine. Adenosine activates the enzyme adenylate cyclase which leads to increased cyclic AMP (cAMP) synthesis. Dipyridamole also inhibits the enzyme phosphodiesterase which normally breaks down cAMP. cAMP impairs platelet aggregation. The glycoprotein (GP) IIb/IIIa inhibitors are involved in the final common pathway to platelet aggregation and coronary thrombus formation. After platelet activation, GP IIb/IIIa becomes a receptor for fibrinogen increasing thrombus formation. There are three GP IIb/IIIa receptor inhibitors: abciximab (ReoPro®), tirofiban (Agrastat®), and eptifibatide (Integrilin®).[50]

Development of adjunctive pharmacotherapy

The first human clinical trial using the self-expanding stainless-steel mesh stent showed favorable results in reducing sudden closure of PTCA treated arteries and preventing restenosis,[13] but the observation of thrombotic occlusion and acute thrombosis led investigators to design intensive antithrombotic regimens. The BENESTENT and STRESS studies, the pivotal studies for the first FDA approved Palmaz-Schatz stent, were actually designed with full doses of heparin, dextran, and warfarin, along with aspirin and dipyridamole in an attempt to prevent stent thrombosis and restenosis. Although these studies showed a lower rate of stent thrombosis, the regimen resulted in the necessity for prolonged hospital stays due to excessive bleeding.[15,16]

Several different approaches were tested to avoid bleeding complications as well as preventing stent thrombosis. The development of the heparin-coated stents aimed at

preventing stent thrombosis allowed for a lower and safer antithrombotic drug regimen, without oral anticoagulation (Table 3).[23]

Table 3. Comparison of clinical outcome of BENESTENT study and BENESTENT II study [15,23]

	BENESTENT	BENESTENT II
Stent	Bare Metal Stent	Heparin-Coated Stent
Adjunctive Medication Regimen	• Aspirin and dipyridamole began the day before the procedure and continued for 6 months. • Heparin and dextran administered during procedure. • Heparin and coumadin began after procedure, heparin decreased progressively for 36 hours and coumadin continued for 3 months.	• Aspirin and diltiazem began the day before the procedure, aspirin continued for 6 months and diltiazem continued until discharge. • Heparin administered during procedure. • Heparin and coumadin replaced by ticlopidine and continued for 1 month.
Stent Thrombosis	3.5 %	0 %
Event free rate	80 %	86 %
Bleeding Complication	13.5 %	0 %
Hospital Stay	8.5 days	3.1 days

Moreover, with the finding that rather than coagulation activation, the platelet activation is the principal factor in stent thrombosis, several randomized trials (ISAR, FANTASTIC, STARS, and MATTIS) were conducted and showed that optimal stenting combined with aspirin and ticlopidine, as compared with aspirin and oral anticoagulant therapy, was associated with a lower incidence of cardiac events which can be attributed

to a reduction of thrombotic occlusion of the stented vessel (Figure 9).[51-54] Since then, dual antiplatelet therapy with aspirin plus the ADP receptor antagonist ticlopidine instead of oral anticoagulant became standard care after coronary stenting. For the patients with diabetes, the GP IIb/IIIa inhibitors were used on the basis of the Evaluation of IIb/IIIa Platelet Inhibitor for STENTing (EPSTENT) trial that showed significant reduction of MACE rates of the combined treatment with stenting and abciximab in the diabetic patients.[55]

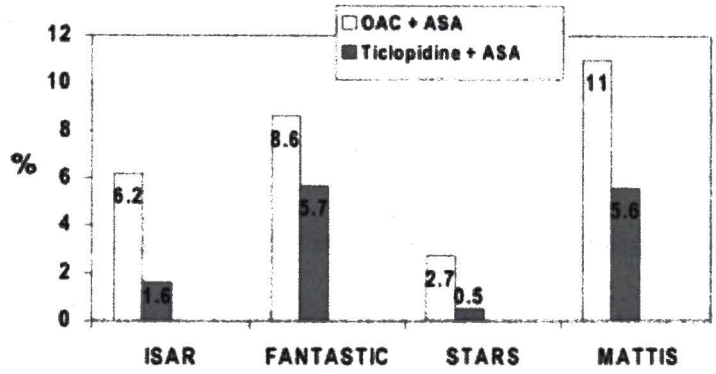

Figure 9. Incidence rates for MACE (death, myocardial infarction, revascularization) in ISAR, FANTASTIC, STARS, and MATTIS trials. OAC=Oral anticoagulant; ASA=Acetylsalicylic acid (aspirin) [51-54]

However, ticlopidine was found to be associated with up to a 2.4% rate of neutropenia, thrombotic thrombocytopenia, and aplastic anemia. These issues have led many investigators to consider the introduction of clopidogrel as an alternative to ticlopidine. The safety of clopidogrel (plus aspirin), a drug with the same mechanism of action, but a more rapid onset of action was proven to be superior to that of ticlopidine (plus aspirin) in the CLASSIC study. Although there were several other studies which

assessed optimal initiation and duration of clopidogrel, a four weeks therapy with clopidogrel plus aspirin, including the 300-mg loading dose of clopidogrel, has been presently established as the standard antithrombotic regimen during coronary stenting.[56]

The development of the drug-eluting stents that resulted in dramatic reduction of the in-stent neointimal proliferation has not brought significant changes in the profile of the adjunctive pharmacotherapy, but a concern that late stent thrombosis may develop in patients who are treated with drug-eluting stents has led most recent trials to extend clopidogrel treatment to 3 to 6 months after PCI, in addition to aspirin therapy. Dual antiplatelet therapy of clopidogrel and aspirin continuing 2 and 3 months has been tested with the sirolimus-eluting stents, and duration of 6-month therapy with paclitaxel-eluting stents.[38-40, 43-46]

In the efforts to maximize the effect of the adjunctive pharmacotherapy to coronary stenting, the regimen has been modified a lot along with the stent evolution. The currently used regimen for coronary stenting consists of the following: aspirin administration (80 to 325 mg) is mandatory in all non-allergic patients at least 2 hours before PCI and should be continued indefinitely. Clopidogrel, 300mg loading dose followed by 75mg daily given orally, is recommended as an alternative to ticlopidine. During PCI, a bolus of UFH in doses of 60-100 IU/kg is administered to maintain an activated clotting time (ACT) of 300 seconds. LMWH or DTI is recommended as an alternative to heparin. A Glycoprotein (GP) IIb/IIIa receptor inhibitor can be used as an adjunct to heparin for the high-risk patients with positive troponins, diabetes, and thrombotic lesions. After BMS implantation, clopidogrel is recommended to continue for

2 weeks to 3 months, and a minimum of 3 months and more than 6 months is recommended for after DES.[47, 50]

Table 4. Summary of stent evolution and adjunctive pharmacotherapy

Approach	Stent name / Coating / Antithrombotic regimen	Effect	Problem	Strategy
Bare Metal Stent (BMS)	• Gianturco-Roubin stent • Palmaz-Schatz stent	Reduction of restenosis rate by 50% • reduction of lesion elastic recoil • inhibit negative remodeling	Stent-associated complication • acute vessel occlusion/closure (within 24 hours of stenting) • subacute thrombosis (between 1 and 30 days) • late in-stent restenosis (between 3 weeks and 6 months)	▸ employ adjunctive pharmacotherapy ▸ change stent design and coating materials
Intensive Antithrombotic Regimen	Full doses of • heparin • dextran • warfarin • aspirin • dipyridamole	A lower rate of stent thrombosis	Prolonged hospital stay due to excessive bleeding and vascular complications	▸ low antithrombotic regiment without oral anticoagulation
Coated stent	Inorganic compounds: • gold • iridium-oxide • carbon • silicon-carbide Synthetic polymer: • phosphorylcholine Immobilized drug: • heparin • paclitaxel • abciximab	Reduction of incidence of subacute stent thrombosis to less than 1%	No reduction of neointimal hyperplasia, a main cause of late in-stent restenosis • 10% to 30% of in-stent restenosis	▸ concept of Prolonged local drug administration to the site of injured vessel using a drug-eluting stent

Table 4. Summary of stent evolution and adjunctive pharmacotherapy (continued)

Approach	Stent name / Coating / Antithrombotic regimen	Effect	Problem	Strategy
Low Antithrombotic Regiment	• aspirin + ticlopidin • aspirin + clopidogrel • glycoprotein (GP) IIb/IIIa inhibitor for high-risk patients	• low incidence of bleeding • low incidence rates for MACE (death, MI, and revascularization)	• no effect on the late in-stent restenosis • side effects	▸ drug-eluting stent ▸ search for optimal initiation, duration, and loading dose
Drug-Eluting Stent (DES)	• CYPHER sirolimus-eluting stent • TAXUS paclitaxel-eluting stent	Dramatic reduction of the in-stent restenosis rate by inhibiting the development of neointimal proliferation • in-stent restenosis rate necessitating additional therapy < 10 % • MACE free survival rate > 90 %	• delayed endothelialisation • late stent thrombosis	▸ longer duration of combined antiplatelet therapy

MACE=Major Adverse Cardiac Event; MI=Myocardial Infarction

Implementation of a new drug-eluting stent clinical trial at Baylor

Because of the proprietary nature of this clinical trial, detailed information regarding study protocol or result can not be disclosed. This report will focus on the regulatory requirements and guidelines governing stent development and on the process and efficiency of subject enrollment.

FDA regulations on Drug-Eluting Stents (DES) [57,58]

Medical devices are classified into 3 classes: class I (General Controls), class II (Special Controls), and class III (Significant risk devices). Device risks and regulatory control increase from class I to class III. Most class I devices are exempt from Premarket Notification 510(k); most class II devices require Premarket Notification 510(k); and all class III devices require Premarket Approval (PMA). (21 CFR part 860) Examples of class I devices include elastic bandages, examination gloves, and hand-held surgical instruments. Examples of class II devices include powered wheelchairs, infusion pumps, and surgical drapes. Examples of Class III devices include replacement heart valves and silicone gel-filled breast implants. Coronary artery stents are significant risk devices that are intended to be implanted in the human body and remain there for a period of 30 days or more. Stents are classified as class III devices and the clinical investigations of stents are conducted under an Investigational Device Exemption (IDE) application in accordance with 21 CFR Part 812. The review of marketing applications is conducted under a Premarket Approval (PMA) application in accordance with 21 CFR Part 814.

Drug-eluting stents are further defined as combination products that combine drug and device components. After combination products were first referenced in the Safe Medical Devices Act (SMDA) of 1990, the guidelines on these products were established through the Intercenter Agreements between the device, drug, and biologic centers and the Requests for Designation (RFD) process. Since the Medical Device User Fee and Modernization Act (MDUFMA) of 2002 established the Office of Combination Products (OCP), the regulatory issues on these products have been more clear and the assignment of the responsible center is determined on the basis of the product's primary mode of action. (21 CFR part 3) The primary mode of action for the drug-eluting stents has been concluded as the device action by the Food and Drug Administration (FDA). The FDA has assigned the Center for Devices and Radiological Health (CDRH) primary regulatory responsibility for drug-eluting stents and the Center for Drug Evaluation and Research (CDER) consulting role for the review of drug safety. Therefore, the safety and efficacy of drug-eluting stents are still reviewed under the same regulation as that for the bare metal stents. The offices that review the IDE and PMA applications for drug-eluting stents include the Office of Device Evaluation (ODE/CDRH), the Office of Science and Technology (OST/CDRH), the Office of New Drugs (OND/CDER), the Office of Pharmaceutical Science (OPS/CDER), and the Office of Clinical Pharmacology and Biopharmaceutics (OCPB/CDER).

To collect safety and effectiveness data required to support a PMA application, the investigator should conduct a human clinical trial under an IDE. FDA has 30 days to review an IDE application and an investigation may not begin until 30days following the

submission. An investigation also requires Institutional Review Board (IRB) approval and must be conducted in accordance with the IDE regulation. To initiate the clinical evaluation of devices, informed consent, labeling for investigational use only, study monitoring, and preliminary evidence of product safety based on the results from both acute and chronic animal studies are also required. (21 CFR part 812)

To market a class III device, the sponsor must receive FDA approval of the PMA application. FDA regulations provide 180 days to review the PMA, but the review time is normally longer. Scientific and regulatory documentation in support of the PMA application usually consists of data from non-clinical laboratory studies and clinical investigations. Non-clinical laboratory studies include information on microbiology, toxicology, immunology, biocompatibility, stress, wear, shelf life, and other laboratory or animal tests. Clinical investigations include study protocols, safety and effectiveness data, adverse reactions and complications, device failures and replacements, subject information, subject complaints, tabulations of data from all individual subjects, results of statistical analyses, and any other information from the clinical investigations. (21 CFR part 814)

Table 5. FDA regulations and applicable standards for Drug-Eluting Stents [57]

Code of Federal Regulations, Title 21	
21 CFR 50	Protection of Human Subjects
21 CFR 54	Financial Disclosure by Clinical Investigators
21 CFR 56	Institutional Review Boards
21 CFR 803	Medical device reporting
21 CFR 812	Investigational Device Exemptions (IDE)
21 CFR 814	Premarket approval (PMA)
21 CFR 820	Design Controls of the Quality System Regulation
International Standards Orgarnization (ISO) Standards	
10993	Biological Evaluation of Medical Devices
25539-1	Cardiovascular Implants – Endovascular Devices • Part 1 – Endovascular Prostheses, Annex D – In vitro Testing and Reporting
American Society for Testing and Materials (ASTM) Standards	
F746	Standard Test Method for Pitting or Crevice Corrosion of Metallic Surgical Implant Materials
F748	Standard Practice for Selecting Generic Biological Test Methods for Materials and Devices
F2004	Standard Test Method for Determination of Transformation Temperature of Nickel-Titanium Alloys by Thermal Analysis
F2052	Standard Test Method for Measurement of Magnetically Induced Displacement Force on Passive Implants in the Magnetic Resonance Environment
F2079	Standard Test Method for Measuring Intrinsic Elastic Recoil of Balloon expandable Stents
F2081	Standard Guide for Characterization and Presentation of the Dimensional Attributes of Vascular Stents
F2082	Standard Test Method for Determination of Transformation Temperature of Nickel-Titanium Shape Memory Alloys by Bend and Free Recovery
F2119	Standard Test Method for Evaluation of MR Image Artifacts from Passive Implants
F2129	Standard Test Method for Conducting Cyclic Potentiodynamic Polarization Measurements to Determine the Corrosion Susceptibility of Small Implant Devices
F2182	Standard Test Method for Measurement of Radio Frequency Induced Heating Near Passive Implants During Magnetic Resonance Imaging
F2213	Standard Test Method for Measurement of Magnetically Induced Torque on Passive Implants in the Magnetic Resonance Environment
G71	Standard Guide for Conducting and Evaluating Galvanic Corrosion Tests in Electrolytes

Study Design

The ongoing study that I was involved in during my internship at Baylor was an industry-sponsored study to investigate a new drug-eluting coronary artery stent. This study was a prospective, multi-center, randomized, single-blind, controlled clinical trial designed to assess the equivalence in safety and efficacy of a new drug-eluting stent when compared to an FDA-approved drug-eluting coronary stent for the treatment of single *de novo* lesions in native coronary arteries. Enrollment of a total of 1,548 patients from up to 70 active sites in the United States and up to 10 active sites in Canada was scheduled. Patients were subsequently randomized to receive either the study stent or control stent in a 1:1 ratio and were blinded to their assignment throughout the 12 months follow-up period. For the first 328 subjects enrolled, another angiographic/intravascular ultrasound (IVUS) evaluation at 8 months was assigned. Follow-up clinic visits at 30 days and at 8 and 9 months, and follow-up assessment at 6, 12 months, 2, 3, 4, 5 years, were required per protocol. Our site was planning to enroll about 20 subjects.

Study Stent and Adjunctive medication regimen – The investigational stent system was made of the sponsor's FDA-approved coronary artery stent system and a new drug-eluting polymer coating. The phosphorylcholine (PC) polymer coating acts as a carrier for the immunosuppressive rapamycin derivative drug. All patients received aspirin (a minimum of 75 mg daily within 24 hours prior to procedure and continued indefinitely post-procedure) and clopidogrel ($\geq$300 mg loading dose administered orally and 75 mg daily continued for a minimum of 6 months). During the procedure, heparin or bivalirudin was administered intravenously.

Study End Points – The primary end point was the nine-month incidence of target vessel failure (TVF) rate. TVF rate was defined as the composite of cardiac death, recurrent myocardial infarction, or clinically-driven target vessel revascularization (TVR) rate of the treated vessel. The secondary end points included acute success (device, lesion, and procedure), angiographic parameters (in-stent and in-segment) in a subset of patients at eight-month, major adverse cardiac event (MACE) rate at 30 days and at 6, 9, and 12 months, and target site/vessel revascularization (TSR/TVR) rate at 9 months post-procedure.

Patient Selection Criteria – Eligible study patients had to be at least 18 years of age with clinical evidence of ischemic heart disease (stable or unstable angina) due to stenosis lesions of *de novo* native coronary arteries. General exclusion criteria included evidence of an acute myocardial infarction (MI) within 72 hours before enrollment, previous or planned PCI of the target vessel, history of an allergic reaction to the materials of the study stent or drugs used as adjunctive pharmacotherapy during procedure, a serum creatinine level of more than protocol criteria, and a left ventricular ejection fraction of less than protocol criteria.

Randomization – Randomization was accomplished in the Cath lab upon determination of angiographic eligibility, using an Interactive Voice Response System (IVRS) (See Appendix D).

Preparation before study initiation

Institutional Review Board (IRB) Approval - All clinical research conducted at

Baylor Health Care System (BHCS) facilities should be approved by the Baylor Research Institute (BRI) Institutional Review Board (IRB) and administered by BRI. A new research protocol submitted for IRB review is initially pre-reviewed by BRI's Office of Research Subject Protection for requirements and suggested modifications. When the IRB approves the research study, the Office of Research Subject Protection generates the IRB approval letter and obtains the IRB Chairman's signature on the approval letter. All IRB approval letters are forwarded to the Office of Sponsored Research, and the IRB letter is sent to the principal investigator (PI) when the clinical research agreement has been executed with the sponsor and the initial payment has been received.[59] This study was approved by the Baylor Research Institute (BRI) Institutional Review Board (IRB) in April 2005. The IRB approval letter and IRB-approved informed consent form along with protocol and protocol amendments were filed in the Regulatory Binder.

Budget and Contract - The sponsored clinical study budget is forwarded to BRI's Office of Sponsored Research for review and submission to the Clinical Study Sponsor. Budget and payment terms are negotiated with the sponsor. The negotiated budget amount is submitted to the Research Coordinator and PI of the clinical study for final approval. The proposed study contract is reviewed and negotiated by the Office of Sponsored Research. The contract is executed by sponsor, BRI's Vice President and the PI of the study.[59] The contract and budget agreement of this study were signed and sent to the sponsor in April 2005.

Financial Disclosure – Investigators for industry sponsored clinical trials are required to disclose financial interests that they may have with the sponsor in accordance with 21

CFR 54. A signed Financial Disclosure statement is sent to the sponsor. A copy of this form is also sent to the Office of Sponsored Research.[59] Financial disclosure signed by all the principal investigators of this study was sent to the sponsor and filed in the Regulatory Binder.

Study Materials – With the exception of the study devices, all the study materials including regulatory binder, manual of operations binder, abridged pocket card, patient information packets, stent implant card, study demonstration stents, case report forms (CRF), and Code of Federal Regulation were received in May 2005 and stored at BRI's Clinical Trials Office. The study devices were obtained on June 9, 2005 after the sponsor's study initiation visit occurred on June 7, 2005.

Study Initiation and Training – Once a site has received IRB approval and the budget and contract have been completed, the sponsor's representative visits a site to initiate the study. The study initiation visit for this study occurred on June 7, 2005. The principal investigator, sub investigators, and study coordinators involved with this study attended the meeting. The sponsor's representative first provided a brief review of the protocol during the weekly catheterization laboratory (Cath Lab) meeting. This was important to introduce a new study and initiate the Cath Lab staff. After the meeting, the sponsor's representative provided training to the personnel involved in the study. All aspects of the protocol and case report form (CRF) were reviewed in detail, and regulatory requirement issues were discussed. The training sheet was signed by each person and filed in the Regulatory binder. For my involvement in this study, the approvals from both BRI's IRB and sponsor were required. I completed the seven IRB Credentialing modules in the

Baylor Learning Network (BLN) as required by the IRB. The delegation of authority form was signed by the PI and me, and sent to the sponsor with my curriculum vitae (CV). The sponsor issued a "GO-Letter" as an approval for my involvement in this study.

Study Implementation

Patient Screening – All of the patients scheduled for catheterization between June 17 and October 24, 2005 were evaluated for study eligibility. The medical and cardiac histories of these patients at Baylor Heart and Vascular Hospital (BHVH) and Baylor University Medical Center (BUMC) were reviewed. Symptoms of chest pain, shortness of breath, and a positive stress test were found as the most common reasons for patients to be scheduled for catheterization. Out of 272 charts reviewed, 216 patients were considered eligible pending the result of their angiographic assessment as required by the protocol (Figure 10). Fifty six patients did not meet the protocol's general inclusion criteria, the predominant reason being previous MI (Figure 11).

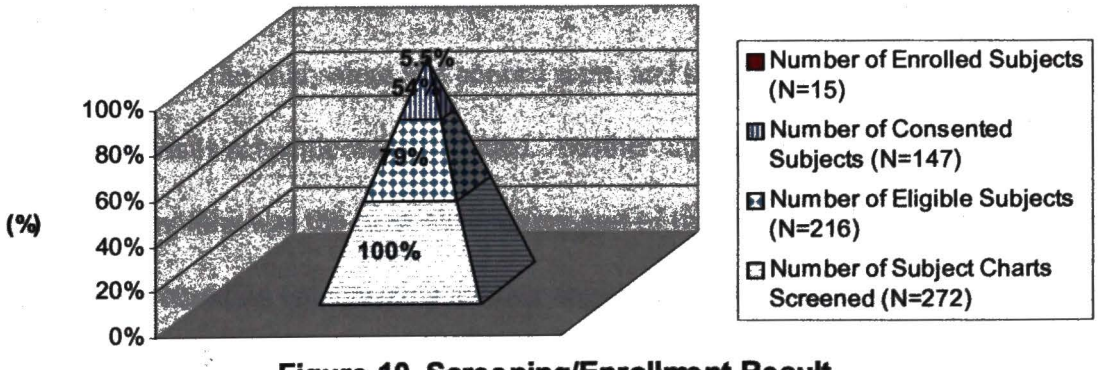

Figure 10. Screening/Enrollment Result

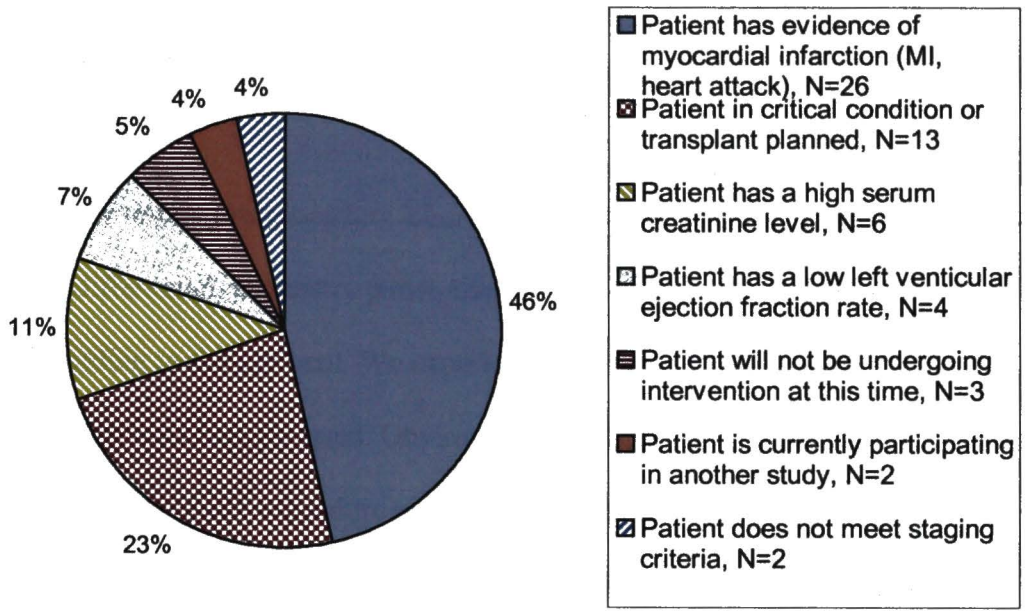

Figure 11. The conditions of general exclusion (N=56)

Informed Consent – Once the patients were determined to be eligible for the study through the chart review, we visited the patient room and introduced the ongoing study to the patients. It was interesting to find that many patients were very knowledgeable about the PCI procedure and even drug-eluting stents. We usually first provided the general information about the study stent and control stent, and then the benefits of the study and the follow-up visits schedule were provided. Another angiographic/IVUS evaluation schedule at 8 months was the most challenging part of the informed consent process. Our efforts were focused on emphasizing another angiogram as the benefit to have the chance to make sure the stented lesion kept from re-narrowing after the procedure. We met with

216 prescreened patients of which 147 patients (68%) consented to participate in the study and 69 patients (32%) refused to participate in the study (Figure 10). Prior to the procedure, the written informed-consent form was signed and dated by the patients (see Appendix C).

Laboratory tests – Pre-procedure laboratory tests including a complete blood count (CBC) with differential, chemistry panel, liver function tests, and lipid panel were ordered according to the protocol. We experienced some protocol noncompliance due to some laboratory tests being missed. Obviously, role of the Cath Lab charge nurses was very important for the pre-procedure requirements to be performed correctly. Once the BHVH nurse desk and laboratory set up a new code for our study, we never had that issue again.

Subject Enrollment – After the informed consent, only subjects meeting all of the angiographic inclusion criteria and none of the angiographic exclusion criteria were randomized and enrolled in the study. Therefore, the principal investigator or sub-investigator assessed angiographic eligibility for inclusion while the patient was in the Cath Lab. In the Cath Lab, the cardiac catheterization team consisting of cardiologists and clinical staff performed diagnostic angiography and angioplasty with stent placement. They threaded a catheter through a blood vessel and injected contrast material into the coronary arteries. The contrast allowed the team to see if the coronary arteries were narrowed or blocked through the digital imaging system.

The study had very strict inclusion/exclusion criteria. Most of our activities at the Cath Lab were assisting the PIs to determine the angiographic eligibility for inclusion through

providing accurate information on the protocol requirements. Randomization was accomplished in the Cath lab through an Interactive Voice Response System (IVRS) (see Appendix D). Because this study was a multi-center clinical trial designed to assign the subject either to the study stent or control stent in a 1:1 ratio, an IVRS system was very helpful to randomize subjects quickly. The control stents were always ready in the Cath Lab, but the study devices were stored in the cabinet of the Cath Lab at BHVH and kept locked during the study with access limited to the approved research personnel of this study. The study devices had the labeling of "CAUTION - Investigational device. Limited by Federal law to investigational use." Once the subject was randomized to the treatment group, we assisted the clinical staff to record all the required angiographic assessment results and checked the administration of concomitant medication regimen according to the protocol.

From 147 consented subjects, only 15 subjects were enrolled in the study (Figure 10). The enrollment rate based on subject charts screened was 5.5% (15/272), for eligible subjects was 6.9% (15/216), and for consented subjects was 10.2% (15/147), respectively (Figure 12). Of the subjects not included after the angiographic assessment (N=132), 45% did not require intervention and 55% had target or vessel lesion conditions that did not meet angiographic criteria (Table 6). These results emphasize the low success rate for patient enrollment in this type of stent studies, regardless of the enthusiasm and dedication of the clinical research team. These findings should allow the PI's to estimate more realistically their sites' potential contribution to future multi-center clinical studies of this nature.

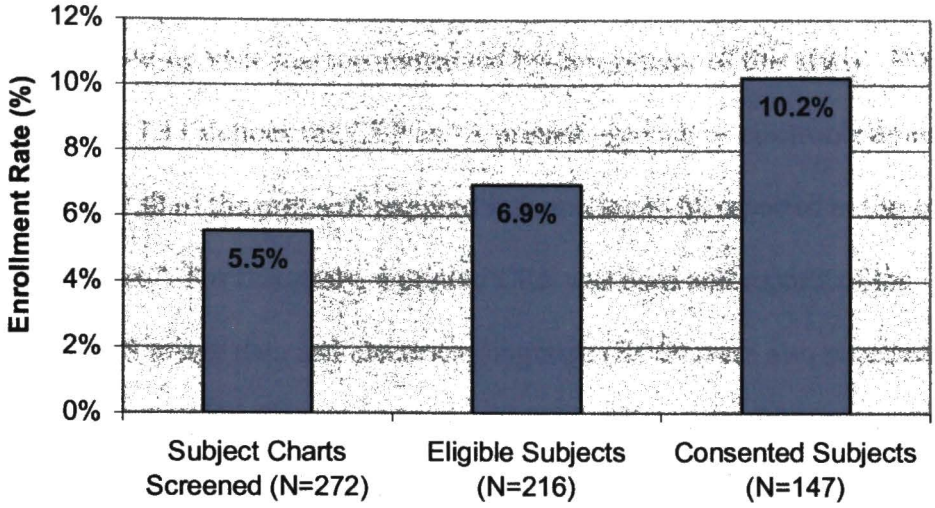

Figure 12. Enrollment Rate based on Subject Charts Screened, Eligible Subjects, and Consented Subjects (N=15)

Table 6. The Conditions of Angiographic Exclusion

	Description	N	%
1	Patient will not be undergoing intervention at this time (Normal)	60	45%
2	Target / Vessel conditions not met angiographic criteria	72	
2-1	Target lesion is not a single de novo lesion (in-stent or graft lesion)	(33)	
2-2	Target lesion is longer than protocol criteria	(7)	
2-3	PIs does not want patient in study	(6)	
2-4	Patient sent for bypass surgery	(4)	
2-5	Target vessel has stent implanted	(4)	
2-6	Patient has a planned PCI within 30 days post-procedure	(3)	
2-7	Patient has left ventricular ejection fraction rate lower than criteria	(3)	55%
2-8	Target vessel involves side branch	(3)	
2-9	Target vessel has other lesions with stenosis greater than criteria	(2)	
2-10	Patient does not meet staging criteria	(2)	
2-11	Target lesion involves a bifurcation	(2)	
2-12	Target lesion is severely calcified	(1)	
2-13	Target vessel diameter is out of criteria range	(1)	
2-14	Target lesion is at bend lesion	(1)	
Subjects excluded based on angiographic assessment		132	100%

Case Report Form (CRF) – Completion of the CRFs within 7 days after patient enrollment or follow-up visit was recommended by the sponsor of this study. ICH GCP Guideline, Section 1.11 defines the CRF as "A printed, optical, or electronic document designed to record all of the protocol-required information to be reported to the sponsor on each trial subject ". For this study, a printed CRF was used and reports of the angiographic/IVUS image data and electrocardiograms (ECG) were also required by the protocol. The CRF for this study was designed to record the medical condition of the subjects before involvement in the study to verify eligibility for the general criteria, description of device implantation procedure for the angiographic evaluation, concomitant medications, and description of adverse events. To collect all the information, review of hospital charts, laboratory notes, and Cath Lab log was primarily performed. The CRF was very detailed and seemed to require all information from the charts when I first reviewed it. I first had to figure out how the clinical research coordinator transferred information from the charts to the CRFs. To read cursive handwriting in the chart or to find out the intention of the medication treatment was not easy and I had to frequently ask for help from the staff at the office. Periodic monitoring visits from the sponsor were very helpful to understand the protocol clearly, complete the CRFs accurately, and reduce protocol deviation. The protocol for this study required adverse events to be recorded on the CRFs and reported to the sponsor. Any serious adverse event (SAE), defined as major adverse cardiac event (MACE) including death, myocardial infarction (MI), and target site revascularization (TSR), and unanticipated adverse device event (UADE), defined as a problem associated with a study device, were

required to be reported to the sponsor and IRB within one working day after the investigator first learned of the event.

Discussion

The stent system used in the ongoing study at Baylor consisted of a new drug absorbed into a phosphorylcholine polymer and the sponsor's FDA-approved stent system. This new drug is a rapamycin derivative, and pre-clinical data has demonstrated that this drug has potent effects on smooth muscle cell growth and inhibits intimal hyperplasia. The adjunctive medication regimen was generally following the currently established adjunctive pharmacotherapy to coronary stenting. The combination of an anti-proliferation agent (rapamycin derivative), combined with the adjunctive use of heparin, an anticoagulant, as well as aspirin and clopidogrel used for their antiplatelet properties, is currently the major optimal regimen to maximize the clinical success of coronary stenting. It has taken a decade to develop the knowledge on which today's study is based. Well designed and well conducted clinical trials will continue to be performed with newer stents and pharmaceutical agents, as we continue to set higher standard for clinical outcomes.

Clinical research requires a team of people, and teamwork is critical to the successful completion of any clinical trial.[60] The composition of a team might include the sponsor, site administrative office, site IRB, study subject, PI, CRC, and FDA. The sponsor, site administrative office, and site IRB, and FDA play an important role for the pre-clinical trial and post-clinical trial. The sponsor is responsible for preparing protocol and CRF, selecting site and PI, and acquiring FDA approval. The site administrative office' role involves the budget, contract, and financial part of the study. The site IRB reviews and approves the study protocol and informed consent form prior to study initiation. For the

active-clinical trial, the major roles are played by the study subject, PI, CRC, and monitor. Given that the ultimate goal of the clinical trial is to produce efficient data to support FDA approval, the active-clinical trial is the most important part of the clinical trial process.

This clinical trial of a DES was unique with respect to the process of patient screening and enrollment, and was educational to help me understand the critical role of the CRC. The patients scheduled for the catheterization procedure were hospitalized on the same day of procedure, mostly in the morning, and their staying time in the patients' room was very short. Therefore, the CRC needed to arrive at the hospital early enough for reviewing medical history and had to be fast in evaluating eligibility for general inclusion criteria. The informed consent process was challenging and required a specially trained and skilled CRC to be successful. This study was designed to demonstrate equivalence of the study DES to the already FDA-approved DES. Since the DES was commercially available, the patients seemed to find less benefit from participating in this study. Also, another angiographic/IVUS evaluation at 8 months was considered to reduce their interests in this study. Based on these environments, the CRC should be very efficient in presenting the study and obtaining consent without coercing the patient.

The enrollment rate of this study was lower than our expectation at study initiation. The enrollment rate was approximately 5.5% (N=15) and overall screen failure rate was approximately 94.5% (N=257) (Figure 12). Enrollment rate of eligible subjects was 6.9% and of consented subjects was 10.2%, which is low compared to other type of studies.

Reasons for patient ineligibility were mainly influenced by protocol requirements and consisted of the following;

1) General inclusion criteria not met (N=56): 20.6%

2) Patients did not consent because they did not want to return for follow up procedures (N=69): 25.4%

3) No intervention was necessary at this time (N=60): 22.1%

4) Target lesion/vessel did not meet angiographic criteria (N=72): 26.5%

Both reasons of 3) and 4) occurred at the Cath Lab. That means, 48.6% of screened patients had angiographic exclusions. Because the CRC knows details of the protocol so well, there is a better guarantee that during the Cath Lab procedure eligible patients would get included, and that ineligible patients would not be included, thereby adhering strictly to the protocol. Even though enrollment rate was lower than expected, this is often a consequence of strict protocol criteria which are out of the control of the clinical investigators and the CRCs.

In addition, the protocol required many kinds of pre-procedure, procedure, and post-procedure tests (laboratory tests and EKG tests). Protocol deviations could occur at so many stages for which the CRC was not directly responsible. For example, the blood sample for the laboratory tests of pre- and post-procedure was drawn by the floor charge nurses and the test result was reported by the laboratory technician. During procedure, timely administration of concomitant medication, timely measurement of physiological condition, detailed recording of treatment procedure were done by the Cath Lab staff. In order to be compliant with the protocol requirement, the CRC should always ensure that

the needs and the education of other staff members are met and he/she should be very communicative with all members of other staff.

The collection and recording of the data of this study also required more efforts from the CRC than the simple role of timely and accurate transferring data from the source document to the CRF. The coronary stenting procedure was accompanied by a variety of adjunctive medication to improve the outcome. Therefore, the CRC should be very knowledgeable about adjunctive pharmacotherapy to coronary stenting.

Summary

There have been numerous advances in interventional cardiology techniques since the first percutaneous transluminal coronary angioplasty (PTCA) was performed to treat coronary artery disease (CAD). The growth has been accelerated with the adoption of coronary stenting. In efforts to reduce the stent-associated complications such as acute or sub-acute thrombosis and late in-stent restenosis, a number of stents have been developed using different kinds of coatings and eluting drugs, and the use of adjunctive pharmacotherapy has improved outcomes after coronary stent deployment. At present, cardiologists have access to a wide variety of approved stent designs, drug eluting or not, as well as many different adjunctive drug regimens.

While the search for safer and better stents and treatments remains ongoing, I had the opportunity to be involved in an ongoing clinical trial of a new drug-eluting stent during my internship. While observing and assisting a clinical research coordinator (CRC), I learned how to implement a clinical trial with an investigational stent, communicate with staff members, maintain regulatory files, and transfer information from the source documents to the Case Report Form (CRF). Out of 272 subject charts screened, 15 subjects were ultimately enrolled in this study. The enrollment process and pitfalls are described and the critical role of the CRC highlighted.

CHAPTER III

INTERNSHIP EXPERIENCE

Description of Internship Site

I did my internship at the Baylor Research Institute (BRI) Clinical Trials Office from May 31, 2005 to October 31, 2005. BRI, the research arm of Baylor Health Care System, was founded in 1982 and currently has approximately 100 employees, including scientists, laboratory assistants and research coordinators. Located in the Zelig H. Lieberman Research Building at downtown Dallas, BRI houses the Baylor Institute for Immunology Research (BIIR) along with the administrative offices. Investigators of BIIR primarily focus on studying the immune system and developing novel approaches to treat cancer, autoimmune disease and infectious diseases. With the concept of bench-to-bedside, BRI focuses on basic science, clinical trials, and healthcare effectiveness and quality of care research. BRI is currently conducting more than 500 active researches including clinical trials of Heart and Vascular Disease, Cancer, Diabetes, and CyberKnife® Research Study.

The BRI administrative offices include the Clinical Trials Office, Research Subject Protection Office, Office of Sponsored Research, Office of Financial Management, and Research Quality Assurance. The Research Subject Protection Office is responsible for reviewing all research protocols that involve the use of human and animal subjects incorporating the Institutional Review Board (IRB), the Institutional Animal Care and

Use Committee (IACUC), and BioSafety. Office of Sponsored Research is in charge of grants submission, grant management, and contract management. The Office of Financial Management oversees the budget and accounting aspects of ongoing studies. Research Quality Assurance is responsible for reviewing compliance with federal and state regulation.

The Clinical Trials Office was opened in 2002 to make available a number of resources for physicians on staff at Baylor Health Care System. The Director of Clinical Trials Office, Betsy Stein, CCRC, is managing a variety of activities of this office: education and training of research staff; operating procedures for trials; biostatistical assistance; preparation of documents for the IRB; budget development; screening, registration, and coordination of study patients; completion of case report forms; and function as liaison with study sponsors. She is supervising more than 45 research nurses, research coordinators, and research assistants throughout Baylor Health Care System. The Clinical Trials Office is currently providing support for 25 NIH-sponsored research and coordinating 250 IRB-approved clinical trials.

Journal Summary

My internship took place under the supervision of Betsy Stein, Director of Clinical Trials Office at BRI. Exposed to the various activities of this office, I received hands-on training and gained insight into all aspects of clinical research. Some of my activities as an intern included attending monthly BRI Clinical Research Coordinators' meetings, Focus on Research meetings, and occasional trainings for clinical research staff. The

monthly BRI Clinical Research Coordinators' meeting was necessary to introduce the new research staff, inform about new developments, discuss issues, and exchange ideas. Seminars presented during this meeting were very informative. The topics of seminars included budget negotiations, subject recruitment-targeted enrollment, process for research order sets, and clinical transformations. The "Focus on Research" meeting was held monthly to educate and inform physicians and researchers about ongoing research throughout Baylor Health Care System. This meeting gave me a chance to learn their latest research activities. Workshops on regulatory issues and in-service training were occasionally provided by outside professionals. I attended BRI's "Clinical Research Best Practice for Coordinators" presented by MedTrials for two days. Each session started with a brief review followed by an exercise and group discussion. This interactive workshop gave me a chance to review the whole process of clinical trial conduct from the initiation to the close-out.

The main project I worked on as an intern at BRI was a prospective, multi-center, randomized, single-blind, controlled clinical trial of a drug-eluting coronary stent system versus a Food and Drug Administration (FDA) approved drug-eluting coronary stent system in *de novo* native coronary artery lesions. This ongoing study was designed to assess the equivalence in safety and efficacy of the experimental drug-eluting stent system as compared to the FDA-approved drug-eluting stent system. My activity for this project was performed through observing and assisting Emily Laible, a clinical research coordinator (CRC), in the implementation of this study at Baylor Heart and Vascular

Hospital (BHVH). Emily worked three days a week. Accordingly, I spent these three days at BHVH and the other two days at the office.

The activities at BHVH began early morning to screen the patients scheduled for the catheterization procedure. We started the day with reviewing the medical history and evaluating eligibility for general inclusion criteria. If the patients met the general criteria, we met with the patients and obtained the informed consent forms. After the informed consent process, the rest of the activities at BHVH occurred at the catheterization laboratory (Cath Lab). At the Cath Lab, we assisted the principal investigator (PI) assessing angiographic eligibility for this study by providing the accurate information of the protocol. If the subject met all of the inclusion criteria, the randomization and enrollment followed right after the assessment. From this activity, I learned how to coordinate the study from screening to the enrollment. Most of the screened patients did not meet the inclusion criteria and were not enrolled. While experiencing the repeated procedure, I reflected on how important the patience and enthusiasm of the research staff are in doing clinical research.

In the middle of my internship, I had an opportunity to attend the investigator meeting for this stent trial in Chicago. The meeting room was packed with so many investigators and CRCs from US and Canadian sites. The meeting began with the trial update followed by reviews on the protocol. There were quite detailed discussions on the criteria. For the last part of this meeting, the sponsor provided recruitment strategies to enhance study enrollment at the sites. A PI of one of the sites introduced their successful story to enroll 15 subjects in 13 weeks. He considered "Enthusiasm" as their top strategy.

I had a great time with this meeting to understand how important it is to share successes or challenges experienced at the sites through this kind of meeting.

I spent two days a week at the office. Part of this time was used for my research focus on the history of coronary stenting and the role and evolution of adjunctive pharmacotherapy. The rest of the time was devoted to completing the Case Report Forms (CRF). The CRF was divided into sections of baseline, index hospitalization, and follow-up visits. Right after the enrollment, the sections of baseline and index hospitalization had to be completed. To complete these sections, the chart and catheterization log were used. Capturing the chart and the catheterization log was usually conducted before the subject was discharged from the hospital the day following the stenting procedure. Transferring information from the source documents to the CRF was very detailed work and required accuracy. I was surprised to find a lot of errors indicated by the monitor even though I was very careful to complete the CRF.

All my experiences and interactions have given me a thorough understanding of the role and responsibilities of the CRC and the entire clinical research team, and are invaluable for my career in the clinical profession.

APPENDICES

TABLE OF CONTENTS

Page

APPENDIX A:

ACONYMS AND/OR ABBREVIATIONS

ACC	American College of Cardiology
ACT	Activated clotting time
ADP	Adenosine diphosphate
AHA	American Heart Association
ASA	Acetylsalicylic acid
ASTM	American Society for Testing and Materials
AT	Antithrombin
BENESTENT trial	Belgium Netherlands STENT Trial
BHCS	Baylor Health Care System
BHVH	Baylor Heart and Vascular Hospital
BIIR	Baylor Institute for Immunology Research
BMS	Bare metal stent
BLN	Baylor Learning Network
BRI	Baylor Research Institute
BUMC	Baylor University Medical Center
CABG	Coronary artery bypass graft
CAD	Coronary artery disease
cAMP	Cyclic AMP
Cath lab	Catheterization lab
CBC	Complete blood count
CCRC	Certified clinical research coordinator
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health

CFR	Code of Federal Regulations
CK	Creatine kinase
CK-MB	Creatine kinase myocardial-band isoenzyme
CRC	Clinical Research Coordinator
CRF	Case report form
CRO	Contract Research Organization
CTO	Clinical Trials Office
CV	Curriculum vitae
DCA	Direct coronary atherectomy
DES	Drug-eluting stent
DTI	Direct thrombin inhibitor
ECG	Electrocardiogram
EKG	Electrokardiogram
EPSTENT trial	Evaluation of IIb/IIIa Platelet Inhibitor for STENTing trial
FDA	Food and Drug Administration
FIM	First-in-man
GCP	Good Clinical Practice
GP IIb/IIIa inhibitor	Glycoprotein IIb/IIIa inhibitor
IACUC	Institutional Animal Care and Use Committee
ICH	International Conference on Harmonization
IDE	Investigational Device Exemption
IRB	Institutional Review Board
ISO	International Standards Organization

IVRS	Interactive Voice Response System
IVUS	Intravascular ultrasound
LAD	Left anterior descending coronary artery
LCX	Left circumflex coronary artery
LIMA	Left internal mammary artery
LMWH	Low molecular weight heparin
LVEF	Left ventricular ejection fraction
MACE	Major adverse cardiac event
MI	Myocardial infarction
MDUFMA	Medical Device User Fee and Modernization Act
NICE	The National Institute for Clinical Excellence
NIH	National Institutes for Health
OAC	Oral anticoagulant
OCP	Office of Combination Products
OCPB	Office of Clinical Pharmacology and Biopharmaceutics
ODE	Office of Device Evaluation
OND	Office of New Drugs
OPS	Office of Pharmaceutical Science
OST	Office of Science and Technology
PAMI trial	Primary stent in Acute Myocardial Infarction trial
PC	Phosphorylcholine
PCI	Percutaneous coronary intervention
PI	Principal investigator

PTCA	Percutaneous transluminal coronary angioplasty
PMA	Premarket approval
RAVEL trial	RAndomized study with the sirolimus-elution bx VElocity balloon-expandable stent in the treatment of patients with de novo native coronary artery Lesions trial
RCA	Right coronary artery
RFD	Request for Designation
RIMA	Right internal mammary artery
SAE	Serious adverse event
SIRIUS trial	SIRolImUS-eluting bx velocity balloon-expandable stent trial
SMDA	Safe Medical Devices Act
STRESS trial	STent REStenoSis trial
TAXUS trial	pacliTAXel-elUting Stent trial
TSR	Target site revascularization
TVF	Target vessel failure
TVR	Target vessel revascularization
UADE	Unanticipated adverse device event
UFH	Unfractionated heparin

APPENDIX B: GLOSSARY [61]

Anesthesia
Loss of sensation with or without loss of consciousness; general anesthesia usually implies loss of consciousness.

Angina
(also known as Angina Pectoris) - Chest discomfort, pain, tightness, or pressure; may also have associated pain in neck, jaw, back, or arm; may include profuse sweating, nausea, or shortness of breath. Angina may be a single symptom or a combination of these symptoms. Angina occurs when the demand for blood by the heart exceeds the supply provided by the coronary arteries.

Angioplasty
Balloon angioplasty (or percutaneous transluminal coronary angioplasty [PTCA]) is a technique used to widen the narrowing in your artery without surgery. The basic idea of angioplasty is to position a catheter with a small inflatable balloon on the end within the narrowed section of the artery. The balloon is then inflated and pushes outward against the narrowing and surrounding wall of the artery. The inflated balloon opens the narrowed artery by splitting and compressing the plaque and slightly stretching the wall of the artery. The balloon may be inflated several times during angioplasty. Each balloon is made of special materials that allow it to inflate to a specific size. Your doctor will select a balloon that will be approximately the same size as your artery. It is possible that the first balloon will be removed and other, larger balloons will be used if additional expansion is required.

Anticoagulant
A substance that slows, suppresses, or prevents the clotting of blood.

Antiplatelet
A medicine that reduces the clumping of platelets in the blood. An antiplatelet medicine helps thin the blood to prevent clot formation.

Atherosclerosis
A disease process in which fatty substances (plaque), such as cholesterol, are deposited on the inner lining of blood vessels.

Balloon Angioplasty
See Angioplasty.

Balloon Catheter
Coronary stent implantation usually follows balloon angioplasty, which requires inserting a balloon catheter into the femoral artery in the upper thigh. When this catheter is positioned at the location of the blockage in the coronary artery, it is slowly inflated to widen that artery, and is then removed.

Brachytherapy
See Intravascular Brachytherapy.

CABG
See Coronary Artery Bypass Grafting.

CAD
See Coronary Artery Disease.

Cardiac
Relating to the heart.

Cardiac Catherization
Cardiac catheterization involves the passage of a catheter (a thin flexible tube) into the right or left side of the heart. Generally this procedure is performed to obtain diagnostic information about the heart or its blood vessels or to provide therapeutic interventions in certain types of heart conditions.

Catheter
A tube used for gaining access to the body's cavities or blood vessels. In angioplasty, a catheter provides access to the heart's arteries.

Catheterization (Coronary Angiogram)
A test used to diagnose coronary artery disease using the catheterization procedure. Contrast dye is injected into the coronary arteries via a catheter, and this allows the doctor to see, on an X-ray screen, the exact site where the artery is narrowed or blocked.

CAT Scanning
See Computed Tomography Scanning.

Cholesterol
A substance that circulates in the blood and plays a role in the formation of blockages. Cholesterol originates in foods that are rich in animal fats.

Computed Tomography Scanning
A technique for producing cross-sectional images of the body in which X-rays are passed through the body at different angles and analyzed by a computer; also called CT scanning or CAT scanning.

Coronary
Related to the arteries that supply blood to the heart.

Coronary Angiogram
See Cardiac Catheterization.

Coronary Arteries
The coronary arteries are special blood vessels that supply the heart with necessary oxygen and nutrients. The heart does not function properly without enough oxygen.

Coronary Artery Bypass Grafting (CABG)
An operation in which a section of vein or artery is used to bypass a blockage in a coronary artery; performed to prevent myocardial infarction (heart attack) and to relieve angina.

Coronary Artery Disease (CAD)
Atherosclerosis of the coronary arteries.

CT Scanning
See Computed Tomography Scanning.

Cytostatic Drugs
Drugs known as cell-cycle inhibitors that selectively stop cell division by blocking cell-cycle progression.

Diabetes
A disease that affects the metabolism of glucose (sugar), thus causing changes in blood vessels. These changes may aid in the development of coronary artery disease.

ECG
See Electrocardiogram.

Electrocardiogram (ECG)
A test that measures and shows the electrical activity of the heart muscle.

Exercise Electrocardiogram
See Stress Test.

FDA
See Food and Drug Administration.

Fluoroscope
Equipment used in a cardiac catheterization procedure that captures a "motion picture" X-ray image of the heart and coronary arteries.

Food and Drug Administration (FDA)
The agency of the American federal government that oversees, regulates, and approves new drugs and devices for sale in the United States.

In-stent Restenosis
A re-narrowing or blockage of an artery within a stent.

Intervention
An action that produces an effect or that is intended to alter the course of a disease process.

Interventional Cardiologist
A doctor specializing in the minimally invasive procedures to treat the heart.

Interventional Cardiology
A field of heart medicine dedicated to research and technology for minimally invasive heart procedures.

Intravascular Brachytherapy
The administration of a therapeutic dose of radiation from within a vessel to a specific area of vascular disease to reduce the reoccurrence of an obstruction or narrowing.

Ischemia
Lack of or insufficient oxygen to tissue (in this case, the heart muscle). Ischemia is a reversible condition if normal blood flow is restored.

Left Ventricle
The largest chamber of the heart which is responsible for pumping blood throughout the body.

Lesion
A blockage in a blood vessel; also known as plaque or stenosis.

Magnetic Resonance Imaging (MRI)
A diagnostic study, similar to a CT or CAT scan, that creates an image using electromagnetic waves instead of X-ray.

MRI
See Magnetic Resonance Imaging.

Myocardial Infarction
Commonly called a "heart attack." Involves irreversible damage to heart tissue/muscle. Insufficient oxygen reaching the heart muscle via the coronary arteries may cause angina, heart attack (myocardial infarction), or even death to the affected area of the heart.

Percutaneous
Performed through a small opening in the skin.

Percutaneous Transluminal Coronary Angioplasty (PTCA)
See Angioplasty.

Plaque
The accumulated material that causes a blockage in a blood vessel; also known as a lesion or stenosis.

Platelets
Blood cells that are involved in the formation of a clot.

PTCA
See Percutaneous Transluminal Coronary Angioplasty and Angioplasty.

Reintervention
The act of reintervening by performing additional procedures to prevent serious injury or correct complications from a prior procedure. The purpose of reintervention in cardiac cases is to open an artery that has become re-blocked following an initial procedure. This is also called revascularization.

Restenosis
A re-narrowing or blockage of an artery at the same site where angioplasty was previously done.

Revascularization
A procedure that must be conducted to open or bypass an artery that has become blocked. If it needs to be done again, it is called a reintervention.

Sirolimus
A drug that helps limit the overgrowth of normal tissue in your artery as the healing process occurs following coronary stent implantation. Overgrowth of normal tissue is thought to be a major factor responsible for re-narrowing of the artery after stent implantation.

Stenosis
A narrowing of any canal, especially one of the cardiac vessels.

Stent
An expandable, slotted metal tube that is inserted into a vessel and acts as a scaffold to provide structural support.

Stent Implantation
A stent is a small, latticed, metal scaffold that is introduced into a blood vessel on a balloon catheter. The doctor maneuvers the catheter into the blocked artery and inflates the balloon. Inflation causes the stent to expand and press against the vessel wall. Once the balloon has been deflated and withdrawn, the stent stays in place permanently, holding the blood vessel open and improving blood flow.

Stress Test
(also known as Exercise Electrocardiogram) - A test that measures electrical changes in the patient's heart (ECG) while the patient is doing controlled exercise. The stress test can show if there has been damage to the heart or if there is decreased blood flow to areas of the heart.

Target Lesion Revascularization (TLR)
Repeat intervention of a previously treated lesion (or blockage) using balloon angioplasty, stent implantation, or bypass graft surgery.

Thrombosis/Late Thrombosis
A blockage caused by clumping of cells. Late thrombosis occurs after 30 days.

Transluminal
Through the inside opening of an artery.

Triglycerides
Substances in the blood that are a component of the "bad" type of cholesterol.

Vessel
Any channel for carrying a fluid, such as an artery or vein.

APPENDIX C:

EXAMPLE OF INFORMED CONSENT DOCUMENT

BAYLOR HEART AND VASCULAR HOSPITAL
PARTICIPATION EXPLANATION AND CONSENT FORM

PROJECT TITLE: A RANDOMIZED CONTROLLED TRIAL OF THE [redacted] DRUG ([redacted]) ELUTING CORONARY STENT SYSTEM VERSUS THE [redacted]-ELUTING CORONARY STENT SYSTEM IN DE NOVO NATIVE CORONARY ARTERY LESIONS

PRINCIPAL INVESTIGATOR: Robert Stoler, MD

TELEPHONE NUMBER: 214-824-8721

INTRODUCTION:

Before you say that you will be in this clinical trial (a kind of research study) you need to read this form. It is important for you to understand all the information in this form. This form will tell you what the clinical trial is about and how it will be done. It will tell you about some problems that might happen during the clinical trial. It will also tell you about the good things that might happen for you during the clinical trial. When you read a paper like this to learn about a clinical trial it is called "informed consent." The people who are doing this clinical trial are giving you very important information about the clinical trial. When you give your consent for something, it is the same as giving your permission. This consent form may contain words that you do not understand. Please talk with one of the doctors or their staff if you have questions. Do not sign this consent form unless all your questions have been answered and you feel comfortable with the information you have read. You will be given a copy of the form to keep.

You are being asked to take part in this study because you have been diagnosed as having a blockage in one of your coronary arteries.

Why Is This Study Being Done?

The purpose of this study is to test the safety and effectiveness of the [redacted] Drug Eluting Coronary Stent System when compared to the [redacted]-Eluting Coronary Stent System in subjects with a coronary artery blockage.

What is the Status of the Drugs (Devices or Procedures) involved in this study?

One stent used for this study is the [redacted] Drug Eluting Coronary Stent System (called the [redacted] stent). The [redacted] stent is based on the Health Canada TPD and

USFDA-approved [redacted] Coronary Stent System (3.0 mm to 3.5 mm stent size) and investigational [redacted] Coronary Stent System currently under clinical evaluation (2.5 mm stent size). The [redacted] are stents without drug. The [redacted] Drug Eluting Coronary Stent System is an investigational drug and device that is not approved by the US Food and Drug Administration.

The [redacted]-Eluting Coronary Stent System is currently approved by the US Food and Drug Administration. The [redacted] stent has been shown to create a wider channel in narrowed heart arteries with a diameter between 2.5 mm and 3.75 mm (less than a quarter inch) and less than 28 mm (about one inch) in length that have not been previously treated. The long-term (greater than one year) outcome of patients with the [redacted] stent is not yet known.

How Many People Will Take Part In The Study?

About 1548 people will take part in this study in up to 80 medical centers in the United States and in Canada. About 20 of these individuals will participate at this location.

What Is Involved In The Study?

- If you agree and are chosen to be in this study, you will have blood drawn (about 6 tablespoons) to check complete blood counts and chemistry, kidney and liver function, the rate at which your blood clots, and to determine if there is any heart damage. This is the usual treatment before this procedure.

- If you are female and able to have children, you will have a pregnancy test. You cannot be in this research study if you are pregnant or plan to become pregnant during the course of the study.

- You will need to take Aspirin 325 mg (one tablet) and Plavix 300 mg (4 tablets – a one time higher dose) or Ticlid (unless you have already taken them) to help decrease the chances of blood clotting which is the usual treatment before this procedure.

- You will have an electrocardiogram (ECG – electrical tracing of your heart function). This is a standard test for patients undergoing balloon angioplasty/stent placement.

- Your doctor will first perform a coronary angiogram (heart catheterization). Fluoroscopy (a type of x-ray imaging device) will be used to obtain a clear picture of the placement of the stent in the heart. Fluoroscopy is a device that uses x-rays to see through your body and create a movie like image of what is seen. This procedure starts with a small needle puncture in your groin or upper arm after the area has been numbed with medicine. A small flexible guidewire and catheter

(small plastic tube) will be moved through a blood vessel from your groin (or arm) to your heart. Your doctor will then inject dye into your coronary arteries to find the blockage and determine if you can still be in the study. You may feel a warm sensation from the dye, but this feeling will usually go away after a short period.

- You will be randomly assigned (like flipping a coin) to receive one of two treatments. You will receive either the [redacted] stent or the [redacted] stent. The [redacted] stent has been approved by the Food and Drug Administration while the [redacted] stent has not. You will not know which treatment you have been assigned throughout the twelve-month follow-up period. Once the blockage has been located, your doctor will use a balloon catheter to open the artery. You may feel some pressure or slight pain at this time. The pain will usually go away after the balloon is deflated. Your doctor will then place either the [redacted] or [redacted] stent in the newly opened area and expand it with a balloon. The stent is a tiny, metal cage-like device designed to prop open the artery and prevent it from collapsing. He will then inject more dye into your artery and take x-rays to be sure the stent is in the right place and the artery is open. A small tube (sheath) will be left in place in your leg (or arm) for a period. The entire procedure will take 1-2 hours.

  If you are randomized to the [redacted] stent, the amount of drug ([redacted]) you will be exposed to is directly related to the total amount of stent length implanted in your heart artery. If more than 48 mm (about two inches) of the [redacted] stent or [redacted] stent is required to treat your heart artery, you may receive additional treatment devices. If your doctor is not able to place the study stent in the heart artery, he/she may choose to treat your artery with an approved device.

- After the procedure, you will be moved to the recovery area where you will be on bed rest for up to twelve hours. There you will receive standard care for stent patients. You will receive heart monitoring, groin/arm checks, and ECG and blood test. About 2 tablespoons of blood will be drawn while your sheath is in place to check the rate at which your blood clots. After the sheath has been removed, pressure will be placed over the area with a clamp to stop the bleeding. You will be transferred to a patient room in the hospital where your heart will be monitored. You will be asked to take 325mg of Aspirin every day from now on and Plavix 75mg (one tablet) or Ticlid for at least 6 months to help decrease the chance of blood clots in the stent.

- During the next 24 hours, you will have three more blood tests to check for any heart damage (about 6-8 tablespoons). The increase in the number of tests for heart damage is being required by the study sponsor and will be paid for by the sponsor.

- You will be required to return for a follow-up clinic visit about 30 days after your stent placement. The visit is to see whether you have had any symptoms, problems or needed medical care since your procedure. At this visit you will have blood tests (about 2 tablespoons) performed to check your platelets (cells that help your blood clot) and white blood cells (cells that fight infection). You will also have a scheduled clinic visit at 9 months to see whether you have had any symptoms, problems or needed medical care since your procedure or last clinic visit. A research nurse or doctor will assess you by phone after your procedure at 6 months and once a year for 5 years.

- If you are one of the first 328 patients enrolled in the study, you will be part of an assigned group (Angiographic/IVUS group) and return to the hospital for a repeat angiogram (x-ray filming of the blood vessel) and IVUS 8 months after the stent implantation. In order to maintain study blinding, a doctor other than the doctor who implanted your stent may perform angiography and IVUS at the 8 month clinic visit. **This test is for research purposes and is not medically indicated and will be paid for by the sponsor.** The same risks apply for this procedure that apply for the first angiogram. (See "Risks That May Occur During The Study" section). This test will be paid for by the study sponsor.

- If you are treated with more than one stent in your heart artery, you will return to the hospital at 8 months after your stent implantation for repeat angiography and IVUS (Multi-stent group). **This test is for research purposes and is not medically indicated and will be paid for by the sponsor.** If you are selected to return for the 8 month visit, the doctor will ask you if you have had any symptoms or problems since your last visit. These additional tests would not be done if you were not in this study.

How Long Will I Be In The Study?

After you are discharged from the hospital, your doctor will see you at one, 8, and 9 months for a follow-up visit. At 6 months and once a year for 5 years after your procedure, the research nurse or doctor will contact you by phone to evaluate your medical status and record any medical problems that you may be having. All patients will be required to have a follow-up angiogram at 8 months. The angiogram will give your doctor more detailed information of what the interior of the stented blood vessel looks like so that the long-term results of the stent placement can be assessed.
Your responsibility to return to your doctor's office will be complete after the 9-month follow up visit. You will continue to be followed once a year by phone for 5 years after the study procedure. Each phone call will take approximately 5 minutes. After completion of the 9-month follow-up you will be free to enroll in other clinical trials.
You can stop participating in this study at any time. However, if you decide to stop participating in the study, we encourage you to talk to the researcher and your regular doctor first.

Your doctor may withdraw you from this study without your consent, if the study is cancelled by the Sponsor and, if for other reasons that are in your best interest.

What Are The Risks of The Study?

The risk of using the [redacted] stent is currently not known. It is expected to be similar to the Health Canada TPD and USFDA-approved stents used for treating coronary (heart) artery disease. The risks of the stent are expected to be similar to those that are associated with standard procedures.
The [redacted] stent is composed of an alloy containing the following metals: cobalt, chromium, molybdenum, and nickel. Other permanently placed devices such as artificial hip joints, heart pacing wires and blood vessel filters have used similar alloys. The risk of the material for use as a stent is thought to be minimal.

Note: If you are allergic to cobalt, chromium, molybdenum, nickel, ticlopidine (Ticlid), clopidogrel (Plavix) and/or aspirin you should not take part in this study.

Other risks from these devices are the same as treatment procedures for a narrowed heart artery. Some problems with standard balloon angioplasty and stenting include, but are not limited to the following. The following Anticipated Events have been identified as possible complications:

Angiogram and Stent related:

Most likely risks:

- Bruise or bleeding at the catheter insertion site in the groin or arm
- Pain at the catheter insertion site

Less likely risks:

- Irregular heart beats, possibly life threatening
- Chest pains during and after the procedure
- Decreased or increased blood pressure
- Re-narrowing of the heart artery (10-30% over six months)

Rare Risks:

- Tearing, puncture or rupture of the heart artery
- Air, pieces of devices or fragments of clots blocking the coronary artery
- Complete blockage of the heart artery, which may require a repeat procedure to re-open the heart artery (2-4%)
- Bleeding around the heart
- Heart attack

- Damage to the stent or injury to the heart artery requiring emergency heart surgery
- Bleeding requiring transfusion or surgery
- Allergic reaction (may include x-ray dye, drugs cobalt, chromium, nickel)
- Infection
- Nerve Injury
- Aneurysm (weakening of a portion of the wall of a blood vessel)
- Failure to release the stent from the catheter
- Stent misplacement in the artery
- Movement of the stent from where it was placed
- The balloon used to expand the stent may break
- Shock
- Stroke
- Death

Radiation Risk:

The initial angiogram and stent placement procedure will last 1 to 2 hours with approximately 30 to 45 minutes of fluoroscopy (x-ray radiation exposure) time, to allow visualization of the placement of the stent into the heart. The second angiographic procedure is expected to only use 3 minutes of fluoroscopy time to view the status of the stent. The amount of radiation that you receive from both angiogram fluoroscopy x- ray exposures is estimated to be about what you would receive naturally by living on earth for about 14 years from background radiation. This dose is similar to the maximum amount of radiation that is allowed for someone who works with radiation over one year and should represent a minimal amount of risk.

In addition, there is a very slight chance that the risk of cancer could increase due to radiation exposure, which is estimated to be less than 0.1%. There is also chance that the fluoroscopy procedure, with a concentrated beam of x-rays, could cause skin reddening, and if the procedure lasts an unusually long time, skin death could possibly occur. This is very unlikely to occur.

Some minor discomfort you might experience includes:

- Soreness or pain at the catheter insertion site and blood draw areas
- Soreness form lying in one position 6-10 hours

Risks associated with the [redacted] stent coated with the investigational drug:

The [redacted] stent is composed of an alloy containing the following metals: cobalt,

chromium, molybdenum, and nickel. Other permanently placed devices such as artificial hip joints, heart pacing wires and blood vessel filters have used similar alloys. The risk of the material for use as a stent is thought to be minimal.

The actual risks of the investigational drug are not yet fully known. Your exposure to the investigational drug is directly related to the total amount of stent length implanted. The risks that might occur due to the use of the investigational drug on the [redacted] stent include but are not limited to:

- Blood in the urine and/or diarrhea
- Diarrhea
- Dry skin
- Fatigue
- Headache
- Infection
- Pain (abdominal, joint, injection site)
- Skin reaction (at injection site)
- Tingling feeling around the mouth

Risks associated with the [redacted] stent coated with [redacted] and a polymer coating:

Exposure to [redacted] and the polymer coating is directly related to the number of implanted stents. The risks that might occur due to the use of the drug ([redacted]) or polymer coating on the [redacted] stent include but are not limited to:

- Abnormal liver values
- Allergic or immunologic reaction the drug ([redacted])
- Allergic reaction to the polymer [redacted] or polymers with similar chemical structures
- Anemia
- Blood transfusion
- Decrease of white and red blood cells and platelets
- Changes of the tissue in the vessel wall including inflammation, cell injury, and cell death
- Disturbances of the gastrointestinal (GI) tract and stomach
- Loss of hair
- Muscle pain/joint pain
- Nerve disease in arms and legs

Risks and side effects from the required medications:

There are possible risks associated with the medication required as part of this study. For example, there is a small risk of bleeding if you have an ulcer in your stomach or at the puncture site in the groin or arm area where the study device was inserted. Please inform your doctor about any unusual bleeding that you experience. You should also inform your physician or dentist that you are taking blood-thinning medication before any procedure.

Plavix® as well as Aspirin can cause rash, headache, dizziness, stomach pain, nausea, diarrhea, indigestion, increased cholesterol, and a drop in the number of white blood cells and platelets. Stomach upset, rash, and headache are the most common side effects. The drop in white blood cells could cause an increase in infections, and a drop in platelets (TTP) could cause an increase in bleeding. A decrease in white blood cell count has been observed in less than 2% of the cases. If you are unable to take Plavix, the drug Ticlid will be prescribed. Administration of Ticlid can lead to abnormal liver values that usually normalize after discontinuing the medication.

Risks for Women of Childbearing Potential:

The effect of the X-Rays used during the heart study, medication used in the study, and the experimental device on pregnant women, unborn, or newborn children is unknown. Pregnant or women of childbearing age, not using proper birth control, are not allowed to join this trial. You should use effective contraception before your procedure and twelve weeks after your stent implant. Please let the doctor know right away if this applies to you. Proper birth controls are surgical sterilization (tubal ligation, hysterectomy), oral contraceptives (birth control pills for a least 2 months), intrauterine devices, implantable contraceptives (Depo-Provera, Norplant), and no sexual activity.

It is not known whether [redacted] or [redacted] is excreted in human milk. The potential adverse reactions in nursing infants from [redacted] or [redacted] have not been determined. A pregnancy test will be performed on women of childbearing potential before enrollment into the study.

You should report any unusual effects that occur after your discharge from the hospital to Robert C. Stoler, MD, or the sub-investigators at 214-824-8721.

Your doctor may be an investigator in this research study. If so, he is interested both in your medical care and in the conduct of this research. Before you sign up for this study or at any time during the research, you may discuss your care with another doctor who is not associated with this research project. You are not under any obligation to participate in any research study offered by your doctor.

This treatment may involve other risks to you that are not known at this time.

Are There Benefits to Taking Part in The Study?

If you agree to take part in this study, there may or may not be direct medical benefit to you. We hope that the information learned from this study will benefit other patients with this disease in the future. The [redacted] stent is a Health Canada TPD and USFDA-approved product whereas the safety and effectiveness of the investigational [redacted] stent is being evaluated from this study.

What Other Options Are There?

Alternate treatments for your narrowed coronary (heart) artery may include:

- The use of other currently approved stents, including stents without any drugs applied to them
- Standard balloon angioplasty
- Atherectomy (a cutting device which removes the tissue from inside the clogged artery)
- Heart artery surgery (coronary artery bypass surgery)
- Other interventional treatments

You may choose not to join this study. If you decide not to participate, you will be treated with the standard procedure chosen by your doctor such as placement of a drug coated stent approved by the FDA. You may quit the study at any time without penalty or loss of benefits that you are entitled to. If you want to end your participation in the study, your doctor will tell you the best way to do it.

What About Confidentiality?

You have a right to privacy. This means that only people working on the study can look at all the information about you from this study. The results of this study may be published in a scientific book or journal. If this is done, your name will not be used. All information about you from this research project will be kept in a locked office.

Sometimes other groups of people need to look at your health information to review the results of the study and make sure the study is done correctly. The kinds of health information that might be given to these people include information in your existing medical records that is relevant to the study and information obtained as part of the study and may include results from lab tests or other tests like x-rays. This information might also be notes written by your doctor from your medical record or notes written by your doctor asking for tests to be done on you. These groups include people who work for Baylor Research Institute, some government agencies like the US Food and Drug Administration, the Office for Human Research Protections and the Association for the Accreditation of Human Research Protection Programs and medical device/drug approval agencies or regulatory bodies in other countries who will be overseeing this study, and [redacted] (the study sponsor) and its Contract Research Organizations and

monitors involved with the study. The privacy law requires that Baylor Research Institute and the investigators and their staff involved with the study get your permission before giving any of your health information to other people or groups. Some of these people or groups might need to look at or copy your information while they are examining the study. We usually remove your name from the information, but the people or groups looking at this information may not be required to follow the privacy law, or they may be able to figure out who you are. If that happens, we cannot promise that your information will still be protected by this law. When you sign this form you are saying it is okay for the Baylor Research Institute and the investigators and their staff involved with the study to give these other people or groups information about your health if they need it to Review the results of the study and make sure the study is done correctly. When you sign this form you are also saying it is okay for your other health care providers to give information about your health to the Baylor Research Institute in order to conduct this study.

You do not have to give your permission for us to release this information, and it is all right to refuse to sign this form. But if you do not sign this form, you cannot be in the research study. If you decide not to be in the study, your doctor will still treat you and your insurance company will still pay your medical bills (according to their policy).

If you change your mind and later want to withdraw your permission, you may do so. You must notify Baylor Research Institute in writing at 3434 Live Oak, Suite 125, Dallas, TX 75204. If you decide to do this, it will not apply to information that was given before you withdrew your permission.

You may not be allowed to look at your health information during this study. However, at a later time, you will be able to look at this information. This later time will be sometime after the study is completed.

Unless permission is withdrawn, this permission will not expire at the end of the study. Also if you withdraw your permission, you will not be permitted to continue to be in the research study.

How the Study Sponsor will use your Health Information?

The Study Sponsor ( ) will keep your health information confidential in accordance with all applicable laws and regulations. may use your health information for this study and to conduct this research. will use it for additional purposes, such as overseeing and improving the performance of its device, new medical research, and proposals for developing new medical products or procedures, and other business purposes. Any reports or publications about the study or and other research will not include your name or your description. Information received during the study will not be used to market to you; your name will not be placed on any mailing lists or sold to anyone for marketing purposes.

What Are The Costs?:

Taking part in the study may lead to added costs to you and your insurance company. Please ask about any expected added costs or insurance problems. You or your insurance carrier will be billed for the treatment you would have received anyway as part of standard care.

In other words, you or your insurance company will be responsible for the cost of the procedures and studies that are being done as a normal part of your medical care. All study-related medical procedures and laboratory evaluations will be provided at no cost to you. There will be no other cost to you for your participation in this study.

The investigator conducting this study is being paid for conducting this trial. This means that you or your insurance company will not be billed for a portion of his time and services.

Will I Be Paid For Participating in This Study?

You will not be paid for being in this study.

What If I Am Injured Or Become Ill While Participating In This Study?

The people doing this research project will do everything they can to make sure you do not get hurt during the project. If you do get hurt, there are some rules about research you need to know:

- The people doing the research project have not set funds aside to pay you money if you are hurt.
- **Baylor Health Care System** has not set funds aside to pay you money if you are hurt.
- **Baylor Research Institute** has not set funds aside to pay you money if you are hurt.
- **Baylor Heart and Vascular Hospital** has not set funds aside to pay you money if you are hurt.
- [redacted] has not set funds aside to pay you money if you are hurt.
- If you have an emergency illness during the project, the people working with you will provide emergency care. You or your insurance company may need to pay for the emergency care if that happens.
- You have not given up any of your legal rights by signing this form.

What Are My Rights As A Participant?

Taking part in this study is voluntary. You may choose not to take part or may leave the study at any time. If you agree to take part and then decide against it, you can withdraw for any reason. At certain times during the treatment, it may be unsafe for you to withdraw, so please be sure to discuss leaving the study with the principal investigator or your regular physician. Deciding not to be in the study, or leaving the study early, will not result in any penalty or loss of benefits that you would otherwise receive.

We will tell you about any new information that may affect your health, welfare, or willingness to stay in this study.

All of the people working on the project must be careful not to carelessly harm you. If you are hurt during this project, you have the right to seek legal counsel. Nothing in this consent form takes away that right if you are hurt during this research.

Whom Do I Call If I have Questions or Problems?

If you have questions about the study or have a research-related injury, contact the ***Robert Stoler, MD*** at ***214-824-8721.***

For questions about your rights as a research subject, contact Lawrence R. Schiller, M.D., IRB Chair, at 214-820-2687.

Statement of Person Obtaining Consent:

I have explained to _____ the purpose of the research project, the procedures required and the possible risks and benefits to the best of my ability. They have been encouraged to ask questions related to participation.

_____ _____

Signature of Person Obtaining Consent Date and Time

Statement of Principal Investigator:

As Principal Investigator of this study, I confirm that to the best of my knowledge this subject has voluntarily agreed to participate in this study and has had an opportunity to ask questions and has received answers to these questions. If another individual was responsible for obtaining informed consent, then this individual has signed above.

_____ _____

Signature of Principal Investigator Date and Time

Confirmation of Consent by Research Subject:

You are making a decision about being in this research study. You will be asked to give your written consent if you want to be in the study. Giving consent is like giving permission. You should not give your permission to be in this study until you have read and understood all the pages in this form. If you cannot read, then someone can read the form to you. Make sure that all your questions about this research project have been answered before you sign this form. When you sign this form, you are giving your permission to be in the study. By signing this form, you have not given up any of your legal rights or released anyone from liability for negligence.

_____ has explained to me the purpose of the research project, the study procedures that I will have, and the possible risks and discomforts that may happen. I have read (or have been read) this consent form. I have read the explanation about this study and have received the [redacted] and [redacted] Patient Guides prior to making an informed decision. I have been given a chance to ask questions about the research study and the procedures involved. I believe that I have enough information to make my decision. I have also been told my other options. To the best of my knowledge, I am not in any other medical research. Therefore, I agree to give my consent to participate as a subject in this research project.

_____ _____

Signature of Subject Date and Time

APPENDIX D:

EXAMPLE OF RANDOMIZATION WORKSHEET

[redacted] Trial
Clinical Protocol [redacted]

Randomization – Worksheet

1. Provide the following information:

Caller Information:

User ID: ☐☐☐☐☐ Enter your assigned PIN ****** (4-6 digits)

2. Call [redacted] Phone, Toll-Free: **800-[redacted]**

3. Answer the following questions:

Subject Information:

Subject Date of Birth: ☐☐ / ☐☐ / ☐☐☐☐
dd *mm* *yyyy*

Subject Initials: ☐☐☐

The following guideline is used when entering patient initials.
All letters match the keypad on the telephone.
The caller will be instructed to use 1 key for dash, Q and Z.

Example: if C is first initial select "2"

Then the system will prompt for each letter
To enter A, press 1.

Dash(-) QZ 1	ABC 2	DEF 3
GHI 4	JKL 5	MNO 6
PRS 7	TUV 8	WXY 9
Return to previous *	Help 0	Return to Main Menu #

Is Subject Diabetic? Yes ☐ No ☐

4. Record the information provided by the system.

Randomization Number: ☐☐☐☐☐☐☐☐

Treatment Assignment:
☐ [redacted] Drug Eluting Coronary Stent System
☐ [redacted]-Eluting Coronary Stent System

Subset Assignment:
☐ Angiographic/IVUS subset
☐ Not applicable

A confirmation will be faxed/emailed to you within one hour. Place this worksheet and confirmation in the Stent Treatment Information Envelope.

APPENDIX E:

DAILY INTERNSHIP JOURNAL

Week 1

05/31/05 (Tue)

I spent the morning reviewing the new employee handbook of Baylor Research Institute (BRI) Clinical Trials Office (CTO). Through this handbook, I could get some information on the activities of the CTO. Betsy introduced me to the BRI staff members and escorted me to the department of Public Safety to get a parking permit decal and photo ID badge. In the afternoon, I was given a tour of Baylor Cancer Center and Baylor Heart and Vascular Hospital (BHVH). During a tour, Betsy introduced me to the on-site staff members.

06/01/05 (Wed)

I spent most of the day working on my research proposal and tried to narrow the focus of my research topic. Betsy introduced her Study Manager Project team members to Nanette and me. The 'Study Manager' is the name of the clinical trial project management software whose web-based version is to be expected later this year.

06/02/05 (Thu)

In the morning, I attended the BRI new employee orientation and I learned about the history and organization of BRI. Today, I signed the confidentiality agreement and Betsy gave me the interventional cardiology protocol of a clinical trial that I will follow during my internship. In the afternoon, Betsy and I discussed my research proposal and narrowed the topic on 'Review of the stent evolution and how the different outcomes impact the clinical practices.' I spent the afternoon reading the electronic journal Medical Science Monitors to collect reference information. Betsy and I met Dr. Fenves who is the principal investigator of a nephrology clinical trial and I observed their meeting while they discussed a response to an internal quality assurance audit.

06/03/05 (Fri)

I spent most of the day reviewing the protocol to prepare me for the launch of the trial scheduled for next Tuesday. This clinical trial is about the drug-eluting coronary stent system. In the afternoon, Betsy and I went to the BHVH where I met many cardiology research staff there.

Week 2

06/06/05 (Mon)

This morning I met with Leah who will work at the Clinical Trials Office for a month covering Emily's maternal leave. I spent the day doing research on the stent evaluation guidelines by the American College of Cardiology (ACC) and the American Heart Association (AHC) to get some ideas for the study design of my research proposal.

06/07/05 (Tue)

Today I began the day at 7:00 a.m. to attend the study initiation meeting for a new clinical trial at BHVH. I met Leah and Emily there. A clinical research associate from the sponsor company introduced the trial synopsis to the Cath lab staff members. Because there was a concern from one of staff members of the Cath lab regarding our attending their meeting, we got out of the room right after the introduction. Therefore we received training from the sponsor person. After reviewing the whole method of this trial, we met Dr. Stoler, Principal Investigator and Dr. Choi, one of the sub-investigators of this trial.

06/08/05 (Wed)

I reviewed the journal 'Clinical Trials Compliance' and got some notes about their recommendations in responding to the FDA's 483 letter and I spent most of the day looking up information through Pub Med to find sources on the current drug-eluting stents (DES).

06/09/05 (Thu)

I spent the entire day researching on the adjunctive pharmacotherapy to coronary stenting and started to write my research proposal draft.

06/10/05 (Fri)

I continued writing my research proposal draft.

I also went to Baylor Research Institute Employee Appreciation Picnic during lunchtime and enjoyed talking to the BRI employees.

Week 3

06/13/05 (Mon)

I started the day reviewing the newsletters "Clinical Trials Administrator" and "Clinical Trials Advisor". I then spent the rest of the day completing the draft of my research proposal.

06/14/05 (Tue)

In the morning, Betsy and I went to BHVH to meet Susan Aston, research nurse for Dr. Grayburn. Betsy helped Susan with developing the study budget for an upcoming device clinical trial. I observed the process of budgeting and I felt how supportive the Clinical Trials Office is to investigators. At noon, I went to 'Focus on Research', a monthly conference on current research topics held in the Folsom Room, 17 Roberts. This month's topic was "Autoimmunity through cytokine-induced dendritic cell activation" presented by Dr. Pascual. Through this lecture, I learned about the factors in developing juvenile arthritis and SLE (Systemic Lupus Erythematosus) and the diagnosis methods using IFN-α signature.

06/15/05 (Wed)

In the morning, Betsy and I reviewed my research proposal draft and she gave me her suggestions on the sentence structure and rewording. After making some corrections, I sent it to my major professor, Dr. Bens by e-mail. In the afternoon, Nanette, BRI Business Development Specialist, gave me Dr. Grayburn's research paper to review. I enjoyed reading his paper about a novel technique that uses ultrasound targeted microbubble destruction (UTMD) to deliver genes to pancreatic islet cells.

06/16/05 (Thu)

In the morning, Leah informed me that the subject screening and enrollment will begin tomorrow for the new device trial. I spent most of the day reviewing the protocol focusing on the inclusion and exclusion criteria for the patients' screening.

06/17/05 (Fri)

Today was the first day to start subject enrollment for the clinical trial. I met Emily and Leah on the 3rd floor of BHVH at 7:00 a.m. Emily and Leah first checked the schedule of Dr.Stoler's patients and reviewed patients' charts briefly. They made a note for the patients' medical history and laboratory history to make sure that they met the inclusion criteria. We met 5 patients, but two of them did not want to get involved in the trial and three of them consented. We entered Cath Lab to observe the catheterization procedure being performed by Dr. Stoler. All of the patients who signed consent forms ultimately did not meet the inclusion criteria. The first patient had multiple lesions in a single vessel. The second patient's obstruction of the coronary artery was severe and needed invasive surgery. The third patient had no stenosis lesion in the coronary artery. We came back to the office in the afternoon and discussed my research proposal with Dr. Bens over the phone for a while. I edited my proposal based on her suggestions and sent it to other committee members for review.

Week 4

06/20/05 (Mon)

Leah and I started the second day of subject screening by reviewing charts of Cath Lab patients. The first patient was a woman in her late forties. Although she was young, her heavy family history of CAD (coronary artery disease) seemed to make Leah consider her as a possible study subject. We spent over 30 minutes answering her questions, but finally she decided not to participate in the study because she did not want to return to the hospital for follow-up visits. We met two other patients scheduled for the Cath Lab in the morning. Both of them had a history of CABG (Coronary Artery Bypass Graft) and one patient had a pacemaker. Leah obtained informed consent from them and we observed the angiography procedure. Dr. Stoler told us that the two patients could not be included in the study because most lesions of their coronary arteries were not native. In the afternoon, one patient was added in the schedule for Cath Lab and the patient was in the Jonsson Hospital. Leah and I went over to the Jonsson Hospital and reviewed his chart first. I observed while Leah explained the study to the patient. The patient had an 18-year-history of drug abuse and I could not hear him very well. The patient consented and we observed the angiography procedure. Dr. Stoler found a stenosis lesion in his artery, but Dr. Stoler did not want to include him in the study. He was concerned that the patient would not return for follow-up procedures.

06/21/05 (Tue)

Four patients were on the schedule list for Cath Lab. Leah and I reviewed the charts and Leah found that the patients did not meet the inclusion criteria. Two other patients were in the Jonsson Hospital and we went there to review the patient charts. The patients also did not meet the inclusion criteria. At 9:00 I came back to CTO to attend BRI Clinical Research Coordinators' Meeting. In the beginning of the meeting, Betsy introduced a new staff member and me to the other staff members. Betsy presented a seminar on effective budget negotiations and the use of budgeting software. At noon, I attended the Investigator Training course in Folsom Room. Ms. Barbara Richardson of MedTrials explained how to integrate research and clinical activities. The remainder of the day, I edited my research proposal to incorporate suggestions from the committee members on the specific goals.

06/22/05 (Wed)

In the morning Betsy reviewed and signed my final research proposal. She also explained to me about the request from the Radiation Safety Committee regarding the stent clinical trial. I was sad to hear that the trial should be on hold until we got the review result. I hope to get a positive result and resume the subject screening and enrollment soon. I spent most of my hours reviewing literature regarding the interventional procedure.

06/23/05 (Thu)

At 8:00 a.m., I arrived at CTO and Betsy told me that Leah got an approval e-mail from the Radiation Safety Committee. I was so glad to have good news and went to BHVH to meet Leah. Leah had already obtained the consent forms from two patients and we ran to the Cath Lab to check their condition. Both of them were pretty normal and we went to Jonsson Hospital to screen the third patient on the schedule list. We reviewed the chart first and the patient's history and labs were satisfactory for inclusion into the study. We obtained the consent form from the patient and came back to BHVH to meet the fourth patient. She was willing to be involved in the study and signed the consent form. Leah and I went to the Cath Lab and Dr. Stoler told us the third patient was perfect for this study. We were so excited to have the first subject for the study and Leah called to the sponsor to acquire the randomization number. The patient was randomized to the study stent and Dr. Stoler seemed to be satisfied with the study stent. The fourth patient was normal even though the patient had a history of 30% blockage. There were so many things we had to do right after the subject enrollment: flag the patient chart so that everyone involved would know that this was a study patient; set the 30-day follow-up visit schedule for the patient through Dr. Stoler's office; give the information package and the copy of the informed consent form to the patient; make a post-procedure Laboratory order; request CD for angiogram to be sent to the sponsor; and print out the Cath procedure log. We screened the last patient, but Dr. Stoler did not want to do angiography for the patient because the patient had done angiography 8 months ago. We came back to the office and made a list for tomorrow.

06/24/05 (Fri)

Today, Leah and I first copied the chart of our first study patient before she was discharged. We obtained two consent forms in the early morning, but we had to wait for a while. Dr. Stoler seemed to be busy with his previous schedule. At 8:30 a.m. Dr. Stoler started a catheterization and found no blockage lesion from the patients. We checked the schedule board and one patient was added on. Her CK-MB (creatine kinase - MB isoenzyme) was a little higher than normal range, but we met her and obtained the consent form. Before the procedure, Leah confirmed with Dr. Stoler that the patient's CK-MB result was fine to be included in the study. However, the patient's coronary arteries were normal. Before lunch, we met two patients, but they refused to be in the study. Six patients were scheduled for the Cath Lab in the afternoon. They were all to be transferred from other hospitals. We waited for one hour until the BHVH had one patient, but the patient was excluded due to the MI (Myocardiac infarction) history within 72 hours. For the rest of the patients, the sign "NHY (not here yet)" on the board was not changed and Leah and I decided to come back to the office. Leah filled out the screen log and told me that we screened 24 patients this week.

Week 5

06/27/05 (Mon)

At 7:00 a.m., I arrived at BHVH. I had several hours before the appointment with the committee members at 11:00 a.m. I waited for Leah in the patient room area as usual, but she did not show up. Because one of the nurses there told me she saw her, I could not leave there and I checked everywhere in the hospital. It was weird. I decided to come back to CTO and drove to UNT HSC to meet Dr. Ratka and Dr. Oglesby. They greeted me and reviewed my final proposal. After signing, they encouraged me to do my best in doing internship. I had lunch with my friend and met Ms. Carolyn to leave my proposal for Dr. Bens.

06/28/05 (Tue)

Dr. Stoler had a schedule for the office this afternoon. Eight patients were scheduled in the morning and Leah and I had to quickly screen patients. We reviewed the chart of the first scheduled patient. He had an angioplasty without stenting in 1993 and we thought he might be a study subject. However, he did not want to return in 8 months for another angiography. The second patient was young woman and she was expecting bypass surgery today, because her CT (Computerized Tomography) scan result showed severe calcification in her coronary artery. Leah explained this study to her, but she did not want to be in the study. Two patients stayed in Jonsson Hospital and we went there to review their charts. Leah explained to me that both patients did not meet the inclusion criteria; one had high CK-MB level and the other had a renal disease. We came back to BHVH and talked to two of patients. Both of them complained of chest pain and shortness of breath and consented to be in the study. We observed the angiography procedure for them, but they were normal. The next two patients that we met were the patients of Dr. Choi, a sub-investigator of this study. It was the first time I observe the angiography procedure performed by Dr. Choi. One patient was normal and the other patient had two stenosis lesions. Dr. Choi wanted to treat one stenosis lesion with a stent and the other lesion with bypass surgery. The patient was excluded.

06/29/05 (Wed)

Today was Dr. Stoler's office day and Leah took the day off. The inclusion and exclusion criteria were still not clear to me. I spent the day reviewing the protocol and related literatures. I also checked the list of the pre-procedure and post-procedure laboratory tests.

06/30/05 (Thu)

Leah and I met five patients in the morning and obtained two consents. The main reason that the patients did not want to be in study was the second angiography in 8 months. Leah asked me to make a pre-Lab order for the consented patients. I went to the nurse

desk and ordered pre-Lab tests. I was so glad to have helped Leah with something. We observed the angiography procedure and the first one was normal. The second patient had one stenosis lesion, but the lesion was too long to meet the criteria. One patient was added in the afternoon schedule. When we visited his room, he was watching the video for Cath Lab procedure. Leah did not want to interrupt him and we watched the video with him. Leah and I were impressed that the video was informative even to us. The patient consented, but was normal. We waited for an hour, but saw no more patients. So we went back to CTO.

07/01/05 (Fri)

I checked the room numbers of Dr. Stoler's patients while I was waiting for Leah. I did not expect many patients before Holiday weekend, but many patients were on the board. Today, we met nine patients and obtained five consent forms. Two were normal and the other patients had stenosis lesions, but none met the criteria. The first one had a lesion in the bypass graft and the second one showed blockage in too small vessel. The third one had perfect de novo lesion for stent implantation, but Dr. Stoler did not want to put him into the study. The patient had many other small blockage lesions, so Dr. Stoler wanted to see the patient earlier than 8 months.

Week 6

07/04/05 (Mon)

Independence Day Holiday – Office Closed

07/05/05 (Tue)

At 7:00 am, I met Leah in front of the Cath Lab and she told me that she received the e-mail from the sponsor regarding IVUS last Friday. She explained to me that the protocol required using the auto pull back IVUS system, but the Cath Lab was using the manual system. The patient screening should be on hold before the Cath Lab got the auto pull back IVUS system. Leah talked to a manager of the Cath Lab to order the system and we came back to CTO. Even though I reviewed the protocol several times, I did not catch this requirement. This incident made me review the protocol again in the afternoon. Betsy told me that the disposable auto pull back IVUS system was ordered and it would not be long to get it.

07/06/05 (Wed)

In the morning, I received training on Study Manager, the PC based software program that Baylor Health Care System has implemented to manage the clinical trials. I thought

this program was really helpful to track the clinical trials and generate the appropriate reports. I spent the afternoon reviewing the newsletters "Clinical Trials Administrator" and "Clinical Trials Advisor".

07/07/05 (Thu)

At 9:00 am, I first went to the Lieberman building to attend a meeting with Betsy. Baylor Institute for Immunology research was located at the second floor. The meeting was about the clinical trial of the Dendritic Cell (DC)-based cancer vaccines. I observed the DC clinical staff to discuss the steps of the clinical trial at the beginning stage. It was interesting to see their efforts to find an effective way for managing calls from the interested subjects. In the afternoon, I attended another meeting with Betsy. There was a presentation for the web-based Study Manager software program specifically on the financing module. I enjoyed the live presentation from Seattle, WA and the staffs' participation in a phone conference to exchange their opinion on the software program.

07/08/05 (Fri)

I spent the day reviewing the regulatory documents of the clinical trial in which I was involved. Because I took a class on organizing the FDA regulatory documents, it was exciting to compare the real FDA regulatory documents with the fake FDA regulatory documents. After reviewing, I added the clinical study to Study Manager and transferred information on the regulatory documents to the system.

Week 7

07/11/05 (Mon)

I spent another day reviewing the regulatory documents. The study correspondence was helpful for reviewing the history of issues that had happened before I was involved in this study. Betsy's explanation on my questions was also helpful to understand IRB documents and procedures.

07/12/05 (Tue)

At 7:00 am, I attended the BHVH staff meeting. Betsy and Elizabeth gave a presentation to the cardiology staff members regarding the clinical trials. I thought they made an impressive presentation. The rest of day, I finished transferring study information to the Study Manager system and asked Betsy to add procedures and sub-investigators to the Study Manager system. In the afternoon, Leah confirmed that she got the disposable IVUS auto pullback systems and the screening could be resumed on Thursday.

07/13/05 (Wed)

I spent the morning reviewing the Clinical Research Agreement and Budget Agreement on the study that I was involved in. Deborah explained to me the contract documents, even though she had no time to spare. Nanette and Regi also gave me great information on budget issues. In the afternoon, I first reviewed the guidelines for the Case Report Form (CRF). We had one subject enrollment and I tried to figure out how Leah transferred information from the source document to the CRF. I had to struggle to match data on the subject's chart to the one on the CRF. It would seem necessary for me to practice more to get used to doing it.

07/14/05 (Thu)

Leah and I resumed screening patients. We met four patients and obtained three consents in the morning. Two of them were excluded because their target lesions involved bifurcation and multiple blockades respectively. However, the third patient was enrolled in the study. We were so excited, because we have been screening without enrollment since we enrolled the first subject three weeks ago. Dr. Stoler first used the IVUS auto pullback system on the second study subject. He did not seem to like it, because it took over 25 minutes to pull the system back from the vessels. I went out for a lunch at Cremona's with many BRI staff to celebrate Cheryl's birthday. My birthday was on next week and Betsy treated me to lunch as well. It was a nice place and I enjoyed the food. After lunch, I went over to BHVH. Leah and I obtained three more consents. The angiogram procedures were unusually slow this afternoon. We had to wait until 5:00 pm, but all subjects did not meet the criteria.

07/15/05 (Fri)

Leah had outside training for the school nurses and asked me to do some works relating to the second study subject. I went to BHVH at 7:00 a.m. and copied the patient's chart before he was discharged this morning. I concerned about getting and copying the chart by myself, but all the nurses were quite willing to help me. The next thing I had to do was picking up the CDs for the angiogram. And then, I came back to CTO and sent out two CDs and the copy of ECG to the sponsor site. Leah also asked me to report the weekly screening log to the sponsor. I did use caution in filling in a screening log form and faxing it. The remainder of time, I added two subjects in the Study Manager system and built the follow-up schedules for them.

<u>Week 8</u>

07/18/05 (Mon)

Emily returned from her maternity leave and Leah will overlap with Emily for a while. Today, Emily wanted to observe the way Leah screened patients and organized documents. There were many patients on the schedule board and I felt it would be busy today. The first patient had a stent in his subclavian vein. He consented, but he had so many blockages needing CABG. Before the angiogram of the second consented patient, we went over to Jonsson and reviewed the chart first. The patient had so many exclusions and was not a good candidate for the study. When we checked the board again, we found most of the patients scheduled after lunch were dialysis patients. Leah explained to me dialysis patients were not good for the study. The second patient had one blockage lesion, but the vessel was too small to be in the study. We all came back to CTO and checked the related documents together. We drew up an IRB protocol deviation form regarding the IVUS system and also drew up an IRB protocol revision form based on the sponsor letter. Before we went home, we left the regulatory binder with Janet for the monitor visiting tomorrow.

07/19/05 (Tue)

The first patient was an orthopedist. Even though he had a history of CABG in May of this year, he asked a lot of questions about the procedure. Leah explained a lot about the procedure and the study. He was interested in the study, but we found he was currently involved in a drug study. His condition was so bad that Dr. Stoler had to spend almost one hour on him. Most of Dr. Stoler's patients had complications and we could obtain consent from only one without enrollment in the morning. Leah and I came back to CTO and met a monitor from the sponsor. The monitor pointed out some expiration on the licenses and lab certificates. In the afternoon, we screened Dr. Choi's patients. None wanted to return for another angiogram in 8 months and thus rejected to be in the study.

07/20/05 (Wed)

I started the day with creating an Excel spread sheet for the patient follow-up visits, because Emily wanted to see the whole schedule in one spreadsheet. I spent the rest of the day reviewing references for my thesis.

07/21/05 (Thu)

We first checked the Cath Room Schedule list. Dr. Stoler and Dr. Choi were expecting many patients today. It did not seem busy to me, because Leah and I reviewed the chart of the patients in Jonsson while Emily met the BHVH patients. All the Jonsson patients had exclusions and we did not obtain consents. Emily obtained three consents from BHVH patients, but none met the criteria.

07/22/05 (Fri)

After spending several hours in the Cath Lab, Emily took Leah and me to Cardiology

Consultants of Texas. It was located on the fourth floor of BHVH and Dr. Stoler's and Dr. Choi's offices were there. We first picked up the copy of Dr. Choi's license for the Regulatory binder and prepared some documents for the first subject's 30-day follow-up visit. When the first study patient came into the office, she seemed healthy. Emily assessed her angina status and adverse effects after the procedure without finding anything wrong. The patient was excited about her planed trip with her family members this weekend.

Week 9

07/25/05 (Mon)

Most of the patients' charts we reviewed did not appear good for the study. Many had internal defibrillators and malignant cancers. Because they did not have exact exclusions, we obtained five consents from them and observed their angiograms at the Cath Lab. One patient had two lesions, but one blockage was not severe enough to be treated. Dr. Choi wanted to put the patient in the study. Leah helped Emily to randomize the subject and order the follow-up laboratory tests. After the procedure, we realized Dr. Choi did not pre-dilatate the target lesion. I was concerned about that because the protocol did not allow for direct stenting. Emily told me that we have to file a protocol deviation form.

07/26/05 (Tue)

In the morning, I first went to Jonsson to copy the patient's chart before she was discharged. Most of the information except the post-procedure ECG report was filed in the chart. The patient's nurse helped me to find it, but we could not find it. I had to wait until the re-order was done. After picking up the cine film CDs, I joined Leah in screening patients. We met six patients and no one was put in the study. No more patients were added on the schedule list, so we went back to the office. In the afternoon, Betsy took me to the site initiation meeting for the study that Dr. Fink was involved in. Betsy told me that Dr. Fink was planning to move to BUMC from the UT Southwestern Medical Center and this meeting was for transferring the existing study. I observed the monitor inspecting the doctor's office and pharmacy. We toured the Investigational Drug Pharmacy and met Jabeen John, PharmD. In the evening, Betsy and I went to the Creative Cancer Concept program at the Hotel ZaZa. Ms. Elaine DeMeyer gave a presentation on antibody dependent cellular cytotoxicity. I really enjoyed her speaking and the dinner.

07/27/05 (Wed)

I started the day entering information of the third enrolled subject to the Study Manager system. After reviewing the chart, I realized that I did not collect the pre-procedure ECG report. The patient was already discharged from the hospital, but I went to the nurse desk

to ask where I could get it. One of the nurses instructed me to go to the medical records department in the basement. After signing the request document, I could copy the ECG report. And then, I sent out the cine film CDs and ECG reports to the sponsor. The remainder of the day I read research papers for my thesis.

07/28/05 (Thu)

Dr. Choi sees patients in the office on Thursday, so we screened Dr. Stoler's patients. All the charts were looking good for the study, but they did not meet the criteria after the angiogram. At the office, Emily and I prepared some documents for my involvement in the study. I signed the delegation authority form and faxed it to the sponsor with my CV. Betsy and Elizabeth assigned me the seven IRB Credentialing modules in the Baylor Learning Network.

07/29/05 (Fri)

Today was Leah's last day working on this study. Emily and I rechecked the criteria and documents before she left. Leah wanted to observe while Emily screened patients. Emily and I met six patients, but no one was enrolled today. One of Dr. Choi's patients had unique coronary arteries. Two major coronary arteries, the right coronary artery (RCA) and the left main artery (LM), arise from the aorta, and the left main artery branches into two large arteries, the left anterior descending artery (LAD) and the circumflex artery (Cx). However, the LAD and Cx of the patient branched from the RCA. Dr. Stoler explained that it was called a coronary anomaly and he has seen five such cases.

Week 10

08/01/05 (Mon)

We started out the day with a middle-aged man who had angioplasty several times before. He already had eight stents in his coronary arteries about eight years ago and he knew very well about the procedure. This case was good for me to see how well stents work on blockages without restenosis. His vessels looked good and no other stent was needed at this time. Three more patients who consented were all heavy smokers. Two of them had multi-blockage lesions and were to be excluded from the study. One was normal.

08/02/05 (Tue)

Today, I read several journals that BRI CTO subscribed. One interesting article was about 'clinical trial drift'. The author pointed out trial drift as the No.1 problem to cause high PI turnover and low patient recruitment. According to this article, the cause of the trial drift was an inadequate investigator and clinical trial staff training about the protocol.

Because we also experienced some problems from an insufficient understanding of the protocol, I quite agreed with this opinion. Many BRI staff went out for a lunch celebrating Elizabeth's 40th birthday. Her office was decorated with forty balloons and cute stuff. I was impressed with her pictures taken when she was young.

08/03/05 (Wed)

I started the day working on the IRB Credentialing module in the Baylor Learning Network (BLN). To pass the module I needed to make a 100 %. Most of the modules had short questions, but it was not easy to get 100 % the first time, so I had to retake it several times. My major professor, Dr. Bens visited BRI office to have a lunch with Betsy and me. Another student who was starting her internship at MedTrials also joined us. We enjoyed talking about the internship program over the great food treated by BRI. In the afternoon, I attended the "Training to Ship Diagnostic Specimens and Infectious Substances" class instructed by Dr. Phillips, BRI's Biosafety Officer. I learned about the IATA (International Air Transport Association) regulations on the special label for the diagnostic specimens.

08/04/05 (Thu)

It was a pretty slow day and we just met four patients today. It was interesting to hear that all of them considered the second angiogram as a good thing. They were willing to consent, but no one was put in the study. The last case had one blockage lesion and I thought she was a fit for the study. Dr. Stoler explained that he did not want to treat her at this time, because she was currently on high doses of the Coumadin treatment. Back in the office, I reviewed the Coumadin related articles and I found that the blood thinners such as the Coumadin should be stopped for a period of time prior to the stent implantation procedure. I then went to Baylor Cancer Center with Betsy. I met Dr. Fay, an oncologist of Texas Oncology PA. Betsy told me that he has been her mentor since she started working here at Baylor hospital 22 years ago.

08/05/05 (Fri)

In the morning, many patients were on the schedule list for Dr. Stoler and Dr. Choi. Emily and I were busy meeting patients at BHVH and Jonsson, then back and forth. Many were pre-operation patients. Emily was skeptical to have them in the study, because they usually had so many follow-up issues. One of them had one de novo lesion and was perfect for the study, but Dr. Stoler had the same opinion as Emily's on the follow-up complications.

Week 11

08/08/05 (Mon)

Dr. Stoler was away on vacation this week and Emily told me that this week was going to be slow. We reviewed the charts of Dr. Choi's patients. The first two patients were both positive on the cocaine test. Emily did not want drug abusers for the study, because we could not trust them in follow-up visits. The next patient had an elevated level of both CK and CK-MB. Emily suspected that this patient had an acute MI and excluded him. The last patient also did not seem to be a possible study subject due to his high level of troponins. Emily explained to me that the troponins level should be low and even slight elevation indicated some damage to the heart. However, we obtained consent from him and observed the angiogram procedure. His coronary arteries had so many blockages and he was excluded.

08/09/05 (Tue)

Emily wanted to review more lab results to complete the CRF of the third enrolled subject. The stent study monitor was due arrive here next week to look over the CRFs and the regulatory binder. I went to the medical record department to review the chart. There seemed to be filed more updated lab results in the chart. I captured all of the information on the labs needed for the CRF and reviewed it at the office. I found a physician order on the hepatic function panel and CK-MB was not executed correctly. The two tests should be completed before the procedure, but the tests were done after procedure. I marked down several questions to ask Emily on Thursday.

08/10/05 (Wed)

I spent most of the day figuring out how Emily transferred information from the charts to the CRFs for the stent study. I read through three CRFs and practiced filling in the boxes by myself. The CRFs were very detailed and seemed to require all information from the charts. After practicing, I felt more confident on CRF entry than I did when I first reviewed it. In the afternoon, I went to Study Manager Workshop. Site research nurses were there and the workshop was on the issues regarding Trait data of Web Edition compared to PC Edition.

08/11/05 (Thu)

In the morning, I spent with Emily looking through the CRFs. Emily kindly answered my questions on the CRFs. We also documented the protocol deviation on the lab tests of the third enrolled subject. Everything seemed to be ready for the monitor visit next week. The rest of the day, I reviewed the papers regarding the pharmacokinetic of the drug contained in the stent.

08/12/05 (Fri)

Today was another slow day for the Cath Lab. There were four patients listed for Dr. Choi but only one consented to participate in the study. Emily and I stayed for a while at the Cath Lab hoping for some transferred patients, but no more patients were added on. We came back to the office before lunch. I spent the afternoon reading papers for my thesis.

Week 12

08/15/05 (Mon)

Today was a very full day. Dr. Stoler was back from his vacation and had lots of patients scheduled for the catheterization. Dr. Choi also had many patients at Jonsson. We spent quite a bit of time reviewing charts. Most of the patients at Jonsson were scheduled to have transplant surgery. We obtained two consents and one was excluded after the angiogram. The other was scheduled after lunch. While waiting for the angiogram procedure, we collected signatures from the sub-investigators, Dr. Schussler and Dr. Schumacher, for a "GO" Letter. Our goal is to increase the number of investigators, so that we can screen more patients for the study. In the afternoon, we enrolled the fourth subject. This subject had a perfect blockage lesion for the study stent implantation. Because we experienced several protocol deviations for the previous subject, we paid careful attention to make sure everything was done according to the protocol. However, we found the pre-lab tests were not done correctly again. The nurse in charge of the subject said she was sorry, but she did not seem to fully realize how important the tests were for the study.

08/16/05 (Tue)

This morning I started out with visiting the fourth subject in his room. He was glad to see me. I gave him the copy of the consent form and the patient guidebook. After making copies of his charts, I attended BRI Clinical Research Coordinators' Meeting held at BUMC. Betsy started the meeting with the introduction of new staff and upcoming events. After BRI Biosafety Update by Dr. Phillips, Nanette and Betsy gave a presentation on "Subject Recruitment-Targeted Enrollment". The most interesting part of today's meeting was the group discussion on the recruitment method. The meeting attendees were divided into three different groups: Within site, Healthcare community, and General Public. We discussed the specific methods for the group and then had time to share the top five ideas from different groups. I was impressed by their great ideas and learned a lot about recruitment strategies. I spent the afternoon reviewing the charts that I copied this morning to check if there was enough information to fill out the CRF.

08/17/05 (Wed)

I spent most of the day reading papers on the Drug-Eluting Stents. In the afternoon, I added the fourth subject to Study Manager system. And then I went to BUMC to copy the updated lab reports at Jonsson and pick up the cine films at BHVH.

08/18/05 (Thu)

Today Emily and I started out with the patients at BHVH. We met two patients and both of them were first in catheterization. They seemed to be very nervous and did not want another angiogram. We went to Jonsson and met one patient. He had no exclusion, but his condition was so bad. We did not enroll him. Emily did not even explain the study to him. We obtained no consent this morning. Back at the office, we filled out the CRF and sent out the cine films to the sponsor. After lunch, we went to the Cath Lab, but no more patients were added. I spent the afternoon reviewing the CRFs and marked several pages for correction by Emily.

08/19/05 (Fri)

The first patients of Dr. Choi and Dr. Stoler both consented. Emily entered Cath Lab 6 with Dr. Stoler and I observed by myself the procedure done by Dr. Choi at Cath Lab 4. Dr. Choi's patient was normal and I moved to Cath Lab 6. Dr. Stoler's patient had a single blockage lesion and was randomized to the study stent. The problem was that the study stent did not have a size between 9mm and 18mm. The target lesion was 8mm long and Dr. Stoler wanted to use 12mm or 15mm on the target lesion. After a while, he decided to treat the patient with the study stent of 9mm. We enrolled the fifth subject today and felt great to have two subjects enrolled this week.

Week 13

08/22/05 (Mon)

This morning we screened five patients and obtained two consents. Dr. Stoler's patient was a young man and had no blockage lesion. While we were waiting for Dr. Choi's catheterization, I went to BHVH medical records department to copy the chart of the fifth subject that we enrolled last Friday. They were stricter than BUMC to give me permission to access the patient record. They requested my ID and IRB approval number. After capturing everything for the CRF, I went to the Cath Lab. The subject had a history of bypass surgery. His angiogram showed that his graft lesion was fine, but he had an 80% stenosis lesion in his native right coronary artery. Dr. Choi put him into the study and we enrolled the sixth patient. Emily confirmed that the sponsor issued a "Go Letter" for me and I could complete the CRFs.

08/23/05 (Tue)

Today I started out with visiting the sixth subject in his room. I gave him the copy of informed consent form and the patient guidebook. After reminding him of next month's follow-up visit, I went to the nurse's desk to copy the chart. I first checked that all the post-procedure tests were done and copied the chart for the CRF. At the office, I started to fill in the CRF of the fifth subject. I had to spend all afternoon to complete the CRF, but I could understand the criteria much better through this work.

08/24/05 (Wed)

In the morning, I collected the cine films from BHVH and sent them out to the sponsor. And then, I spent several hours transferring data from the chart to the CRF for the sixth subject. I felt more confident than when I first completed the CRF yesterday. I still made some errors, but I seemed to be getting faster on this. While completing the CRFs, I found the calcium test and the GGT (Gamma glutamyl transferase) test were not included in i-Stat 6+ test and the liver function test respectively. I called the lab and they confirmed that we should add the calcium and GGT tests on those above tests. I marked it to be informed to Emily. Sherece informed me that the IVUS pull back systems had already arrived on Monday. I found them at Betsy's office and brought them to the Cath Lab.

08/25/05 (Thu)

Today we screened three patients and one patient consented. The patient had a perfect stenosis lesion for the stent implantation. Because the patient's vessel was somewhat calcified, Dr. Stoler wanted to treat this patient with the study stent. However, the patient was randomized into Taxus stent and Dr. Stoler was not allowed to use the study stent. Dr. Stoler seemed to consider that the study stent was more flexible than Taxus stent. We enrolled the seventh subject today. Back at the office, the monitor had already arrived and was reviewing the CRFs. Emily and I spent the afternoon working with her. We made some corrections according to her suggestions, but she told us that we did a pretty good job on the CRFs.

08/26/05 (Fri) ~ 08/27/05 (Sat)

I flew to Chicago to attend the investigator meeting for the stent trial. The hotel was located at the O'Hare airport and it was easy to get there with complimentary shuttle service. The meeting room was packed with so many Investigators and Clinical Research Coordinators from the US and Canada sites. The meeting began with the trial update by the sponsor clinical team. And then, the Principal Investigator of this study, Dr. David Kandzari from Duke Clinical Research Institute took several hours reviewing the protocol. There were quite detailed discussions on the criteria and many sites seemed to have the same opinions on the strict protocol. The most arguable part of the protocol was

an exclusion criterion on the pre-procedure CK and CK-MB tests. Dr. Kandzari promised to review this part again and send us follow-up data within a week. For the last part of this meeting, the sponsor provided recruitment strategies to enhance study enrollment at the sites. Dr. Solomon from Methodist Hospital at Houston introduced their successful story to enroll 15 subjects in 13 weeks. He considered "Enthusiasm" to be their top strategy. I had a great time at this meeting understanding how important it is to share successes or challenges experienced at the sites.

Week 14

08/30/05 (Tue)

I took Monday off after the weekend meeting in Chicago. This morning, I first checked the messages from Emily. Most of the messages were about the enrollment yesterday. She enrolled the eighth subject. I went to BHVH and met the subject. He was a nice man in his mid-sixties. He told me that he was willing to participate in this study. He seemed to feel great about being a part of this study. I gave him the copy of the informed consent form and a 30 day-follow-up visit schedule. After collecting his chart information, I came back to the office. I spent the afternoon transferring data to the CRF.

08/31/05 (Wed)

I had a car accident on the way to the office this morning. My car had the bumper and light broken. The other driver said it was his fault and would like to pay all the costs. I took some time and went to the collision center to get an estimate. I hope it will not take long to clear this case. In the afternoon, I got a call from the sponsor regarding the IVUS base form. We had been sending out the cine films with the Cath lab logs, but the sponsor wanted to see information in the IVUS base forms instead of the Cath lab logs. I spent the afternoon filling in the IVUS base forms for all the enrolled subjects.

09/01/05 (Thu)

Emily and I screened the patients scheduled for Dr. Schumacher and Dr. Stoler. We first entered the Cath lab to observe the procedure done by Dr. Schumacher. Because it was the first study case for him, he asked a lot of questions regarding the criteria. We observed two more cases by Dr. Stoler, but no one was enrolled today. At the office, I spent the afternoon transferring the subject information to Study Manager system.

09/02/05 (Fri)

Today was a busy day. There were about fifteen patients scheduled for Dr. Stoler and Dr. Choi. We had to run back and forth between the patient rooms and the Cath labs. Dr.

Choi seemed to be more aggressively enrolling the subjects after attending the investigator meeting. We obtained seven consents and enrolled the ninth subject.

Week 15

09/05/05 (Mon)

Labor Day Holiday – Office Closed

09/06/05 (Tue)

Today, I first went to BHVH medical records department to collect the chart information of the subject that we enrolled last Friday. During chart review, I checked that all the information that I needed for the CRF was filed. Everything was on file except the pre-procedure CK-MB result. Back at the office, I transferred the chart information to the CRF.

09/07/05 (Wed)

I started the day reviewing the journals "Clinical Trials Administrator" and "Clinical Trials Advisor" and I spent the rest of the day reading the papers for my thesis.

09/08/05 (Thu)

Dr. Choi did not have the Cath Lab scheduled today so we screened Dr. Stoler's patients. Most of them were BHVH patients. Emily and I felt easy to screen BHVH patients. Because the nurses there are very much aware of this study, we did not have to be as detailed when we ordered the pre-laboratory tests for the study patients. We screened seven patients and obtained three consents. None of them met the criteria, thus were not put into the study.

09/09/05 (Fri)

I arrived at the Cath Lab at 6:40 a.m. this morning to have enough time to review the patient chart before I entered the patient room. Emily was off and I had to meet the patients by myself. Emily already spoke with two of the scheduled patients over the phone yesterday and she said they wanted to be in the study. I first met those two patients, but they said they changed their mind. There were three more patients on the schedule list and I met them. I was a little bit nervous and was not as fast as Emily. I tried to explain the study and obtained one consent. We could not enroll the subject, but I had a great experience today.

Week 16

09/12/05 (Mon)

Today, Emily and I were busy screening patients and observing their angiographies. We screened twelve patients and obtained six consents. It was the first time we enrolled two subjects on one day. We used up two IVUS systems. Because we had two more consented patients scheduled for the angiography, we drove to the office to check the status of the order. The systems have not arrived yet and we returned to the Cath Lab. Dr. Stoler was wondering whether he could use the manual system. Emily tried to contact the sponsor to ask about it, but she was unable to reach her CRA (Clinical Research Associate). We left the Cath Lab hoping to get the systems this week.

09/13/05 (Tue)

I started the day visiting the subjects at Jonsson and BHVH before they were discharged. After giving them the follow-up schedule and information guide on the stent, I collected the chart information. Some of the lab results were not updated in the chart and I requested the laboratory to fax them to the office. I spent the afternoon reading papers for my thesis.

09/14/05 (Wed)

I spent most of the day transferring the chart information to the CRFs of two subjects that we enrolled on Monday. In the afternoon I stopped by the health fair for diabetes research with Nanette on the way to pick up the cine films. The research coordinators from the Endocrine Center were providing glucose level tests with advertisement materials to people around BUMC. Nanette explained to me that this fair would be helpful to recruit subjects not only for their ongoing studies but also for their future studies.

09/15/05 (Thu) ~ 09/16/05 (Fri)

I attended Baylor Research Institute's "Clinical Research Best Practice for Coordinators" presented by Medtrials for two days. For this interactive workshop, there were pre-assignments on a Protocol and a Case Report Form. Because the protocol was the same one that I used for my group presentation last semester, I was confident on the content of the protocol. Every session started with a brief review followed by an exercise and group discussion. I loved this presentation format. We had a chance to review the whole process of the clinical trial from the initiation to the close-out. The most interesting part of this workshop was the informed consent process.

Week 17

09/20/05 (Tue)

I took Monday off after traveling to Seattle to visit my sister-in-law over the weekend. In the morning, I attended Baylor Research Institute Clinical Research Coordinators' Meeting. There were reviews on the Billing Compliance Update and BRI Finance Update followed by a presentation on the New Process for Research Order Sets by the Director of Health Information Management. At noon, I went to 'Focus on Research', a monthly conference on current research topics held in the Folsom Room, 17 Roberts. This month's topic was "Anti-HCV Immune Globulin for Prevention of Graft Reinfection after Liver Transplantation" presented by Dr. Davis. I spent the afternoon reading journals.

09/21/05 (Wed)

I spent most of the day writing the medication log on the CRFs to prepare for the Monitor visit. The CRF requests the generic names and I had to look up the drug list to find the generic names and indications for the brand names on the charts.

09/22/05 (Thu)

There was a long list of patients on Dr. Stoler's schedule. Emily and I obtained six consents, but no one fit the criteria. In the morning, we had two 30-day follow-up visit subjects. Both of them looked great and they did not report any adverse effects. Back at the office, I organized the consent forms by IRB number and made boxes to be shipped to the storage.

09/23/05 (Fri)

Emily was off today to attend the investigator meeting. I went to Dr. Stoler's office to collect the lab reports of the 30-day follow-up visit subjects and spent the morning completing the CRFs. It seemed that everything was ready for the Monitor visit. I spent the afternoon reading papers for my thesis.

Week 18

09/26/05 (Mon)

Today was a very busy day. Emily and I spent quite a long time reviewing the patients' charts. Many of today's patients had unique enzymatic profiles and past histories. We had to check if these issues were in the exclusion criteria. We met seven patients and obtained

four consents. No one fit the angiographic criteria. Back from the Cath Lab, I spent time at the library.

09/27/05 (Tue)

For the most of the day I reviewed articles for the literature review part of my report.

09/28/05 (Wed)

I spent the day reviewing reference papers at the office.

09/29/05 (Thu)

The first three patients scheduled for Dr. Stoler all consented to be in the study. One of them had a great lesion for the study and we enrolled the twelfth subject. At 10:00 a.m. Emily and I met a 30-day follow-up visit subject at Dr. Stoler's office. The subject still complained of chest pain, but it seemed less severe than before the procedure. No more patients were added on the schedule and we went back to the office.

09/30/05 (Fri)

All the patients we met this morning did not want to come back in eight months for another angiogram. While we were waiting for another patient to be added, Emily and I organized the study devices. We checked out the devices that expired in October and replaced them with new ones. No more patients were added. Back at the office, I filled in the CRF for the 30-day follow-up visit subject of yesterday. In the afternoon, I attended an informational meeting for writing CRM Internship Practicum Report at UNTHSC.

Week 19

10/03/05 (Mon)

Emily and I obtained two consents this morning. Both patients were scheduled for the same time for Dr. Choi and Dr. Stoler, so I observed by myself the procedure done by Dr. Choi. Dr. Choi's patient was normal and I moved to Cath Lab 6. Dr. Stoler's patient had a good blockage lesion for our study and we enrolled the thirteenth subject today!

10/04/05 (Tue)

I started the day visiting the subject at BHVH before he was discharged. He seemed to feel better after treatment with a stent. I scheduled his follow-up visit and collected the chart information. I was glad to check all the labs were done according to the protocol. I spent the afternoon transferring the chart information to the CRFs of the two subjects that we enrolled.

10/05/05 (Wed)

A Monitor arrived at the office around 9 AM. Because our site has enrolled about ten subjects since her last visit, this month's monitoring was scheduled for two days. I thought I was very careful to fill in the CRFs, but she pointed out a lot of errors. I spent most of the day with the Monitor correcting errors on the CRFs. Today I realized again how important the monitoring visit is for the clinical research.

10/06/05 (Thu)

Emily and I had lots of work to be done today. We first screened patients and collected signatures from Dr. Stoler and Dr. Choi for the CRFs while we were waiting for the Cath Lab procedure for the consented patients. No one was put into the study. And then, we met a 30-day follow-up visit subject at Dr. Stoler's office. Back at the office, we helped the monitor to collect some part of CRF pages for data analyzing. We received the update letter from the sponsor and found out site ranked fifth for the enrollment. It was exciting!

10/07/05 (Fri)

We obtained one consent today. The patients still did not want to return for anther angiogram. In the afternoon the sponsor announced that the enrollment of 328 IVUS/Angiogram subsets has been completed, so no more subjects have to return for a second angiogram. Emily and I were really excited to hear this news. We hope our enrollment will be faster next week. I spent the afternoon at the library writing my internship report.

Week 20

10/10/05 (Mon)

Today was the first day of screening patients after the enrollment of IVUS/Angiogram subset was completed last week. The fact that patients do not need to return for another angiogram seemed to make patients more willing to participate in the study than before. We obtained four consents, but no one was put into the study.

10/11/05 (Tue)

I spent most of the day writing my internship practicum focus report regarding the stent evolution and adjunctive pharmacotherapy.

10/12/05 (Wed)

I spent today writing my report at the office.

10/13/05 (Thu)

Today, Dr. Stoler was off to observe the Jewish holiday, Yom Kippur. Dr. Choi instead had a schedule at the Cath Lab. He usually has an office schedule on Thursday. Emily and I met at BHVH. No patient was scheduled for Dr. Choi this morning. After we met a 30-day follow-up visit patient, we checked the schedule list again finding no patient added to it. I spent the rest of the day at the library writing my report.

10/14/05 (Fri)

Four patients consented to participate in the study. One of them was found to have a severe blockage lesion in the left coronary artery. Dr. Choi first wanted to treat that lesion with a regular stent, but he decided to put him into the study. We enrolled the fourteenth subject today. The subject scheduled for the 30-day follow-up visit did not show up today. Emily called him and re-scheduled his visit. The subject wanted to visit the office out of window date. I was so worried about the schedule, but Emily told me we should not make the subjects visit if they don't want to.

Week 21 ~ Week 22

10/17/05 (Mon) ~ 10/31/05 (Mon)

During this time, while screening patients and observing the Cath lab procedures, I more focused on writing my internship practicum report and met with committee members to revise the contents of the report.

October 31, 2005 was the last day of my internship at Baylor Research Institute.

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