

Keeton, Kamaryn. A Retrospective Study on Delayed Graft Function after Deceased-Donor Kidney Transplantation. Master of Science (Clinical Research Management), December, 2017, 87 pages, 6 figures, bibliography, 20 titles.

Delayed graft function (DGF) following renal transplantation may be more severe in kidneys from deceased vs. living donors due to ischemia-reperfusion. Data was analyzed from 40 living and 49 deceased donor-recipient pairs from January 2012-13 at two centers. DGF incidence was greater in kidneys from deceased (52.1%) vs. living donors (12.1%). Comparison of DGF incidence in deceased vs. living donor kidneys yielded $\chi^2 = 14.225$ and $p = 0.0002$. Regression analyses of post- vs. pre-graft changes in serum creatinine vs. cold ischemic time, donor body mass index, donor age and terminal serum creatinine were not significant. These results indicate delayed functional recovery of transplanted kidneys from deceased vs. living donors, which is important when determining a plan of care for these patients.

A RETROSPECTIVE STUDY ON DELAYED GRAFT
FUNCTION AFTER DECEASED-DONOR
KIDNEY TRANSPLANTATION

Kamaryn E. Keeton, B.S.

APPROVED:

Robert Mallet, Ph.D, Major Professor

Harlan Jones, Ph.D., Committee Member

Theresa Cheyne, RN, Committee Member

Stephen Mathew, Ph.D., Department Chair

Johnny He, Ph.D., Interim Dean
Graduate School of Biomedical Sciences

A RETROSPECTIVE STUDY ON DELAYED GRAFT
FUNCTION AFTER DECEASED-DONOR
KIDNEY TRANSPLANTATION

THESIS

Presented to the Graduate Council of the
Graduate School of Biomedical Sciences

University of North Texas

Health Science Center at Fort Worth

In Partial Fulfillment of the Requirements

For the Degree of

MASTER OF SCIENCE

By

Kamaryn Keeton, B.S.

Fort Worth, Texas

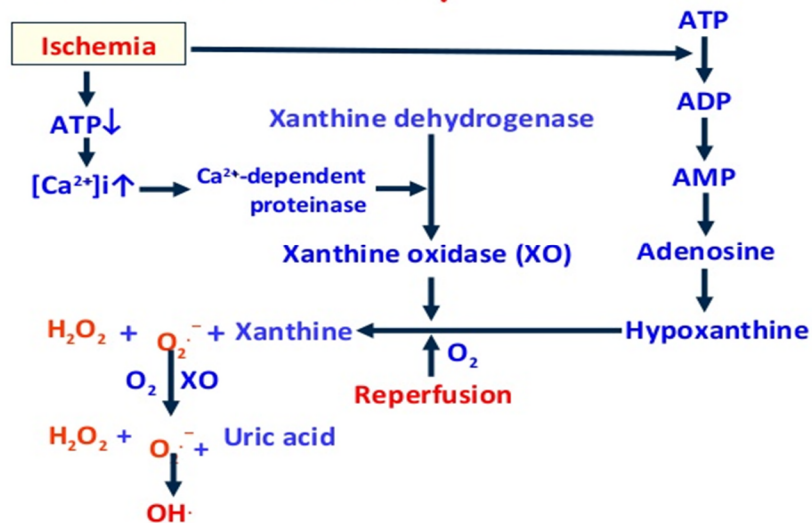
December 2017

TABLE OF CONTENTS

	Page
LIST OF FIGURES.....	iv
Chapter	
I. INTRODUCTION.....	1
II. A RETROSPECTIVE STUDY ON DELAYED GRAFT FUNCTION AFTER DECEASED-DONOR KIDNEY TRANSPLANTATION.....	3
Background and Literature.....	3
Specific Aims.....	5
Significance.....	6
Materials and Methods.....	7
Results.....	8
Discussion.....	9
Summary and Conclusions.....	12
III. INTERNSHIP EXPERIENCE.....	13
Description of Internship Site and Internship Experience.....	13
Journal Summary.....	13
APPENDIX.....	15
A. Daily Journal.....	16
BIBLIOGRAPHY.....	77

LIST OF FIGURES

Xanthine Oxidase Pathway

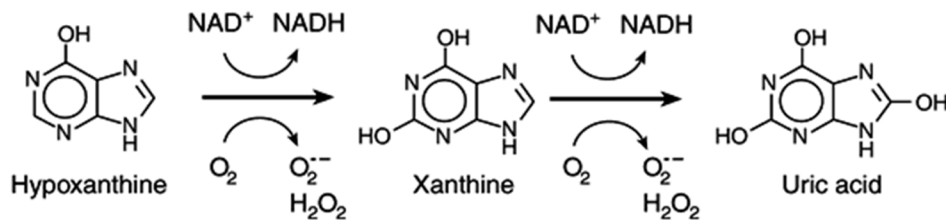


Hunan Normal University Medical College, Department of Pathology. Xanthine Oxidase Pathway.

Digital Image. N.p., 10 July 2015. Web. 06 Nov. 2017. <https://www.slideshare.net/prabeshrajjk/09-ir-injury-50388722>>. Ischemia Reperfusion Injury, Slide 22.

Figure 1: While calcium has a direct role in the contraction of renal arteriolar smooth muscle, it also activates calcium-dependent proteinase in the conversion of xanthine dehydrogenase to xanthine oxidase. The result of this pathway is the production of uric acid, hydrogen peroxide and a superoxide anion, which, under normal conditions, is converted to a hydroxyl radical that is then converted to water. In the event of ischemia-reperfusion injury, superoxide anions accumulate to a level that overshadows the ability of antioxidants to maintain homeostasis.

Xanthine dehydrogenase (XOR_D)



Xanthine oxidase (XOR_O)

Raivio, Kari O., Saksela M., Lapatto R. Conversion of Hypoxanthine to Uric Acid by Xanthine

Dehydrogenase and Xanthine Oxidase. Digital image. The Online Metabolic & Molecular Bases of Inherited

Disease, n.d. Web. 06 Nov. 2017. < <https://ommbid.mhmedical.com/data/books/971/ch111fig2.png> >.

Figure 2: Under normal conditions, xanthine dehydrogenase and xanthine oxidase function simultaneously in the conversion of hypoxanthine to uric acid; xanthine dehydrogenase acts as a reductant in the conversion of NAD^+ to NADH , while xanthine oxidase functions as an oxidant in the conversion of molecular oxygen to a superoxide anion and hydrogen peroxide.

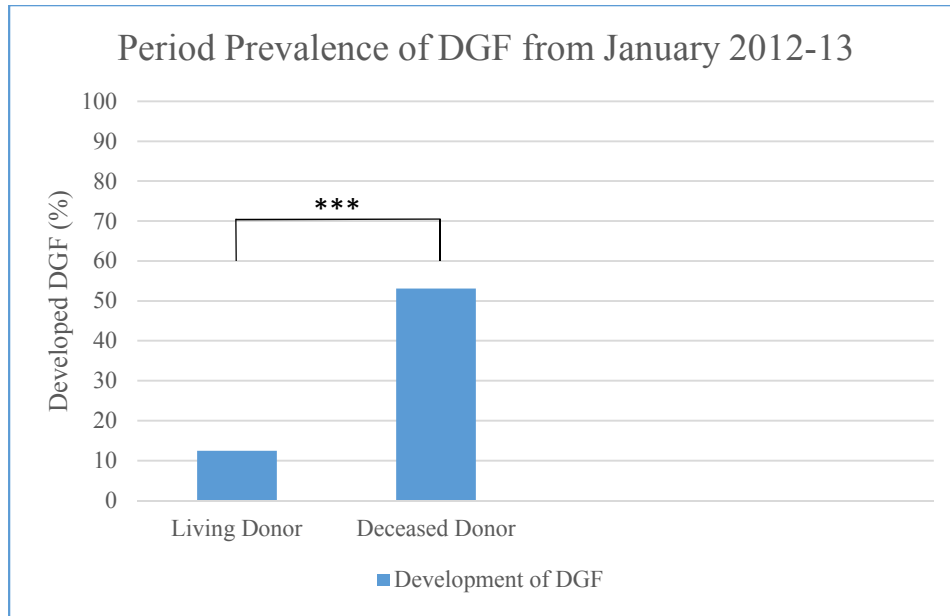


Figure 3: Prevalence of DGF over a 1 year period at BAS and BUMC. Living-donor kidney recipients (n = 40) showed a prevalence of 12.5%, while deceased-donor recipients (n = 49) showed a prevalence of 53.1%. A Chi-squared statistic of $\chi^2 = 14.225$ showed strong statistical significance at $p = 0.0002$ (***), further demonstrating that the frequency of DGF is significantly different within the two populations.

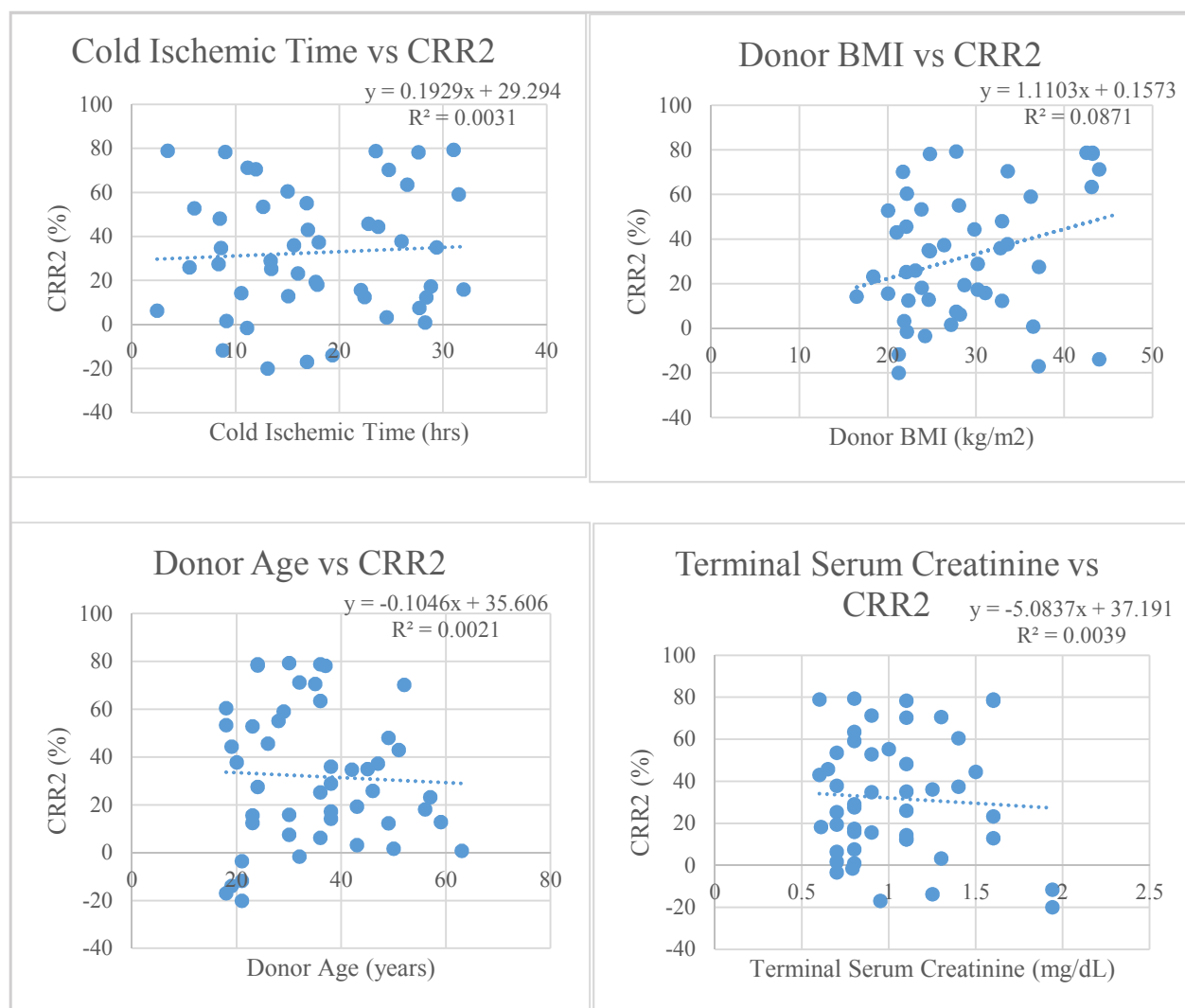


Figure 4: Linear regressions of CRR2 vs. cold ischemic time, donor BMI, donor age and terminal serum creatinine, using immediate, post-transplant serum creatinine values as day 1. Donor BMI and CRR2 showed the strongest relationship, followed by terminal serum creatinine, cold ischemic time, and then donor age. But the R^2 values for the linear regression analyses of cold ischemic time ($R^2 = 0.00314$), donor BMI ($R^2 = 0.08706$), donor age ($R^2 = 0.00207$), and terminal serum creatinine ($R^2 = 0.0039$) do not demonstrate statistically significant relationships between these variables and CRR2 in this population.

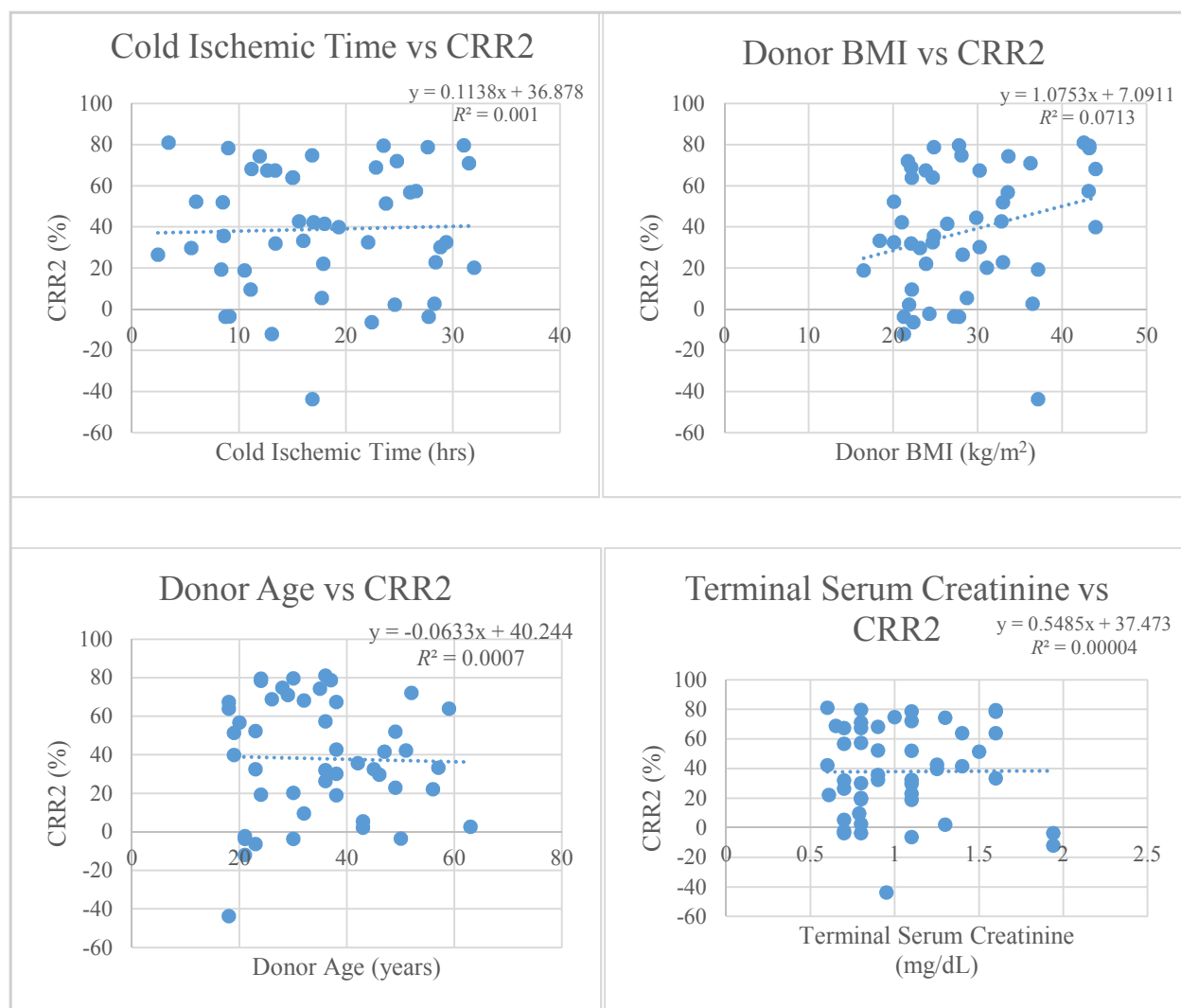
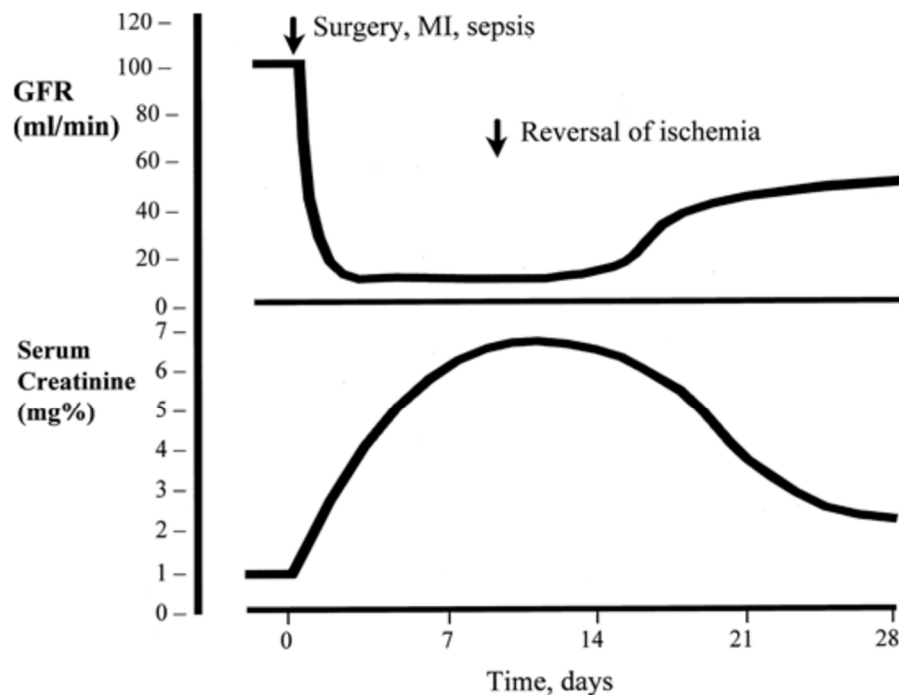


Figure 5: The R^2 values for the linear regression analyses of cold ischemic time ($R^2 = 0.00095$), donor BMI ($R^2 = 0.07134$), donor age ($R^2 = 0.00066$), and terminal serum creatinine ($R^2 = 0.00004$) were even lower when CRR2 was calculated using pre-transplant creatinine values as day 1. In this analysis, donor BMI vs CRR2 also showed the strongest relationship, followed by cold ischemic time, donor age, and then terminal serum creatinine.



Source: Hall JB, Schmidt GA, Wood LDH: *Principles of Critical Care*, 3rd Edition: <http://www.accessmedicine.com>
 Copyright © The McGraw-Hill Companies, Inc. All rights reserved.

Figure 6: Serum creatinine concentrations are dependent upon the lean muscle mass and catabolic state of the patient (19). After the onset of kidney injury, GFR experiences a sharp decrease; however, because it must be produced metabolically, serum creatinine takes days to build up to a level that reflects this loss of renal function.

CHAPTER I

INTRODUCTION

Delayed graft function (DGF) is most simply defined as the absence of immediate function of a transplanted kidney. When transplanted kidneys fail to function, the patient is at risk for extended hospital stay, increased morbidity, post-transplant dialysis and increased cost of care (1,2) . When DGF is complicated by acute cellular rejection, there is also an increased risk of allograft failure (3). A 2008 study found the occurrence of DGF to be 4-10% after donation of a kidney from a living donor, and 5-50% after transplantation of a kidney from a deceased donor (1). A 2015 study by Chaumont et al. reported that incidences of DGF after deceased-donor transplants have remained within the range of 15-30% for the past 30 years (3).

The majority of studies on DGF define the condition as the use of dialysis within the first week of transplantation (2,3). The application of this definition alone would result in inclusion of patients who were dialyzed for reasons other than ischemia-reperfusion-induced DGF, which is a common complication of transplantation and a known causative factor of delayed graft function (1). Another risk of using a dialysis-based definition alone is that a patient's need for renal replacement therapy is dependent upon the physician's subjective assessment (1). Studies using this definition may fail to include patients whose creatinine clearance is inadequate in the immediate days post-transplant, but who are deemed sufficiently stable for discharge without dialysis. Other studies have opted for a urine output-based definition of DGF, but this definition fails to account for residual kidney function which may vary within patients (1). Clinicians

evaluate graft function from the patient's clinical presentation in the hours and days post-transplant; this includes monitoring of urine output, daily metabolic panels, vital signs, ultrasounds and biopsy when necessary. Results may be confounded if patients who do have DGF are erroneously included in the cohort of immediately-functioning grafts, or if patients who have other comorbidities with clinical presentations resembling are included in the DGF cohort; therefore, it is important that the inclusion and exclusion criteria of delayed graft function are rigorously defined.

In this study, delayed graft function was identified in two ways: dialysis-requiring DGF (D-DGF) and non-dialysis-requiring DGF (N-DGF). D-DGF was defined as the use of dialysis within the first 7 days of transplant for reasons other than acute cellular rejection, surgical complications or comorbidities that were not due to ischemia-reperfusion injury (1,4). N-DGF was identified by a creatinine reduction ratio on post-transplant day 2 (CRR_2) $\leq 30\%$, in the absence of the aforementioned comorbidities (2,5,6). The creatinine reduction ratio directly measures kidney function by comparing the serum creatinine on days 1 and 2 post-transplant, and the rate at which creatinine is being excreted by the kidneys. In severe cases of DGF, the creatinine will fail to fall ($\text{CRR}_2 = 0\%$), or may even increase post-transplant ($\text{CRR}_2 < 0\%$). In other cases, the kidneys fail to excrete creatinine at a sufficient rate ($0 < \text{CRR}_2 \leq 30\%$). It is important for physicians to understand the risks associated with the first 2 days post-transplant due to the potential for hyperkalemia, which can lead to muscle weakness or paralysis, cardiac arrhythmias and conduction abnormalities (7).

CHAPTER II

A RETROSPECTIVE STUDY ON DELAYED GRAFT FUNCTION AFTER DECEASED-DONOR KIDNEY TRANSPLANTATION

Background and Literature

The generation of reactive oxygen species (ROS) due to hypoxemia has been identified as a mechanism of ischemic kidney injury during the pre-procurement period (1,3,8). Hypoxic conditions are especially manifested after death or trauma. ROS are a natural by-product of cellular metabolism and their presence in the human body is normally balanced by the presence of antioxidants. When the ROS outweigh the antioxidants, the patient is considered to be under oxidative stress. ROS normally function to induce apoptosis and necrosis; this action is important in the context of DGF because acute tubular necrosis is a common result of ischemia-reperfusion injury which can be seen microscopically via biopsy. Siedlecki et al. attribute renal oxidative stress to the failure of 3 primary processes: vasoconstriction of the renal afferent arteriole, xanthine dehydrogenase activation (XD) and heme oxygenase-1 (HO-1) (8).

The renal afferent arteriole delivers blood from the renal arteries to the glomerulus, and changes in its diameter are responsible for maintaining an appropriate renal perfusion pressure and glomerular filtration rate. When blood flow to the renal afferent arteriole is reduced, baroreceptors in the juxtaglomerular cells detect the decreased blood pressure (8). Renin is released by juxtaglomerular cells and subsequently the concentration of angiotensin II is increased (8). Angiotensin II acts as a vasoconstrictor at the afferent and efferent arterioles via

the tubuloglomerular feedback mechanism, resulting in decreased renal blood flow and decreased glomerular filtration rate (8,9,10). Angiotensin II also promotes calcium release from the sarcoplasmic reticulum in afferent arteriolar vascular smooth muscle, further promoting renal vasoconstriction (8,9,10). Additionally, endothelin-1, a vasoconstrictor released by vascular endothelial cells, and thromboxane A₂, a ligand released by platelets that functions as a prothrombotic agent, are released to increase intravascular perfusion pressure (8). These constrictive forces- which, under normal conditions, function to regulate perfusion pressure and mean arterial pressure- only further exacerbate the lack of blood flow to the kidney in the pre-procurement period.

Heme oxygenase-1 catabolizes iron-containing molecules under anaerobic conditions; failure of HO-1 to function causes a build-up of iron-containing molecules in the cell cytosol (8). Iron overload is particularly dangerous in this case because of its ability to catalyze, via Fenton chemistry, the conversion of hydrogen peroxide to cytotoxic free-radicals which damage cellular membranes, compromise transcellular electrolyte gradients, promote DNA cleavage and activate proteases that degrade the basement membrane of the proximal tubule (8,11).

Xanthine dehydrogenase (XD) has an anti-oxidative effect, but it has the opposite effect when it is converted by Ca²⁺-activated proteases to xanthine oxidase (XO) (8,12) (Figure 1). Under normal conditions, xanthine dehydrogenase and xanthine oxidase function simultaneously in the conversion of hypoxanthine to uric acid; xanthine dehydrogenase acts as a reductant in the conversion of NAD⁺ to NADH, while xanthine oxidase functions as an oxidant in the conversion of molecular oxygen to a superoxide anion and hydrogen peroxide (Figure 2). A 2010 study found significant changes in xanthine metabolizing enzyme activity after transplant, and suggested that measurements of this activity could be useful in distinguishing immediate, slow

and delayed recovery of graft function (12). While hypoxic conditions are present in all patients during the death process and after severe trauma, brain death and cardiac death have different physiological pathways, and so it is reasonable to expect that they result in different effects on the renal system.

Donation after cardiac death (DCD) refers to the recovery of organs after withdrawal of life support when a patient has suffered severe brain damage, but does not meet the formal criteria for brain death (13). For example, if a patient suffers a traumatic brain injury resulting in irreversible brain damage, are being maintained by life support, but are not formally considered brain-dead, their kidneys may be donated after life support is removed. This would be considered donation after cardiac death due to the asystole that occurs after removal of life support. Kidneys donated after cardiac death are at an increased risk of delayed graft function due to the significant warm ischemic time, which is the time that the organ remains at body temperature between asystole and the cold perfusion of the explanted organ (3,8). Warm ischemic time is minimal in donation after brain death (DBD). However, prolonged cold ischemic time, which is the time between organ cooling and reperfusion, is also a recognized risk factor for DGF (3,8).

Other risk factors associated with DGF are recipient and donor age, African American race, donor obesity, donor history of hypertension or diabetes, cold storage in contrast to machine perfusion, and an array of immunologic factors (3).

Specific Aims

The purpose of this study was to investigate the risk factors for DGF within the Baylor system using specific inclusion and exclusion criteria to define delayed graft function. This definition allows the condition to be studied as a single morbidity rather than it being

confounded by concurrent diseases. Based on previous research, it was expected that living donor kidneys would have the lowest prevalence of DGF due to the lack of death or trauma-induced renal ischemic injury in living donors. Secondly, it was expected that kidneys from older donors, donors with high terminal serum creatinine levels or BMI, or prolonged cold ischemic times would be more susceptible to the development of DGF following transplantation. Lastly, it was expected that kidneys donated after cardiocirculatory death would have a higher prevalence of DGF compared to DBD kidneys (8,15).

Significance

Siedlecki et al. reported that the incidence of delayed graft function after deceased kidney donation has increased with the expansion of donation criteria, and that this increase coincides with a 40% decrease in graft survival (8). This trend is clinically important because disease incidence would be expected to decrease as medical knowledge in a given field advances. Extended criteria donors are defined as any donor over the age of 60 at time of death, or any donor aged 50-59 presenting with one of the three following conditions: history of hypertension, terminal serum creatinine > 1.5 mg/dl, or history of stroke (16). The donor criteria were expanded to include this population in order to meet the increased demand for donor kidneys.

The impact of DGF on long-term graft survival is not without controversy (3,8,15,17). In 2015, Chaumont et al. found that when DGF is compounded with early graft rejection, patients are at a higher risk of graft failure, and these authors suggested that previous studies reporting an association between DGF alone and graft failure failed to take acute rejection into account (3). Singh et al. found donor age and early rejection to be the only significant risk factors for graft failure in DCD transplants, while DGF was not a significant risk factor (15). Even if there is no

long-term impact on graft survival or patient mortality, DGF is still an important clinical problem because of the risk for extended hospital admission, hyperkalemia, increased morbidity, post-transplant dialysis and increased cost of care (1,2).

Materials and Methods

This study was approved by the Baylor Scott & White IRB and the University of North Texas Health Science Center IRB. Data was collected on patients receiving deceased and living-donor kidney transplants at Baylor Scott & White All Saints Medical Center (BAS) and Baylor University Medical Center (BUMC) over the period of January 1, 2012- January 31, 2013. During this time, there were 40 living donations and 49 deceased donor-recipient pairs which met all of the criteria for this study. Donor and some recipient data came from spreadsheets provided by the United Network for Organ Sharing (UNOS) through BAS Transplant Informatics. Data was abstracted for deceased and living donors and recipients. Only donors over the age of 18 years were included in this study. Each donor-recipient pair was de-identified and assigned a unique number (n = 1, 2, 3...). Rejection episodes were identified by UNOS data and electronic medical records. Recipient pre- and post-transplant serum creatinine values were also abstracted from electronic medical records. Baseline serum creatinine concentrations were taken from the most recent basic metabolic panel prior to transplant. If dialysis was provided preoperatively then the pre-dialysis value, if available, was taken as the baseline value. Day 1 creatinine clearance was collected from the basic metabolic panel taken in the immediate hours after transplant. Day 2 creatinine clearance was collected from lab results taken 24-48 hours after the day 1 value, and were obtained at approximately the same time each day post-transplant. CRR2 (%) was calculated using the following equation:

$$\frac{(\text{CCR day 1} - \text{CCR day 2})}{(\text{CCR day 1})} * 100, \quad \text{CCR} = \text{creatinine clearance}$$

The clinical course of each recipient's hospital visit was verified by radiological findings, progress notes, OR reports, discharge and transplant summaries. Patients with acute cellular rejection, surgical complications and bacterial infections were excluded from this study. Patients who received multiple organ transplants were also excluded from this study.

A chi-square analysis was used to determine independence between deceased and living donors. Yates's correction for continuity was applied (18). Multi-kidney donors were paired with their corresponding recipients. Due to the small DCD sample size ($n=7$), Fisher's exact test was used to determine independence within deceased donors after brain death and cardiac death (18). An online calculator was provided by Social Science Statistics for Fisher's exact test. Microsoft Excel was used for the linear regressions, and graphs were produced showing donor age, terminal serum creatinine, donor BMI and cold ischemic time vs CCR2 for deceased donors. CCR2 was calculated using the post-transplant creatinine levels as CCR day 1 (Figure 4), and then again using pre-transplant, baseline values as CCR day 1 (Figure 5). R^2 values were produced via Microsoft Excel.

Results

Figure 3 shows that of the 40 living donations, 5 recipients developed DGF (12.5%). Of the 49 deceased-donor transplants, 26 patients developed DGF (53.1%). A chi-square analysis was used to analyze living donor kidneys vs. deceased donor kidneys (both DBD and DCD) in the development of DGF. A chi-square statistic of $\chi^2=14.225$ was calculated with a two-tailed P value = 0.0002, which was statistically significant. In the analysis of DCD and DBD donors, the

Fisher exact test statistic value was 1, and the result was not statistically significant at $p < 0.05$.

The R^2 values for the linear regression analyses of cold ischemic time ($R^2 = 0.00314$), donor BMI ($R^2 = 0.08706$), donor age ($R^2 = 0.00207$), and terminal serum creatinine ($R^2 = 0.0039$) did not indicate statistically significant correlations when CRR2 was calculated using post-transplant creatinine values as day 1 (Figure 4). Relatively, donor BMI and CRR2 showed the strongest correlation, followed by terminal serum creatinine, cold ischemic time, and then donor age. The R^2 values for the linear regression analyses of cold ischemic time ($R^2 = 0.00095$), donor BMI ($R^2 = 0.07134$), donor age ($R^2 = 0.00066$), and terminal serum creatinine ($R^2 = 0.00004$) were even lower when CRR2 was calculated using pre-transplant creatinine values as day 1 (Figure 5). In this analysis, donor BMI vs CRR2 also showed the strongest relationship, followed by cold ischemic time, donor age, and then terminal serum creatinine.

Discussion

The first hypothesis of this study was supported by the finding that the prevalence of DGF amongst living-donor kidney recipients (12.5%) was much lower than that of deceased-donor kidney recipients (53.1%) over the one year period of January 2012-13. This outcome supports the literature stating that renal ischemia-reperfusion injury is a primary driving force for DGF, since this type of kidney injury is minimal in living donations (1,3,7). The chi-square value ($\chi^2 = 14.225$) showed strong statistical significance at $p = 0.0002$, further demonstrating that the frequency of DGF is significantly different in recipients of kidneys from living vs. deceased donors.

The second hypothesis of this study was not supported by the linear regression plots (Figures 4 and 5). Very low R^2 values indicated that the independent variables- donor age, donor

BMI, terminal serum creatinine and cold ischemic time- do not individually explain the variation in CRR2. The low R^2 values do not show significant relationships between various risk factors and DGF. The regression analyses do suggest that graft function does not recover well during the first two days post-transplant, since none of the measured variables showed a significant effect on the development of disease during the two-day time period. The results showing that cold ischemic time alone did not show a significant impact on CRR2 in this population are important when studying the timing of the onset of injury leading to delayed graft function. The length of the storage time did not show a significant effect, positive or negative, on CRR2. This could suggest that the inciting event occurs prior to organ procurement rather than during machine perfusion or cold storage; alternatively, there could be a risk factor in the recipient that, in combination with prolonged cold ischemia time, leads to DGF. Further studies are required to address these two possibilities. One limitation of this analysis was that data was not recorded concerning whether or not the kidneys underwent machine perfusion or cold storage preservation, as it has been shown that machine perfusion reduces the risk of delayed graft function (14). Another limitation is due to the nature of creatinine itself; serum creatinine concentrations are dependent upon the lean muscle mass and catabolic state of the patient (19). After the onset of kidney injury, GFR experiences a sharp decrease; however, because it must be produced metabolically, serum creatinine takes days to build up to a level that reflects this loss of renal function (Figure 6). A future study might analyze the effects that the variables analyzed in this study have on day 5 and day 7 creatinine reduction ratios, 1 year graft survival and chronic graft survival in this population. A larger sample size might also reveal more significant relationships and larger R^2 values.

Due to the small sample size ($n = 7$) of DCD kidney recipients for this 13-month period at these two centers, this study was not able to support the alternative hypothesis concerning DCD and DBD kidneys. While the percentage of DCD kidney recipients which developed DGF (57.1%, $n = 4$) was marginally higher than the percentage of DBD kidneys that developed DGF (52.4%, $n = 22$), the results of the Fisher exact test were not significant at a p value of 0.05. An expanded study period to capture more cases could permit more robust analyses of graft function between these two groups. This study initially intended to compare extended criteria donors as well, however donor stroke history was not recorded in the UNOS data so these patients could not be completely identified.

Concerning Figure 5, a limitation worth noting is that pre-dialysis creatinine values were not always available. This could potentially make the value for C_{CR} day 1 smaller than it would be at baseline, leading to a smaller value for CRR2 and a potentially false diagnosis of N-DGF. It was also not always possible to determine when each recipient's most recent dialysis treatment was prior to hospital admission. Having variance in the pre-transplant time without dialysis might cause some patients to be misdiagnosed as well due to high variance in baseline and post-transplant creatinine levels.

These findings are clinically important when developing a plan of care for patients who have received kidneys from deceased donors. Because the prevalence of DGF is higher in those patients, medical professionals should take precautions to avoid hyperkalemia and the need for dialysis in these recipients- especially in the first two days post-transplant.

Summary and Conclusions

The results of this study showed that while kidneys from deceased donors resulted in significantly higher frequencies of DGF in comparison to kidneys from living donors, the individual effects of donor age, donor BMI, terminal serum creatinine and cold ischemic time were not significant determinants of DGF for this population. There are multiple factors at play in the development of delayed graft function due to ischemic reperfusion injury, and this study was primarily concerned with the effects of the donor. Future studies should include a larger sample size and evaluate long term outcomes, different measures of creatinine clearance such as day 5 and day 7 reduction ratios, and both donor and recipient immunologic and non-immunologic data. Recipient age was not collected in this study, so Δ GFR was not included in the linear regression due to the requirements of the MDRD equation:

$$[\text{GFR} = 175 \times (\text{serum creatinine})^{-1.154} \times (\text{age})^{-0.203} \times 0.742 \text{ (if female)} \times 1.212 \text{ (if black)}].$$

CHAPTER III.

INTERNSHIP AT BAYLOR SCOTT & WHITE RESEARCH INSTITUTE

Description of Internship Site and Internship Experience

This internship took place at Baylor All Saints Medical Center at Fort Worth in the department of Transplant and Clinical Research. Most of the studies were nephrology or hepatology studies, but there were some women's studies as well. The internship started on May 30, 2017 and will terminate on November 24, 2017. Most of the clinical research coordinators were registered nurses (RNs), but there was also a coordinator with a post-graduate education, and there was another who specifically handled regulatory affairs. Additionally, there was a clinical research assistant who was also a former CRM student.

Journal Summary

I was able to experience many different aspects of clinical research at this site. Initially, I shared an office with the clinical research assistant. She taught me about the different studies that were taking place at this site, and I was able to observe her ship labs. I also helped her with inventory in the supply room and learned a lot about the correspondence between the site and the sponsor in regards to collection samples. Although I could not handle specimens for this internship, I watched her and asked questions when I had them. I also completed dangerous goods training online through Mayo Medical Laboratories. Also, during the first part of my internship, Sandra Morones asked me to perform a literature review for one of the nephrologist's

PI-initiated studies. I really enjoyed this, and I was thrilled to be able to write that section of the proposal draft.

I later shared an office with an RN coordinator. My favorite experience with her was when I had the opportunity to attend a kidney transplant. I was able to observe her and other coordinators give informed consent, and it was interesting seeing the different styles of each coordinator while presenting the same information. I admired how each coordinator ensured that the patients understood their rights and the voluntariness of the studies. I was able to attend patient visits with other coordinators as well, and I enjoyed watching them prepare for the visits and interact with patients. I learned about the data entry that takes place after the visit, which goes directly to the sponsor and is frequently a topic of discussion during monitor visits. Most importantly, by interacting with patients I received further insight into their feelings and the different reasons why patients decide to join studies in the first place.

For the later portion of my internship, I shared an office with the regulatory coordinator, Maria. Theresa asked me if there was anything that I especially wanted to focus on during the internship, and I told her that I wanted to gain a working knowledge of regulatory affairs. Maria taught me how each study binder was organized, and she was always available and willing to help when I did not understand something. Eventually, I learned to create informed consent documents based on the constant correspondence between the sponsor, the site, and the IRB. I learned to process IND safety reports and to put them in the correct format for Baylor's IRB. I was also able to attend an IRB meeting with Maria at BUMC in Dallas.

I spent the final portion of this internship working on my study. Theresa and Sandra M. were incredibly helpful whenever I needed advice or expertise. I feel that my time here has prepared me for a future career in research and in medicine.

APPENDIX A
DAILY JOURNAL

Week 1

Tuesday, May 30, 2017

On my first day at Baylor Scott and White Research Institute, I was given a tour of the site and was introduced to the staff. I was told to report to Sandra Morones, Transplant Research Supervisor, RN, BSN, MSPH, CCRC, until my site mentor Theresa Cheyne, RN, Manager, Clinical and Transplant Research, returned from vacation on Thursday, June 8th. During the tour I found out that I would be sharing an office with Holy, the clinical research assistant and former CRM student. I received my network account ID as a part of my login information, but I was told that it would take 3-5 business days for a password and so I would not be able to start my CITI training yet. At lunch time, however, I was able to attend a free Lunch and Learn provided for the nurses' Continuing Education. The topic was Enhancing End of Life Care through Hospice, and the luncheon was held by VITAS Healthcare, the contracting hospice service for the hospital. This was also the day that I made contact with my advisory committee to ask about their availabilities. At the end of the day, I discussed the process of writing and defending a thesis with Holy.

Wednesday, May 31, 2017

On day 2 of my internship, I helped organize and break-down expired kits. Kits are packages of materials sent from the sponsor to be used by the site for collection of specimens and data. They contain materials such as test tubes, syringes, pipettes and requisition forms. Paperwork from expired kits was to be disposed of in the shredding bins generally used for documents containing protected health information.

Thursday, June 1, 2017

On this day, my complete login information was acquired and I gained computer access and access to my BSWhealth email account. However, I was still unable to complete the Baylor Learning Network training on this day. I was able to follow research RNs, Sandra and Ava, to visit Dr. Gautam, a hepatologist and one of the principal investigators (PI). I introduced myself and Sandra asked if she needed help on any of her studies. Dr. Gautam was excited to have an intern and said that she would like to meet with me privately on another day to talk about my internship goals. Sandra had previously discussed with me that Dr. Gautam had a study up for review, and that working with her could help me think of a topic for my research proposal.

Friday, June 2, 2017

The end of my first week consisted of patient visits. The first patient Sandra and I visited in Day Surgery was still in the screening stage of a double-blinded study on non-alcoholic steatohepatitis. Sandra explained to me that "randomized control trials are performed so that you have a comparator" when analyzing experimental data. The patient wanted to know the details of her first liver biopsy which would determine her eligibility for the study. The biopsy would be performed via the transjugular vein, and the tissue sample results would determine whether or not she was a candidate. This particular patient had already received and given her initial informed consent, but understandably she was still hoping that she would be healthy enough to not qualify.

The second patient I visited in Day Surgery was with Ava, and this was the initial informed consent visit for this patient. Ava explained that it was difficult to enroll patients in this study because it focuses on acute mediated rejection within a year post-kidney transplantation.

Ava reiterated to the patient that participation in the study "would not change the course of [the patient's] treatment, it would just be an addition." The patient had a history of two unilateral transplants, with the most recent one being 10 months prior. The patient was not aware of her rejection status yet, so after we left I asked about the reasoning behind recruiting at this point in time. The nurse explained that she likes to give patients time in advance to think about enrollment, so that if they are a candidate they can already have an idea about what they want to do.

The third patient I visited was with Ava as well, this time on the admissions floor. The patient was already enrolled in a study and had a history of unilateral kidney transplant and focal segmental glomerulosclerosis (FSGS). The study required the mean of 3 blood pressure readings to be recorded, and blood samples were later taken as well. The patient presented with hypertension and edema to the upper extremities.

Week 2

Monday, June 5, 2017

Today started with a patient visit. The patient was here with his wife for an evaluation for a liver transplant. There is a physician here conducting a study evaluating kidney function in transplant patients, so it was important that we recruit this patient for the study. Ava gave the informed consent and explained that participation was completely voluntary. She explained that he would be receiving a test that is usually very expensive for free, and she pointed out that it would also be personally beneficial to the patient to know about his kidney function. She explained that the primary inconvenience would be the 3 hours of testing and drawing of blood. Both the patient and his wife said “we probably will do it,” since he had a history of UTI and they were concerned about his recovery from that. The couple took the informed consent form so that they would have time to think about it. Ava said she makes sure to tell every patient who comes in for evaluation that “research is always voluntary” and that they “would still be receiving the gold standard of care.”

The next patient visit was for the same study; however it was a different person giving the informed consent. Verbally it was not word-for-word, but the same benefits were explained. She also mentioned that the patient could not have any PO intake for 1 hour before testing. The patient had previously mentioned that he and his wife lived over an hour away, so Sandra did acknowledge that the travel time to the hospital, the 3 hours of testing and the travel time home might not make him the best candidate for the study. I thought this was very considerate on her part because it shows that she was listening and that she had the patient’s best interests in mind. Surprisingly, he agreed and signed the informed consent in the room. We found out that he was actually a nurse, and so he understood the importance of research and was willing to help. He

explained that he had been unable to do his job for the past year due to being diagnosed with primary Wilson's disease. After the signature was obtained, Sandra thanked the patient and reminded him again of the voluntariness of participation.

While walking back to the office, we had a discussion about the use of controls and placebos. I told her that the way the nurses here explained it to the patients helped me understand the concept better. I had always thought that some patients would be receiving nothing, while some receive the experimental medication, and during class I struggled to understand how that was ethical. However the reality is that some patients receive the experimental medication, while others receive whatever the standard of care is at that time. That way, researchers can determine whether or not the results represent an actual improvement in care.

Tuesday, June 6, 2017

Today I received an email from the chief compliance officer to complete the Baylor Scott & White Health (BSWH) FY2016 Conflict of Interests Program Disclosure Statement, which is an online form that must be filled out annually to disclose any potential financial conflicts of interests. It asked about my own financial investments in Baylor or in any company who does business with Baylor. It also asked about my relationships with people who work at Baylor or who have the ability to influence someone who makes decisions at Baylor. Unfortunately I was absent on this day due to personal reasons, but I let Sandra know ahead of time.

Wednesday, June 7, 2017

Today I completed the FY2016 BSWH Disclosure Statement online. I also attended a multidisciplinary Breast Tumor Conference for lunch. It was a case review of 3 current patients

presented by Baylor physicians. Presenters included 3 oncologists, a radiologist and a pathologist. I listened as they discussed current investigational drug studies for chemotherapy treatments and debated about the clinical significance of the findings. One case in particular involved a 32 year old female with a family history of breast cancer who was diagnosed with invasive ductal carcinoma (IDCA) in her right breast. Her physician said she responded extremely well to her first round of chemo, but the patient still required one final surgery and radiation of her entire chest wall. The patient had received implants in the past, so she maintained a relationship with her plastic surgeon who was also in contact with her oncologist. She had asked about the possibility of a nipple-sparing mastectomy (NSM), but her oncologist was skeptical due to the lack of literature on patients with her specific criteria. Prior to receiving chemotherapy, she would not have qualified for the surgery due to the proximity of the tumor to the nipple, but after treatment the tumor had minimized to a size that made her technically a candidate. Her physician explained to her that she could technically perform the surgery, but she also explained her discomfort due to the lack of research in the area. Although she still wanted the more cosmetically appealing surgery, the patient did not want to increase her risk of relapse after responding so well to the first treatment. The physician told her she would ask her colleagues for their opinions. One of the physicians argued that since she would be having chest-wall radiation afterwards, an NSM followed by implants would be a reasonable option. However, most of the physicians agreed that there was an increased risk due to the lack of literature.

Later this day, I observed the clinical research assistant and learned about the shipping process of labs. Depending on the study protocol, some labs were to be shipped at ambient temperature while others were to be shipped frozen. As previously stated, specimens from the

same patient requiring two different transportation conditions each require their own requisition forms and shipping labels. There are some combination boxes that allow both specimens to be shipped together. These also require two different requisition forms, however there only needs to be one shipping label. It is standard to use the label for frozen specimens since one of the packages is on dry ice. Ambient packages typically contain gel packs to control for fluctuating temperatures.

Thursday, June 8, 2017

While working on the correlative studies section for one of the nephrologist's research protocols, I started brainstorming ideas for my research topic. I thought it would be interesting to analyze some of the psychosocial changes in donors before and after transplantation. I would use a questionnaire to collect demographic data, relationship to the recipient, and emotions experienced before, immediately after, and years after donation. I also considered possibly analyzing the differences between kidney and liver donation as well, since the recovery processes are so different for each. Some of the challenges to this study would be the formulation of appropriate questions, finding the proper statistical tests to analyze qualitative data, getting IRB approval, developing my own informed consent forms and recruiting and interviewing patients. Donor follow-up is particularly challenging compared to recipient follow-up because they are not as closely followed by the hospital. Also, it would not be appropriate to survey patients about feelings that they had years in the past.

I discussed my ideas with Sandra who suggested that I focus on kidney transplants instead of liver since most of the liver transplants are performed at the Dallas campus. She also told me about a behavioral health study that she had done in the past looking at patients with

lung cancer, their relationships with their primary care givers and how that affected their recoveries. This gave the idea of maybe doing a survey among current kidney recipients and their caregivers, and then analyzing the health practices and overall health of the two. Theresa came back from vacation today so I also spoke with her about my ideas. She agreed that coming up with the right questions would be the next step, but it might also be challenging since I'm not a behavioral health professional. That was something that I was concerned about too because I didn't want to get into the diagnostics since I am not licensed. We also talked about the committee meeting time and location, which would take place at the UNTHSC campus.

Friday, June 9, 2017

Today I watched Holy, the research assistant, process and package labs and helped her organize the supply room. I also continued to brainstorm proposal ideas. I plan to think about it more over the weekend and reassess on Monday.

Week 3

Monday, June 12, 2017

Today I discussed three different proposal ideas with my site mentor Theresa and the supervisor Sandra.

1. Survey evaluating patient competency of their immunosuppressants/medications

The importance of this study would be to measure the current effectiveness of patient education. Upon receiving a kidney, the patient's body immediately starts fighting the foreign body. For this reason, recipients typically require immunosuppressants for the rest of their lives. Because missing even one dose of immunosuppressants could cause a patient to experience kidney rejection, it is important that they understand all of the medications that they are taking, what they are for, and that they have a system in place so that they don't forget to take their medicine. I would probably need a way to survey the primary caregiver as well. I think these questions may be difficult to formulate because I wouldn't want to come across as accusatory, but I would also need to get an accurate measure of their understanding.

2. Factors associated with decreased hypertension among kidney recipients

I learned that many recipients experience hypertension and require medications after kidney transplant, so I thought it would be interesting to compare patients who don't develop hypertension to those who do.

3. A retrospective study evaluating the relationship between cause of death of deceased kidney donors and graft failure

This is my favorite of the three. My interest in this topic stemmed from reading a correspondence letter from researchers in The New England Journal of Medicine who had done a

study on machine perfusion vs cold storage of kidneys in donation after cardiac death and brain death. They concluded that machine perfusion showed lower rates of failure in donors after cardiac death, but not with donors after brain death (20). They concluded that “this finding could suggest a different type of delayed graft function in kidneys donated after circulatory death, as compared with those donated after brain death” (20). I talked to Sandra about the study and she informed me that almost every deceased donor kidney, even those travelling within the neighborhood, are machine perfused. I think it would make an interesting study keeping this variable constant, but I would still need to make my hypotheses more narrow and specific. Theresa and Sandra also told me more about the databases that I would have access to: UNOS, which is a national database that LifeGift uses to store donor information, and 3M, which is Baylor's HER system that combines information from LifeGift and connects it to recipient medical records.

Tuesday, June 13, 2017

Initially, I was going to look at the relationship between cause of death in deceased kidney donors and the development of graft failure in recipients. However, this would come with many limitations that I was uncomfortable with. There are many possible reasons for graft failure such as non-compliance with medications/immunosuppressants, loss of insurance coverage and development of exacerbating comorbidities that may have contributed, and there was no feasible way of distinguishing between them.

Instead, I would like to examine the relationships between extended criteria donors (ECD), donation after cardiac death (DCD), donation after brain death (DBD), (potentially)

living donor donation, and the onset of delayed graft function (DGF)- stratifying by age, BMI, sex, race, and cold ischemic time. DGF is defined as the lack of renal function immediately after transplantation; however I will need to come up with a more specific definition of DGF for my study. It was cited that one of the factors that makes studying the relationship between DGF and graft failure so complex is "due to the time lapse between inciting event and outcome" (7). I decided that narrowing the window of time to DGF would be stronger evidence for a correlation, because I wouldn't have to worry about all of the confounding variables that can occur years after surgery.

I initially struggled to come up with a topic for my research proposal because I wanted it to be interesting and challenging, yet feasible enough for the allotted time. I also wanted the research to be scientifically relevant and useful. I decided to read more on the physiology behind renal transplantation, because I thought that having a better understanding of the overall process and mechanisms behind the surgery would allow me to ask better questions. I then came across an article in the American Journal of Transplantation by Siedlecki et al titled, "Delayed Graft Function in the Kidney Transplant." It provided in-depth discussions about the pre-procurement, procurement, peri- and post-operative periods, as well as both current and future treatments for DGF. In the introduction it states that "the reported incidence of DGF in deceased donors has increased over time despite the progress in acute rejection treatment and translates to a 40% decrease in long-term graft survival" (7). It goes on to state that "the increase has been contemporaneous with the use of expanded criteria donors and donation after cardiac death" (7).

This trend is important because as medical knowledge increases, we obviously like to see dysfunctions decrease- not the other way around. The reason for expanding the criteria for kidney donors to include older patients, patients with hypertension and with increased serum

creatinine levels was due to a shortage in available organs. The alternative to expanding the criteria would be to narrow to the previous standards; this would leave many patients with end stage renal disease (ESRD) without the current most effective treatment, which is transplantation. Therefore, my goal is to provide insight for future researchers so that they can better identify the patients most at risk for delayed graft failure, and then continue working to develop preventative treatments. I believe the "real" mechanistic answer is molecular in nature and is probably going to be discovered through genetic studies, but I hope that my research will at least give insight to the broad understanding of DGF.

Later, I spoke over the phone with a clinical transplant employee to ask about Baylor's living donor program. He gave me the number of living donations performed at this hospital each year for the past 5 years. I needed this information because I needed to know if I would have enough data to use them as a comparison group in my study. I now need to consult with a statistician to determine the appropriate population size, since there are relatively few live donors compared to deceased donors.

Today was also the day of the first committee meeting. I presented these ideas to the committee who then encouraged me to think about more specific hypotheses.

Wednesday, June 14, 2017

Today we had a staff meeting. Theresa recognized staff who had been awarded for excellent service, and encouraged the team to set goals for themselves and to honestly assess their work. The managers decided to move my workspace into Ava's office so that I could work more closely with her and learn more about the everyday responsibilities of an RN coordinator, so I'm really looking forward to that.

Thursday, June 15, 2017

Today, a monitor from a pharmaceutical company came in for a site initiation visit (SIV). The meeting was between the monitor, the RN coordinator and the clinical research assistant. She asked for a list of everyone who would be involved in the study. She described this process as a "2-step SIV." She explained that the second step would consist of a 20 minute teleconference with the PI. She provided a PowerPoint presentation of the research protocol and discussed the responsibilities of the PI and the coordinator, diagnoses parameters, inclusion and exclusion criteria, the schedule of events, protocol for reporting adverse events, and drug accountability.

Friday, June 16, 2017

I changed offices today. Other than that, there was not much going on in the clinic, so I worked on formatting my journal and research proposal. I wanted to use the number system in my actual thesis since it looks neater, but I already referenced two sources in my journal and I do not yet know in which order they will appear in the thesis.

Week 4

Monday, June 19, 2017

Today I met with Maria, the regulatory specialist. We talked about an upcoming study on NASH and she showed me how to create an informed consent document from the hospital template. Basically, the sponsor sent their own template with all of the information that they wanted included in the document, but Baylor has their own template and so I have to combine the information from the sponsor with the consent form from Baylor. Baylor specifically wanted their document to be at an 8th grade reading level.

Tuesday, June 20, 2017

Today I shadowed Trista for a routine visit for a separate NASH study. She asked the patient about changes in meds, health, new habits like smoking. She then collected vitals, abdominal measurements and blood samples. She placed an order electronically for the study drug with the pharmacist downstairs, and then took the patient for ultrasound imaging. We discussed the use of placebo, and how some multi-dose studies are organized in such a way that only 33% of patients are in the control group. We also discussed the difficulty in patient retention once a new treatment becomes available. There is no pill at the moment for NASH. Later today, I was able to work on my research proposal, and I also met with one of the hepatologists who asked me to help her with data abstraction for one of her studies.

Wednesday, June 21, 2017

Today was relatively uneventful, so I was able to continued working on proposal and on the informed consent document. The informed consent form contained information about the timeline, duration and risks associated with the study. It was a women's study so there were a lot of reproductive risks to be included.

Thursday, June 22, 2017

Today there was 12 lead EKG placement training for the staff which I was able to observe. I continued to work on my proposal, and I finished a large portion of the informed consent document.

Friday, June 23, 2017

Today I finished the draft for my research proposal and sent it to my major professor. I was also able to show Maria my progress on the informed consent document. We planned to meet later next week once I have completely finished it.

Week 5

Monday, June 26, 2017

Today I helped Maria file documents in the binder for an upcoming study. It included the study protocol, personnel CVs, licensing information, financial disclosure forms, FDA 1572 forms and other documents related to the study. She told me it was important for the site to maintain the same documents as the sponsor. I also helped Holy organize the supply room for a while.

Tuesday, June 27, 2017

There was a monitor visit today from a Canadian sponsor. I took her to the research pharmacist downstairs and observed her do drug accountability. The pharmacist indicated that the temperature in the refrigerator had been 0.1 degree lower than required for a period of 10 minutes, and that was something that had to be documented and explained to the sponsor. After this, I helped Maria organize documents by their protocol numbers. Later, Dr. Gautam hosted teaching rounds in the CVICU. The patient was a middle-aged woman with what initially presented as fatty-liver disease, but, after an unknown acute incident, caused her to go into renal failure, require intubation and present with extremely high lab values. After rounds, I attended a meeting between the monitor, coordinator (Sandra G.) and Dr. Gonzales, the PI for a study on hepatorenal syndrome. They discussed the status of the study and she inquired about any problems with recruitment. I also added the changes that my major professor suggested for my research proposal.

Wednesday, June 28, 2017

Another monitor came today for an SIV, but this time it was for two separate studies that were closely related but had different protocol requirements. The monitor discussed amendments, inclusion/exclusion criteria and the research protocol. She wanted to know specifically which coordinators would require access to the sponsor's electronic program for lab results. This particular study was a multicenter study with 400 sites, and so the hospital only has to recruit 2 patients. I also went on a patient visit with Theresa today. It was for a device study involving incontinence. I was able to observe a patient's bladder being filled and emptied via a catheter, which was very interesting.

Thursday, June 29, 2017

Today, I helped Holy take inventory and organize the kit room. I also met with Maria and she asked me to help her organize a binder containing the licensing information of different employees involved in research. She wanted me to create an excel document listing the expiration dates of everyone's training certificates, CVs and medical licenses. I printed from the computer what was not in the binder already, and printed labels for the dividers. In between those projects, I was able to work on my proposal more and think about the statistical relationships that I wanted to analyze. I talked about my ideas with Sandra M. at the end of the day, who gave me advice on how to divide my subgroups.

Friday, June 30, 2017

After finishing Maria's binder this morning, I was able to finish the corrections to my research proposal. I added a table that will hopefully clarify the exact comparisons that I wish to

make. I showed the table to my mentor Theresa who agreed with the plan. She instructed me to create a spreadsheet containing all of the data which I wish to collect so that I can submit it to the IRB for approval. She also sent me the final copy of the informed consent document that I helped create. I saw that she changed some of the sponsor's language so that it would be at an 8th grade reading level as Baylor wanted it. For example: "participate" was changed to "take part", "medication" was changed to "medicine," and "approximately" was changed to "about." I feel like I now have a better understanding of the type of language they want.

Week 6

Monday, July 3, 2017

Since today was the day before a holiday, there were no patients and a lot of the staff had the day off. I did come in for a while to create the data sheet for submission to the IRB, which I sent to the committee via e-mail. Dr. Mallet suggested adding sodium and bicarbonate concentration in addition to the potassium concentration in recipients so that their acid-base chemistry could be better evaluated. I asked the staff members who were present if they needed help with anything, and they all declined because they were leaving early.

Tuesday, July 4, 2017

The facility was closed for Independence Day.

Wednesday, July 5, 2017

I submitted my final research proposal to the committee today after making changes suggested by Theresa. She suggested expanding the study to include data from BUMC in Dallas as well as Baylor All Saints in Fort Worth, which I thought was a good idea since DGF is not something that happens frequently. Later, I helped Holy organize the supply room and take inventory. There were a lot of kits that had expired at the end of June, so those had to be broken down. There were also a lot of new kits that had arrived today.

Thursday, July 6, 2017

Today I helped organize the kit room again. Later in the afternoon, Sandra M. asked me to help her create source documents for an upcoming study. Holy sent me the protocol to read over and said that we would start working on them tomorrow. They are due by Tuesday the 11th.

Friday, July 7, 2017

Today I started working on the source documents for the upcoming study. Holy gave me a pocket-sized protocol from the sponsor, so I followed the schedule of events and made sure the documents contained all of the protocol requirements for each specific visit. Theresa also asked when I planned on submitting my proposal to the IRB, so I will start that process soon. I also completed dangerous goods training through Mayo Medical Laboratories today. Although I cannot handle specimens here, I thought it would be good information to know for my own personal understanding, and it is also a useful certification for future jobs.

Week 7

Monday, July, 10, 2017

Today, I completed another FY 2017 BSWH Disclosure Statement online. I also completed all of the source documents and sent them to Holy, who combined them with her half and then sent them to Sandra. They were basically the documents that the coordinator would take with them and fill out at each visit. Each consisted of a checklist of tasks that were to be completed at that visit, and a more detailed form that was to be completed by the study coordinator.

Tuesday, July, 11, 2017

Today I logged into Iris and started a new project for submission to the IRB. Theresa was out sick today and I was confused about some of the questions, so I decided to wait and ask her tomorrow since no one else had knowledge about those specific questions.

Wednesday, July 12, 2017

Today, we had another breast tumor conference. The same physicians presented as last time, but the cases were different. This conference seemed to focus more on treatment plans than on research, but I did learn a little bit about tumor classification. Also today, Maria sent me a new template from the sponsor that I previously created the informed consent document for. There had been updates and so I had to recreate it using the new information. They also added an optional pharmacogenetic study, so I had to create a form for that too. She said we would discuss it more tomorrow in the morning. Theresa was still not feeling well so I plan to ask her about the IRB submission tomorrow.

Thursday, July 13, 2017

Today I met with Maria and she gave me the instructions for the new informed consent documents, which she needs by tomorrow. I finished most of the informed consent for the main study, and I plan to finish formatting it tomorrow. This time, I made sure the wording was at the appropriate reading level using the changes that Theresa made to the first document. I also met with Theresa today and we went over the IRB application together. They wanted to know basic information about the study such as the purpose, plans for confidentiality, types of data to be collected, where the funding was coming from and the roles of everyone involved in the study- specifically the roles and names of those who would have access to the actual data.

Friday, July 14, 2017

I finished the informed consent for the main study today and sent it to Maria and Theresa. Maria said I could submit the consent form for the optional pharmacogenetic study to her on Monday, but I still finished it so that all of the new information was transferred into the template. I will complete the formatting on Monday.

Week 8

Monday, July 17, 2017

Upon arrival, I finished formatting the pharmacogenetic study informed consent document and sent it to Theresa and Maria. I also moved from Ava's office to Maria's office, so that over the next few weeks I can learn about the role of the regulatory specialist. I helped her file documents into the study-specific binders. There are active studies from a variety of sponsors, and while I was filing I noticed that they each pretty much followed the same format as far as tabulation was concerned. Sandra M. came in earlier today and said that she sent the research proposal that I helped write the background for to the nephrologist. She said it was "excellent" and that it provided a good rationale for the existence of that specific study by discussing the debates in the current literature. I met with Theresa later today and we discussed my progress in the internship. She suggested that I be more vocal with the coordinators and ask what they are doing every day.

Tuesday, July 18, 2017

This morning, I submitted my application to the IRB. I notified the committee of this and also of the updates to my proposal and data collection sheet. In the application, the IRB wanted me to justify why I needed to collect certain data, and I realized that I did not actually need dialysis end dates for my study. Length of dialysis may have some impact on graft survival, but this study focuses more on the immediate problem of DGF. Maria asked me to make sure the essential documents were in place for a particular study that has an upcoming SIV. She explained that these documents are the most important and are what the monitor will look for when he/she comes. These include CVs, medical licenses, FDA 1572 forms, financial disclosures and signed

protocol signature pages stating that they have read and understand the protocol. Later today, I helped Holy with the new kit shipment in the supply room.

Wednesday, July 19, 2017

I was absent this day due to illness.

Thursday, July 20, 2017

I was absent this day due to illness.

Friday, July 21, 2017

A few shipments came in this morning containing kits and updated lab manuals from sponsors. Holy was on vacation today so I opened the boxes and put everything where it belonged in the storage room. I also updated the inventory and removed all of the kits that would be expiring at the end of this month. After that, I worked on GCP training through the CITI website. I then finished making a table for Theresa listing each active study and the lead and back-up coordinators for each one.

Week 9

Monday, July 24, 2017

This morning, I worked on CITI training for good clinical practice (GCP). In the afternoon, I shadowed Theresa on a women's study visit. She let me review the protocol in the binder for this particular subject so that I could see what all would be performed for this visit. It was basically just vitals and monitoring for any changes in medication or condition. Compliance with study drug was also assessed, and leftover drugs were collected from the patient. This visit also required a few questionnaires to be filled out by the subject. After the exam by the coordinator, the PI came and performed a trans-vaginal ultrasound (TVU) and a trans-abdominal ultrasound (TAU). The protocol had a specific list of images that were required as well as captions for labelling purposes. I then watched Theresa fill in the patient's electronic chart via the sponsor's EDC system.

Tuesday, July 25, 2017

Today I worked on GCP training, but I had to leave early due to persistent illness.

Wednesday, July 26, 2017

Today, I did some GCP training but mostly helped Maria file documents and create regulatory binders for an upcoming study.

Thursday, July 27, 2017

Today I worked on GCP training which I have almost finished. I also helped Holy in the kit room and filed some regulatory documents for Maria.

Friday, July 28, 2017

I completed GCP training and received my certificate today. While all of the training was relevant, the section that I found the most interesting was the lesson on investigator initiated studies. Basically, when a PI initiates his/her own study, they then take on the responsibilities of both the PI and sponsor. This includes signing the form FDA 1571, which is between the sponsor and the FDA, and also implementing a system for managing compliance, records and safety of a trial as well as reporting adverse events and protocol deviations. Later today, I went to the UNTHSC campus to sign and deliver my intent to graduate form.

Week 10

Monday, July 31, 2017

Today I completed the two stipulations that the IRB sent back for my study approval. I then updated Dr. Mathew on the status of the IRB approval. Maria later sent me e-mails of some amendments that were made to the informed consent documents for two studies, to be completed by the end of the day on Wednesday. The sponsor tracked the changes that they made to the original version of the ICF, so I will make those changes accordingly in the Baylor template.

Tuesday, August 1, 2017

Today consisted of a monitor visit with Ava. We first met with the PI, who is a nephrologist at the hospital, and the monitor discussed the upcoming investigators meeting, which is a meeting that the sponsor holds to review the protocol with all of the investigators participating in their study. I then sat with Ava and the monitor as they went over some discrepancies in the EDC. This afternoon, I finished the informed consent document for the first study and sent it to the regulatory specialist Maria and my site mentor Theresa.

Wednesday, August 2, 2017

This morning I finished the second informed consent document and sent it to Maria and Theresa for review. I then helped Holy receive new kits and take inventory in the kit room. Maria asked me to create a new regulatory binder for an existing study so that general correspondence could be documented properly. Today at lunch, I attended another breast tumor conference. Later today, Maria sent me 3 informed consent document templates from a different

sponsor to be completed by Friday. She also sent me a spreadsheet containing studies that are up for continuing review to be discussed tomorrow morning.

Thursday, August 3, 2017

This morning I finished incorporating the amendments for the 3 informed consent forms. I sent the updated versions to Maria and Theresa. Maria and I then left for the IRB meeting at the Dallas campus. We found out that the IRB would actually be reviewing two of our studies today. The meeting took place in a formal conference room at BUMC. Maria showed me a list of the different IRBs that Baylor uses, and it showed the constitution of the board while leaving names anonymous. The list primarily consisted of MDs with a few social workers and other professionals. One woman identified herself as a nurse at Baylor and a cancer survivor, which I think gives her an interesting and valuable perspective as a board member. During the meeting, the chair of the board led the discussion and went down a list of studies. Each study had been previously assigned to a reviewer, so at the time of the meeting the reviewer presented any concerns he/she had with the protocol. One member simply suggested a language change to an informed consent document because it used medical terminology without ample explanation. Maria explained that if the board had to vote on a particular study, they would ask if there were any representatives from the site present and ask them to leave the room. I really enjoyed this experience as it gave me a better perspective on how the IRB actually functions. By learning this, I feel that I will be able to make better decisions as a coordinator in the future.

Friday, August 4, 2017

Today, Theresa gave me an email from a monitor listing documents needed for her next visit. I located them in the regulatory binders and scanned them all to Theresa. The monitor was specific about the dates that she wanted, and she included instructions on corrections to be made to the training log. The former coordinator for this study no longer works here, but the sponsor still needs her training records since she was on the study at one point. This afternoon, I helped Holy organize the kit room. Maria also sent me another informed consent document to be completed by the end of the day on Monday.

Week 11

Monday, August 7, 2017

This morning I finished the informed consent document and sent it to Maria and Theresa. Trista came back today so I asked her what she had going on and she informed me that she had a patient visit tomorrow morning, so I plan to go to that with her. There is also a monitor visit tomorrow and she said we would go to that when we returned from the Diabetes Thyroid Center (DTC). Maria also gave me some more regulatory documents today so I filed them in the appropriate binders.

Tuesday, August 08, 2017

This morning I met Trista at the hospital and we drove to the DTC for a patient visit. Trista explained that this drug was stored at the diabetes center rather than at Baylor with the research pharmacist because that was the location that it would be dispensed and because that was the location of the PI. She explained how it was important to show PI oversight at the location of drug dispensing, and that when the monitor comes they go to the address that is on the form FDA 1572. She used the sponsor's IWRS (interactive web response system) to print the drug dispense form prior to the visit, which told her exactly which bottles to dispense. The IWRS is also what randomizes patients for drug assignment. At the patient visit, she took vitals, dispensed study drug, and reviewed concomitant meds and medication changes. A con-meds list is taken at the beginning of the study, and at each visit changes in medication must be logged on the source document and in the EDC. Aside from the more serious meds, the list also included supplements and common OTC medications. Patients sometimes don't remember the start and stop dates for medications, so sometimes medical records have to be pulled. Trista says that she

has her subjects sign consent forms periodically for the release of medical information in case she has to request records. Keeping an updated consent form prevents her from having to fax a form, obtain consent, and then request records every time she needs them. After everything in the protocol for this visit was completed, the coordinator collected the expired study drug and we left. On the way back, we talked about the importance of documentation via a progress note, which I am familiar with from working as a scribe. These should be included in the subject binder, and can either be entered through the hospital's EMR, or typed, signed and dated. The progress note does not go into the EDC however; that is solely for data from the source document. I later watched Trista enter the data from this visit into the EDC. One interesting thing that I learned was that when entering concomitant drugs, some sponsors prefer generic names while others prefer brand names, and for drugs that contain multiple compounds at different dosages, these sometimes have to be entered separately. To maintain the accuracy of the EDCs, sponsors employ data monitors who ensure the completion and accuracy of the data entries and submit queries for the study coordinator to correct if there are discrepancies. The EDC is also where adverse events are logged electronically. This particular patient reported that she recently started pain medication for arthritis in her hip. Baylor requires that all unanticipated AEs be reported to the IRB, but for this study, the sponsor only wants to know about specific cardiovascular AEs. To know whether an AE is unanticipated or not, the coordinator has to look at the investigator brochure, which contains all of the pre-clinical and current drug information.

Wednesday, August 09, 2017

This morning we learned that a donor kidney had become available and that the recipient was potentially eligible for a study. I went on the informed consent visit with Sandra Garcia.

This was particularly interesting because the patient was a vulnerable subject. He and his family were Spanish-speaking, and neither the patient nor his wife could read or write. The coordinator had to read the informed consent and the questionnaires out loud to him. The questionnaires were basically about the state of his health currently and over the last 4 weeks. It also asked about his mental health and his physical capabilities. The patient said he had been on the waiting list for the past 6 months but denied any recent major changes in health. The subject's adult son was able to read the consent form as well. I thought it was interesting that today was the subject's first day of hearing about the study and he still agreed to participate in it. This particular study requires multiple blood draws and a one-time administration of study drug during the surgery, and then of course a few years of follow-up. For this part of the visit, I accompanied Ava in the OR for a few hours.

Thursday, August 10, 2017

Today we had a dip party because one of the coordinators, Trista, will no longer be working here. Before she left she made her subjects aware that she would no longer be providing care for them, but reassured them that another qualified coordinator would pick up where she left off. Because she was involved in the studies, her training records still have to be maintained in the regulatory binders at Baylor and with the sponsor.

Friday, August 11, 2017

Today I worked more on the spreadsheet that Theresa asked me to help her with. Later, I helped Maria with filing regulatory binders.

Week 12

Monday, August 14, 2017

Today I started on the 6 new stipulations that the IRB sent back. Most of them were small changes, such as replacing “N/A” with “No known risks.” But one of them stated that I had to include a risk-to-benefit analysis coverage in my proposal, even though I had already stated the potential future benefit. I asked Theresa for advice on how to do that, and she suggested calling the IRB representative directly and asking what they meant. I called the IRB office number that was provided on IRIS and left a voicemail. I was also granted access to Allscripts today, which is one of the EMRs that I will use for my project.

Tuesday, August 15, 2017

Today, Maria taught me how to prepare IND safety reports using Baylor’s template and the report sent from the sponsor. I learned that the sponsor sends these reports to every site involved in their study whenever a serious adverse event occurs. The report has information about the patient, their medical history and the event. The Baylor template includes a table at the end describing the event, the severity, whether the event was unexpected and if it required a changed to the informed consent form. Later this morning, Shawnta and Theresa asked me to help them in the storage room where the closed studies are located. For the studies that had been closed for over 6 months, I was asked to box them according to the study and to separate the patient files from the non-patient files. I preserved the functional binders and disposed of the broken binders. I then organized all of the empty binders so that they fit neatly on the shelves. I also tried calling Heather, the manager of regulatory affairs, a few times today to address the questions I had about the stipulation, but there was no answer.

Wednesday, August 16, 2017

This morning, I tried calling Heather again with no answer. I updated Dr. Mathew on the status of the IRB submission, and he offered advice on how to address the final stipulation. Maria later informed me that there were some SIVs upcoming next week and that she wanted me to make sure the corresponding binders contained up to date documents including: medical licenses, CVs and laboratory credentials. She also wanted me to make sure that everybody who was listed on the FDA form 1572 was also listed on the DOA, and if they were not then they needed to have an end date listed on the DOA. I was not able to do this today because the shared drive was having systemic issues. I later met with Theresa about a spreadsheet that I had created for her. She wanted me to use the DOA log to include everyone assigned to each study.

Thursday, August 17, 2017

This morning we had a staff meeting. Maria suggested creating a miscellaneous folder in for each study in the shared drive to prevent misfiling. After the meeting, I updated my protocol to contain the last IRB stipulation and submitted the changes. I then received another message from the IRB, but this time I was able to get in contact with the person assigned to my study via email. We worked out the remaining issues and I received the notification that my project was up for expedited review. Maria sent me 3 new ICFs to be completed by Monday, 8/21, and an IND safety report as well. I finished the safety report, sent it back to her and started on the ICFs, but she reminded me that she needed the documents for the upcoming monitor visit by tomorrow so that's what I spent the rest of the day doing.

Friday, August 18, 2017

Today I was absent due to a personal emergency that I had to attend to.

Week 13**Monday, August 21, 2017**

This morning I finished the informed consent forms and sent them all to Maria. I later helped her file documents, and I also had my weekly meeting with Theresa. I updated her on the status of the IRB submission and she said that I should have approval by the end of the week since it was up for expedited review.

Tuesday, August 22, 2017

This morning, I completed another ICF and sent it to Maria and Theresa. I then worked on the spreadsheet and added Holy and Maria to the table per Theresa's request. Maria explained to me that box 6 on form 1572 was only for investigators and sub-investigators, while the DOA listed everyone involved on the study. I also went on a visit with Ava and a monitor to see one of the PIs. Ava stayed behind to finish the meeting and I walked the monitor back to the site. We talked about school and she explained that she worked as a coordinator before becoming a monitor, so that was nice to be able to talk to her about the differences between those two positions. At the end of the day, I sent the completed spreadsheet to Theresa.

Wednesday, August 23, 2017

Today I attended the breast tumor conference, which was interesting as usual. Holy and I were going to ask one of the oncologists if we could shadow her for a while, but she had to leave and we were unable to speak with her. I then helped Holy organize the supply room, but I had to leave early for a meeting with Dr. Mathew. He encouraged me to get more experience with non-regulatory aspects of the internship, and reminded me to send him the approval letter along with other requested documents when I receive it. Later this evening, I received the outcome letter from the IRB, so I plan to send that along with the other required documents tomorrow.

Thursday, August 24, 2017

After completing the UNTHSC conflict of interest training, I submitted the required documents to Dr. Mathew via email. Maria sent more IND safety reports to complete, so I completed those today. At first, I did them as all separate documents since they were initial and follow-up reports for 3 different events. Maria taught me that it was okay to include them all on the same table, as long as they were from the same study. I fixed this mistake and sent the corrected version back to her and Theresa.

Friday, August 25, 2017

Today I did another IND safety report. I also helped Maria prepare for an upcoming monitor visit for one of the women's studies. She wanted me to go through the study binder and assure that all CVs, licenses IATA and GCP training certificates were up to date. I located updated versions of the documents that were expired and filed them appropriately.

Week 14

Monday, August 28, 2017

This morning I met with Theresa because I thought I could start on my project today, however I still have not received IRB approval from UNTHSC and I also don't have access to UNOs or 3M. Theresa put in those requests for me, so that should be arriving soon.

Tuesday, August 29, 2017

Today I worked on a new informed consent document for an upcoming study. I completed most of it but will finish the rest tomorrow morning. I also helped Holy in the kit room, and I filed regulatory documents that Maria emailed to me.

Wednesday, August 30, 2017

Maria emailed me this morning asking me to print and file email correspondence between her and a monitor, to complete regulatory action items for an upcoming monitor visit, to complete new IND safety tables and to file some regulatory documents. I completed the ICF that I started yesterday, however I noticed that the template that the sponsor sent had combined the consent document for their main study with the consent for 3 optional pharmacokinetic, genetic and biopsy studies. I remembered that Baylor usually creates separate consent forms for optional studies, so I asked Maria if I should create separate ones or leave it combined. She said to wait until she finds out which optional studies this site will be performing, and then to create separate documents based on that. I then printed the list of action items sent by the monitor. I went to the coordinators involved and asked them to sign the DOA log, and updated some of the expired

licensing. I then asked Sandra Morones to send me a template so that I could create a note-to-file that the monitor requested. She showed me where she keeps all of her templates on the shared drive, so I got one from there, filled it out, printed it and had Maria sign it. I then filed it in the appropriate section of the binder. Now that the DOA is up to date, the PI has to initial the newly added start and end dates. Later, I added a PI's GCP training to all of his study binders and updated his training in the staff training records. Also today I was approved to gain access to 3M. All that I need now is to gain access to UNOs which has been requested, and for IRB approval from UNTHSC.

Thursday, August 31, 2017

This morning Maria notified me of an upcoming monitor visit. She asked me to go through the shared drive and ensure all of the CVs, licenses, training and lab certifications were up to date, and if not to replace them with current versions. After I completed this, I helped one of the coordinators by setting up the electronic device for a new study. Patients will use that device to answer questionnaires during their study visits. I liked how the protocol had very thorough instructions on setting the device up, keeping the device charged, and knowing which passcodes to use in different scenarios. For example, there was one code that was to be used for creating investigator accounts, one for investigator training, one for subject training and one for adding subjects.

Friday, September 1, 2017

This morning I did a safety report for Sandra G. It was a follow-up report for one that I had already done, but addressed to a different PI for another study. I noticed that the sponsor

sends safety reports to sister-studies, even when the event technically occurs in a separate study. After this I helped Holy pick up shipments and break down kits in the storage room. Shawnta and Theresa then asked me to box some more closed studies. Maria then emailed me saying that there will be a monitor visit when we return from break so I helped her get those documents ready. I then filed everything from the filing tray at the end of the day.

Week 15

Monday, September 4, 2017

The facility was closed today due to Labor Day.

Tuesday, September 5, 2017

There was a monitor visit today for one of the studies with Sandra Garcia and Ava. I had already filed the essential documents last week per Maria's request, so the regulatory binder was up-to-date and ready for the visit. The monitor started by asking questions about the IRB, such as how often they meet and how far in advance amendments have to be submitted. She also inquired about whether or not Baylor allowed advertisements. Sandra informed her that we do utilize ads created by the sponsor after they have been approved by the IRB. She then passed around an SIV attendance log which required names and roles of all personnel present. The monitor explained how she currently has ~30 sites assigned to her, and how this particular study uses an adaptive monitoring plan which allows for less frequent visits (every 3-6 months rather than every 2-4 weeks). In addition to the assigned monitor, this study also has a central monitoring associate that will be available for questioning. We then discussed the recent name change of the sponsor and study, since they were bought out by another company and then later realized there was an existing study/drug with a similar name. The name change required a protocol amendment as well as changes to the ICF. The new protocol provided a table outlining the roles of the sponsor vs the roles of the CRO. At the investigator's meeting for this study, many PIs had comments and suggestions at the end of the presentation. Interestingly, the sponsor was open to the suggestions and released a second version of the protocol taking these concerns into account. For example, some of the inclusion/exclusion criteria were expanded. This was

surprising to me because I didn't think the investigators had any control over the design of a study, but this sponsor was actually receptive to their ideas. One reason for this may be due to the length of this study- it is expected to last for 8 years. It is international and the criteria are very specific, and so they are already concerned about patient retention. The monitor mentioned an anticipated screen failure rate of over 50%, so I can see why they were willing to make amendments to make this process easier for PIs and patients. Another way the sponsor wants to combat decreases in the retention rate is to have the coordinators encourage honesty from patients about drug compliance. Although there is a desired minimum percentage for compliance, due to the length of this study, falling below that percentage is not an end-all for participation. The monitor also wanted to know about different procedures, if they were performed on site and if the PI would be interpreting the results herself. The monitor discussed difficulties that some sites have with getting source documentation, protocol and GCP training for pathology/radiology staff who are not directly involved with research. She said that in place of adding these personnel to the DOA, an NTF would be sufficient as long as it states that the radiologist would not be making assessments or eligibility decisions related to the study, that they have been informed/trained about procedural guidelines, and that the PI will be overseeing the process. The monitor also wanted to know specifications about the hospital's temperature-controlled lab equipment, as well as the standard operating procedure (SOP) for transporting study drug between locations. After reviewing the rest of the protocol we went to meet with the PI. The monitor and PI discussed inclusion/exclusion criteria, concomitant meds, pharmacokinetic information about the study drug and SAE reporting. Something that many PIs, including ours, had concerns about, was the lack of an open-label protocol for placebo non-responders who develop a worsening illness. Although there is no current drug therapy for this

disease, the monitor said that the sponsor is aware of the possibility of a treatment coming to market next year and that they are considering creating a protocol for this event.

After meeting with the PI, we went to the interventional radiology wing and let the monitor look around and ensure its legitimacy. After this, I ate lunch and returned to my desk. I asked Theresa about the ICF that I was working on and she said to make a separate one for the optional genetic study. Sandra G then asked me to print copies of CVs to take to the monitor.

Wednesday, September 6, 2017

Today, I asked Theresa and Maria about the informed consent that I was working on. The sponsor had sent one ICF for the main study, an optional genetic study and two other optional studies- all merged into one document. Baylor prefers separate consent forms for genetics studies, so Theresa instructed me to create a separate ICF for that part of the study, and to leave the other two optional studies in the ICF for the main study. I completed that, however I then noticed that the sponsor included another two consent pages at the end of their ICF: one for continued follow-up after early withdrawal, and one for re-entering the main study after potential liver injury. I had to make an additional two consent forms for these using the Baylor template and the information provided by the sponsor. The ICF for restarting study drug was tricky, because on one hand, I had to treat it like a new, separate study, while on the other hand the patient would actually be re-entering the main study. For example, the purpose of the study and the risks and approval status of the study drug were still the same, and I also decided to keep the consent section for the two optional studies that were included in the main ICF. I figured they would have to re-consent for those, regardless of when they re-enter, since those blood draws happen over the course of the study. For the continued follow-up after withdrawal, I asked

Theresa about the risks section. She said that the only risk for a study like that would be the risk of loss of confidentiality. I sent the completed ICFs to Maria, who told me to do the best that I could and explained how there was constant communication between the site and the sponsor before submission to the IRB. Today I also received an email from Dr. Mathew stating that my study had been approved by the UNTHSC IRB, so I was really happy to hear that. Later, I asked Holy what all she had to do today and I asked if I could help her create source documents for two NASH studies. I wanted to practice reading protocols for more complicated studies and I thought making source docs would be a good way to do that. She gave me the miniature protocol booklets from the sponsor and showed me how to use the schedule of events, procedure descriptions and EDC screenshots to create the documents. Before leaving, I made sure the filing tray was empty.

Thursday, September 7, 2017

There was supposed to be a patient visit this morning for Sandra G. but the patient cancelled so I was not able to go to that. When I arrived this morning, I met with Theresa and we talked about how I would be able to match UNOs numbers (from deceased donors) to their corresponding recipients. She said that Ava would know more about that, so I met with Ava and she told me about a binder in the transplant clinic that had the numbers. I cannot take the binder from the room that it is in, so I will have to sit there and collect data as necessary. I later helped Theresa format tables on an ICF that she was working on, I helped Holy break down kits, helped Maria fill out a 1572, met with Theresa about action items for one of the women's studies, and filed everything from the filing tray before leaving.

Friday, September 8, 2017

Today I sat with Sandra G. and Ava as Maria taught them how to create IND safety report tables. There was supposed to be a patient visit today but the patient cancelled. Although she had already taught me how to make these tables, I still learned new things and ways to improve my reports in the future. She explained why the wording on our table had to be an exact match to the IND report from the sponsor, per the IRB's request. She said that all of the other sites that she worked at simply requested that the PI sign the report that came from the sponsor, and then file it appropriately; however, Baylor's IRB was unique because they want both the sponsor's report and a Baylor report.

Week 16

Monday, September 11, 2017

Today I updated expired documents for the off-site study at the Diabetes Thyroid Center. This was one of the action items that I met with Theresa about last Thursday, but it took a while to get the information because this PI is not a part of the Baylor system and his clinic is not on campus. I then had a discussion with Maria about IND safety reports. She said that the nurses would no longer be submitting individual reports to the IRB, but instead would submit them all at once when the study was up for continuing review. That way, the PI would be able to sign everything in one sitting, and one table per study could be submitted. We agreed that this method was not perfect, and I suggested reviewing and submitting them at the beginning of each month rather than annually. I think each nurse will figure out what works best for them with time. Later, we talked more about keeping track of new amendments. Theresa sent me a sample spreadsheet and said to add to it if I had any new ideas. At the end of the day, I filed everything from the filing tray before leaving.

Tuesday, September 12, 2017

This morning, I asked Ava if she would have time to go with me to the transplant clinic and show me where the transplant binder is, and she said she would that afternoon. Meanwhile, I helped Maria by printing and filing documents in preparation for a monitor visit tomorrow. I also began coordinating thesis defense dates with the advisory committee. Later today, Ava and I went downstairs where she introduced me to one of the transplant nurses and showed me the UNOs binder.

Wednesday, September 13, 2017

So today I planned to start collecting data, but I realized that although I had access to Allscripts and 3M, I still did not have access to UNOs. I asked Sandra M. if the woman she e-mailed to give me access ever followed up with her, and she said that she had not responded. Sandra e-mailed Betsy, director of transplant operations, again and she responded quickly. She also put me in contact with Jennifer, director of transplant informatics. They asked me questions about my project and I sent them my proposal and data collection sheet. Betsy then asked if I had been approved by the transplant research committee, and informed me that transplant studies had to be approved by the committee before the IRB. The next committee meeting would not be until October 4th. Fortunately, she spoke with the chair of the committee, Dr. Asrani, and he gave me his contact information in case I had any questions. Theresa and I called and spoke with him over the phone and he agreed to approve the project if he looked over the proposal and found no problems with it. Later today, he emailed us back and expressed concerns about the feasibility of the project. He forwarded it to one of the hepatology PIs, Dr. Gonzalez, who agreed to look over it and provide feedback as well. At this point, I started looking at ways to cut back on the data being collected. Today I also helped Sandra Garcia create a safety report table.

Thursday, September 14, 2017

This morning, Dr. Gonzalez replied with his feedback. He was in agreeance with Dr. Asrani and was concerned about the feasibility amongst other things. After further correspondence explaining the purpose of the project, they suggested that I speak with a nephrologist. Ava and I went looking for one of the nephrology PIs, but we could not find him so we plan to try again tomorrow morning before his clinic. Also today I started helping Sandra G.

set up an electronic tablet for one of the new studies. She was not present today so I wasn't able to create password hints for her, so I will have to complete this tomorrow when she comes back.

Friday, September 15, 2017

This morning Theresa and I went and found Dr. Yango to show him my proposal. He agreed with the feedback of the other two physicians in that my study was not going to discover anything new, but said that since I did not have much time it would be okay to perform the study. Theresa and I updated Dr. Asrani, Jennifer and Betsy on the approval as well as my plans to only analyze data from January 2012- January 2013. Jennifer sent me sample documents for the information that would be in the UNOs database, and we determined that the study would still require access to that data. Dr. Asrani said that he would update the research committee on the project. Today I also finished setting up the electronic tablets for Sandra G.

Week 17

Monday, September 18, 2017

Today after further communication with Jennifer and Theresa, we discussed the possibility of me updating one of the transplant databases since I would be accessing them anyways. Jennifer later sent me a spreadsheet with the data for living donors and she said that she requested the data for deceased donors as well. This has most of the information that I need so I don't think I will need access to the actual UNOs registration sheets.

Tuesday, September 19, 2017

This morning I received the deceased donor data from Jennifer for 2012-2014. I noticed that a lot of the data was encoded numerically, and Theresa later explained that this was so that the computer could understand when they ran the data. Jennifer said that she would send me the cross references for these numbers upon request. Later today, I completed the amendment spreadsheet that Maria asked me for and sent that back to her.

Wednesday, September 20, 2017

I've been sick since Sunday and was still running a fever so I decided to stay home today.

Thursday, September 21, 2017

The informed consent document for one of the studies was rejected by the IRB because a large section of the document contained a complicated chart that was difficult to follow. I offered to work on it and started creating a new, less-complicated table using their protocol, but Maria

and Theresa decided it would be better to provide the information in bullet form rather than the chart. I finished the new ICF and emptied the filing tray before leaving.

Friday, September 22, 2017

This morning I arrived early to go to grand rounds. The presentation was given by a physician who discussed the links between endometriosis and cancer. She discussed cases that she had seen in the past and she also provided statistical data about the incidence of different types of cancers. I believe the presentation counted towards continuing education for some of the staff. Later today I fixed an ICF for Theresa so that the procedure tables fit within the margins. I also started looking at the donor data and thinking about how this would change my data collection sheet and proposal, since I now have to resubmit to the IRB. I will only be collecting less information at this point, not adding new data, so I am not anticipating any delays with them.

Week 18

Monday, September 25, 2017

This morning I emailed Derrick about reserving a room for the thesis defense, which we decided should be on Tuesday, November 7th at 10am. I later helped Holy in the kit room and emptied the filing tray before leaving.

Tuesday, September 26, 2017

Today I mostly filed regulatory documents and helped Holy in the supply room. The end of the month is approaching and so inventory has to be done for the study supplies. There are a lot of them expiring at the end of September and October so they have to be broken down and current inventory has to be recorded.

Wednesday, September 27, 2017

Today I went to the breast tumor conference again. There was only one oncologist presenting today, but others were there and were involved in the discussion. There were two pathologists present as well. It's always interesting hearing them debate treatment options. There was one patient whose initial labs showed that her disease was not systemic, however most of the physicians agreed that based on her history and the extent of the tumor, it was highly unlikely that the cancer was not systemic. This reminded me of something I read about in MCAT psych/soc called the Recognition-Primed Decision model. The book used the example of a physician determining that a patient was having an MI without even looking at the ECG, due to having seen the preceding series of events so often. They attribute this model to physician intuition, so I thought it was interesting to see a real-life example of this.

Thursday, September 28, 2017

Today I started collecting data for my study. I had a goal of collecting data on 64 patients a day (32 recipient-donor sets), but since today was the first day I was still figuring out how to go through the spreadsheet and collect data in the most efficient way. I collected data for a total of 50 patients, but it did get easier towards the end so I think I will be able to meet my goal tomorrow.

Friday, September 29, 2017

Today I mostly collected data all day. I was able to finish the last 14 patients from yesterday and also met the goal of 64 patients for today. I also emailed Derrick again this morning about reserving a room for the thesis defense. One thing that I changed on my data collection spreadsheet is that I no longer need the dialysis start date. This is because on the spreadsheet that Jennifer sent me, it says “dialysis required in the first week” and they say “Y” or “N.” So at this point, I also plan to delete the “Date of transplant” column as well since that is identifiable information that I no longer need. I was not able to get the donor history of stroke from the data provided, so I will have to email Jennifer for that information as well as the cross-references for patient ethnicity and cause/mechanism/circumstances of death. I plan to submit my amended proposal to the IRB next week now that I know exactly what changes will be made. No new information is being collected.

Week 19

Monday, October 2, 2017

Today I met my goal for data collection of 65 patients. I would like to finish data collection within the next 2 weeks so I've been calculating how many I need to complete per day. I also got the room reserved for my thesis defense on November 7th. One unanticipated problem that I encountered was that some of the deceased donors donated both of their kidneys and so they were listed twice. I wasn't sure if I should exclude those patients, or only count them once during the data analysis. I was worried that having more recipients than donors might throw off the results. I asked Dr. Mallet about this and he suggested assigning a half value of 0.5 to each of the donor-recipient pairs during the analysis. If this is not possible, he said I could use the first pair and exclude the second. Hopefully I can do the first option, because there are some cases where one recipient develops DGF and the other does not, and I would hate to lose valuable data like that. Also today, I started editing the proposal that I submitted to the IRB to include the new dates and changes to the study.

Tuesday, October 3, 2017

Today I was able to collect data for 90 patients. Since I was able to collect more than I anticipated, I set a new goal of collecting data on 125 subjects per day. I later submitted the updated research proposal and data collection sheet to the Baylor IRB, and filed regulatory documents before leaving.

Wednesday, October 4, 2017

This morning I finished filing the remaining regulatory documents. Also, I met my goal and collected data for 126 patients. Shawnta asked me to help her create a spreadsheet so she could keep track of dry ice shipments, so I did that for her. Later, I helped Ava find informed consent documents for one of her studies. The sponsor was requesting a copy of the most recently consented patient's ICF signature page. I went through all of the subject binders and found the subject with the most recent date and scanned the page to her.

Thursday, October 5, 2017

Today I collected data on 178 patients. I am almost finished collecting data on deceased donors so I plan to move on to living donors soon; however, I still have to go in Allscripts and gather the serum creatinine levels for each recipient. I think that will be the most time-consuming part of data collection for me. Later today, Ava told me that the sponsor actually wanted the signature page with the patient's name redacted so she asked me to redact the signatures and resend it to her. After this, I went to UNTHSC campus and got my intent to defend form signed by Dr. Jones and Dr. Mallet.

Friday, October 6, 2017

Today, I collected data on the remaining cadaveric donors and filed regulatory documents before leaving.

Week 20

Monday, October 9, 2017

Today I completed data collection for 101 living donors and recipients. I also helped Holy in the storage room because boxes for 3 different studies arrived today. I later emptied the filing tray before leaving.

Tuesday, October 10, 2017

Today I finished collecting data for all patients from the spreadsheet. I plan to start going through Allscripts tomorrow to collect creatinine levels from recipient charts. Today I also updated Dr. Mathew with the most recent IRB approval paperwork from Baylor. I later emailed Jennifer about some data that was missing from some of the spreadsheets, and also to get the cross references for some of the coding used by UNOS. Some of the recipients had “U” in place of their cold ischemic times, which is understandable for cadaveric donors whose deaths may have been at unknown times, but there were quite a few unknowns for living donors which I did not expect to see. There were also some donors who did not have corresponding recipients, so I highlighted these as well and sent the spreadsheets back to her. I emptied the filing tray before leaving.

Wednesday, October 11, 2017

Today Holy showed me how to look up patients using Allscripts. However, I encountered a problem with some of the data. Patients are given a metabolic panel immediately after surgery, and then again at 3 AM the same or following day- no matter when the surgery took place. This creates a less-than-ideal range of time elapsed between the surgery’s end time and the day 1

creatinine clearance measurement. I discussed this with Dr. Mallet via email and phone and he said that I would have to come up with a range of hours that I would accept as day 1 and another range for day 2, and then apply this standard to all patients. After giving it more thought, I think I want to use 6-30 hours as day 1, and then 30-54 hours as day 2. That way, any transplant ending after 9 PM with less than 6 hours between the day 1 reading and the end of surgery will roll over to the next 3 AM reading, rather than the one on the same night. I'm still not sure if that is a good plan though, because the difference in creatinine clearance 6 hours post-op compared to 30 hours is still pretty significant, and this can cause some patients to be misdiagnosed with N-DGF. Perhaps I should use a narrower time frame and just exclude any patients who do not meet the criteria.

Thursday, October 12, 2017

Today I mostly collected data and filed regulatory documents before leaving. Jennifer sent me updates on some of the missing data that we had discussed.

Friday, October 13, 2017

Today I continued to collect data and filed regulatory documents before leaving. Jennifer also sent me updates on the remainder of the missing data via email.

Week 21

Monday, October 16, 2017

Today I continued data collection. I emailed Dr. Mallet about some questions I had and he suggested that I collect pre-transplant values as baseline between groups in order to characterize the population. Jennifer was really helpful in sending me the data for patients with missing cold ischemia times. She also sent me a list of patients with official DBD vs DCD causes of death.

Tuesday, October 17, 2017

Today I noticed that the prevalence of N-DGF was unusually high; 12/20 patients that I collected data on. I asked Sandra M. about it and she asked me to explain my study to her. We concluded that the incidence was not so surprising given the hospitals practices at the time. Also, since 6 of the 12 were from 3 of the same donors, this was actually a pretty accurate reflection of the population at the time. She reassured me that it would become more accurate with the more patients I included. I asked her for information on the changes that the transplant department has made since then.

Wednesday, October 18, 2017

Today I collected data and met with Dr. Mallet afterwards to talk about the data analysis. We agreed that I would continue data collection until Wednesday and then begin the statistical analysis and writing.

Thursday, October 19, 2017

Today I continued data collection, and I also helped Maria who sent me correspondence emails to print and file for a study.

Friday, October 20, 2017

Today I continued data collection and completed all of the data for cadaveric recipients in 2012.

Week 22

Monday, October 23, 2017

Today I finished collecting data on all cadaveric-kidney recipients from BUMC and BAS. I also finished data on living recipients from BAS today.

Tuesday, October 24, 2017

Today I completed collecting data on living recipients from BUMC through January 2013. I decided to exclude patients from BAS after January 2013 so that the timeline would be consistent with the deceased-donation recipients. I plan to spend tomorrow finding donor stroke history in DonorNet, since Dr. Mallet agrees that my sample size is adequate now.

Wednesday, October 25, 2017

Today after getting access to DonorNet I was not able to find stroke history as it was not collected by UNOS. I plan to look at donor age and terminal serum creatinine individually since I cannot technically classify patients as extended criteria donors without stroke history. I sent my data to Dr. Mallet today and we met and talked about options for the statistical analysis.

Thursday, October 26, 2017

Today I started writing my thesis and also the statistical analysis. I originally planned to use a t-test but after further discussion with Dr. Mallet he suggested a chi-squared analysis instead, since I no longer have the ECD group. He showed me how to calculate the chi-squared value using the 2x2 contingency table, and we discussed either analyzing two-kidney donors as

two separate experiments, or taking the first donor-recipient pair in each instance and excluding the second. I decided to analyze them as two separate transplants.

Friday, October 27, 2017

Today I continued writing and downloaded a statistics software. Holy informed me that linear regression could be calculated in Excel, so I decided to use that instead since the interface was more familiar.

Week 23

Monday, October 30, 2017

Today I continued writing my thesis and creating graphs for the regression analysis.

Tuesday, October 31, 2017

Today I continued writing my thesis and working on the statistical analysis. I noticed that the R-squared values were extremely low, and this was not at all expected for the variables that have been pretty well established as risk factors for DGF. I plan to meet with Dr. Mallet in the morning to discuss these results.

Wednesday, November 1, 2017

Today I continued writing after meeting with my major professor, who reassured me of the validity of my results. He offered ideas as to why the results were not showing strong relationships and about the clinical importance of those results. I was not expecting to get data so drastically different from the literature, so my discussion is going to be different than I originally planned.

Thursday, November 2, 2017

Today I sent the completed version of my Thesis to my major professor and Dr. Mathew. I will add a figure demonstrating the prevalence of DGF amongst living and deceased-donor kidney recipients per Dr. Mallet's suggestion. I also filed regulatory documents before leaving.

Friday, November 3, 2017

Today I sent the completed version of my thesis to the committee including the new figure. I also finished filing regulatory documents for Maria. I then started preparing for the presentation which I will continue to do this weekend.

BIBLIOGRAPHY

- (1) Yarlagadda SG, Coca SG, Garg AX, et al. Marked variation in the definition and diagnosis of delayed graft function: a systematic review. *Nephrol Dial Transplant*. 2008;23(9):2995-3003.
- (2) Vilar E, Varagunam M, Yaqoob MM, Raftery M, Thuraisingham R. Creatinine reduction ratio: a useful marker to identify medium and high-risk renal transplants. *Transplantation*. 2010;89(1):97-103.
- (3) Chaumont M, Racapé J, Broeders N, et al. Delayed Graft Function in Kidney Transplants: Time Evolution, Role of Acute Rejection, Risk Factors, and Impact on Patient and Graft Outcome. *J Transplant*. 2015;2015:163757.
- (4) Avihingsanon Y, Ma N, Pavlakis M, et al. On the intraoperative molecular status of renal allografts after vascular reperfusion and clinical outcomes. *J Am Soc Nephrol*. 2005;16(6):1542-8.
- (5) Rodrigo E, Ruiz JC, Piñera C, et al. Creatinine reduction ratio on post-transplant day two as criterion in defining delayed graft function. *Am J Transplant*. 2004;4(7):1163-9.
- (6) Govani MV, Kwon O, Batiuk TD, Milgrom ML, Filo RS. Creatinine reduction ratio and 24-hour creatinine excretion on posttransplant day two: simple and objective tools to define graft function. *J Am Soc Nephrol*. 2002;13(6):1645-9.
- (7) Mount, D. B., MD. (2015, September 24). Clinical manifestations of hyperkalemia in adults (R. H. Sterns MD & J. P. Forman MD, MSc, Eds.). Retrieved November 02, 2017, from https://www.uptodate.com/contents/clinical-manifestations-of-hyperkalemia-in-adults?source=search_result&search=Hyperkalemia&selectedTitle=3~150
- (8) Siedlecki A, Irish W, Brennan DC. Delayed graft function in the kidney transplant. *Am J Transplant*. 2011;11(11):2279-96.
- (9) Liu R, Persson E. Angiotensin II Stimulates Calcium and Nitric Oxide Release From macula Densa cells Through AT₁ Receptors. *Hypertension*. 2004;43:649-653.
- (10) Berne R. M., Koeppen B. M., Stanton B. A. (2010). *Berne & Levy physiology*. Philadelphia, PA: Mosby/Elsevier. pp 561-566, 573-577.
- (11) Emerit J, Beaumont C, Trivin F. Iron metabolism, free radicals, and oxidative injury. *Biomed Pharmacother*. 2001;55(6):333-9
- (12) Dołęgowska B, Błogowski W, Domański L. Clinical evidence of the association between serum perioperative changes in xanthine metabolizing enzymes activity and early post-transplant kidney allograft function. *J Am Coll Surg*. 2010;211(5):587-95.

- (13) Transplant Center, UC Davis. Donation After Cardiac Death (DCD). Retrieved October 31, 2017, from http://www.ucdmc.ucdavis.edu/transplant/nonlivingdonors/nonliving_after_cardiac.html
- (14) Moers C, Smits JM, Maathuis MH, et al. Machine perfusion or cold storage in deceased-donor kidney transplantation. *N Engl J Med*. 2009;360(1):7-19.
- (15) Singh RP, Farney AC, Rogers J, et al. Kidney transplantation from donation after cardiac death donors: lack of impact of delayed graft function on post-transplant outcomes. *Clin Transplant*. 2011;25(2):255-64.
- (16) Rao PS, Ojo A. The alphabet soup of kidney transplantation: SCD, DCD, ECD--fundamentals for the practicing nephrologist. *Clin J Am Soc Nephrol*. 2009;4(11):1827-31.
- (17) Yarlagadda SG, Coca SG, Formica RN, Poggio ED, Parikh CR. Association between delayed graft function and allograft and patient survival: a systematic review and meta-analysis. *Nephrol Dial Transplant*. 2009;24(3):1039-47.
- (18) Glantz SA. *Primer of Biostatistics*, 7th Ed. New York: McGraw-Hill, 2012, pp. 80-99
- (19) Reddy B, Murray P. Chapter 75. Acute Renal Failure. In: Hall JB, Schmidt GA, Wood LH. eds. *Principles of Critical Care, 3e* New York, NY: McGraw-Hill; 2005. <http://accessmedicine.mhmedical.com/content.aspx?bookid=361§ionid=39866447>. Accessed November 15, 2017.
- (20) Moers C, Pirenne J, Paul A, Ploeg RJ. Machine perfusion or cold storage in deceased-donor kidney transplantation. *N Engl J Med*. 2012;366(8):770-1.