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Early Detection of Acute Kidney Injury in Neonates After Cardiopulmonary Bypass

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EARLY DETECTION OF ACUTE KIDNEY INJURY IN NEONATES AFTER CARDIOPULMONARY BYPASS

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ABSTRACT

Prophylactic peritoneal dialysis (PD) in neonates undergoing cardiac surgery with cardiopulmonary bypass (CPB) has proven to be safe and improve outcomes. Understanding which neonates would most benefit from prophylactic PD is needed to optimize care.

Objective: We sought to validate patient-specific characteristics associated with the need for PD in neonates requiring CPB. We hypothesized serum creatinine (SCr), pre-operative weight, or open chest post-operatively are associated with the need for PD.

Methods: We evaluated neonates in the cardiac ICU requiring cardiac surgery with CPB from March 2019 through March 2021 with our new protocol for PD catheter placement. Neonates were classified as those who "needed PD" and those who "did not need PD." Those who "needed PD" had a PD catheter placed in the OR that was used for >48 hours, or those who did not have a PD catheter placed in the OR, but in retrospect would have benefited from PD based on predetermined clinical findings. Those who "did not need PD" did not have a PD catheter placed and would not have benefitted from PD, or if placed it was removed or put to drain ≤ 48 hours post-operatively.

Results: Of the 97 neonates, 29% were categorized as "needed PD" and 71% as "did not need PD." Neonates with higher STAT scores were associated with needing PD (Median = 5 [4-5] versus 4 [3-4.25], $p<0.0001$, 95% CI (0.52 to 1.09)). Neonates with an open chest post-operatively were more likely to need PD ($p<0.0001$). After adjusting for STAT

score, neonates with an open chest post-operatively were 14 times more likely to need PD (AOR=14.00; p=0.0038, 95% CI (1.53 to 127.89). After adjusting for open chest, for every 1 unit increase in STAT score there was a 2.54 higher odds for needing PD (AOR=2.54; p=0.0461, 95% CI (0.94 to 6.88)).

Conclusion: Implementation of our risk-based assessment has improved our ability to provide prophylactic PD to neonates requiring CPB. In contrast to our retrospective analysis, only having an open chest post-operatively was associated with needing PD in our prospective analysis. Additional larger prospective studies are needed to further validate our findings.

Keywords: acute kidney injury (AKI), cardiopulmonary bypass (CPB), peritoneal dialysis (PD), neonates

DEDICATION

I dedicate this thesis to my extremely supportive husband, Brandon, and to my adorable children Onyx and Satchel. Without their love, patience, support and understanding I would not have been able to accomplish this goal.

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LIST OF ABBREVIATIONS

AKI	acute kidney injury
CPB	cardiopulmonary bypass
ECMO	extracorporeal membrane oxygenation
IQR	interquartile range
KST	kidney support therapy
OR	operating room
PD	peritoneal dialysis
SCr	serum creatinine
STAT	Society of Thoracic Surgeons-European Association for Cardio-Thoracic Surgery

INTRODUCTION

Peritoneal dialysis (PD) is a common modality of kidney support therapy (KST) in smaller patients, especially infants. In neonates who undergo cardiopulmonary bypass (CPB), PD has been associated with improved outcomes; however, there is no consensus on which neonates would most benefit from prophylactic PD [1-3]. Several studies have demonstrated prophylactic PD to improve outcomes, including better fluid balance, fewer electrolyte abnormalities, shorter duration of mechanical ventilation and decreased length of ICU stay [3-5]. In fact, when placed in the operating room (OR), PD has proven to be safe with very few adverse events [3, 6, 7]. Prophylactic PD has been compared to the use of furosemide for fluid overload in infants after cardiac surgery. Those who received furosemide were more likely to have worse outcomes including 10% fluid overload [4].

Although we and others have shown that PD after CPB improves clinical outcomes, currently most pediatric hospitals do not have protocols in place for managing severe AKI and fluid overload post-operatively with early PD. While there is no definitive consensus on when PD should be initiated in this population, understanding the benefits of prophylactic PD is important. In addition, identification of neonates who will most benefit from prophylactic PD minimizes unnecessary procedures, including placement of PD catheters in neonates who ultimately will not require KST. Answers to these clinically relevant questions will help provide care for the right patients, thus improving outcomes while reducing medical expenditures. Such a model of protocol-

based initiation of PD may be applied to other critically ill pediatric and adult populations.

We have substantial preliminary data that a risk-based assessment prior to CPB may help identify neonates who will benefit from early preventive PD but this needs to be validated prospectively. We sought to test the hypothesis that patient-specific characteristics including pre-operative weight, pre-operative serum creatinine (SCr) and having an open chest post-operatively are associated with the need for PD in neonates who have undergone cardiac surgery requiring CPB. We hypothesize that our predetermined patient risk factors (SCr $\geq$ 0.8 mg/dL, pre-operative weight $\leq$ 2.5 kg or open chest post-operatively) are associated with the need for PD in neonates who have undergone cardiac surgery and placed on CPB.

METHODS

Population

Preliminary data/Era 1: We performed a single-center retrospective chart review of neonates with congenital heart disease who required cardiac surgery with CPB from October 2012 through June 2016 at Children's of Alabama. Inclusion criteria included all neonates less than 30 days of age who required CPB during cardiac surgery. Exclusion criteria included neonates who were started on KST prior to cardiac surgery. Institutional review board approval was obtained and a waiver of informed consent was included.

Current study/Era 2: We performed a prospective observational study of neonates with congenital heart disease who required cardiac surgery with CPB from March 2019 through March 2021, during which time our new protocol from Era 1 (preliminary data) for PD catheter placement had been implemented. Inclusion criteria included all neonates less than 30 days of age who required CPB during cardiac surgery. Exclusion criteria included neonates who were started on KST prior to cardiac surgery. Institutional review board approval was obtained and a waiver of informed consent was included. Utilization of the new protocol required PD catheters to be placed in the OR at the time of cardiac surgery based on the predetermined patient-specific characteristics (SCr $\geq$ 0.8 mg/dL, pre-operative weight $\leq$ 2.5 kg or open chest post-operatively) from Era 1. Those who did not meet the predetermined patient-specific characteristics did not have a PD catheter placed in the OR with the exception of those having a Norwood procedure due to the surgical complexity and expected illness of the patient post-operatively.

Perioperative characteristics

Perioperative characteristics evaluated for both eras included age at time of surgery, sex, birthweight, gestational age, the Society of Thoracic Surgeons-European Association for Cardio-Thoracic Surgery (STAT) score, CPB time, lowest pre-operative SCr, pre-operative weight, and open chest post-operatively **(Tables 1 and 2**).

Defining the need for PD

We classified neonates as those who "needed PD" and those who "did not need PD" based on prior experience of those requiring KST in the cardiac ICU. Neonates defined as "needed PD" had a PD catheter placed in the OR that was used for more than 48 hours, or those who did not have a PD catheter placed in the OR but in retrospect would have benefited from PD based on the neonate having 10% fluid overload plus one of the following: intubated for more than 48 hours, had an open chest for more than 48 hours and/or required extracorporeal membrane oxygenation (ECMO). Neonates defined as those who "did not need PD" had a PD catheter placed in the OR but it was removed or put to drain ≤ 48 hours post-operatively or who did not have a PD catheter placed in the OR and would not have benefitted from PD based on our above criteria (**Table 3**).

Participant Allocation

Neonates were classified into four groups based on the 2 x 2 table below for the variables of whether or not a PD catheter was placed in the OR and whether they "needed PD" vs "did not need PD." The cohort was divided into the following 4 groups:

- Group 1 were those that had a PD catheter placed and "needed PD."

- Group 2 were those that had a PD catheter placed and “did not need PD.”
- Group 3 were those that did not have a PD catheter placed and “needed PD.”
- Group 4 were those that did not have a PD catheter placed and “did not need PD.”

These four groups were finally categorized into those that “needed PD” (Groups 1 and 3) and those that “did not need PD” (Groups 2 and 4) as shown in **Tables 1 and 2**.

Table 1

Descriptive statistics for Era 1

Variable	Total N=148 (%)	ERA 1 Needed PD N=67 (%)	ERA 1 Did not need PD N=81 (%)	p-value (95% CI)
Age at surgery (days)				
Mean ± SD	9.66 ± 6.76	8.44 ± 5.89	10.68 ± 7.29	**0.0446**
Median, IQR	7.32 (5.35-11.38)	6.40 (4.49-9.32)	8.31 (5.52-13.96)	**(-0.42 to 0.05)**
Sex (Male)	92 (62.59)	45 (67.16)	47 (58.02)	0.1729
Birthweight (kg)				
Mean ± SD	3.11 ± 0.5	3.02 ± 0.55	3.19 ± 0.54	0.0829
Median, IQR	3.09 (2.75-3.46)	3.00 (2.67-3.40)	3.3 (2.88-3.50)	(-0.35 to 0.02)
Gestational Age (weeks)				
Mean ± SD	38.21 ± 1.61	38.04 ± 1.44	38.36 ± 1.76	0.2523
Median, IQR	39 (37-39)	39 (37-39)	39 (37.25-39)	(-0.84 to 0.22)
STAT				
Mean ± SD	3.84 ± 0.92	4.10 ± 0.84	3.63 ± 0.93	**0.0015**
Median, IQR	4 (3-4)	4 (4-5)	4 (3-4)	**(0.18 to 0.76)**
CPB (min)				
Mean ± SD	114.43 ± 50.65	122.58 ± 49.41	107.79 ± 50.98	0.075
Median, IQR	108.5 (86-133.75)	117 (92-144)	102 (74.5-128)	(-1.52 to 31.30)
Pre-op SCr (mg/dL)				
Mean ± SD	0.50 ± 0.14	0.53 ± 0.14	0.47 ± 0.14	**0.0099**
Median, IQR	0.5 (0.4-0.6)	0.5 (0.4-0.7)	0.5 (0.4-0.6)	**(0.01 to 0.11)**
Pre-op weight (kg)				
Mean ± SD	3.19 ± 0.55	3.09 ± 0.51	3.28 ± 0.56	**0.0381**
Median, IQR	3.20 (2.81-3.50)	3.10 (2.67-3.46)	3.24 (3.00-3.62)	**(-0.36 to -0.01)**
Open chest (yes)	63 (42.57)	42 (62.69)	21 (25.93)	**<0.001**

All values are N (%) except for those with ± which represent mean and standard deviation or median with IQR. P-values represent chi-square test for categorical variables and independent T-Test for continuous variables. PD (peritoneal dialysis), STAT (Society of Thoracic Surgeons-European Association for Cardio-Thoracic Surgery), CPB (cardiopulmonary bypass), SCr (serum creatinine)

Table 2

Descriptive statistics for Era 2

Variable	Total N=97 (%)	ERA 2 Needed PD N=28 (%)	ERA 2 Did not need PD N=69 (%)	p-value (95% CI)
Age at surgery (days)				
Mean ± SD	7.94 ± 4.67	6.39 ± 2.99	8.57 ± 5.08	**0.0509
Median, IQR	7 (5-9.5)	6.5 (5-7.75)	7 (5.5-10.5)	(-3.83 to -0.52)
Sex (Male)	46 (47.42)	11 (39.29)	35 (50.72)	0.305
Birthweight (kg)				
Mean ± SD	3.09 ± 0.53	3.11 ± 0.44	3.08 ± 056	0.8516
Median, IQR	3.04 (2.73-3.45)	3.01 (2.82-3.45)	3.05 (2.68-3.45)	(-0.23 to 0.28)
Gestational Age (weeks)				
Mean ± SD	38.05 ± 1.33	38.15 ± 1.26	38.01 ± 1.37	**0.6279
Median, IQR	39 (37-39)	39 (37-39)	38 (37-39)	(-0.45 to 0.74)
STAT				
Mean ± SD	4.13 ± 0.84	4.69 ± 0.47	3.89 ± 0.85	****<0.0001**
Median, IQR	4 (4-5)	5 (4-5)	4 (3-4.25)	**(0.52 to 1.09)**
CPB (min)				
Mean ± SD	121.42 ± 49.25	128.79 ± 35.50	118.43 ± 53.79	**0.0771
Median, IQR	118 (89-146)	132 (108.25-156.5)	114 (85-139)	(-8.22 to 28.93)
Pre-op SCr (mg/dL)				
Mean ± SD	0.53 ± 0.14	0.57 ± 0.14	0.51 ± 0.13	**0.0534
Median, IQR	0.51 (0.43-0.6)	0.53 (0.47-0.66)	0.50 (0.41-0.58)	(-0.01 to 0.12)
Pre-op weight (kg)				
Mean ± SD	3.19 ± 0.53	3.14 ± 0.41	3.22 ± 0.57	**0.4144
Median, IQR	3.19 (2.84-3.58)	2.99 (2.89-3.40)	3.27 (2.82-3.61)	(-0.28 to 0.13)
Open chest (yes)	55 (56.70)	27 (96.43)	28 (40.58)	**<0.0001**

All values are N (%) except for those with ± which represent mean and standard deviation or median with IQR. P-values represent chi-square test for categorical variables, independent T-Test for continuous variables or Wilcoxon signed rank test indicated by **

PD (peritoneal dialysis), STAT (Society of Thoracic Surgeons-European Association for Cardio-Thoracic Surgery), CPB (cardiopulmonary bypass), SCr (serum creatinine)

Table 3

Defining the need for PD

Condition 1 (Needed PD)	Condition 2 (Did not need PD)
• PD catheter placed in the OR and used for > 2 days	• PD catheter not placed in the OR
• PD catheter not placed in the OR but in retrospect would have benefited based on > 10% fluid overload PLUS one of the following: o intubated > 48 hours o open chest > 48 hours o ECMO	• PD catheter placed in the OR but it was removed or put to drain </= 48 hours post-op

PD (peritoneal dialysis), OR (operating room), ECMO (extracorporeal membrane oxygenation)

STATISTICAL ANALYSIS

We identified statistically significant differences in patient characteristics between the two groups: those who needed PD versus those who did not need PD. Descriptive statistics were performed using percentages for categorical variables. Chi-square was used to compare differences in categorical variables, independent t-test for continuous variables and Wilcoxon signed rank test for continuous variables that were not normally distributed. Continuous variables that were normally distributed were reported as means with standard deviation and variables that were not normally distributed we reported as medians with interquartile ranges (IQR). For Era 1 we were able to invoke the central limit theorem for continuous variables that were not normally distributed. For Era 2 we used the Wilcoxon signed rank test for continuous variables that were not normally distributed. The STAT score represents the estimated risk of mortality associated with cardiac procedures and ranges from categories 1-5, with 5 having the highest mortality risk. While the STAT score is ordinal data, we treated it as a continuous variable because it has five levels. For the regression analysis, we were interested in the association of multiple independent variables with the need for PD. The dependent variable, needed PD, was a categorical variable with two-levels, therefore a binary logistic regression analysis was performed to predict the need for PD (yes or no). For our statistical model, we used the variables with statistical significance based on the bivariate analysis. We then used a combination of forward and backward selection with step-wise regression to further determine the most parsimonious model for predicting the need for PD, using $p=0.10$. For

Era 1, we adjusted for open chest post-operatively, pre-operative SCr and pre-operative weight. For Era 2, we adjusted for open chest post-operatively and STAT score. All statistical analyses were performed using JMP Pro 16.

RESULTS

Era 1

Era 1 is our preliminary data in which we performed our retrospective chart review and represents our findings prior to implementing the protocol for PD catheter placement. There was a total of 148 neonates evaluated who had cardiac surgery requiring CPB. There were no neonates excluded from the analysis. The study included a total of 148 neonates and there was no missing data. The Lack of Fit was not statistically significant (p=0.2226) meaning we had good model fit. The confusion matrix indicated that 69.59% of the cases were correctly classified so model fit was satisfactory. The chi-square whole model test was statistically significant ($X^2_{(3)}$=29.86378; p<0.0001) meaning that our current model was better than the null model. In assessing the model assumptions, none of the correlations were greater than 0.8 therefore there was no evidence of multicollinearity with the predictor variables and the dependent variable had an acceptable split between needed PD (45%) and did not need PD (55%).

Of the 148 neonates in the study, 99/148 (67%) had PD catheters placed in the OR.

- 58/99 (59%) of neonates with PD catheters placed needed PD and were classified as Group 1.
- 41/99 (41%) of neonates with PD catheters placed did not need PD and were classified as Group 2.

Of the 148 neonates in the study, 49/148 (33%) did not have PD catheters placed in the OR.

- 9/49 (18%) of neonates without PD catheters placed needed PD and were classified as Group 3.
- 40/49 (82%) of neonates without PD catheters placed did not need PD and were classified as Group 4 (**Table 4**).

Demographic data were categorized by the outcome variables needed PD and did not need PD (**Table 1**). Of the 148 neonates evaluated, 67/148 (45%) needed PD and 81/148 (55%) did not need PD. Of the 67 neonates in the needed PD group, 9/67 (13.4%) did not have a PD catheter placed in the OR while of the 81 neonates in the did not need PD group, 41/81 (50.6%) had a PD catheter placed (**Table 4**). Bivariate analysis revealed that those who needed PD were younger on the day of surgery (Median= 6.40 [4.49-9.32] days versus 8.31 [5.52-13.96] days; p=0.04, 95% CI (-0.42 to -0.05) and had a lower pre-operative weight on the day of surgery (Mean= 3.09 ± 0.51 kg versus 3.28 ± 0.56 kg; p=0.04, 95% CI (-0.36 to -0.01). The lowest pre-operative SCr was equal for both groups (0.5 mg/dL) but differed in IQR (IQR= 0.4-0.7 versus 0.4-0.6; p=0.01, 95% CI (0.01 to 0.11). The neonates who had an open chest post-operatively were more likely to need PD, $p<0.001$. Neonates with higher STAT scores were associated with the need for PD (Median = 4 [4-5] versus 4 [3-4], p=0.0015, 95% CI (0.18 to 0.76)). There were no significant differences in sex, birthweight, gestational age, and CPB time between groups. After performing a combination of forward and backward selection with step-wise regression we found the most parsimonious model for predicting need for PD, using p=0.10: pre-operative SCr, pre-operative weight or open chest post-operatively with an AUC=0.7. For every 0.1 mg/dL increase in SCr the odds of needing PD increased by 36%, controlling for pre-operative weight and open chest post-operatively (AOR 1.36;

p=0.0169, 95% CI (1.06 to 1.79). Neonates with an open chest post-operatively were 4.73 times more likely to need PD, controlling for SCr and pre-operative weight (AOR 4.7; p<0.001, 95% CI (2.32 to 9.96)) (**Table 5**). While pre-operative weight did not reach significance (AOR 0.53; p=0.0636, 95% CI (0.26 to 1.04)) we included it as a predictor in our final model for our prospective analysis because it neared significance. Using the Prediction Equation we were able to determine a 70% probability that a neonate with a SCr ≥ 0.8 mg/dL, preoperative weight ≤ 2.5 kg or having an open chest post-operatively would need prophylactic PD.

Table 4

2x2 table of Era 1 need for PD

	Needed PD	**Did not need PD**	**Total**
PD catheter placed (YES)	58 (Group 1)	41 (Group 2)	99
PD catheter placed (NO)	9 (Group 3)	40 (Group 4)	49
Total	67	81	148

PD (peritoneal dialysis)

Table 5

Era 1. Mixed step-wise logistic regression predicting need for PD

Variable	**Crude OR**	**P-value**	**95% CI**	**AOR**	**P-value**	**95% CI**
Pre-op SCr (mg/dL)	1.36	**0.0095**	1.07 to 1.74	1.36	**0.0169**	1.06 to 1.79
Pre-op weight (kg)	0.52	**0.0362**	0.27 to 0.96	0.53	0.0636	0.26 to 1.04
Open chest (yes)	4.8	**<0.0001**	2.41 to 9.84	4.73	**<0.0001**	2.32 to 9.96

PD (peritoneal dialysis), SCr (serum creatinine)

Era 2

Era 2 represents our findings after implementation of our new protocol for PD catheter placement. The study included a total of 97 neonates; however, upon logistic regression analysis the total sample size was 88 so we were missing 9% (N=9) of the data. The Lack of Fit was not statistically significant (p=0.9221) meaning we had a good model fit. The Confusion Matrix indicated that 75.00% of the cases were correctly classified so model fit was satisfactory. The chi-square whole model test was statistically significant ($X^2_{(2)}$=29.65288; p<0.0001) meaning that our current model was better than the null model. In assessing the model assumptions, none of the correlations were greater than 0.8 therefore there was no evidence of multicollinearity among the predictor variables and the dependent variable had an acceptable split between needed PD (29%) and did not need PD (71%).

Of the 97 neonates in the study, 46/97 (47%) had PD catheters placed in the OR.

- 28/46 (61%) of neonates with PD catheters placed needed PD and were classified as Group 1.
- 18/46 (39%) of neonates with PD catheters placed did not need PD and were classified as Group 2.

Of the 97 neonates in the study, 51/97 (53%) did not have PD catheters placed in the OR.

- 0/51 (0%) of neonates without PD catheters placed needed PD and were classified as Group 3.
- 51/51 (100%) of neonates without PD catheters placed did not need PD and were classified as Group 4 (**Table 6**).

Table 6

2x2 table of Era 2 need for PD

	Needed PD	Did not need PD	Total
PD catheter placed (YES)	28 (Group 1)	18 (Group 2)	46
PD catheter placed (NO)	0 (Group 3)	51 (Group 4)	51
Total	28	69	97

PD (peritoneal dialysis)

Demographic data were categorized by the outcome variables needed PD and did not need PD (**Table 2**). Of the 97 neonates evaluated, 28/97 (29%) needed PD and 69/97 (71%) did not need PD. Of the 28 neonates in the needed PD group, 0/28 (0%) did not have a PD catheter placed in the OR while of the 69 neonates in the did not need PD group, 18/69 (26.1%) had a PD catheter placed (**Table 6**). Bivariate analysis demonstrated that neonates with higher STAT scores were associated with the need for PD (Median = 5 [4-5] versus 4 [3-4.25], p<0.0001, 95% CI (0.52 to 1.09)). The neonates who had an open chest post-operatively were more likely to need PD (p<0.0001). There were no significant differences in age at surgery, sex, birthweight, gestational age, CPB time, pre-operative SCr or pre-operative weight between groups. After performing a combination of forward and backward selection with step-wise regression we found the most parsimonious model for predicting the need for PD, using p=0.10: STAT score and open chest post-operatively. After adjusting for open chest, for every 1 unit increase in STAT score there was 2.54 higher odds for needing PD (AOR=2.54; p=0.0461, 95% CI (0.94 to 6.88)). After adjusting for STAT score, neonates with an open chest post-operatively were 14 times more likely to need PD than not need PD (AOR=14.00; p=0.0038, 95% CI (1.53 to 127.89)) (**Table 7**).

Table 7

Era 2. Mixed step-wise logistic regression predicting need for PD

Variable	Crude OR	P-value	95% CI	AOR	P-value	95% CI
STAT	5.69	**<0.0001**	2.5 to 15.18	2.54	**0.0461**	0.94 to 6.88
Open chest (yes)	39.54	**<0.0001**	7.71 to 725.25	12.64	**0.0038**	1.54 to 127.89

PD (peritoneal dialysis), STAT (Society of Thoracic Surgeons-European Association for Cardio-Thoracic Surgery)

DISCUSSION

In this prospective observational study we sought to test the hypothesis that patient-specific characteristics including pre-operative weight, pre-operative SCr and having an open chest post-operatively are associated with the need for PD in neonates who have undergone cardiac surgery requiring CPB. These risk factors were determined after performing a single-center retrospective analysis of 148 neonates requiring CPB after cardiac surgery. It was determined that SCr $\geq$ 0.8 mg/dL, pre-operative weight $\leq$ 2.5 kg or having an open chest post-operatively were associated with the need for PD. Our current study demonstrated that having an open chest post-operatively was associated with needing PD after adjusting for STAT score (AOR=14.00; p=0.0038, 95% CI (1.53- to 127.89); however, we did not find that SCr or pre-operative weight were associated with the need for PD as hypothesized.

Prior studies have investigated SCr as a risk factor for developing AKI in infants undergoing cardiac surgery requiring CPB and have found associations with both a lower pre-operative SCr and a higher pre-operative SCr. In a retrospective analysis, Aydin and colleagues reviewed individuals 18 years of age and younger who underwent cardiac surgery. After multivariate logistic regression analysis of approximately 85 neonates, they demonstrated that a lower pre-operative SCr was independently associated with AKI [8]. On the other hand, Blinder and colleagues retrospectively evaluated approximately 400 infants who underwent cardiac surgery and found that a higher pre-operative SCr was associated with postoperative AKI [9].The discrepancy in these findings is likely to

be multifactorial. An overall challenge is the difficulty in defining neonatal AKI due to multiple confounders including maternal SCr, neonatal prematurity and proximal tubular immaturity [10-12]. The initial SCr seen is neonates is often reflective of maternal SCr and can take weeks to reach its nadir. Consequently, it is expected for SCr to decrease during the first week of birth and therefore it is difficult to determine the baseline SCr or the degree of AKI in neonates who have cardiac surgery within the first few days of life [13]. Another contributor is the variation in the classification used to define AKI which differs based on changes in SCr and urine output. Currently, it has been generally accepted to use the neonatal modified Kidney Diseases: Improving Global Outcomes (KDIGO) criteria for defining AKI in neonates; however, some prior studies have used other classifications including the risk, injury, failure, loss and end-stage renal disease (RIFLE) classification, pediatric RIFLE (pRIFLE) and Acute Kidney Injury Network (AKIN) [14, 15]. While the abovementioned studies discuss the association of SCr to the development of AKI, our study specifically focused on the association of SCr and the development of severe AKI requiring KST.

Our prospective analysis also did not find an association between pre-operative weight and the need for PD as we hypothesized. This was not a huge surprise because when we adjusted for pre-operative SCr and having an open chest post-operatively in our multivariable regression analysis, pre-operative weight was no longer significant with p=0.0636. We included pre-operative weight in our prospective analysis to increase the sensitivity because it neared significance and we did not want to miss any neonates who may have needed PD. In retrospect, including the pre-operative weight as a criteria for PD catheter placement may have contributed to us not having a significant improvement

in neonates who did not need PD but had a PD catheter placed (41% vs 39%).

Aside from our hypothesis, we found that the STAT score was associated with the need for PD after adjusting for open chest post-operatively (AOR=2.54; p=0.0461, 95% CI (0.94 to 6.88)). While the p-value is significant, we do interpret this association with caution due to our reported 95% confidence interval of 0.94 to 6.88. In our retrospective analysis (Era 1), bivariate analysis demonstrated that the STAT score was statistically significant between groups; however, once included in our statistical model it was no longer significant. When we compare Era 1 to Era 2 for overall differences between groups, we find that the groups differed for STAT scores, with neonates in Era 2 having higher STAT scores than Era 1 neonates. This may account for the difference seen between both Eras. We do not feel that the association of the STAT score and need for PD in Era 2 should be ignored but should be further investigated with larger studies.

The strength of this study is that this is one of the first studies to proactively identify and later validate risk factors associated with the need for PD in neonates who have undergone cardiac surgery requiring CPB. It is known that prophylactic PD improves outcomes in neonates requiring cardiac surgery; however, we do not know which neonates would benefit most [1-3]. We are one of very few pediatric hospitals who perform prophylactic PD in this population. This study has assisted our institution with actively developing a protocol for managing severe AKI post-operatively. Proactively identifying these risk factors avoids delays in initiating PD therefore mitigating worsening outcomes including fluid overload, prolonged mechanical ventilation, prolonged ICU length of stay and mortality. This protocol has the potential to not only improve patient outcomes but reduce medical expenditures. This study also demonstrated

that we were able to decrease the number of neonates who needed PD but did not have a PD catheter placed between Era 1 and Era 2 from 13.4% to 0%, respectively. Also, we were able to decrease the number of neonates who did not need PD but had a PD catheter placed between Era 1 and Era 2 from 50.6% to 26.1%, respectively. There are some limitations to this study including single-center retrospective analysis and small sample size which is often seen in other pediatric studies. Increasing the sample size can potentially strengthen the study which can then be further validated in larger prospective studies. Additionally, there is no accepted consensus of when KST should be initiated. Opinions on when to start KST vary between institutions and even among nephrologists at the same institution. After thoughtful discussion and consideration, our definition of who needs PD was decided by the nephrologists and cardiac intensivists at our institution based on prior experience of neonates in the cardiac ICU who required PD. Therefore, the definition of who needs PD is not generalizable. Having a more universal consensus on which patients actually require PD is needed and can possibly be accomplished by surveying various pediatric institutions who perform KST.

While acknowledging both the strengths and limitations of our study, it has allowed us to establish a starting point for standardizing care for these neonates. Future multi-center prospective studies will further enhance our findings.

CONCLUSION

Implementation of our risk-based assessment prior to CPB has improved our ability to provide prophylactic PD to neonates who will likely have severe AKI requiring KST at our institution. Of the three patient-specific characteristics that we found in our retrospective analysis to be associated with the need for PD, we only found having an open chest post-operatively in our prospective analysis to be significant. Additional larger prospective studies are needed to further validate our findings.

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APPENDIX A

IRB Approval letter

THE UNIVERSITY OF ALABAMA AT BIRMINGHAM
Office of the Institutional Review Board for Human Use

470 Administration Building
701 20th Street South
Birmingham, AL 35294-0104
205.934.3789 | Fax 205.934.1301 |
irb@uab.edu

APPROVAL LETTER

TO: Borasino, Santiago

FROM: University of Alabama at Birmingham Institutional Review Board
Federalwide Assurance # FWA00005960
IORG Registration # IRB00000196 (IRB 01)
IORG Registration # IRB00000726 (IRB 02)

DATE: 26-Jun-2019

RE: IRB-160624007
Description of Acute Kidney Injury in Neonates Undergoing Cardiac Surgery with Cardiopulmonary Bypass

---

The IRB reviewed and approved the Continuing Review submitted on 25-Jun-2019 for the above referenced project. The review was conducted in accordance with UAB's Assurance of Compliance approved by the Department of Health and Human Services.

Type of Review:	Expedited
Expedited Categories:	5
Determination:	Approved
Approval Date:	26-Jun-2019
Approval Period:	Expedited Status Update (ESU)
Expiration Date:	25-Jun-2022

Although annual continuing review is not required for this project, the principal investigator is still responsible for (1) obtaining IRB approval for any modifications before implementing those changes except when necessary to eliminate apparent immediate hazards to the subject, and (2) submitting reportable problems to the IRB. Please see the IRB Guidebook for more information on these topics.

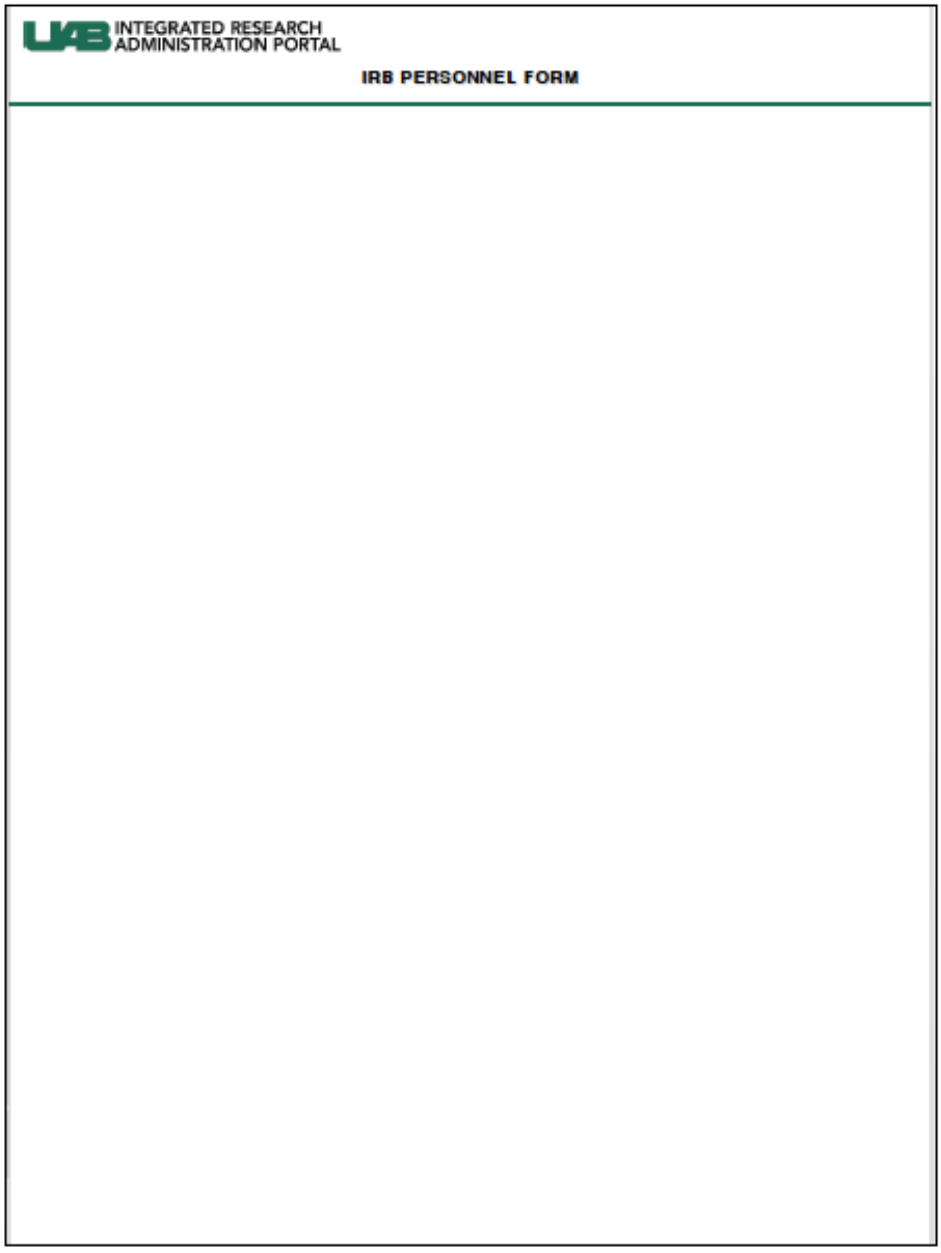
The following apply to this project related to informed consent and/or assent:

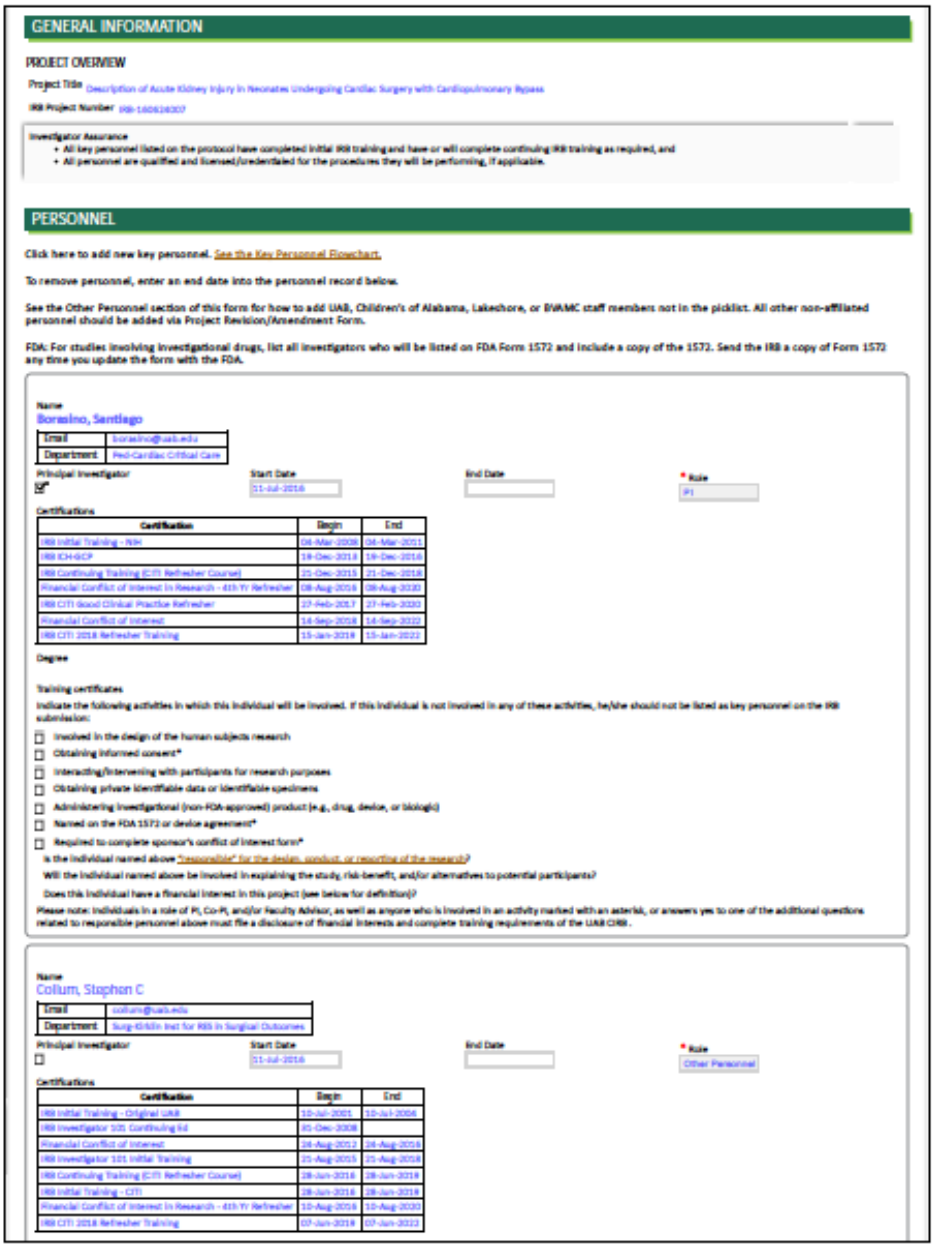
- Waiver of Informed Consent
- Waiver of HIPAA

This protocol has now been transitioned to the 2018 Revised Common Rule and no longer requires continuing review. An Expedited Status Update (ESU) is required at least every three years. Details regarding the process for the ESU can be found on the IRB website.

APPENDIX B

IRB Personnel Form


INTEGRATED RESEARCH
ADMINISTRATION PORTAL
IRB PERSONNEL FORM



GENERAL INFORMATION

PROJECT OVERVIEW

Project Title: Description of Acute Kidney Injury in Neonates Undergoing Cardiac Surgery with Cardiopulmonary Bypass

IRB Project Number: IRB-160626007

Investigator Assurance
- All key personnel listed on the protocol have completed initial IRB training and have or will complete continuing IRB training as required, and
- All personnel are qualified and licensed/credentialed for the procedures they will be performing, if applicable.

PERSONNEL

Click here to add new key personnel. See the Key Personnel Flowchart.

To remove personnel, enter an end date into the personnel record below.

See the Other Personnel section of this form for how to add UAB, Children's of Alabama, Lakeshore, or BVAMC staff members not in the picklist. All other non-affiliated personnel should be added via Project Revision/Amendment Form.

FDA: For studies involving investigational drugs, list all investigators who will be listed on FDA Form 1572 and include a copy of the 1572. Send the IRB a copy of Form 1572 any time you update the form with the FDA.

Name
Borasino, Santiago

Email	borasino@uab.edu
Department	Ped-Cardiac Critical Care

Principal Investigator: ☑ | Start Date: 01-Jul-2016 | End Date: | * Role: PI

Certifications

Certification	Begin	End
IRB Initial Training - NIH	04-Mar-2008	04-Mar-2011
IRB ICH-GCP	19-Dec-2013	19-Dec-2018
IRB Continuing Training (CITI Refresher Course)	21-Dec-2015	21-Dec-2018
Financial Conflict of Interest in Research - 4th Yr Refresher	08-Aug-2016	08-Aug-2020
IRB CITI Good Clinical Practice Refresher	27-Feb-2017	27-Feb-2020
Financial Conflict of Interest	14-Sep-2016	14-Sep-2022
IRB CITI 2018 Refresher Training	15-Jan-2018	15-Jan-2022

Degree

Training certificates

Indicate the following activities in which this individual will be involved. If this individual is not involved in any of these activities, he/she should not be listed as key personnel on the IRB submission:

- ☐ Involved in the design of the human subjects research
- ☐ Obtaining informed consent*
- ☐ Interacting/intervening with participants for research purposes
- ☐ Obtaining private identifiable data or identifiable specimens
- ☐ Administering investigational (non-FDA-approved) product (e.g., drug, device, or biologic)
- ☐ Named on the FDA 1572 or device agreement*
- ☐ Required to complete sponsor's conflict of interest form*

Is the individual named above "responsible" for the design, conduct, or reporting of the research?

Will the individual named above be involved in explaining the study, risk-benefit, and/or alternatives to potential participants?

Does this individual have a financial interest in this project (see below for definition)?

Please note: Individuals in a role of PI, Co-PI, and/or Faculty Advisor, as well as anyone who is involved in an activity marked with an asterisk, or answers yes to one of the additional questions related to responsible personnel above must file a disclosure of financial interests and complete training requirements of the UAB CIRB.

Name
Collum, Stephen C

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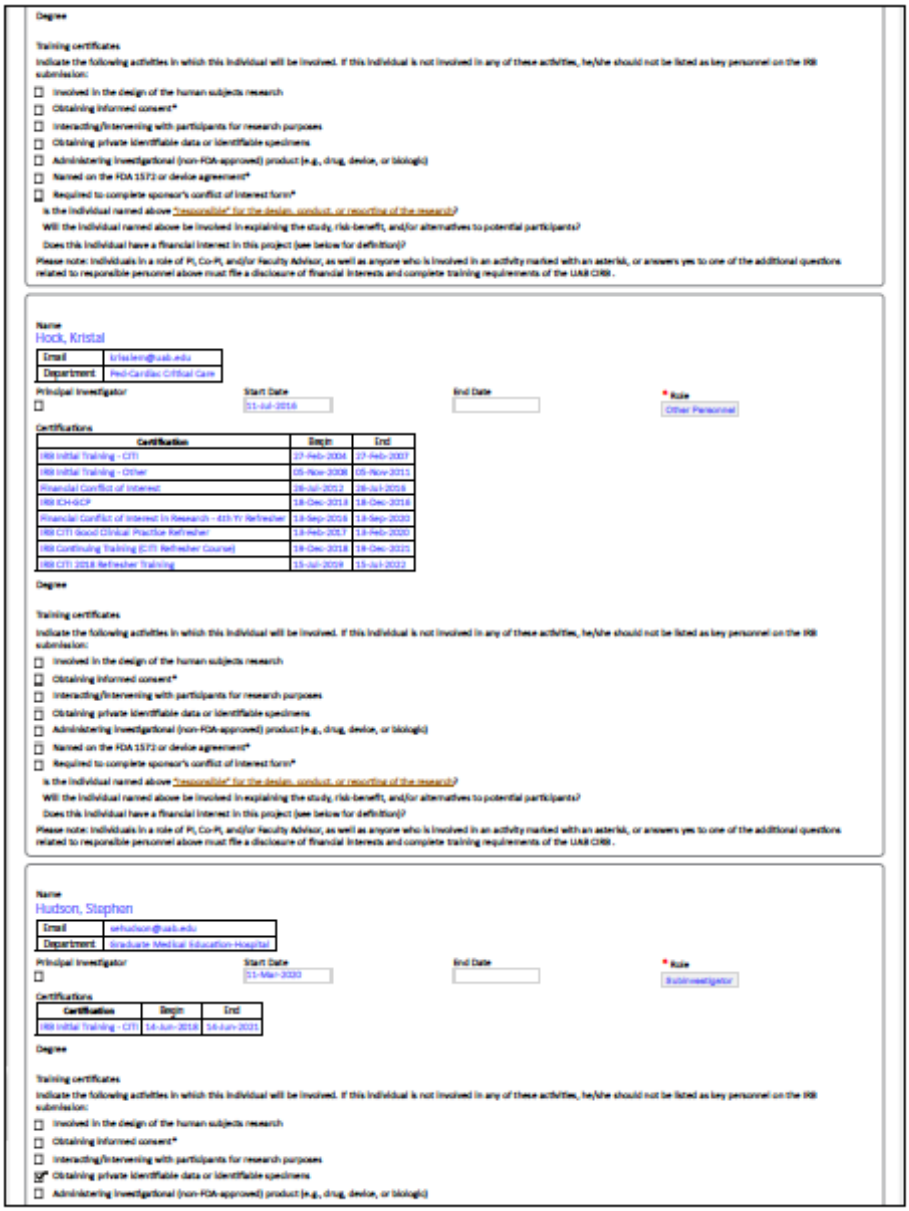
Principal Investigator: ☐ | Start Date: 01-Jul-2016 | End Date: | * Role: Other Personnel

Certifications

Certification	Begin	End
IRB Initial Training - Original UAB	10-Jul-2001	10-Jul-2006
IRB Investigator 101 Continuing Ed	01-Dec-2008	
Financial Conflict of Interest	24-Aug-2012	24-Aug-2018
IRB Investigator 101 Initial Training	21-Aug-2013	21-Aug-2018
IRB Continuing Training (CITI Refresher Course)	28-Jun-2014	28-Jun-2014
IRB Initial Training - CITI	28-Jun-2014	28-Jun-2014
Financial Conflict of Interest in Research - 4th Yr Refresher	10-Aug-2016	10-Aug-2020
IRB CITI 2018 Refresher Training	07-Jun-2018	07-Jun-2022



Degree

Training certificates

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Name

Hock, Kristal

Email	krisslen@uab.edu
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Principal Investigator ☐ | Start Date 01-Jul-2016 | End Date | * Role Other Personnel

Certifications

Certification	Begin	End
IRB Initial Training - CITI	27-Feb-2004	27-Feb-2007
IRB Initial Training - Other	05-Nov-2008	05-Nov-2011
Financial Conflict of Interest	28-Jul-2012	28-Jul-2016
IRB ICH-GCP	18-Dec-2014	18-Dec-2018
Financial Conflict of Interest in Research - 4th Yr Refresher	18-Sep-2016	18-Sep-2020
IRB CITI Good Clinical Practice Refresher	18-Feb-2017	18-Feb-2020
IRB Continuing Training (CITI Refresher Course)	19-Dec-2018	19-Dec-2021
IRB CITI 2018 Refresher Training	15-Jul-2019	15-Jul-2022

Degree

Training certificates

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Name

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Principal Investigator ☐ | Start Date 01-Mar-2020 | End Date | * Role Subinvestigator

Certifications

Certification	Begin	End
IRB Initial Training - CITI	14-Jun-2018	14-Jun-2021

Degree

Training certificates

Indicate the following activities in which this individual will be involved. If this individual is not involved in any of these activities, he/she should not be listed as key personnel on the IRB submission:

- ☐ Involved in the design of the human subjects research
- ☐ Obtaining informed consent*
- ☐ Interacting/intervening with participants for research purposes
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- ☐ Administering investigational (non-FDA-approved) product (e.g., drug, device, or biologic)

☐ Named on the FDA 1572 or device agreement*
☐ Required to complete sponsor's conflict of interest form*
No Is the individual named above "responsible" for the design, conduct, or reporting of the research?
No Will the individual named above be involved in explaining the study, risk-benefit, and/or alternatives to potential participants?
No Does this individual have a financial interest in this project (see below for definition)?
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Principal Investigator ☐ | Start Date 11-Jul-2016 | End Date | * Role Other Personnel

Certifications

Certification	Begin	End
IRB Investigator 101 Initial Training	29-Jun-2015	29-Jun-2018
IRB ICH-GCP	13-Dec-2018	13-Dec-2018
Financial Conflict of Interest	09-Mar-2017	09-Mar-2021
IRB CITI 2018 Refresher Training	14-Jan-2018	14-Jan-2022
IRB CITI Good Clinical Practice Refresher	18-Dec-2018	18-Dec-2022

Degree

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Does this individual have a financial interest in this project (see below for definition)?
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Name
Kirklin, James K

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Principal Investigator ☐ | Start Date 11-Jul-2016 | End Date | * Role Other Personnel

Certifications

Certification	Begin	End
IRB Initial Training - Original UAB	25-May-2000	25-May-2004
IRB Initial Training - CITI	07-Feb-2008	07-Feb-2008
Financial Conflict of Interest	16-Aug-2012	16-Aug-2016
IRB ICH-GCP	18-Sep-2014	18-Sep-2018
IRB Continuing Training (CITI Refresher Course)	21-Dec-2015	21-Dec-2018
Financial Conflict of Interest in Research - 413 Yr Refresher	09-Aug-2016	09-Aug-2020
IRB CITI Good Clinical Practice Refresher	15-Feb-2017	15-Feb-2020
IRB CITI 2018 Refresher Training	06-Mar-2018	06-Mar-2022

Degree

Training certificates
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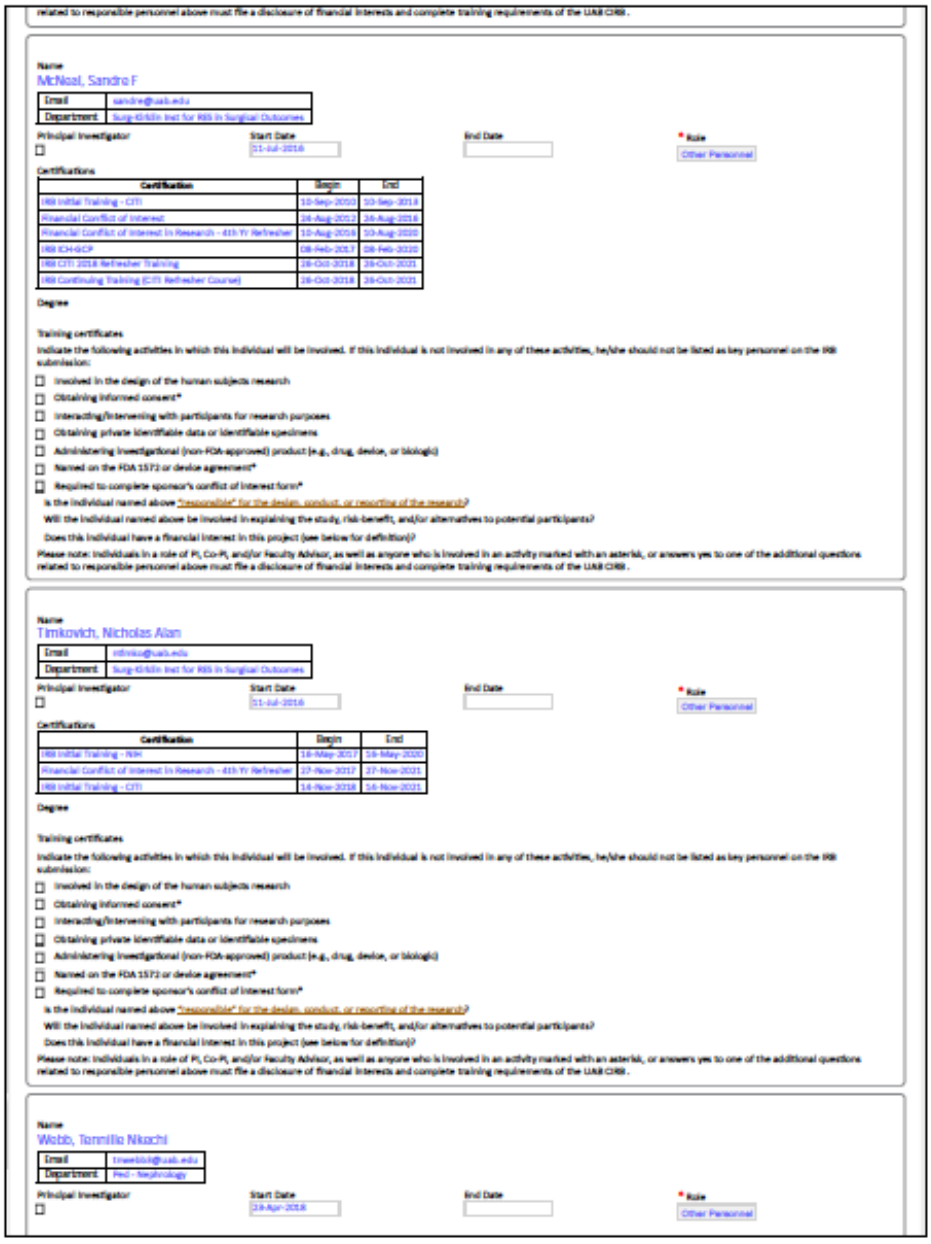

related to responsible personnel above must file a disclosure of financial interests and complete training requirements of the UAB CIRB.

Name
McNeal, Sandra F

Email	sandra@uab.edu
Department	Surg-Ctr/Div Inst for Rsh in Surgical Outcomes

Principal Investigator ☐ | Start Date 11-Jul-2016 | End Date | * Role Other Personnel

Certifications

Certification	Begin	End
IRB Initial Training - CITI	10-Sep-2010	10-Sep-2013
Financial Conflict of Interest	24-Aug-2012	24-Aug-2016
Financial Conflict of Interest in Research - 4th Yr Refresher	10-Aug-2016	10-Aug-2020
IRB ICH-GCP	08-Feb-2017	08-Feb-2020
IRB CITI 2018 Refresher Training	28-Oct-2018	28-Oct-2021
IRB Continuing Training (CITI Refresher Course)	28-Oct-2018	28-Oct-2021

Degree

Training certificates

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Name
Timkovich, Nicholas Alan

Email	ntimko@uab.edu
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Principal Investigator ☐ | Start Date 11-Jul-2016 | End Date | * Role Other Personnel

Certifications

Certification	Begin	End
IRB Initial Training - NIH	16-May-2017	16-May-2020
Financial Conflict of Interest in Research - 4th Yr Refresher	27-Nov-2017	27-Nov-2021
IRB Initial Training - CITI	16-Nov-2018	16-Nov-2021

Degree

Training certificates

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- ☐ Required to complete sponsor's conflict of interest form*

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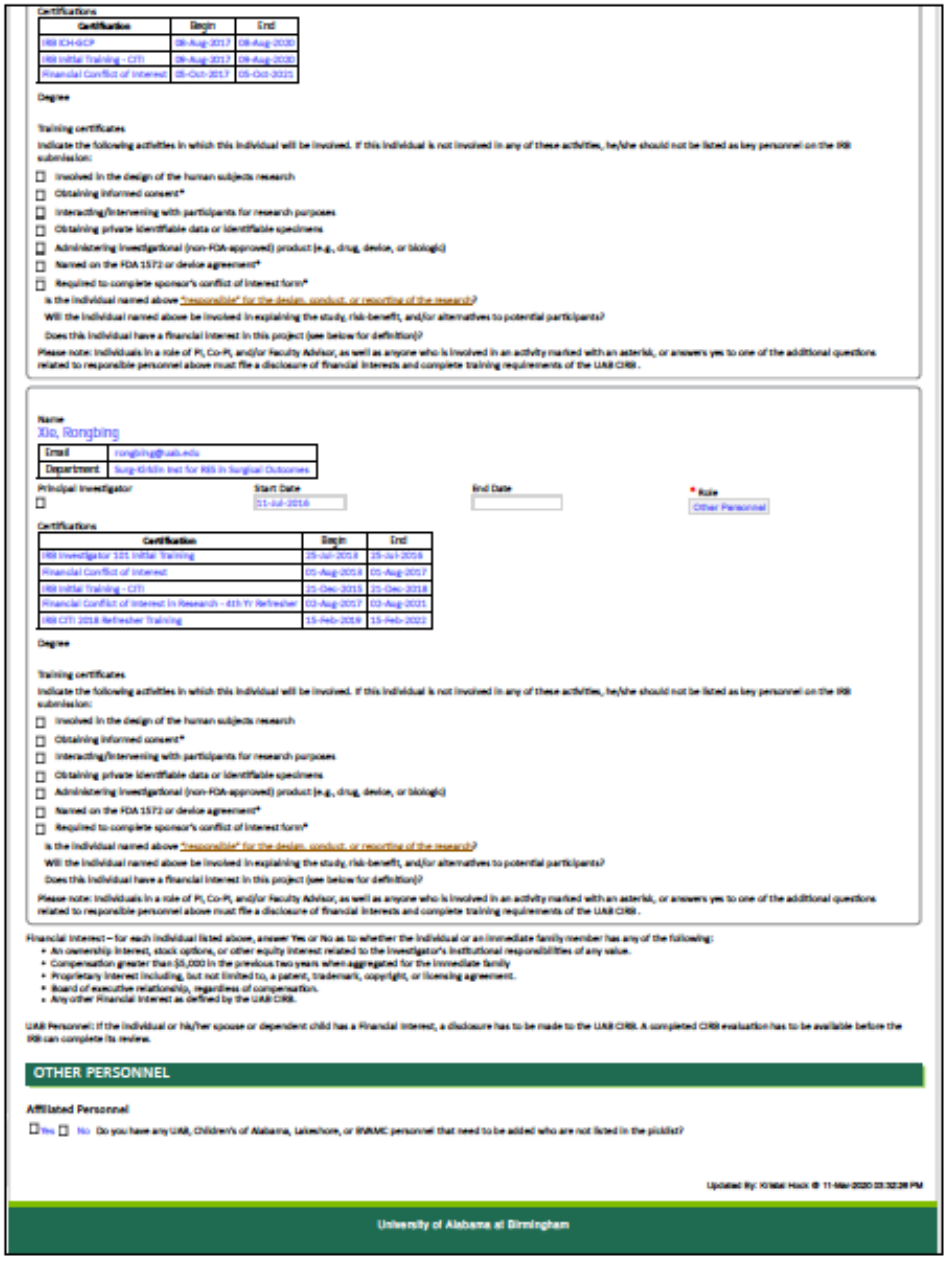
Name
Webb, Tamillia Nkachi

Email	tnwebb@uab.edu
Department	Ped - Nephrology

Principal Investigator ☐ | Start Date 19-Apr-2018 | End Date | * Role Other Personnel



Certifications

Certification	Begin	End
IRB ICH-GCP	08-Aug-2017	08-Aug-2020
IRB Initial Training - CITI	08-Aug-2017	08-Aug-2020
Financial Conflict of Interest	05-Oct-2017	05-Oct-2021

Degree

Training certificates

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- ☐ Named on the FDA 1572 or device agreement*
- ☐ Required to complete sponsor's conflict of interest form*

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Name

Xie, Rongbing

Email	rongbing@uab.edu
Department	Surg-Ortho Inst for RES in Surgical Outcomes

Principal Investigator ☐ | Start Date 01-Jul-2016 | End Date | * Role Other Personnel

Certifications

Certification	Begin	End
IRB Investigator 101 Initial Training	25-Jul-2014	25-Jul-2018
Financial Conflict of Interest	05-Aug-2014	05-Aug-2017
IRB Initial Training - CITI	21-Dec-2015	21-Dec-2018
Financial Conflict of Interest in Research - 4th Yr Refresher	02-Aug-2017	02-Aug-2021
IRB CITI 2018 Refresher Training	15-Feb-2018	15-Feb-2022

Degree

Training certificates

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- ☐ Administering investigational (non-FDA-approved) product (e.g., drug, device, or biologic)
- ☐ Named on the FDA 1572 or device agreement*
- ☐ Required to complete sponsor's conflict of interest form*

Is the individual named above "responsible" for the design, conduct, or reporting of the research?

Will the individual named above be involved in explaining the study, risk-benefit, and/or alternatives to potential participants?

Does this individual have a financial interest in this project (see below for definition)?

Please note: Individuals in a role of PI, Co-PI, and/or Faculty Advisor, as well as anyone who is involved in an activity marked with an asterisk, or answers yes to one of the additional questions related to responsible personnel above must file a disclosure of financial interests and complete training requirements of the UAB CIRB.

Financial Interest – for each individual listed above, answer Yes or No as to whether the individual or an immediate family member has any of the following:

- An ownership interest, stock options, or other equity interest related to the investigator's institutional responsibilities of any value.
- Compensation greater than $5,000 in the previous two years when aggregated for the immediate family
- Proprietary interest including, but not limited to, a patent, trademark, copyright, or licensing agreement.
- Board of executive relationship, regardless of compensation.
- Any other Financial Interest as defined by the UAB CIRB.

UAB Personnel: If the individual or his/her spouse or dependent child has a Financial Interest, a disclosure has to be made to the UAB CIRB. A completed CIRB evaluation has to be available before the IRB can complete its review.

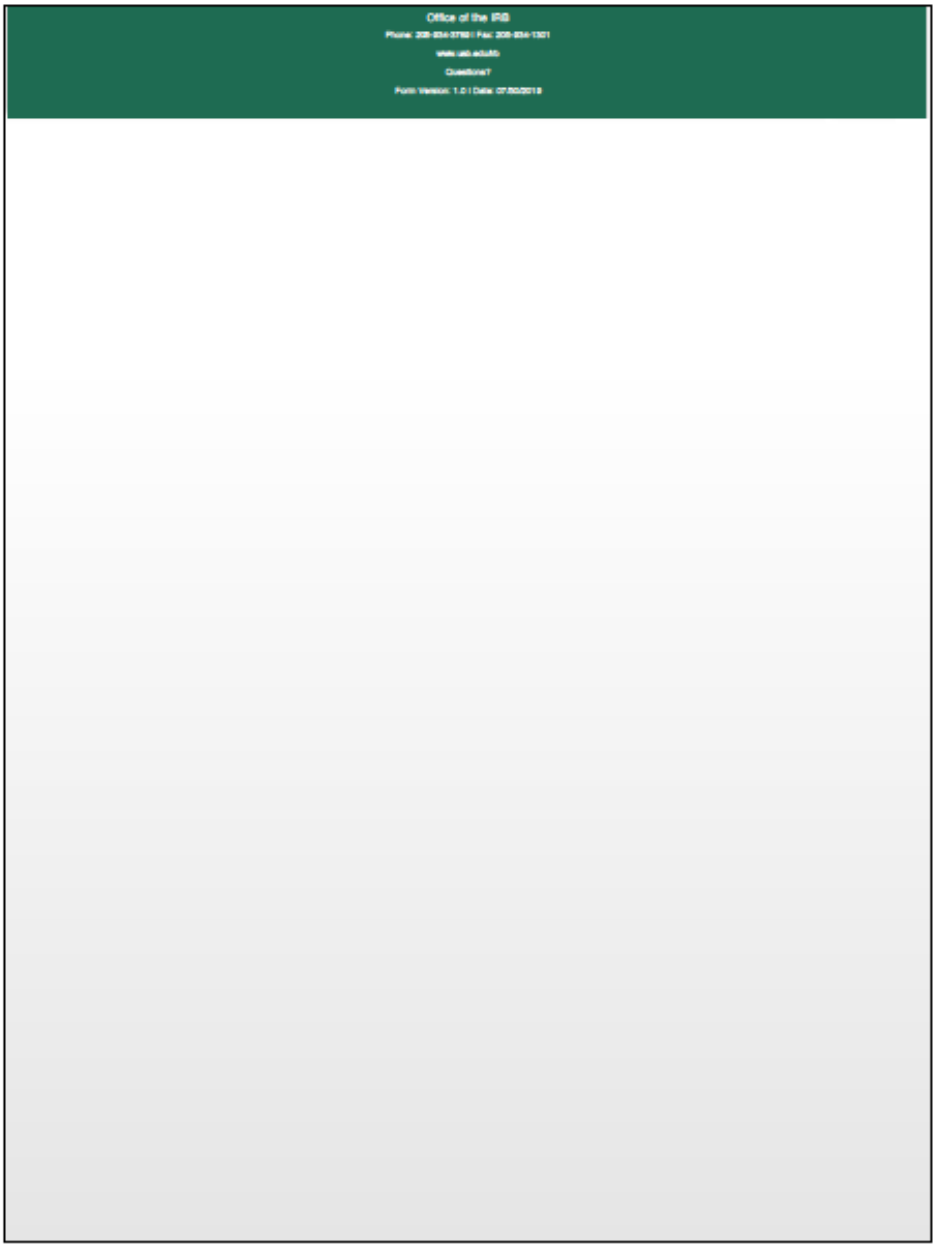
OTHER PERSONNEL

Affiliated Personnel

☐ Yes ☐ No Do you have any UAB, Children's of Alabama, Lakeshore, or RVRMC personnel that need to be added who are not listed in the picklist?

Updated By: Kristal Hack @ 11-Mar-2020 03:32:28 PM

University of Alabama at Birmingham


Office of the IRB
Questions?