A Multi-Center, Pilot Study to Assess the Safety and Efficacy of a Selective Cytopheretic Device (SCD) in Pediatric Patients with Acute Kidney Injury (AKI)

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PROTOCOL SYNOPSIS

Study Title	A Multi-Center, Pilot Study To Assess the Safety and Efficacy of A Selective Cytopheretic Device (SCD) In Pediatric Patients with Acute Kidney Injury (AKI)
Study Phase	Pilot Study.
Product Description	The Selective Cytopheretic Device (SCD) is comprised of tubing, connectors, and a synthetic membrane cartridge. The device is connected in series to a commercially available Continuous Renal Replacement Therapy (CRRT) device. Blood from the CRRT circuit is diverted after the CRRT hemofilter through to the extra capillary space (ECS) of the SCD. Blood circulates through this space and it is returned to the patient via the venous return line of the CRRT circuit. Regional citrate anticoagulation is used for the entire CRRT and SCD blood circuits. The SCD[redacted] is a synthetic membrane with the ability to bind activated leukocytes and when used in a continuous renal replacement extracorporeal circuit in the presence of regional citrate anticoagulation modulates inflammation.
Rationale	Our primary hypothesis is that up to seven sequential 24-hour SCD treatments will improve survival in pediatric patients with Acute Kidney Injury (AKI) as compared to CRRT alone (standard of care). Further, SCD therapy will reduce the duration of maintenance dialysis secondary to AKI due to acute tubular necrosis (ATN). ATN is an acute reversible process and if not reversed in three months, it may not be reversed at all. [1, 2] Studies suggest that approximately 10-20% of AKI patients do not recover renal function [3, 4] and, therefore, require chronic dialysis. Importantly, acute kidney injury is a highly lethal condition in critically ill patients. Despite improvements in acute medical care and advances in dialysis therapies, the mortality rate during the past four decades of this condition has not improved. Critically ill patients with AKI in hospital ICU settings have mortality rates of approximately 50%, including pediatric patients [5, 6, 7, 8, 9, 10, 11, 12] AKI promotes a systemic inflammatory response syndrome (SIRS) which results in systemic microvascular damage and, if severe, multi-organ dysfunction. [13, 14] Activated circulating leukocytes play a central role in this process. [15] Leukocytes,

	especially neutrophils, are major contributors to the pathogenesis and progression of many inflammatory disorders, including SIRS, sepsis, ischemia reperfusion injury, and acute respiratory distress syndrome (ARDS). Many therapeutic approaches are under investigation to limit the activation and tissue accumulation of leukocytes at sites of inflammation to minimize tissue destruction and disease progression. [16, 17, 18]
Primary Objective	To evaluate the safety of the SCD treatment up to seven consecutive 24 hour SCD treatments in the pediatric AKI population being treated with Continuous Renal Replacement Therapy (CVVH, CVVHD, or CVVHDF) with regional citrate anticoagulation.
Secondary Objective	To evaluate the effect of up to seven consecutive 24 hour SCD treatments on all cause mortality and dialysis dependency at day 28, and day 60 in the pediatric AKI population being treated with Continuous Renal Replacement Therapy (CVVH, CVVHD, or CVVHDF) with regional citrate anticoagulation. These outcomes will be compared to a historical data set.
Study Endpoints	In this Pilot study four domains of interest have been designated. The four domains are: • Patient Safety: Safety Endpoint Measures include adverse events, laboratory safety parameters, vital signs, EKG, ventilation status and hemodynamic variables. • Clinical Efficacy: The Primary Clinical Efficacy Endpoint Measure is in-hospital; 28 and 60-day all-cause mortality. Time to renal recovery and necessity for chronic dialysis up to day 60 will also be determined. Additional efficacy endpoints include time to intensive care unit (ICU) discharge, and time to hospital discharge. • Device Integrity and Performance: The Endpoint Measure is SCD use without failure. This measure will help assess the integrity and performance of the SCD device. • SCD Mode of Action: Exploratory Endpoint Measures will include inflammatory cytokines, cell activation parameters and biomarkers at clinical sites with this capability.
Assessment of Device Integrity and Performance	Criteria for assessment of device integrity and performance include: • Significant Clotting within the Device as assessed by visual inspection. • Evidence of leakage (i.e., cracking/breakage of a port, connector, hemofilter cartridge or tubing). • Any unforeseen malfunction that results in the need for

	discontinuation.
Study Populations	Pediatric patients with a body weight (BW) greater than or equal to 15 kg receiving care in the Intensive Care Units of each participating hospital will be screened daily and identified for participation in the trial.
Study Design	This is an open-label, multi-center Pilot study.
Approximate Number of Subjects	Up to 30 patients will be enrolled in this study.
Approximate Number of Centers	Up to 10 Clinical Centers in the United States will participate in this study.
Duration of Subject Participation	Each patient will be followed for 60 days following enrollment.
Inclusion Criteria	1. A patient, or legal representative, has signed a written informed consent form. 2. Must be receiving medical care in an intensive care unit (e.g., PICU, MICU, SICU, CTICU, Trauma). 3. Age less than 22 years. 4. Females of child bearing potential who are not pregnant (confirmed by a negative serum pregnancy test) and not lactating if recently post-partum. 5. Intent to deliver full supportive care through aggressive management utilizing all available therapies for a minimum of 96 hours. 6. Clinical diagnosis of AKI due to etiologies requiring CRRT (see Appendix B). AKI is defined as acute kidney injury with any one of the following: • Increase in SCr by ≥0.3 mg/dL (≥26.5 μmol/L) within 48 hours or; • Increase in SCr to ≥1.5 times baseline, which is known or presumed to have occurred within the prior 7 days or; • Urine volume <0.5ml/kg/h for 6 hours 7. At least one non-renal organ failure (defined as receiving mechanical ventilation or at least one vasoactive medication to treat hypotension) OR presence (proven or suspected) of sepsis. (**Appendix C**).

Exclusion Criteria	1. Threshold blood pressure of 80/40 mmHg-- patients with both a systolic blood pressure of less than 80 mmHg and a diastolic blood pressure of less than 40 mmHg. 2. Irreversible brain damage based on available historical and clinical information. 3. Patients with a solid organ transplant or those with a bone marrow or stem cell transplant in the previous 100 days or who have not engrafted. 4. Acute or chronic use of circulatory support device other than ECMO such as LVADs, RVADs, BIVADs. 5. Presence of preexisting advanced chronic renal failure (i.e., ESRD) requiring chronic renal replacement therapy prior to this episode of acute kidney injury or with pre-existing chronic kidney disease (CKD) defined as a eGFR<30 ml/min/1.73m^2. Patients who have never seen a pediatric nephrologist will be assumed not to have pre-existing CKD. 6. AKI occurring in the setting of burns, obstructive uropathy, vasculitis, scleroderma renal crisis, atheroembolism, functional or surgical nephrectomy, cyclosporine, or tacrolimus nephrotoxicity. 7. Received >12 hour of CRRT (not including SCUF on ECMO) during this hospital admission or prior to transfer from an outside hospital. 8. Received >1 hemodialysis treatment during this hospital admission or prior to transfer from an outside hospital. 9. Metastatic malignancy which is actively being treated or may be treated by chemotherapy or radiation during the subsequent three month period after study therapy. 10. Chronic immunosuppression with the exception of corticosteroids up to a dose of 10 mg per day. 11. HIV or AIDS. 12. Severe chronic liver failure as determined by standard diagnostic requirements. 13. Current Do Not Attempt Resuscitation (DNAR), Allow Natural Death (AND), or withdrawal of care status, or anticipated change in status within the next 7 days. 14. Patient not expected to survive 28 days because of an irreversible medical condition. (This is not restrictive to AKI, and may include situations such as the presence of irreversible brain damage, untreatable malignancy, inoperable life threatening condition, or any condition to which therapy is regarded as futile by the PI.) 15. Any medical condition that the Investigator thinks may interfere with the study objectives. 16. Physician refusal.

	17. Dry weight of <15 kg. 18. Platelet count <15,000/mm^3 at time of screening. 19. Concurrent enrollment in another interventional clinical trial. Patients enrolled in clinical trials where only measurements and/or samples are taken (NO TEST DEVICE OR TEST DRUG USED) are allowed to participate. 20. Use of any other Investigational drug or device within the previous 30 days.
Evaluation Plan	The primary evaluation of this study will be safety and all-cause mortality or dialysis dependency through 60 days post-enrollment. Additional endpoints will be time on CRRT, total ICU and hospital days. Mortality and dialysis dependency rates will be compared to historical controls.

LIST OF ABBREVIATIONS

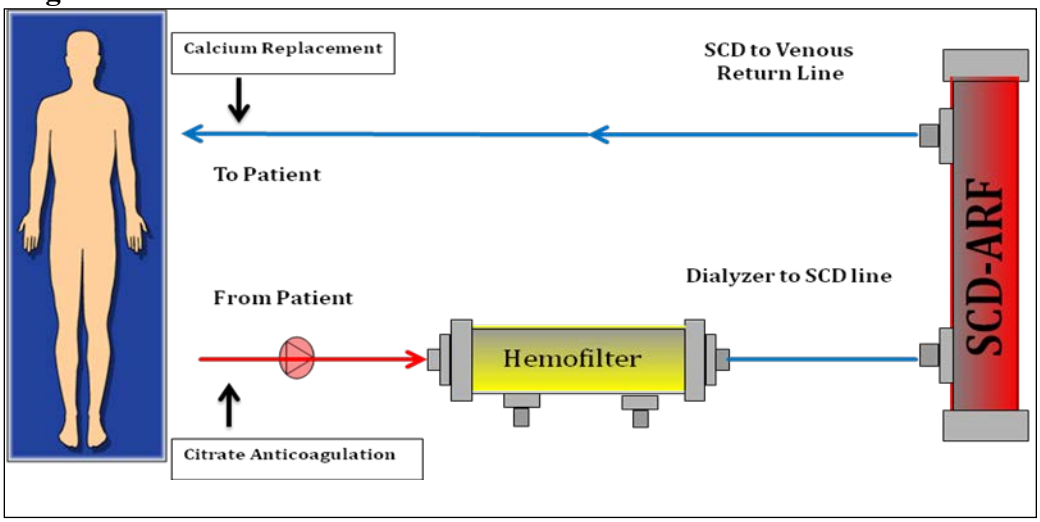
AE	Adverse Event
AKI	Acute Kidney Injury
ARDS	Acute Respiratory Distress Syndrome
ARF	Acute Renal Failure
ATN	Acute Tubular Necrosis
BW	Body Weight
iCa	Ionized Calcium
CBC	Complete Blood Count
CRF	Case Report Form
CRRT	Continuous Renal Replacement Therapy
CTICU	Cardiothoracic Intensive Care Unit
CVVH	Continuous Veno-Venous Hemofiltration
CVVHD	Continuous Veno-Venous Hemodialysis
CVVHDF	Continuous Veno-Venous Hemodiafiltration
ECS	Extra Capillary Space
ICU	Intensive Care Unit
MICU	Medical Intensive Care Unit
nriCa	Non Recommended Ionized Calcium Range
ppCRRT	Prospective Pediatric CRRT Registry
PRISM	Pediatric Risk of Mortality
RAD	Renal Assist Device
riCa	Recommended Ionized Calcium Range
SAE	Serious Adverse Event
SCD	Selective Cytopheretic Device
SICU	Surgical Intensive Care Unit
SIRS	Systemic Inflammatory Response Syndrome
SOFA	Sequential Organ Failure Assessment
WBC	White Blood Cell
UADE	Unanticipated Adverse Device Effect

1. INTRODUCTION

The Selective Cytopheretic Device (SCD) is comprised of tubing, connectors, and a synthetic membrane cartridge. The device is connected in series to a commercially available Continuous Renal Replacement Therapy (CRRT) device. Blood from the CRRT circuit is diverted after the CRRT hemofilter through to the extra capillary space (ECS) of the SCD. Blood circulates through this space and it is returned to the patient via the venous return line of the CRRT circuit. Regional citrate anticoagulation is used for the entire CRRT and SCD blood circuits.

The SCD-[redacted] is a synthetic membrane with the ability to bind activated leukocytes and when used in a continuous renal replacement extracorporeal circuit in the presence of regional citrate anticoagulation modulates inflammation. See **Figure 1**.

Figure 1: Schematic of the CRRT circuit and SCD



1.1 RATIONALE FOR THERAPY

Our primary hypothesis is that up to seven sequential 24-hour SCD treatments will improve survival in patients with Acute Kidney Injury (AKI) as compared to CRRT alone (standard of care). Further, SCD therapy will reduce the duration of maintenance dialysis secondary to AKI due to acute tubular necrosis (ATN). ATN is an acute reversible process and if not reversed in three months, it may not be reversed at all. [1, 2] Studies suggest that approximately 10-20% of AKI patients do not recover renal function [3, 4] and, therefore, require chronic dialysis.

Importantly, acute kidney injury is a highly lethal condition in critically ill patients. Despite improvements in acute medical care and advances in dialysis therapies, the mortality rate during the past four decades of this condition has not improved. Critically ill patients with AKI in hospital

ICU settings have mortality rates of up to 50%, including pediatric patients [5, 6, 7, 8, 9, 10, 11, 12]

AKI promotes a systemic inflammatory response syndrome (SIRS) which results in systemic microvascular damage and, if severe, multi-organ dysfunction. [13, 14] Activated circulating leukocytes play a central role in this process. [15] Leukocytes, especially neutrophils, are major contributors to the pathogenesis and progression of many inflammatory disorders, including SIRS, sepsis, ischemia reperfusion injury, and acute respiratory distress syndrome (ARDS). Many therapeutic approaches are under investigation to limit the activation and tissue accumulation of leukocytes at sites of inflammation to minimize tissue destruction and disease progression. [16, 17, 18] Preclinical studies utilizing a porcine model of septic shock have demonstrated that SCD therapy immunomodulates activated circulating leukocytes. This effect is associated with improvement of multiorgan dysfunction. [19]

2. PRIOR CLINICAL EXPERIENCE

2.1 PHASE II RENAL ASSIST DEVICE STUDY (RAD003 IND NUMBER 11077)[20]

2.1.1 STUDY SUMMARY

The poor outcomes in patients with acute kidney injury (AKI) and end-stage renal disease (ESRD) on chronic dialysis are due to immune dysregulation associated with these disorders. Evolving evidence suggests that the kidney, and specifically renal epithelial cells, plays an important role in the immunological response of leukocytes under disease states. Method: In this regard, the development of two therapeutic approaches utilizing renal epithelial cells and 'smart' immunomodulatory membranes has been tested in preclinical animal models and clinical trials. Results: These two approaches have been demonstrated in phase II human trials to improve the survival of intensive care unit patients with AKI and multiorgan failure. The use of a 'smart' immunomodulatory membrane is also being evaluated in a small exploratory clinical trial to assess its effects on immunoregulation in ESRD patients requiring chronic hemodialysis. Conclusions: The use of renal progenitor/stem cell therapy and/or cytopheretic membranes may result in effective treatments to alter the dysregulated immunological state of acute or chronic renal failure and improve the outcomes of these diseases.

2.1.2 SAFETY RESULTS

All serious adverse events (SAEs) during the first 28 days after randomization were reported to the Medical Monitor within 24

hours of the event. The reported SAEs were consistent with a seriously ill ICU patient population with AKI receiving CVVH.

2.2 ESRD SAFETY AND BIOINFLAMMATORY ASSAY STUDY

2.2.1 STUDY SUMMARY

A study of the SCD was conducted at the Henry Ford Hospital in Detroit, Michigan entitled "A Phase I/II Trial of a Two-Cartridge Hemodialysis System on Inflammatory Markers in Chronic Hemodialysis Subjects". This study was designed to determine what effect one treatment with the SCD would have on the reduction of bioinflammatory markers such as cytokines IL-2, IL-6, IL-8 and IL-10 and white cell activation in chronically inflamed End Stage Renal Disease (ESRD). The study enrolled fifteen subjects at one site, with four of the original 15 patients re-enrolled in what was called "Amendment 2".

2.2.2 SAFETY RESULTS

Fifteen chronic hemodialysis (HD) patients with elevated CRP levels were treated for four hours under standard HD with systemic heparin anticoagulation and, at their next dialysis treatment session, received standard HD plus SCD therapy with regional citrate anticoagulation. The 15 patients have completed the study treatment period and safety data is shown in **Table 1** as follows:

Table 1: Report of Adverse Events - ESRD trial

Adverse Event	Number of Mild Severity Events	Number of Moderate Severity Events
Fever	1	0
Chills	2	0
Headache	1	0
Nausea	3	0
Vomiting	2	1
Diarrhea	1	0
Dizziness	1	1
Visual Disturbances	0	1
Lethargy	0	1
Itching	1	0
Latent TB infection	1	0
Cough	1	0
Left cheek swelling	1	0
Decreased hemoglobin	1	1
Increased CRP level	2	0
Neck swelling cellulites	0	1
Ankle sprain	0	1
Replacement of left dysfunctional IJ catheter for HD	1	0
Dialysis catheter fell off during sleep	0	1
Muscle cramp	0	1

Adverse Event	Number of Mild Severity Events	Number of Moderate Severity Events
Chest pain	0	1
Clotted extracorporeal system. 350 ml blood loss	0	1
L Upper quadrant pain	0	1
Decreased WBC	0	1

2.3 AKI SAFETY, MORTALITY AND DEVICE INTEGRITY STUDY (CHINA)[21]

2.3.1 STUDY SUMMARY

Despite decades of improvements in the provision of renal replacement therapy, the morbidity and mortality associated with acute kidney injury (AKI) in the intensive care unit (ICU) setting remains extremely high. Much of the morbidity and mortality of this disorder is the consequence of systemic cellular damage that results from immune dysregulation. This was a prospective, single-arm, single-center study designed to evaluate the safety and efficacy of treatment with a selective cytopheretic device (SCD) on clinical outcomes in AKI requiring renal replacement therapy in the ICU. The patients enrolled in the trial were compared with historical case-matched controls with respect to age and Sequential Organ Failure Assessment (SOFA) score. The mortality for the case-matched controls was 77.78%, whereas the mortality in the SCD treatment group was 22.22% ($p = 0.027$). Multiple regression analysis identified treatment with SCD as the only significant variable affecting mortality among age, SOFA score, and average change in urine output over the first 7 days during or after treatment. Mean total urine output in the 10 subjects receiving SCD treatment increased from a baseline of approximately 500 ml/d to more than 2,000 ml/d by day 7 of treatment.

2.3.2 SAFETY RESULTS

A total of 12 patients were enrolled in this study. There were no SAEs reported.

In the 9 subjects analyzed on SCD treatment, no neutropenic events were reported. Mean WBC counts remained normal throughout treatment, with a mild decline noted upon initiation of therapy that was shown to rebound by day 7. No bleeding events were reported. Average platelet counts remained in the functional range (above 50,000) throughout treatment, with a mild decline noted upon initiation of therapy that was shown to plateau by day 4 to an average platelet count of 75,000. A summary of all adverse events (AEs) observed in the 9 subjects on SCD treatment is presented in **Table 2**. These events were not attributed to the

device by the investigator, as they commonly occur with CRRT treatment.

Table 2: Adverse event reporting – China Study – n=9 patients

Adverse Event (n=9 patients)	Number of Mild Severity Events	Number of Moderate Severity Events
Hypercalcemia	6	2
Thrombocytopenia	1	0
Hypocalcemia	0	1
Allergic Reaction	1	0
Hypophosphatemia	2	0
Hypernatremia	1	0

2.4 PILOT STUDY USA ARF-002 - IDE [redacted][22]

2.4.1 STUDY SUMMARY

Acute kidney injury (AKI) is characterized by deterioration in kidney function resulting in multisystem abnormalities. Much of the morbidity and mortality associated with AKI result from a systemic inflammatory response syndrome (SIRS). This study described herein was a prospective, single-arm, multicenter US study designed to evaluate the safety and efficacy of the Selective Cytopheretic Device (SCD) treatment on AKI requiring continuous renal replacement therapy (CRRT) in the ICU. The study enrolled 35 subjects. The mean age was 56.3 ± 15. With regard to race, 71.4% of the subjects were Caucasian, 22.9% were Black, and 5.7% were Hispanic. Average SOFA score was 11.3 ± 3.6. Death from any cause at Day 60 was 31.4%. Renal recovery, defined as dialysis independence, was observed in all of the surviving subjects at Day 60. The results of this pilot study indicate the potential for a substantial improvement in patient outcomes over standard of care therapy, which is associated with a greater than 50% 60-day mortality in the literature. The SCD warrants further study in scientifically sound, pivotal trial to demonstrate reasonable assurance of safety and effectiveness.

2.4.2 SAFETY RESULTS

A summary of all adverse events (AEs) observed in the 35 subjects is presented in **Table 3**. The AEs observed were those expected for a critically ill patient population with acute renal failure and/or in an ICU setting.

Table 3: Summary of Adverse Events ARF-002

Adverse Events	Number of Subjects with Events N (% of 35)	Number of Events % of 199 (n/199)
Total adverse events	33 (94%)	199
Serious adverse event	23 (66%)	14.1% (28/199)
Unanticipated Adverse Device Effect	0 (0%)	0.0% (0/199)
Relationship to Study*		
Unrelated to study therapy	32 (91%)	93.5% (186/199)
Possibly related to study therapy	8 (23%)	6.0% (12/199)
Probably related to study therapy	0 (0%)	0.0% (0/199)
Definitely related to study therapy	1 (3%)	0.5% (1/199)
Outcome		
Resolved w/ sequelae	14 (40%)	13.6% (27/199)
Resolved w/out sequelae	25 (71%)	64.3% (128/199)
Continuing	11 (31%)	11.1% (22/199)
Death	11 (31%)	5.5% (11/199)
Reported as Unknown	3 (9%)	5.5% (11/199)
Frequency		
Single Episode	29 (83%)	54.3% (108/199)
Intermittent	16 (46%)	21.1% (42/199)
Continuous	16 (46%)	24.1% (48/199)
Reported as Unknown	1 (3%)	0.5% (1/199)
Severity		
Mild	21 (60%)	34.7% (69/199)
Moderate	25 (71%)	51.8% (103/199)
Severe	19 (54%)	13.6% (27/199)

*Subjects experienced more than one AE, therefore, numbers do not add up to N=22 (number of subjects experiencing any adverse event).

2.5 PIVOTAL STUDY (PROTOCOL SCD-003) - IDE [redacted][23]

2.5.1 STUDY SYNOPSIS

Per the SCD-003 Protocol, our primary hypothesis is that up to seven sequential 24-hour SCD treatments will improve survival in patients with Acute Kidney Injury (AKI) as compared to CRRT alone (standard of care). Further, SCD therapy may reduce the duration of maintenance dialysis secondary to AKI due to acute tubular necrosis (ATN). ATN is an acute reversible process and if not reversed in three months, it may not be reversed at all. [1, 2] Studies suggest that approximately 10% of AKI patients do not recover renal function [3, 4] and, therefore, require chronic dialysis. Importantly, acute kidney injury is a highly lethal condition in critically ill patients. Despite improvements in acute medical care and advances in dialysis therapies, the mortality rate during the past four decades of this condition has not improved. Critically ill patients with AKI in hospital ICU settings have mortality rates of 50 to 80%. [5, 6, 7, 8, 9, 10, 11, 12]

The SCD requires regional citrate anticoagulation be used for the entire CRRT and SCD blood circuits. Per SCD-003, Section 5.1:

Each participating clinical site is to use their regional citrate anticoagulation protocol for the CRRT and SCD-ARF circuits (Study Arm) and for the CRRT only (Control Arm). The recommended ionized calcium level (measured post SCD-ARF) in the CRRT and SCD-ARF blood circuit should be between 0.25 and 0.40 mmol/L.

2.5.2 SAFETY RESULTS AT INTERIM ANALYSIS

The planned interim analysis was initiated at subject 134 and subject enrollment paused on May 24, 2013, to assess the clinical impact on study endpoints. On September 3, 2013, the Data Safety Monitoring Board (DSMB) convened and reviewed the SCD-003 data. Upon completion of their meeting, they stated that there were no safety concerns with the outcomes presented in the following tables.

Table 4 delineates the Summary of Site-reported Serious Adverse Events (SAEs) using site-reported category and term. None of the SAEs were considered 'definitely' device related per the Principal Investigator.

Table 4: Summary of Site-reported Serious Adverse Events (SAEs)

All Subjects N=132*							
	CRRT + SCD N = 69		CRRT Alone N = 63*			Total N =132*	
Category	Ets	Pts % (n/N)	Ets	Pts % (n/N)	Fisher's Exact P-Value	Ets	Pts % (n/N)
Total	80	65.2% (45/69)	71	63.5% (40/63)	0.857	151	64.4% (85/132)
Blood and lymphatic system disorders	9	11.6% (8/69)	4	4.8% (3/63)	0.212	13	8.3% (11/132)
Cardiac disorders	15	17.4% (12/69)	11	15.9% (10/63)	1.000	26	16.7% (22/132)
Gastrointestinal disorders	5	5.8% (4/69)	7	9.5% (6/63)	0.518	12	7.6% (10/132)
General disorders and administration site conditions	4	5.8% (4/69)	7	11.1% (7/63)	0.350	11	8.3% (11/132)
Infections and infestations	14	17.4% (12/69)	11	15.9% (10/63)	1.000	25	16.7% (22/132)
Injury, poisoning and procedural complications	1	1.4% (1/69)	0	0.0% (0/63)	1.000	1	0.8% (1/132)
Investigations	0	0.0% (0/69)	1	1.6% (1/63)	0.477	1	0.8% (1/132)
Metabolism and nutrition disorders	2	2.9% (2/69)	2	3.2% (2/63)	1.000	4	3.0% (4/132)
Musculoskeletal and connective tissue disorders	1	1.4% (1/69)	1	1.6% (1/63)	1.000	2	1.5% (2/132)
Nervous system disorders	6	7.2% (5/69)	1	1.6% (1/63)	0.211	7	4.5% (6/132)
Other	2	2.9% (2/69)	6	7.9% (5/63)	0.258	8	5.3% (7/132)
Psychiatric disorders	0	0.0% (0/69)	1	1.6% (1/63)	0.477	1	0.8% (1/132)
Renal and urinary disorders	1	1.4% (1/69)	3	4.8% (3/63)	0.348	4	3.0% (4/132)
Respiratory, thoracic and mediastinal disorders	13	14.5% (10/69)	10	15.9% (10/63)	1.000	23	15.2% (20/132)
Skin and subcutaneous tissue disorders	0	0.0% (0/69)	2	3.2% (2/63)	0.226	2	1.5% (2/132)
Vascular disorders	7	10.1% (7/69)	4	6.3% (4/63)	0.536	11	8.3% (11/132)

*Two subjects enrolled to CRRT alone arm (012-002, 003-015) however not treated.

60 Day Mortality based on the SCD-003 protocol intent to treat is presented in **Table 5**.

Table 5: 60 Day Mortality

60 Day Mortality	CRRT + SCD N= 69	CRRT Alone N= 65	Overall N=134
All Subjects Enrolled	100.0% (69/69)	100.0% (65/65)	100.0%(134/134)
Alive	61% (42/69)	64% (38/59*)	63% (80/128)
Dead	39% (27/69)	36% (21/59*)	38% (48/128)

*Does not include six subjects LTFU (002-003, 011-002, 004-007, 011-004, 013-002, 007-025)

2.5.3 EFFICACY RESULTS AT INTERIM ANALYSIS

As a result of the mortality in Control Arm (CRRT alone) being approximately 10% lower than published levels of 45-50%, further analysis was undertaken. As a result of the analysis, it was discovered that amount of time the patient was maintained in the recommended ionized calcium range (0.25-0.40 mmol/L per SCD-003 protocol) presented a difference in efficacy outcomes. One reason for the deficiency in clinical trial execution to ensure the protocol's riCa target range of ≤0.40 mmol/L be maintained could be attributed to the national shortage of injectable calcium. If the patient did not experience circuit clotting, the PIs emphasis of achieving and continuously maintaining the patient in the recommended ionized calcium range was not consistently adhered to. In addition, the injectable calcium shortage resulted in 9 of the 21 open clinical sites unable to enroll subjects due to low hospital inventories of injectable calcium.

Of the 134 subjects enrolled in the SCD-003 protocol at the time of the interim analysis, 19 SCD subjects (CRRT+SCD) and 31 control subjects (CRRT alone) were maintained in the protocol's recommended range ((≤0.40 mmol/L) ≥90% of the therapy time).

Table 6 details all cause mortality at day 60 (primary endpoint) of the treated subjects which received the recommended ionized calcium (riCa) and **Table 7** details all cause mortality at day 60 of the treated subjects which did not receive the recommended ionized calcium (nriCa).

Table 6: 60 Day Mortality of Subjects – Recommended Ionized Calcium Range (riCa)

60 Day Mortality riCa	CRRT + SCD N= 19	CRRT Alone N= 27*	Overall N=46
Alive	84% (16/19)	59% (16/27)	70% (32/46)
Dead	16% (3/19)	41% (11/27)	30% (14/46)
Pearson chi2(1) = 3.2793 Pr = 0.070			

*Three subjects LTFU (004-007, 007-025, 011-004). One subject withdrew consent (013-002).

Table 7: 60 Day Mortality of Subjects – Non Recommended Ionized Calcium Range

60 Day Mortality nriCa	CRRT + SCD N= 50	CRRT Alone N= 32*	Overall N=82
Alive	52% (26/50)	69% (22/32)	59% (48/82)
Dead	48% (24/50)	31% (10/32)	42% (34/82)
Pearson chi2(1) = 2.2555 Pr = 0.133			

*Two subjects LTFU (002-003, 011-002). Two subjects enrolled to CRRT alone arm (012-002, 003-015) however not treated.

A borderline statistically significant difference in 60-day all cause mortality (primary endpoint) was found in the cohort where the patient was maintained for ≥90% of the treatment in the protocol's recommended ionized calcium (riCa) target range of ≤0.40 mmol/L over those that were maintained ≤90% of the treatment duration.

The secondary endpoints of renal replacement therapy dependency at day 60, mortality at day 28, number of ventilator free days at day 28 and mortality of the sub population of severe septic patients at day 60 were analyzed. No statistical significance was shown except for the secondary endpoint of dialysis dependency. Dialysis dependency showed a statistically significant difference between the patients maintained for ≥90% of the treatment in the protocol's riCa target range of ≤0.40 mmol/L over those at ≤90% of the treatment duration. **See Table 8**.

Table 8: Dialysis Dependency at Day 60 – Recommended Ionized Calcium Range

Dialysis Dependency at Day 60 riCa	CRRT + SCD	CRRT Alone
N	0/16	4/16
p-value	0.033	

When a composite endpoint of all cause mortality (primary endpoint) or renal replacement therapy dependency (a secondary endpoint) at day 60 is analyzed, a statistical significance is observed. See **Table 9**.

Table 9: 60 Day Combined End Point of All Cause Mortality or Dialysis Dependency – Recommended Ionized Calcium Range

60 Day Combined End Point of All Cause Mortality or Dialysis Dependency -- riCa	CRRT + SCD N=19	CRRT Alone N=27
	15.8%	55.6%
N	3/19	15/27
p-value	0.007	

2.5.4 CONCLUSION AT INTERIM ANALYSIS

The SCD-003 Protocol included one formal interim effectiveness analysis on the primary endpoint of time to all-cause mortality by 60 days for review by the DSMB. On September 3, 2013, CytoPherx received concurrence from the DSMB that they would have recommend continuing the SCD-003 study (with appropriate corrective action to ensure the protocol's riCa target range of <0.40 mmol/L be maintained). However, due to the existing statistical deficit, an increase in sample size to achieve a statistically significant treatment difference on the primary endpoint would have been required. This increase in sample size would be prohibitive for CytoPherx to finance.

Rather than continue SCD-003, CytoPherx terminated the study and intends to submit to FDA a supplement to IDE [redacted] for approval of a new clinical trial protocol (no changes to the SCD device) designed to achieve statistical significance of a death or dialysis dependence composite endpoint.

3. PILOT STUDY (PROTOCOL SCD-PED-01) OBJECTIVES AND ENDPOINTS

3.1 PRIMARY OBJECTIVE

To evaluate the safety of the SCD treatment up to seven consecutive 24 hour SCD treatments compared to historic data on in-hospital mortality and on all cause mortality and dialysis dependency at day 28, and day 60 in the pediatric AKI population being treated with Continuous Renal Replacement Therapy (CVVH, CVVHD, or CVVHDF) with regional citrate anticoagulation.

3.1.1 SECONDARY OBJECTIVE

To assess the effect of SCD treatment on various measures of pediatric patient clinical outcome and to evaluate the integrity of the SCD device and patient safety in SCD treatments from the time of initiation of therapy to as many as seven consecutive 24-hour SCD treatments.

3.2 STUDY ENDPOINT

In this Pilot study four (4) domains of interest have been designated. The four (4) domains are:

1. Patient Safety: Safety Endpoint Measures include adverse events, laboratory safety parameters, vital signs, EKG, ventilation status and hemodynamic variables.
2. Clinical Efficacy: The Primary Clinical Efficacy Endpoint Measure is in-hospital; 28 and 60-day all-cause mortality. Time to renal recovery and necessity for chronic dialysis up to day 60 will also be

determined. Additional efficacy endpoints include time to intensive care unit (ICU) discharge, and time to hospital discharge.

3. Device Integrity and Performance: The Endpoint Measure is SCD use without failure. This measure will help assess the integrity and performance of the SCD device.
4. SCD Mode of Action: Exploratory Endpoint Measures will include inflammatory cytokines, cell activation parameters and biomarkers at clinical sites with this capability.

Endpoints are defined in **Appendix D**.

3.3 ASSESSMENT OF DEVICE INTEGRITY AND PERFORMANCE

Criteria for assessment of device integrity and performance include:

- Significant Clotting within the Device as assessed by visual inspection
- Evidence of leakage (i.e., cracking/breakage of a port, connector, hemofilter cartridge or tubing).
- Any unforeseen malfunction that results in the need for discontinuation.

4. STUDY DESIGN

This is an open-label, multi-center Pilot Study.

5. SELECTION OF PATIENT POPULATION

5.1 STUDY POPULATION

Up to 30 pediatric patients will be enrolled in this study, in up to 10 Clinical Centers in the United States.

Pediatric patients with a body weight (BW) greater than or equal to 15 kg receiving care in the Intensive Care Units of each participating hospital will be screened daily and identified for participation in the trial. See **Appendix E**, CRRT Management.

5.2 INCLUSION CRITERIA

1. A patient, or legal representative, has signed a written informed consent form.
2. Must be receiving medical care in an intensive care unit (e.g., ICU, PICU, CICU, Trauma).
3. Age less than 22 years.
4. Females of child bearing potential who are not pregnant (confirmed by a negative serum pregnancy test) and not lactating if recently post-partum.
5. Intent to deliver full supportive care through aggressive management utilizing all available therapies for a minimum of 96 hours.

6. Clinical diagnosis of AKI due to etiologies requiring CRRT (see Appendix B). AKI is defined as acute kidney injury with any one of the following:
   - Increase in SCr by ≥0.3 mg/dL (≥26.5 μmol/L) within 48 hours or;
   - Increase in SCr to ≥1.5 times baseline, which is known or presumed to have occurred within the prior 7 days or;
   - Urine volume <0.5ml/kg/h for 6 hours
7. At least one non-renal organ failure (defined as receiving mechanical ventilation or at least one vasoactive medication to treat hypotension) OR presence (proven or suspected) of sepsis (**Appendix C)**.

5.3 EXCLUSION CRITERIA

1. Threshold blood pressure of 80/40 mmHg-- patients with both a systolic blood pressure of less than 80 mmHg and a diastolic blood pressure of less than 40 mmHg.
2. Irreversible brain damage based on available historical and clinical information.
3. Patients with a solid organ transplant or those with a bone marrow or stem cell transplant in the previous 100 days or who have not engrafted.
4. Acute or chronic use of circulatory support device, other than ECMO, such as LVADs, RVADs, BIVADs.
5. Presence of preexisting advanced chronic renal failure (i.e., ESRD) requiring chronic renal replacement therapy prior to this episode of acute kidney injury or with pre-existing chronic kidney disease (CKD) defined as a eGFR<30 ml/min/1.73m^2. Patients who have never seen a pediatric nephrologist will be assumed not to have pre-existing CKD.
6. AKI occurring in the setting of burns, obstructive uropathy, vasculitis, scleroderma renal crisis, atheroembolism, functional or surgical nephrectomy, cyclosporine or tacrolimus nephrotoxicity.
7. Received >12 hour of CRRT (not including SCUF on ECMO) during this hospital admission or prior to transfer from an outside hospital.
8. Received >1 hemodialysis treatment during this hospital admission or prior to transfer from an outside hospital.
9. Metastatic malignancy which is actively being treated or may be treated by chemotherapy or radiation during the subsequent three month period after study therapy.
10. Chronic immunosuppression with the exception of corticosteroids up to a dose of 10 mg per day.
11. HIV or AIDS.
12. Severe chronic liver failure as determined by standard diagnostic requirements.

13. Current Do not Attempt Resuscitation (DNAR), Allow Natural Death (AND), or withdrawal of care status, or anticipated change in status within the next 7 days.
14. Patient not expected to survive 28 days because of an irreversible medical condition. (This is not restrictive to AKI, and may include situations such as the presence of irreversible brain damage, untreatable malignancy, inoperable life threatening condition, or any condition to which therapy is regarded as futile by the PI.)
15. Any medical condition that the Investigator thinks may interfere with the study objectives.
16. Physician refusal.
17. Dry weight <15 kg.
18. Platelet count <15,000/mm^3.
19. Concurrent enrollment in another interventional clinical trial. Patients enrolled in clinical trials where only measurements and or samples are taken (NO TEST DEVICE OR TEST DRUG USED) are allowed to participate.
20. Use of any other interventional drug or device within the previous 30 days.

6. STUDY ACTIVITIES

6.1 SCREENING PERIOD

The screening period is the time period when a patient is identified, informed consent is obtained, and the patient is evaluated for inclusion in the clinical trial. Because of the critically ill nature of the study population, it is expected that the majority of patients will not be able to provide informed consent. Where subjects are unable to consent themselves, surrogate informed consent will be sought from the subject's healthcare proxy or other equivalent legal representative. Only adverse events directly related to the screening procedures will be reported during this time.

Medical history and test results must be examined to ensure the patient meets all eligibility criteria. Tests that are specific to this protocol (i.e. not standard of care) require the patient or legal representative to have provided written consent for participation.

Any patients that do not meet study criteria, whether consent was obtained or not, will not be enrolled into the study. These patients will not be counted in the overall study enrollment numbers, but will be listed on the screening log.

Prior to enrollment please contact the study sponsor to validate that the patient has met all inclusion and exclusion criteria.

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Cincinnati Children's Hospital Medical Center (CCHMC)

6.2 CRRT PARAMETERS

6.2.1 CITRATE ANTICOAGULATION

Each participating clinical site will use their regional citrate anticoagulation protocol. The clinical site is responsible to achieve, and maintain a serum post filter ionized calcium level of <0.40 mmol/L throughout the entire observation period (day and night). The serum post filter ionized calcium level will be collected from the CRRT Circuit post SCD[redacted]

To alleviate the metabolic derangements associated with regional citrate based anticoagulation:

a) *Alkalosis*: Patients with an arterial pH <7.40 at enrollment will initiate CRRT with solutions containing either 25 or 35 meq/L

of base as directed by local standard of care. During the study, if the patient's arterial pH increases to >7.45 OR the patient's serum bicarbonate increases to >35 meq/L, the CRRT solution will be changed to a base concentration of 25 meq/L, OR 0.9% NaCl will be added dialysis fluid to correct the alkalosis per local standard of care.

b) *Citrate lock*: If the patient develops citrate lock, as defined by a serum ionCa <0.95 mmol/L and a total serum Ca >12.5 meq/L, the citrate infusion will be discontinued OR the CRRT clearance will be increased by 50% per local standard of care, AND CRRT circuit Ca and patient Ca will be checked at least every one hour. For centers that stop citrate, once the patient ionCa is >1.0 mmol/L, the citrate will be restarted at 50% of the previous rate, and hourly ionCa pairs will be rechecked x 3 to ensure a stable patient ionCa >1 mmol/L and stable circuit ionCa <0.40 mmol/L.

Of importance the clinical plan is to monitor the perfusion circuit iCa levels at least q1h at the initiation of regional citrate anticoagulation (RCA) until a steady state iCa range is between 0.25 to 0.40 mmol/L. Once established, iCa levels both in the circuit and in the patient will be monitored q6h. If the iCa is outside the targeted range or alterations in citrate or calcium infusion rates are made, iCa levels are measured at least q1h until targeted ranges are once again achieved. Of importance, for efficacy of SCD treatment, iCa levels must be maintained in the recommended range at least 90% of the time, based on a sensitivity analysis showing that the mortality endpoint difference was lower with target iCa 80-85% of total treatment in clinical trial SCD-003.

The protocol example identified in **Appendix K** may be utilized.

6.2.2 BLOOD CIRCUIT VOLUME

The additional blood volume for the SCD is 120 ml. This additional circuit blood volume for the standard SCD in >20 kg patients can be handled with blood priming with matched blood similar to the standard practice in neonates. Blood prime will occur if the total extracorporeal circuit volume (ECV) is greater than 10% of the patient's blood volume, based on an estimate of blood volume = 70 ml/kg x patient body weight (kg) [24]. The situation is most commonly encountered in neonatal CRRT, where circuit ECV can represent nearly 50% of patient blood volume, yet the same principles apply for this clinical study. [25]

Hypotension associated with blood priming can occur from transient dilution of vasoactive medications (e.g., norepinephrine), or from exposure to the hyperkalemic, hypocalcemic acidotic nature of blood banked blood, which can cause a bradykinin release syndrome (BRS) when the blood is exposed to the CRRT membrane. The BRS is usually associated with AN-69 membranes that will not be used in this study. Each center has its own blood priming protocol to mitigate the potential for this reaction. However, minimum standards for blood priming in this trial are detailed in Appendix L to ensure patient safety. [26]

Patients with AKI requiring CRRT are often hypotensive prior to initiation of CRRT. Initiation of CRRT itself can improve hemodynamics by correcting acidosis and hypocalcemia. Most patients with hemodynamic instability receive vasoactive medications. Since the age range and associated normal blood pressure parameters is wide for this pediatric study, it is difficult to mandate an age specific lower blood pressure threshold to preclude CRRT initiation, especially if CRRT can address the instability as noted above. However, a threshold BP of 80/40 mmHg-- patients with both a systolic blood pressure of less than 80 mmHg and a diastolic blood pressure of less than 40 mmHg will not be entered into the study.

If a patient develops hypotension or experiences worsening hypotension during CRRT/SCD initiation (defined as a > 10 mmHg decrease in mean arterial pressure (MAP) during the first 15 minutes of CRRT initiation or integration of the SCD into the circuit), the patient will receive a 10 ml/kg crystalloid bolus over 10 minutes. If this bolus does not lead to improvement of MAP within 5 minutes, vasoactive medications will either have their dose increased (if already prescribed) or will be initiated. Each center will select the vasoactive medication that is best suited for the clinical indication.

6.2.3 SCD PLACEMENT IN CRRT / ECMO CIRCUIT

Appendix M illustrates the integration of the CRRT circuit and SCD into the ECMO circuit. The CRRT return will be post pump.

Patients who receive CRRT on ECMO almost always develop their AKI, and hence their need for CRRT, after they have been on ECMO for at least 24 hours. Thus, the additional extracorporeal volume (ECV) associated with the CRRT circuit is not a factor, as the blood volume from ECMO is stable. In fact, the contribution of

the CRRT circuit is decreased (in terms of percent of ECV) since the ECMO circuit adds to the patient blood volume.

The pressure gradients are not an issue with CRRT on ECMO. In the most standard configurations, the CRRT circuit draws blood from the ECMO circuit post-pump and returns blood to the ECMO circuit pre-membrane, which is the safest configuration. The CRRT circuit will therefore see positive pressure from the ECMO circuit, and the current CRRT machines are designed to handle this. The CRRT pumps however, regulate the pressures within the CRRT circuit, so the SCD will see similar pressures compared to a non-ECMO situation.

6.3 BASELINE PERIOD

The Baseline Period begins at enrollment and ends at the start of the Observation Period. It is expected that the patient will begin the Observation Period before the patient has reached 12 hours of CRRT. The following information will be recorded as close to the start of the Observation Period as possible. Data from standard of care tests may be used as baseline data, as long as it is captured within the time frames noted.

- **Demographic Data**
  a) Date of birth
  b) Gender
  c) Race/ethnicity
- **Hospitalization Data**
  a) Hospital Admission Date
  b) Hospital Admission Diagnosis
  c) ICU Admission Date
  d) ICU Admission Diagnosis
  e) Medical History
- **Vital Signs/Physical Assessment (within 12 hours prior to the start of Observation Period unless otherwise indicated)**
  - Temperature
  - Blood Pressure, heart rate,
  - Body weight (within 24 hours if available)
  - PRISM II Score
  - Physical Exam
  - Urine Output (previous 24 hours)
  - ICU percent fluid overload at CRRT initiation (Defined as [(Fluid In (liters) – Fluid Out (liters))/ICU admission weight (kg)] x 100% where Fluid In and Fluid Out are calculated from ICU admission to CRRT initiation.
- **Clinical Laboratory Tests (within 12 hours prior to the start of Observation Period)**
  - CBC with differential
  - BUN/Creatinine
  - Na, K, Cl, HCO_3, Ca, Mg, Ionized Ca, PO_4
  - ALT, AST, Bilirubin, ALP, Total Protein, Albumin, Glucose
  - PT, PTT, INR
  - Urinalysis (if urine available)
- **Respiratory**
  - Status – Ventilator support (yes/no; date of intubation)
  - If on Vent: FiO_2
  - If on Vent with an arterial line: Arterial Blood Gas (12 hours prior to start of Observation Period)
  - If on Vent without an arterial line: Arterial Blood Gas (if available within 12 hours of start of Observation Period)
- **Blood for Research**
  - Blood sample will be sent to an outside laboratory for testing of biomarkers
- **Other (Event-driven)**
  - Acknowledgement (yes/no) to critical medications administered to the patient in the 24 hours prior to start of Observation Period
  - Adverse Events occurring since enrollment
  - Microbiology/culture data (within the last 72 hr.)

6.4 STUDY OBSERVATION PERIOD

The Study Observation Period begins when the patient starts treatment and will continue up to a maximum of 168 hours from the time of Observation Start. **Patient will begin the Observation Period before the patient has reached 12 hours on CRRT.** A patient may begin CRRT therapy and SCD treatment at the same time, which would also mark the beginning of the Study Observation Period.

This observation period has been broken into seven 24 hour time periods. It ends when the patient has reached 168 hours in the observation period or when the patient meets the termination criteria outlined in **Section 7.2** as determined by the Principal Investigator or Medical Team at the participating Clinical Site.

All tests are scheduled on a 24 hour cycle, or once a day, and can be scheduled to be drawn around each participating site's ICU blood drawing schedule, with the exception of any test that requires a specific draw frequency.

The following information will be obtained for patients enrolled during the study observation period on a daily basis unless otherwise specified:

- **Vital Signs/Physical Assessment**
  - Temperature
  - Blood Pressure , heart rate
  - Urine Output (previous 24 hours)
  - Net Fluid Balance (previous 24 hours)
- **Clinical Laboratory Tests**
  - CBC with differential – every 12 hours (+/- 4 hours)
  - BUN, Creatinine
  - Na, K, Cl, HCO_3, Ca, ionized Ca, Mg, PO_4
  - ALT, AST, Bilirubin, ALP, Total Protein, Albumin, Glucose
  - PT, PTT, INR
- **Respiratory**
  - Status – Ventilator support (yes/no; date of extubation)
  - If on Vent: FiO_2
  - If on Vent with an arterial line: Arterial Blood Gas
  - If on Vent without an arterial line: Arterial Blood Gas (if available)
- **Blood for Research**
  - Collect at hours 48, 96, 144, and end of study (+/- 4 hours). If study observation period ends prior to hour 168, collect at end of study observation period. Blood for biomarkers will be collected as close as possible to the time of SCD scheduled changes in the days required (+/- 4 hours) if practical.
  - Blood sample will be sent to an outside laboratory for testing of biomarkers

- **CRRT Parameters (Start at hour 0)**
  - Parameters include modality, blood flow rate, net fluid removal, dialysate or replacement solution flow rate, citrate infusion rate, calcium replacement rate.
  - System performance (circuit survival - event driven)
  - Post filter ionized calcium (+/- 1 hour)

Therapy Initiation	Q 1 hr. until post filter iCa level <0.40 mmol/L; then Q 6hr.
After any Calcium or Citrate rate change	Q 1 hr. until post filter iCa level <0.40 mmol/L; then Q 6hr.
After any Interruption: Recirculation, Procedure, Restart	Q 1 hr. until post filter iCa level <0.40 mmol/L; then Q 6hr.

- **SCD Performance (Start at hour 0)**
  - SCD [redacted] performance (event driven)
  - SCD and SCD Blood Tubing Set Change every 24 hour (+/-4 hour)

- **Other (Event Driven)**
  - Acknowledgement (yes/no) to critical medications administered to the patient
  - Adverse Events
  - Diagnostic/Therapeutic Procedures
  - Microbiology/culture data

6.5 STUDY FOLLOW UP PERIOD

6.5.1 POST END OF STUDY TREATMENT PERIOD

This Study Follow Up period has been broken into five 24 hour time periods. It starts when the patient has reached 168 hours in the observation period or when the patient meets the termination criteria outlined in **Section 7.2**. It ends at 120 hours or ICU discharge, whichever comes first. Record the following data daily in the Study Follow-up Period unless otherwise noted:

- **Vital Signs/Physical Assessment**
  - Blood pressure, heart rate, temperature
  - Physical Exam (first 24 hours only)
  - Urine Output (from previous 24 hours)
  - Net fluid balance (from previous 24 hours)
- **Clinical Laboratory Tests (first 24 hours only)**
  - CBC with differential
  - BUN, Creatinine
  - Na, K, Cl, HCO_3, Ca, Mg, Ionized Ca, PO_4

- **Respiratory**
  - Status – Ventilator support (yes/no)
  - If on Vent: FiO_2
  - If on Vent with an arterial line: Arterial Blood Gas(first 24 hours only)
  - If on Vent without an arterial line: Arterial Blood Gas (if available, first 24 hours only)
- **Renal Replacement Therapy status**
  - RRT status
- **Other (Event Driven)**
  - Microbiology/culture data
  - Adverse Events
  - Acknowledgement (yes/no) to antibacterial agents administered to the patient.

6.5.2 DAY 28 POST ENROLLMENT

This visit may be done via telephone call or office visit. Please record the following information on day 28 (+7 days) following enrollment:

- Presence / date of mechanical ventilation (since last visit)
- Presence / date of renal replacement therapy (since last visit)
- Serious Adverse events (since last visit)
- Serum creatinine (if an office visit takes place)

6.5.3 DAY 60 POST ENROLLMENT

This visit may be done via telephone call or office visit. Please record the following information on day 60 (+7 days) following enrollment:

- Presence / dates of mechanical ventilation (since last visit)
- Presence / dates of renal replacement therapy (since last visit)
- ICU discharge date
- Hospital discharge date
- Serious Adverse events (since last visit)
- Serum creatinine (if an office visit takes place)

7. TREATMENT INTERRUPTIONS – DISCONTINUATION CRITERIA

7.1. TREATMENT INTERRUPTION CRITERIA

The SCD is to be used continuously along with CRRT and changed every 24 hours and at any time the circuit exhibits significant clotting that impairs the functionality of the circuit.

In the event that a procedure is needed (e.g. CT-Scan, MRI), SCD treatment may be interrupted for a maximum of 12 hours (cumulative) per 24 hour period for these indications. In the event a patient needs to initiate ECMO in the middle of the SCD course, SCD treatment may be interrupted for up to 24 consecutive hours. Cumulative interruption of greater than 12 hours (or 24 hours for ECMO) will trigger the end of Observation Period and immediate initiation of the Follow-up period. These patients will not be removed from the study unless consent is withdrawn.

7.2. TREATMENT DISCONTINUATION CRITERIA

Patients may be withdrawn from therapy prior to hour 168 for a variety of reasons. When therapy is discontinued prior to hour 168, the follow-up period will immediately begin and data will continue to be collected per protocol.

The Principal Investigator will assign a primary reason for therapy termination utilizing the categories listed in 7.3 and 7.4 below, and if appropriate, one or more subcategories.

7.3. CLINICAL CRITERIA:

1. **Improvement in Clinical Status**
   If a patient's condition improves (e.g. renal condition has improved to the extent that CRRT can be discontinued or hemodynamic status has improved so that the dialysis modality can be changed from CRRT to IHD) treatment may be discontinued before the 168 hour treatment period. The decision to discontinue treatment based upon improvement in clinical status will be made by the Principal Investigator.

2. **CRRT related medical events**
   Such as persistent leukopenia, neutropenia or thrombocytopenia based upon PI's clinical assessment.

3. **SCD related medical events**
   Such as persistent leukopenia, neutropenia or thrombocytopenia based upon PI's clinical assessment of relationship to SCD.

4. **CRRT Failure/Malfunction**
   Failure of the CRRT device and/or circuit, including inability to maintain vascular access that requires treatment to be discontinued prior to hour 168 of therapy.

5. **SCD Failure/Malfunction**
   Any failure of the SCD[redacted] that requires treatment to be discontinued prior to hour 168 of therapy e.g. clotting or evidence of leakage in the SCD[redacted] or inability to maintain a patent circuit.

6. **Death**

7. **Withdrawal of life support**

8. **Concomitant Medical Conditions**
   Need for medical, surgical or diagnostic procedures that necessitate discontinuation of SCD treatment for longer than the allowable 12 hours per 24 hour period.

9. **Regional Citrate Anticoagulation Intolerance**
   All patients must be able to tolerate and achieve satisfactory regional citrate anticoagulation. Tolerance of regional citrate anticoagulation is defined as achieving:
   - Two (2) consecutive circuit ionized calcium levels of < 0.40 mmol/L (or < 1.6 mg/dL),
   - At least 30 minutes apart, and
   - Within the first 12 hours of CRRT initiation.

   If unable to achieve the specific circuit ionized calcium levels within the time frame above, treatment with the SCD must be discontinued. The patient will progress on to the post-SCD follow up period, unless the patient and/or legal guardian withdraws consent for the study.

10. **Other**
    Any other reason that the Principal Investigator deems appropriate for discontinuation from the Study Observation period must be documented.

7.4. NON-CLINICAL CRITERIA:

- **Withdrawal of participation from study observation period**
  Patients may withdraw their consent to participate in the study observation period at any time. If the patient wishes to remain in the clinical study, the follow-up period will immediately begin at the termination of study observation period. All data will continue to be collected per protocol.

The Principal Investigator will notify the Sponsor's Chief Medical Officer or designee within 24 hours of withdrawal of participation.

- **Withdrawal of consent**
  If a patient or legal representative withdraws consent, all protocol related activities will be immediately discontinued. If study therapy (CRRT+SCD) is being administered at the time of withdrawal, normal procedures will be followed for CRRT+SCD therapy discontinuation (please see SCD Operator's Manual). No further study activity will be conducted.

  The Principal Investigator will notify the Sponsor's Chief Medical Officer or designee within 24 hours of withdrawal of consent.

8. CLINICAL TRIAL TERMINATION CRITERIA

The Sponsor reserves the right to terminate the clinical trial for safety or administrative reasons at any time. If the Sponsor, Principal Investigator, Data Safety Monitoring Board (DSMB), Institutional Review Board (IRB), or Food and Drug Administration (FDA) officials discover conditions during the study indicating that the trial or participation by a clinical site should be discontinued, this action may be taken after appropriate consultation between the Sponsor and the Investigators.

Conditions that may warrant discontinuation of the trial at a specific clinical site may include the following:

- Failure of the Investigator to enroll patients into the trial at an acceptable rate (as defined and agreed upon between the Investigator and the Sponsor).
- Failure of the Investigator to comply with the pertinent FDA regulations.
- Submission of false information by the Investigator from the research facility to the Sponsor or the FDA.
- Failure to achieve and maintain post filter iCa levels of <0.40 mmol/L

Conditions that may warrant discontinuation of the trial may include, but are not limited to, the following:

- Discovery of an unexpected, serious or unacceptable risk to the patients enrolled in the study.
- Decision on the part of the Sponsor to suspend or discontinue testing, evaluation or development of the study product at any time.

9. SAFETY

9.1. ADVERSE EVENTS

An Adverse Event is any sign, symptom, illness, clinically significant abnormal laboratory value or other adverse medical event that appears for the first time or worsens in a subject (control or treatment arm) during this clinical study, regardless of whether or not it is considered related to the device.

- Blood and lymphatic system disorders (e.g., anemia, disseminated intravascular coagulation (DIC), heparin-induced thrombocytopenia (HIT), hypercoagulation, leukocytosis, thrombocytopenia, and thrombocytosis);
- Cardiac disorders (e.g., atrial fibrillation, atrial flutter, bradycardia, cardiogenic shock, non-ST segment elevation myocardial infarction, sinus tachycardia, ventricular fibrillation, and ventricular tachycardia);
- Gastrointestinal disorders (i.e., blood in stool, constipation, distended abdomen, gastrointestinal bleeding, ileus, nausea, pancreatitis, vomiting)
- General disorders and administration site conditions (i.e., chest pain, generalized aching, high temperature, hypothermia, multi-organ failure)
- Infections and infestations (i.e., candidiasis, gangrene, klebsiella pneumonia infection, methicillin-resistant staphylococcus aureus (MRSA) infection, pneumonia, sepsis, septic shock, and urinary tract infection (UTI));
- Injury, poisoning and procedural complications (e.g., post procedural pain);
- Metabolism and nutrition disorders (i.e., hypercalcemia, hyperglycemia, hyperkalemia, hypernatremia, hypervolemia, hypocalcemia, hypoglycemia, hypokalemia, hypomagnesemia, hyponatremia, hypophosphatemia, malnutrition, metabolic acidosis, and metabolic alkalosis);
- Musculoskeletal and connective tissue disorders (e.g., muscle spasm) ;
- Nervous System Disorders (e.g., encephalopathy, mental deterioration, stroke);
- Psychiatric disorders (e.g., agitation, anxiety, confusion, insomnia, mental status changes);
- Renal and urinary disorders (e.g., acute retention of urine, renal failure);
- Respiratory, thoracic and mediastinal disorders (e.g., acute respiratory failure, aspiration pneumonia, atelectasis, hypoxemia, pleural effusion, pneumothorax, pulmonary thromboembolism, respiratory failure, and thoracic hemorrhage);
- Skin and subcutaneous tissue disorders (e.g., macular rash, skin ulcer); and
- Vascular disorders (e.g., deep vein thrombosis, hypertension, hypotension, and jugular vein thrombosis).

9.2. SERIOUS ADVERSE EVENTS

Any Adverse Event, whether considered study-treatment related or not, which fits any of the criteria below, is considered a serious adverse event (SAE):

- Results in death
- Is life-threatening (meaning that the patient was at risk of death at the time of the event; this does not refer to an event which might have caused death if it had occurred in a more severe form)
- Requires in-patient hospitalization or prolongs the existing hospitalization
- Is a persistent disability/incapacity
- Is a congenital anomaly or birth defect
- Is considered an important medical event by the Principal Investigator (e.g., surgery, return to ICU, emergency procedures)

9.3. UNANTICIPATED ADVERSE DEVICE EFFECT

Unanticipated adverse device effect (UADE) is any serious adverse effect on health or safety, any life-threatening problem or death caused by, or associated with a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the application; or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects. UADEs are reported to FDA as they occur (e.g., no later than 10 working days after CytoPherx first receives notice of the effect), as mandated by 21 CFR 812.150(b)(1).

9.4. ANTICIPATED ADVERSE EVENT

Co-morbidities and symptoms/laboratory/physiological deviations normally associated with pre-existing conditions (e.g., diabetes, ASHD, other C-V conditions, pneumonia, dialysis shunt problems, neurologic deficits) are considered "anticipated adverse reactions." The investigator is required to take special care in differentiating concomitant illness events from those related to the therapy by use of patient history, relationship to treatment time and cartridge integrity, and other characteristics of clinical circumstances present at the time of the adverse experience, including drug interactions of concomitant medications and effects of surgical and/or medical procedures.

Adverse events associated with CRRT or underlying critical illness are also to be considered "anticipated". Such events include, but are not limited to: thrombocytopenia, hyponatremia, hypokalemia, hypo- or hypercalcemia, hypo- or hyperglycemia, air embolism, hypotension, hemolysis, increased oxygenation requirements, leukopenia, arrhythmias, hypothermia, lactic acidosis, temporary decrease in cardiac output or cardiac index, disruption of skin integrity, bleeding, shock, bacteremia, hypotension, seizure, and death.

In addition, the following adverse events were experienced in the SCD-003 clinical trial and are considered anticipated:

- Blood and lymphatic system disorders (i.e., Anemia, Disseminated intravascular coagulation (DIC), Heparin-induced thrombocytopenia (HIT), Hypercoagulation, Leukocytosis, Thrombocytopenia, Thrombocytosis)
- Cardiac disorders (i.e., Atrial fibrillation, Atrial flutter, Bradycardia, Cardiogenic shock, Non ST segment elevation myocardial infarction, Sinus tachycardia, Ventricular fibrillation, Ventricular tachycardia)
- Gastrointestinal disorders (i.e., Blood in stool, Constipation, Distended abdomen, Gastrointestinal bleeding, Ileus, Nausea, Pancreatitis, Vomiting)
- General disorders and administration site conditions (i.e., Chest pain, Generalized aching, High temperature, Hypothermia, Multi organ failure)
- Infections and infestations (i.e., Candidiasis, Gangrene, Infection Klebsiella pneumonia, Infection MRSA, Pneumonia, Sepsis, Septic shock, UTI)
- Injury, poisoning and procedural complications (i.e., Post procedural pain)
- Metabolism and nutrition disorders (i.e., Hypercalcemia, Hyperglycemia, Hyperkalemia, Hypernatremia, Hypervolemia, Hypocalcemia, Hypoglycemia, Hypokalemia, Hypomagnesemia, Hyponatremia, Hypophosphatemia, Malnutrition, Metabolic acidosis, Metabolic alkalosis)
- Musculoskeletal and connective tissue disorders (i.e., Muscle spasm)
- Nervous system disorders (i.e., Encephalopathy, Mental deterioration, stroke)
- Psychiatric disorders (i.e., Agitation, Anxiety, Confusion, Insomnia, Mental status changes)
- Renal and urinary disorders (i.e., Acute retention of urine, Renal failure)
- Respiratory, thoracic and mediastinal disorders (i.e., Acute respiratory failure, Aspiration pneumonia, Atelectasis, Hypoxemia Pleural effusion, Pneumothorax, Pulmonary thromboembolism, Respiratory failure, Thoracic hemorrhage)
- Skin and subcutaneous tissue disorders (i.e., Macular rash, Skin ulcer)
- Vascular disorders (i.e., Deep vein thrombosis, Hypertension, Hypotension, Jugular vein thrombosis).

Any questions as to the expectedness of an adverse event will be discussed with CytoPherx's CMO and/or the DSMB.

9.5. CAUSALITY

All enrolled patients must have all AEs assessed for causality (probability that the AE may have been caused by the study treatment) by the Principal Investigator. The following definitions for causality assessment will be used in this study:

9.5.1. DEFINITELY RELATED

A clinical event, including a significant change in a laboratory test, that occurs in a plausible time relationship to the SCD treatment or other protocol-required activity, and which cannot be explained by concurrent disease or other drugs, chemicals, or procedures and that follows a clinically reasonable response upon withdrawal of the SCD treatment.

9.5.2. PROBABLY RELATED

A clinical event, including a significant change in a laboratory test, that occurs within a reasonable time sequence in relationship to the SCD treatment or other protocol-required activity that is unlikely to be attributed to concurrent disease, other drugs, chemicals, or procedures, and that follows a clinically reasonable response upon withdrawal of the SCD treatment.

9.5.3. POSSIBLY RELATED

A clinical event, including a significant change in a laboratory test, that occurs within a reasonable time sequence in relationship to the SCD treatment or other protocol-related activity that could also be explained by concurrent disease, drugs, chemicals, or procedures. The clinical course after withdrawal of the SCD treatment may be unclear with respect to the contribution of the SCD treatment to the AE.

9.5.4. UNRELATED

An AE, including a significant change in a laboratory test, that occurs with a temporal relationship to the SCD treatment or protocol-required activity that makes an association with the SCD treatment or study activity improbable, and in which other drugs, procedures or underlying disease(s) provide likely explanation.

9.6. SEVERITY – INTENSITY

The intensity of all adverse events should be evaluated using the following definitions:

9.6.1. MILD

An event that requires minimal clinical treatment or an adverse event requiring monitoring but no intervention or treatment; causes slight discomfort.

9.6.2. MODERATE

An event that requires non-routine intervention, (i.e., a new clinical treatment or diagnostic procedure), administered within an hour of the event; causes annoying discomfort.

9.6.3. SEVERE

An event requiring immediate intervention; causes significant discomfort.

9.7. ADVERSE EVENT REPORTING

Adverse event reporting requirements will be based on the time period in which the adverse event occurs. It is understood that many of the signs and symptoms observed with ICU patients are expected. However, these should still be reported as adverse events if they meet the definitions of the Protocol. A "clinical care" event should therefore be reported as an adverse event if it meets any of the definitions. A group of symptoms that can be combined under one diagnosis, should be reported as a single adverse event. If a group of symptoms cannot be combined under one diagnosis, the symptoms should be reported as separate adverse events. These events will be reported as the number of events per time of exposure to the device.

9.7.1. SCREENING PERIOD

Only adverse events, serious and not serious, directly related to the screening procedures will be captured during this period. Unrelated clinical adverse events that occur prior to enrollment will be considered part of the medical history.

9.7.2. ENROLLMENT PERIOD THROUGH END OF STUDY

All adverse events that occur from the time of enrollment will be recorded as follows:

- Serious Adverse Events (identified in **Section 9.2**) will be recorded until Day 60 after enrollment, death, or patient withdrawal of study consent, whichever occurs first.
- Non-serious adverse events will be recorded until end of study follow-up period after enrollment, death, patient withdrawal of study consent or until hospital discharge, whichever occurs first.

Any serious adverse event (regardless of relationship to the treatment) occurring from the time of enrollment through end of study must be reported to CytoPherx Inc, or designee, within 24 hours of knowledge of the event.

Each clinical trial site will be supplied with written SAE reporting

instructions, SAE reporting forms and contact information for reporting of serious adverse events.

For any AE that is ongoing at the time of the initial report, periodic follow-up information will be required until the adverse event is resolved or the patient is no longer in the study, whichever occurs first.

The Investigator is responsible for all adverse events reporting to the Institutional Review Board (IRB) according to the requirements of the IRB and for providing clinical trial monitors with all medical records needed to source-verify the adverse events.

10. DATA SAFETY MONITORING BOARD

An independent Data Safety Monitoring Board (DSMB) will review safety results over the course of the study on a schedule set by CytoPherx, Inc. and the DSMB. The DSMB will comply with the FDA Guidance: "Guidance for Clinical Trial Sponsors on the Establishment and Operation of Clinical Trial Data Monitoring Committees". The DSMB will be formed to provide scientific and medical feedback for the study.

The DSMB will focus on the following areas:

- *Performance* – to assess study conduct and compliance;
- *Effectiveness* – to assess mortality and dialysis dependency;
- *Safety* – to assess the incidence, severity, relationship, and timing of adverse events and to identify safety concerns; and
- *Context* – to assess the study relative to the AKI literature.

The DSMB will reflect the disciplines and medical specialties necessary to interpret the data from the clinical study and to fully evaluate participant safety. The SCD-PED-01 DSMB will be made up of at least 2 medical practitioners with expertise in AKI and critical care medicine. The DSMB will operate under a charter and will identify prospective data display specifications to conduct independent data reviews. The DSMB will make recommendations to the Sponsor to continue the study as planned or to stop the study due to safety. The DSMB will meet to perform safety evaluations and to provide feedback to the Sponsor at least annually as well as after 5, 10 and 16 of the cohort has completed 60 day follow-up. An efficacy evaluation to historical controls will be accomplished after all 16 enrolled patients have completed 60 day follow-up. The DSMB reserves the right to request more frequent evaluations.

11. PROTOCOL ANALYSIS / SCIENTIFIC SOUNDNESS

This study derives from the hypothesis that up to seven or less sequential 24 hour SCD treatments will improve survival in patients with AKI requiring CRRT as compared to historical data. Further, SCD therapy may reduce the duration of maintenance dialysis secondary to acute renal failure (ARF) due to acute kidney injury (AKI).

The precise mechanism of action of the SCD is becoming better understood and appears to be an immunomodulatory process which inhibits leukocyte activation, a trigger of systemic inflammatory response syndrome (SIRS) and multi-system organ failure. The modulation of the pro-inflammatory state is believed to also allow recovery of renal function in AKI and other organ failure. The cartridge in the presence of citrate anticoagulant acts as a selective cytopheretic device to sequester and inhibit potentially damaging circulating leukocytes.

Recent data have demonstrated, that the inflammatory response of neutrophils adhered to a polysulfone dialysis membrane in the presence of low iCa and citrate are released with a normalized apoptotic life span, compared to a delayed apoptotic rate promoted in systemic inflammation. Leukocytes, especially neutrophils, are major contributors to the pathogenesis and progression of clinical inflammatory disorders, including SIRS, sepsis, ischemia/reperfusion injury and ARDS. Further data have demonstrated that monocytes with a proinflammatory phenotype, binds more avidly than monocytes with a reparative phenotype to the membrane in low iCa environment. This selective binding results in a less inflammatory circulating monocyte population in disorders of inflammation. The protocol has been carefully constructed with precise AKI diagnostic criteria, CRRT or comparable mode treatment and definition of patient's age, need to tolerate citrate anticoagulation and placement in the ICU during SCD therapy. Patient exclusion criteria are also detailed so as to provide a well characterized and standardized patient population. Observational periods and a complete schedule of events in the protocol delineate specific efficacy measurements as required to test the study hypothesis, including bio-inflammatory assay markers, and WBC activation studies.

Besides the test of the hypothesis the study is focused on observable, empirical and laboratory determinations of patient safety while on the SCD. Previous human trials have been conducted on the SCD device and the protocol contains a review of AE and SAE data from all SCD human studies and findings from those studies contributed to constructing the investigative safety profile. Safety endpoint measures specified in the protocol include adverse events, laboratory safety parameters, vital signs, ventilation status and hemodynamic variables. Device integrity and performance measurements are also defined as are circumstances which demand premature termination of SCD treatment.

Prolonged exposure to the SCD is anticipated to result in superior outcomes, although as noted above, this pilot study is not designed to assess for efficacy. However, we understand that a minimum amount of exposure to the SCD will be required for an appropriate safety analysis and for making any inference regarding efficacy. The ppCRRT experience demonstrated that the majority of patients (201/370) received CRRT for 1 to 7 days and exhibited 65% survival (Symons et al CJASN 2007 Table7). Assuming our trial includes patients with similar illness severity, we have established a 72 minimum number of hours a patient will be treated with the SCD to be included in the final outcome analysis.

This trial is an early safety efficacy study but is not powered for statistical significance. Insights into a comparison of historical controls matched to SCD treated patients will utilize the ppCRRT Registry to match for: etiology of AKI, co-morbidities, CRRT modality, dose and form of anticoagulant, adverse events. [10].

The ppCRRT Registry has data fields for the primary reason for CRRT, including AKI and its cause, as well as co-morbidities which will be matched for primary organ system involvement. The CRRT modality was evenly distributed between convective and diffusive modality, with 60% of the convective modalities provided as CVVH and 40% as CVVHDF. The anticoagulant protocol will be standardized with ACD-A/$CaCl_2$ and all centers used the same protocol in ppCRRT Registry as outlined in this study protocol. Thus, the ppCRRT Registry dataset will be able to be matched to our study patient cohort. Also as noted above, patients will be matched for age, size and PRISM II score.

The Prospective Pediatric CRRT (ppCRRT) database will be used as a control for the CRRT treatment related factors including: patient age, gender, primary cause of AKI, total treatment duration, CRRT modality (CVVH, CVVHD, CVVHDF), CRRT small solute clearance (ml/1.73m2/hour), baseline estimated GFR (using the original Schwartz formula, which was used in the ppCRRT), urine output in the 24 hours prior to CRRT initiation (ml/kg/hour), percent fluid overload at CRRT initiation based on admission ICU weight, vasoactive medication number at time of CRRT initiation and mean airway pressure at CRRT initiation.

An additional analysis will also evaluate patients who have achieved targeted iCa levels during 90% of treatment time and those who do not.

In summary this protocol meets all criteria necessary for clinical scientific inquiry related to a test of hypothesis in a well monitored environment focused on patient safety during the conduct of the study. Basic statistics will be performed on the data sets along with historical data comparisons and subjected to subset analysis where appropriate. The results will help to guide the design of a future pivotal study of this device.

The rational for therapy, study objectives and endpoints, design, inclusion and exclusion criteria are explicitly defined. Patient safety parameters are well documented including safety reporting, safety observations and assays, procedures for patient withdrawal and study discontinuation criteria along with monitoring device integrity and performance. Lastly, a review of all prior SCD human study safety data is included in the protocol for full disclosure to study investigators and the informed consent document includes a full description of all known and potential risks of the device treatment.

12. DATA COLLECTION – STUDY MONITORING AND AUDIT

The Principal Investigator is responsible for assuring the accuracy and completeness of all study documentation. Monitoring will be conducted within ICH/GCP Guidelines and CytoPherx, Inc. Clinical Monitoring Plan to ensure the following:

- The facilities continue to be acceptable.
- The protocol is appropriately followed.
- Any agreed upon changes to the protocol have been approved by the IRB and approval has been received in writing by CytoPherx, Inc.
- Accurate, complete and current records are maintained and available for all patients.
- For each subject. collection of protocol-required data and entry of that data into the CRFs must be completed as soon as reasonably possible following that subject's last day in each study period.
- The information recorded and submitted to CytoPherx, Inc. is representative of the patient's record and other supporting documentation.
- Accurate, complete and timely adverse event reports for serious adverse events are submitted to CytoPherx, Inc.
- The Principal Investigator continues to assume primary responsibility for the study.

The Investigator or designee must, upon request, provide to the Clinical Research Associate (CRA), Quality Assurance Auditor, or FDA Investigator the necessary study records for a thorough review of the study's progress. These records include, but are not limited to, original documents and records, such as hospital and clinic charts, consent forms, and laboratory records. The Principal Investigator is required to notify the Sponsor immediately of the following:

- Withdrawal of IRB Approval
- Any protocol violations or protocol deviations related to study device use
- Notification that Informed Consent was not obtained or consent was withdrawn
- Any other instance in which the Investigator or Sponsor deems it necessary

13. INVESTIGATOR'S STATEMENT OF RESPONSIBILITY

By my signature, I confirm that my staff and I have carefully read and understand this protocol and agree to comply with the conduct of the specified therein, In particular we have agreed to:

- Conduct the study according to the protocol, amendments, and study guides.
- Obtain Institutional Review Board approval of the study, any amendments to the study and periodic-re-approval, as required.
- Obtain written consent from each study participant or their legal representative.
- Report all serious adverse events to CytoPherx, Inc and to the IRB, as required by the protocol and IRB regulations.
- Assure access by study monitors to original source documents.
- Cooperate fully with any study-related GCP audit as performed by CytoPherx, Inc, their designee, or the Food and Drug Administration (FDA).
- Maintain confidentiality and assure security of confidential documents such as the protocol, consent form, case report form, SCD Operator's Manual, final study reports, manuscript, and/or unpublished data and correspondence.
- Achieve and maintain serum post filter ionized calcium levels of <0.40 mmol/L.

_____ _____

Principal Investigator Signature Date

_____

Printed Name

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15. APPENDICES

APPENDIX A – PEDIATRIC RISK OF MORTALITY (PRISM II) SCORE [27]

ORGAN SYSTEM	MEASURE
Respiration	PaO_2 to FiO_2 Ratio, P_aCO_2, Resp. Rate
Coagulation	Protime, PTT
Liver	Serum Total Bilirubin
Cardiovascular	Systolic BP, Diastolic BP, Heart rate
Central nervous system	Glasgow Coma Score, Pupillary Reflexes
Metabolic	Serum potassium, calcium, glucose, bicarbonate glucose

ORGAN SYSTEM	MEASURE	FINDING	POINTS
Respiration	PaO_2 to FiO_2 Ratio (please see Pulmonary System Conversion Table for Non-ventilated Pts)	200 – 300 mmHg	2
		<200 mmHg	3
	P_aCO_2	51-65 mmHg	1
		>65	5
	Respiratory Rate (breath/min)	51-70	1
		>70 or Apnea	5
Coagulation	Protime or Partial Thromboplastin Time	1.5 x control	2
Liver	Serum Total Bilirubin	>3.5 mg/dL	6
Cardiovascular	Systolic Blood Pressure (mmHg)	150-200 or 65-75	2
		>200 or 50-64	6
	Diastolic Blood Pressure (mmHg)	>110	6
	Heart Rate (beat/min)	>150 or <80	4
Central Nervous System	Glasgow Coma Score	<8	6
	Pupillary Reactions	Unequal or dilated	4
		Fixed and dilated	10
Metabolic	Potassium (mEq/L)	3.0 – 3.5 or 6.5 – 7.5	1
		<3.0 or >7.5	5
	Calcium (mg/dL)	7.0 – 8.0	2
		12.0 – 15.0 or <7.0	6
	Glucose (mg/dL)	40-60 or 250 – 400	8
		<40 or >400	8
	Bicarbonate (mEq/L)	<16 or >32	3

Conventions used for the above table include:

- PaO_2 is in mmHg and FiO_2 in percent from 0.21 to 1.00.

APPENDIX A (Continued)
PEDIATRIC RISK OF MORTALITY (PRISM II) SCORE [27]

GLASGOW COMA SCORE

The Glasgow Coma Score (GCS) is scored between 3 and 15, 3 being the worst and 15 the best. It is composed of the three parameters listed below:

Best Eye Response (4)

1. No eye opening
2. Eye opening to pain
3. Eye opening to verbal command
4. Eyes open spontaneously

Best Verbal Response (5)

1. No verbal response
2. Incomprehensible sounds
3. Inappropriate words
4. Confused
5. Oriented

Best Motor Response (6)

1. No motor response
2. Extension to pain
3. Flexion to pain
4. Withdrawal from pain
5. Localizing pain
6. Obeys commands

A Coma Score of 13 or higher correlates with a mild brain injury, 9 to 12 is a moderate injury and 8 or less a severe brain injury.

APPENDIX A (Continued)
PEDIATRIC RISK OF MORTALITY (PRISM II) SCORE [27]

PULMONARY SYSTEM CONVERSION TABLE

O_2 Saturation Conversion Table		**Conversion Table for FiO_2**
Pulse oximetry O_2 saturation may be used for calculating PaO_2/FiO_2 ratio when ABG not available		When measured on mask or nasal cannula

SaO_2 (%)	Calculated PaO_2
80	44
81	45
82	46
83	47
84	49
85	50
86	52
87	53
88	55
89	57
90	60
91	62
92	65
93	69
94	73
95	79
96	86
97	96
98	112
99	145

Nasal Cannula	
100% O_2 Flow Rate (L/min)	FiO_2 (%)
1	24
2	28
3	32
4	36
5	40
6	44
Oxygen Mask	
100% O_2 Flow Rate (L/min)	FiO_2 (%)
5-6	40
6-7	50
7-8	60
9	90
10	99+
Mask with Reservoir Bag	
100% O_2 Flow Rate (L/min)	FiO_2 (%)
6	60
7	70
8	80

APPENDIX B – DEFINITIONS OF ACUTE KIDNEY INJURY

Acute Kidney Injury

Acute Kidney Injury (AKI) is sudden loss of the ability of the kidneys to excrete wastes, concentrate urine, and conserve electrolytes. AKI is due to a variety of etiologies. These conditions are found in circumstances of acute injury and conform to one of the following criteria:

- Increase in SCr by ≥ 0.3 mg/dl (≥26.5 μmol/L) within 48 hours or:
- Increase in SCr to ≥ 1.5 times baseline, which is known or presumed to have occurred within the prior 7days or:
- Urine volume <0.5ml/kg/h for 6 hours
  (Note: pre-renal, vascular, , and obstructive etiologies are excluded on clinical or other diagnostic grounds.)

AKI develops predominantly due to the injury and necrosis of HPTC (Human Proximal Tubular Cells). AKI is caused by ischemia of the kidneys or by exposure to nephrotoxic agents. Risks for AKI include injury or trauma with resulting damage to the muscles, recent major surgery, blood transfusion reaction, septic shock or other forms of shock, and severe hypotension longer than 30 minutes.

Any condition that causes a reduction in the amount of blood being pumped by the heart may cause AKI. Liver disease and damage caused by diabetes mellitus (diabetic nephropathy) may predispose a person to the condition. AKI can also be caused by exposure to nephrotoxic agents (e.g., aminoglycoside antibiotics), antifungal agents (e.g., amphotericin), medications to prevent rejection of transplanted organs (e.g., cyclosporine), dye used for radiographic studies, and other toxins. In SCD studies, patients with AKI due to a variety of etiologies are eligible for study participation. As noted above, pre-renal, vascular, and obstructive etiologies are excluded on clinical or other diagnostic grounds.

APPENDIX C – DEFINITIONS OF ORGAN FAILURE AND SEPSIS [28]

A. SEPSIS

Sepsis is defined in this protocol as the presence (probable or documented) of infection together with two or more of the following systemic manifestations of infection:

Age	2-5 years	6-12 years	13-18 years	19-22 years
Tachypnea [1] **(breaths / min)**	>22	>18	>14	>14
Tachycardia (beats / min)	>140	>130	>110	>90
Hyper/Hypothermia (all ages)	>38.5ºC or <36ºC			
WBC ($x10^3$ /mm)	>15.5 or <6	>13.5 or <4.5	>11 or <4.5	>12 or <4.0

[1.] Patient meets this criteria if mechanically ventilated, not related to underlying neuromuscular disease or the receipt of general anesthesia.

B. NON-RENAL ORGAN FAILURE

At least one non-renal organ failure (defined as receiving mechanical ventilation [12] or at least one vasoactive medication to treat hypotension) OR presence (proven or suspected) of sepsis.

APPENDIX D – ENDPOINT DEFINITIONS

ALL-CAUSE MORTALITY:
All cause mortality is defined as in-hospital, 28-day and 60-day all cause mortality.

DIALYSIS DEPENDANCY AT DAY 60:
Dialysis dependency at day 60 is defined as patient not receiving any form of intermittent or continuous renal replacement therapy at or within 3 days of 60 days post enrollment in the study with no plans for additional intermittent or continuous renal replacement therapy.

PATIENT SAFETY:
Adverse events, laboratory safety parameters, vital signs, EKG, ventilation status and hemodynamic variables.

DURATION OF RENAL SUPPORT:
The duration of renal support will be defined as the numbers of days from the initiation of renal replacement therapy (start of observation period) to final dialysis treatment. Duration of renal support will be censored if the patient is still dialysis dependent at the time of death or are dependent at day 60.

RECOVERY OF RENAL FUNCTION:
Recovery of renal function will be defined as lack of need for continuous dialysis support on day 28, and will be classified as yes or no at day 28. Subjects who were alive at day 28 will be included in the analysis. Patients who remain dialysis dependent at study completion (day 60) or time of death will be categorized as having no recovery of renal function.

ASSESSMENT OF SCD[redacted] INTEGRITY AND PERMORMANCE:
The SCD[redacted] will be evaluated for the presence of clotting, leaking or any other malfunction.

APPENDIX E – CRRT MANAGEMENT

Continuous Renal Replacement will be provided to all patients enrolled in the SCD-PED-01 Trial using automated equipment with integrated ultrafiltration control.

CRRT Modality:	Continuous
Blood Flow Rate:	Prescribed by Investigator Team – Treating Team
Dialysate Type:	Prescribed by Investigator Team – Treating Team
Dialysate Rate:	Prescribed by Investigator Team – Treating Team
Replacement Fluid Type:	Prescribed by Investigator Team – Treating Team
Ultrafiltration:	Prescribed by Investigator Team – Treating Team
Anticoagulation:	Regional Citrate Anticoagulation Only
Anticoagulation Prescription:	Prescribed by Investigator Team – Treating Team
CRRT Device	Gambro PrismaFlex, B. Braun Diapact
Hemofilter:*	Gambro Prismaflex HF 1000, Renaflow HF 400, Renaflow HF 700, Renaflow HF 1200
CRRT System Change:	Per participating center protocol
SCD[redacted] Change:	Every 24 hours and as needed due to clotting
SCD Blood Tubing Set Change	With each SCD change
CRRT+SCD Interruption:	Up to twelve (12) hours per 24 hour period (or up to 24 hours if interruption was needed to initiate ECMO in the middle of the SCD course)

*Hemofilters can be provided to site by sponsor upon request. The clinical site will agree to use one of the protocol approved hemofilters for therapy.

APPENDIX F – SCD-PED-01 Study Schedule of Events

	Baseline	Hr 0-24	Hr 25-48	Hr 49-72	Hr 73-96	Hr 97-120	Hr 121-144	Hr 145-168	Therapy End
Vital Signs/Physical Assessment									
Temperature , Body Weight (baseline only)	X	X	X	X	X	X	X	X	
Blood Pressure (if no bp, MAP acceptable), Heart Rate	X	X	X	X	X	X	X	X	
PRISM II Score	X								
Physical Exam	X								
Urine Output (previous 24 hours)	X	X	X	X	X	X	X	X	
Net Fluid Balance (previous 24 hours)		X	X	X	X	X	X	X	
Sepsis	X								
ICU Percent Fluid Overload at CRRT Initiation	X								
Clinical Laboratory Testing									
CBC with differential	X	q12h	q12h	q12h	q12h	q12h	q12h	q12h	
BUN/Creatinine	X	X	X	X	X	X	X	X	
Na, K, Cl, HCO_3, Ca, Mg, PO_4, Ionized Calcium	X	X	X	X	X	X	X	X	
ALT, AST, Bilirubin, ALP, TP, Albumin, Glucose	X	X	X	X	X	X	X	X	
PT, PTT, INR	X	X	X	X	X	X	X	X	
Urinalysis (if urine is available)	X								
Respiratory									
Arterial Blood Gas (pH, PaO_2, $PaCO_2$) (if on vent)*	X	X	X	X	X	X	X	X	
Ventilator Settings (FiO_2,)	X	X	X	X	X	X	X	X	
Blood For Research									
Blood for Biomarkers	X		X(hr/48)		X(hr/96)		X(hr/144)		X
Extracorporeal Device Parameters									
CRRT (Settings- Event Driven)	X (hour 0)	X	X	X	X	X	X	X	
Post Filter Ionized Calcium	X (hour 0)	q1h until <0.40mmol/L; then q6h	q6h	q6h	q6h	q6h	q6h	q6h	
CRRT Device and SCD [redacted] Performance (Event Driven)		X	X	X	X	X	X	X	
SCD 24hr. Daily Change		X	X	X	X	X	X	X	
Other (Event-Driven)									
Adverse Events	X	X	X	X	X	X	X	X	X
Critical Medications, Blood products (yes/no) per Appendix J	X	X	X	X	X	X	X	X	X
Diagnosis/Therapeutic Procedures	X	X	X	X	X	X	X	X	X
Microbiology/culture data	X	X	X	X	X	X	X	X	

*Required only if the presence of an A-line; see **Section 6.3** and **Section 6.4** for details

APPENDIX G – SCD-PED-01 Study Schedule of Events: Follow-up Period

Day 1 - 5 or until ICU discharge (whichever occurs first unless otherwise specified)

Measurement	Hour 0 - 24	Hours 25 – 120[1]
Vital Signs/Physical Assessment		
Blood pressure, temperature, and heart rate	X	X
Physical Exam	X	
Urine Output (from previous 24 hours)	X	X
Net Fluid Balance – (from previous 24 hours)	X	X
Clinical Laboratory Tests		
CBC with differential	X	
BUN/Creatinine	X	
Na, K, Cl, HCO_3, Ca, Mg, PO_4, Ionized Calcium	X	
Respiratory:		
Arterial Blood Gas (pH, PaO_2, $PaCO_2$)	X	
Ventilator Settings (FiO_2)	X	X
Other(event driven)		
Renal Replacement Therapy status	X	X
Microbiology/Culture Data	X	X
Adverse Events	X	X
Serious Adverse Event	X	X
Antibacterial Medications (yes/no)	X	X

[1]Events listed in this column are to be performed once per 24 hour time period.

APPENDIX H – SCD-PED-01 Study Schedule of Events: Day 28 and Day 60

Measurement	Day 28[1]	Day 60[2]
Presence of mechanical ventilation (since last visit)	X	X
Presence of renal replacement therapy (since last visit)	X	X
Hospital and ICU Discharge information	X	X
Serious Adverse events (since last visit)	X	X
Serum Creatinine (if office visit takes place)	X	X

[1] This visit may be done via telephone call or office visit. Please record the above information on day 28 (+7 days) following enrollment.

[2] This visit may be done via telephone call or office visit. Please record the above information on day 60 (+7 days) following enrollment.

APPENDIX I – INFORMED CONSENT TEMPLATE

CHILD

A Multi-Center, Pilot Study To Assess the Safety and Efficacy of A Selective Cytopheretic Device (SCD) In Pediatric Patients with Acute Kidney Injury (SCD-PED-01)

INTRODUCTION

We are asking for your permission for your child to be in a research study so that we can learn new information that may help others. If you decide not to give your permission for your child to be in this study, we will still take good care of him/her. If you decide to allow your child to be in this study, you may change your mind at any time during the study and your child can stop being in the study. Take all the time you need to make your choice. Ask us any questions you have. It is also okay to ask more questions after you decide to allow your child to be in the study. You can ask questions at any time.

WHY ARE WE DOING THIS RESEARCH?

In this research study, we want to learn more about the effects of a new device which is similar to a dialysis filter used in the treatment of Acute Kidney Injury (AKI). Because of your child's kidney injury, continuous renal replacement therapy (CRRT) is being used to help your child's kidneys recover. This research involves using an investigational device or filter on the CRRT machine which is called a selective cytopheretic device (SCD). The SCD works by allowing cells that cause kidney injury to be desensitized, inactivated, or stopped from causing more harm.

We are asking your child and other children with AKI and requiring CRRT to be in the research, to understand the safety and effectiveness of the dialysis filter, selective cytopheretic device (SCD).

We are asking 30 children to participate in this research.

WHO IS IN CHARGE OF THE RESEARCH?

_____ is the researcher at _____ that is in charge of this study.

_____is being paid by the National Institutes of Health to do this study.

WHO SHOULD NOT BE IN THE STUDY

Your child cannot be in this study if he/she has any of the following:

- Older than 22 years old
- Not receiving care in an intensive care unit
- Pregnant or lactating
- Heart support devices like, LVAD, RVAD, BiVAD
- History of previous dialysis treatments during this admission
- History of End Stage Kidney Disease
- Severe chronic liver failure
- Cancer
- Chronic immunosuppression
- HIV or AIDS.
- Weight of less than 15kg (33 lbs.)
- Concurrent enrollment in another interventional clinical trial. Patients enrolled in clinical trials where only measurements and/or samples are taken are allowed to participate.
- Use of any other Investigational drug or device within the previous 30 days.

WHAT WILL HAPPEN IN THE STUDY?

The research staff will explain each visit to you. You will be able to ask questions to make sure you understand what will happen to your child.

These are the things that will happen to your child while in the study:

- CRRTas prescribed by your child's doctor with the addition of the SCD filter for up to 7 days
- SCD will be changed once every 24 hours (See below the description of SCD)
- Daily blood work for safety monitoring
- In addition to daily blood work, a blood sample for Complete Blood Count will be done daily in the evening from an existing catheter for safety monitoring (extra 1 mL/day)
- Every other day blood samples for biomarkers (for this and future research) drawn from an existing catheter (total amount 4 mL/during the study period)
- Data collection from your child's medical record for every day the SCD is used, and up to 60 days or discharge from the hospital.
- If your child still needs dialysis after 7 days, your child will be treated r per standard of care without the SCD filter as prescribed by your child's doctor.

The SCD is a synthetic membrane similar to filters used for hemodialysis to filter unwanted substances from the blood. The SCD will be connected to an existing CRRT circuit. Blood from the CRRT machine is flowed through the SCD, then returned back to the CRRT machine, and then returned back to the patient.

To keep the blood from forming clots in the circuit, a solution of citrate is put in the CRRT and SCD. Citrate is a medication that keeps blood from forming clots when the blood is outside the body. Citrate is used with CRRT as part of normal care at this hospital.

Future Research:
Researchers in this study are dedicated to researching biomarkers of kidney disease related to AKI. The data and blood samples collected during this study are important to this study and to future AKI research. With your additional consent, blood collected during this study will be kept in an outside laboratory for an indefinite period of time with samples from other children who have enrolled in this study. All identifying information will be removed from the samples. They will be identified only by a unique study number.

These samples may be used in the future in ongoing research related to biomarkers involved in AKI and other kidney conditions. They will only be studying kidney disease, which your child has already been diagnosed as having. They will not be researching non-kidney related disease.

These samples will be sent to an outside laboratory chosen by the sponsor, CytoPherx, Inc, but we will not give them any information that would personally identify your child. We will not put the results of any tests conducted on these samples in your child's medical record. Your child may still participate in this study even if you do not agree to participate in the sample repository.

WHAT ARE THE GOOD THINGS THAT CAN HAPPEN FROM THIS RESEARCH?

Being in this study may have potential benefit of improved outcome in terms of survival, improved blood pressure stability and a shorter ICU course; however, this cannot be guaranteed. Being in this study may not help your child right now.

When we finish the study, we hope that we will know more about the effects of the new dialysis filter on patients with AKI. The results from this study may help other children with AKI later on.

WHAT ARE THE BAD THINGS THAT CAN HAPPEN FROM THIS RESEARCH?

	Life Threatening	Serious	Mild
Common			General aching Skin rash Nausea Vomiting Low blood pressure Low white blood counts
Uncommon	Irregular heart rate	Infections Electrolyte disorders	Temperature Pain Confusion
Rare		Pneumonia Bleeding from low platelet count Low or high calcium levels	

There may be other risks that we do not know about yet.

WHAT OTHER CHOICES ARE THERE?

Instead of being in this study, you can choose not to have your child be in it. If you choose not to participate, your child will receive CRRT as standard of care.

HOW WILL INFORMATION ABOUT YOUR CHILD BE KEPT PRIVATE?

Making sure that information about your child remains private is important to us. To protect your child's privacy in this research study we will:

- Identifiable data will have limited access, only the appropriate study staff will have access.
- Store all study information in a locked cabinet or password protected file
- Enter de-identified data into a secure password protected system
- Ensure only appropriate study staff will have access to patient information

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This website will not include information that can identify your child. At most, the website will include a summary of the study results. You can search this website at any time.

The Food and Drug Administration (FDA) may choose to inspect your child's records since your child is a subject in this investigation of an unapproved drug/device**.**

WHAT IF WE LEARN NEW INFORMATION DURING THE RESEARCH?

You will be told of any new information that might affect your child's health, welfare, or willingness to allow your child to continue to take part in this study.

WILL IT COST YOU ANYTHING EXTRA FOR YOUR CHILD TO BE IN THE RESEARCH STUDY?

There will be no extra costs to you because your child is participating in this study. You or your child's health plan will pay for all the things you would have paid for even if you were not in the study, including the ICU stay, CRRT, and other hospital related health costs. The SCD study device will be provided at no cost to you or your health insurance provider.

WILL YOU/YOUR CHILD BE PAID TO BE IN THIS RESEARCH STUDY?

Your child will not be paid for participating in the study.

WHAT HAPPENS IF YOUR CHILD IS INJURED FROM BEING IN THIS STUDY?

If you believe that your child has been injured as a result of this research you should contact the Principal Investigator as soon as possible to discuss the concerns. Treatment for injuries is available at the study institution. If your child goes to the Emergency Room or to another hospital or doctor it is important that you tell them that your child is in a research study. If possible, you should give them a copy of this parental permission form.

The study institution follows a policy of making all decisions about compensation for the medical treatment of physical injuries that happened during or were caused by research on an individual basis.

WHO DO YOU CALL IF YOU HAVE QUESTIONS OR PROBLEMS?

For questions, concerns, or complaints about this research study you can contact the study person listed on page 1 of this document.

If you would like to talk to someone that is not part of the research staff or if you have general questions about your research study rights or questions, concerns, or complaints about the research, you can call the institution's Institutional Review Board at _____.

AUTHORIZATION FOR USE/DISCLOSURE OF HEALTH INFORMATION FOR RESEARCH

To be in this research study you must also give your permission (or authorization) to use

and disclose (or share) your child's "protected health information" (called PHI for short).

What protected health information will be used and shared during this study?
The study institution will need to use and share your child's PHI as part of this study. This PHI will come from:

- Your child's study institution medical records
- Your child's research records
- The types of information that will be used and shared from these records include:
- Laboratory test results, diagnosis, and medications
- Reports and notes from clinical and research observations
- Imaging (like CT scans, MRI scans, x-rays, etc.) studies and reports
- If applicable, information concerning HIV testing or the treatment of AIDS or AIDS-related conditions, drug or alcohol abuse, drug-related conditions, alcoholism, and/or psychiatric/psychological conditions (but not psychotherapy notes).

Who will share, receive and/or use your child's protected health information in this study?

- Staff at all the research study sites (including this study institution)
- Personnel who provide services to your child as part of this study
- Other individuals and organizations that need to use your child's PHI in connection with the research, including people at the sponsor and organizations that the sponsor may use to oversee or conduct the study.
- The members of the study institution's Institutional Review Board and staff of the Office of Research Compliance and Regulatory Affairs.

How will you know that your child's PHI is not misused?
People that receive your child's PHI as part of the research are generally limited in how they can use your child's PHI. In addition, most people who receive your child's PHI are also required by federal privacy laws to protect your child's PHI. However, some people that may receive your child's PHI may not be required to protect it and may share the information with others without your permission, if permitted by the laws that apply to them.

Can you change your mind?
You may choose to withdraw your permission at any time. A withdrawal of your permission to use and share your child's PHI would also include a withdrawal from participation in the research study. If you wish to withdraw your permission to use and share your child's PHI you need to notify the study doctor, listed on the first page of this document, in writing. Your request will be effective immediately and no new PHI about your child will be used or shared. The only exceptions are (1) any use or sharing of PHI that has already occurred or was in process prior to you withdrawing your permission and (2) any use or sharing that is needed to maintain the integrity of the research.

Will this permission expire?
Your permission will expire at the end of the study. If the study involves the creation or maintenance of a research database repository, this authorization will not expire.

Will your child's other medical care be impacted?
By signing this document you agree for your child to participate in this research study and give permission to this study institution to use and share your child's PHI for the purpose of this research study. If you refuse to sign this document your child will not be able to participate in the study. However, your child's rights concerning treatment not related to this study, payment for services, enrollment in a health plan or eligibility of benefits will not be affected.

SIGNATURES

[ ] _____ (check box and initial) I AGREE to allow my blood samples to be saved for future biomarker studies.

The research team has discussed this study with you and answered all of your questions. Like any research, the researchers cannot predict exactly what will happen. Once you have had enough time to consider whether your child should participate in this research you will document your permission by signature below.

You will receive a copy of this signed document for your records.

_____
Printed Name of Research Participant

_____ _____
Signature of Parent or Legally Authorized Representative* Date

_____
* If signed by a legally authorized representative,
a description of such representative's authority must be provided

_____ _____
Signature of Individual Obtaining Consent Date

ADULT

A Multi-Center, Pilot Study To Assess the Safety and Efficacy of A Selective Cytopheretic Device (SCD) In Pediatric Patients with Acute Kidney Injury (SCD-PED-01)

INTRODUCTION

We are asking for your permission to be in a research study so that we can learn new information that may help others. If you decide not to give your permission to be in this study, we will still take good care of you. If you decide to be in this study, you may change your mind at any time during the study and you can stop being in the study. Take all the time you need to make your choice. Ask us any questions you have. It is also okay to ask more questions after you decide to be in the study. You can ask questions at any time.

WHY ARE WE DOING THIS RESEARCH?

In this research study, we want to learn more about the effects of a new device which is similar to a dialysis filter used in the treatment of Acute Kidney Injury (AKI). Because of your kidney injury, continuous renal replacement therapy (CRRT) is being used to help your kidneys recover. This research involves using an investigational device or filter on the CRRT machine which is called a selective cytopheretic device (SCD). The SCD works by allowing cells that cause kidney injury to be desensitized, inactivated, or stopped from causing more harm.

We are asking you and other people with AKI and requiring CRRT to be in the research, to understand the safety and effectiveness of the dialysis filter, the selective cytopheretic device (SCD).

We are asking 30 people to participate in this research.

WHO IS IN CHARGE OF THE RESEARCH?

_____ is the researcher at _____ that is in charge of this study.

_____is being paid by the National Institutes of Health to do this study.

WHO SHOULD NOT BE IN THE STUDY

You cannot be in this study if you have any of the following:

- Older than 22 years old
- Not receiving care in an intensive care unit
- Pregnant or lactating
- Heart support devices like LVAD, RVAD, BiVAD
- History of previous dialysis treatments during this admission
- History of End Stage Kidney Disease
- Severe chronic liver failure
- Cancer
- Chronic immunosuppression
- HIV or AIDS.
- Weight of less than 15kg (33 lbs.)
- Concurrent enrollment in another interventional clinical trial. Patients enrolled in clinical trials where only measurements and/or samples are taken are allowed to participate.
- Use of any other Investigational drug or device within the previous 30 days.

WHAT WILL HAPPEN IN THE STUDY?

The research staff will explain each visit to you. You will be able to ask questions to make sure you understand what will happen to you.

These are the things that will happen to you while in the study:

- CRRT as prescribed by your doctor with the addition of the SCD filter for up to 7 days
- SCD will be changed once every 24 hours (See below the description of SCD)
- Daily blood work for safety monitoring
- In addition to daily blood work, a blood sample for Complete Blood Count will be done daily in the evening from an existing catheter for safety monitoring (extra 1 mL/day)
- Every other day blood samples for biomarkers (for this and future research) drawn from an existing catheter (total amount 4 mL/during the study period)
- Data collection from your medical record for every day the SCD is used and up to 60 days or discharge from the hospital.
- If you still need dialysis after 7 days, you will be treated per standard of care without the SCD filter as prescribed by your doctor.

The SCD is a synthetic membrane similar to filters used for hemodialysis to filter unwanted substances from the blood. The SCD will be connected to an existing CRRT circuit. Blood from the CRRT machine is flowed through the SCD, then returned back to the CRRT machine, and then returned back to the patient.

To keep the blood from forming clots in the circuit, a solution of citrate is put in the CRRT and SCD. Citrate is a medication that keeps blood from forming clots when the blood is outside the body. Citrate is used with CRRT as part of normal care at this hospital.

Future Research:
Researchers in this study are dedicated to researching biomarkers of kidney disease related to AKI. The data and blood samples collected during this study are important to this study and to future AKI research. With your additional consent, blood collected during this study will be kept in an outside laboratory for an indefinite period of time with samples from other patients who have enrolled in this study. All identifying information will be removed from the samples. They will be identified only by a unique study number.

These samples may be used in the future in ongoing research related to biomarkers involved in AKI and other kidney conditions. They will only be studying kidney disease, which you have already been diagnosed as having. They will not be researching non-kidney related disease.

These samples will be sent to an outside laboratory chosen by the sponsor, CytoPherx, Inc, but we will not give them any information that would personally identify you. We will not put the results of any tests conducted on these samples in your medical record. You may still participate in this study even if you do not agree to participate in the sample repository.

WHAT ARE THE GOOD THINGS THAT CAN HAPPEN FROM THIS RESEARCH?

Being in this study may have potential benefit of improved outcome in terms of survival, improved blood pressure stability and a shorter ICU course; however, this cannot be guaranteed. Being in this study may not help you right now.

When we finish the study, we hope that we will know more about the effects of the new dialysis filter on patients with AKI. The results from this study may help other people with AKI later on.

WHAT ARE THE BAD THINGS THAT CAN HAPPEN FROM THIS RESEARCH?

	Life Threatening	Serious	Mild
Common			General aching Skin rash Nausea Vomiting Low blood pressure Low white blood counts
Uncommon	Irregular heart rate	Infections Electrolyte disorders	Temperature Pain Confusion
Rare		Pneumonia Bleeding from low platelet count Low or high calcium levels	

There may be other risks that we do not know about yet.

WHAT OTHER CHOICES ARE THERE?

Instead of being in this study, you can choose not to participate in it. If you choose not to participate, you will receive CRRT as standard of care.

HOW WILL INFORMATION ABOUT YOU BE KEPT PRIVATE?

Making sure that information about you remains private is important to us. To protect your privacy in this research study we will:

- Identifiable data will have limited access, only the appropriate study staff will have access.
- Store all study information in a locked cabinet or password protected file
- Enter the-identified data into a secure password protected system
- Ensure only appropriate study staff will have access to patient information

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This website will not include information that can identify you. At most, the website will include a summary of the study results. You can search this website at any time.

The Food and Drug Administration (FDA) may choose to inspect your records since you are a subject in this investigation of an unapproved drug/device**.**

WHAT IF WE LEARN NEW INFORMATION DURING THE RESEARCH?

You will be told of any new information that might affect your health, welfare, or willingness to continue to take part in this study.

WILL IT COST YOU ANYTHING EXTRA TO BE IN THE RESEARCH STUDY?

There will be no extra costs to you to participate in this study. Your health plan will pay for all the things you would have paid for even if you were not in the study, including the ICU stay, CRRT, and other hospital related health costs. The SCD study device will be provided at no cost to you or your health insurance provider.

WILL YOU BE PAID TO BE IN THIS RESEARCH STUDY?

You will not be paid for participating in the study.

WHAT HAPPENS IF YOU ARE INJURED FROM BEING IN THIS STUDY?

If you believe that you have been injured as a result of this research you should contact the Principal Investigator as soon as possible to discuss the concerns. Treatment for injuries is available at the study institution. If you go to the Emergency Room or to another hospital or doctor it is important that you tell them that you are in a research study. If possible, you should give them a copy of this permission form.

The study institution follows a policy of making all decisions about compensation for the medical treatment of physical injuries that happened during or were caused by research on an individual basis.

WHO DO YOU CALL IF YOU HAVE QUESTIONS OR PROBLEMS?

For questions, concerns, or complaints about this research study you can contact the study person listed on page 1 of this document.

If you would like to talk to someone that is not part of the research staff, or if you have general questions about your research study rights or questions, concerns or complaints about the research, you can call the institution's Institutional Review Board at _____.

AUTHORIZATION FOR USE/DISCLOSURE OF HEALTH INFORMATION FOR RESEARCH

To be in this research study you must also give your permission (or authorization) to use and disclose (or share) your "protected health information" (called PHI for short).

What protected health information will be used and shared during this study?
The study institution will need to use and share your PHI as part of this study. This PHI will come from:

- Your study institution medical records
- Your research records
- The types of information that will be used and shared from these records include:
- Laboratory test results, diagnosis, and medications
- Reports and notes from clinical and research observations
- Imaging (like CT scans, MRI scans, x-rays, etc.) studies and reports
- If applicable, information concerning HIV testing or the treatment of AIDS or AIDS-related conditions, drug or alcohol abuse, drug-related conditions, alcoholism, and/or psychiatric/psychological conditions (but not psychotherapy notes).

Who will share, receive and/or use your protected health information in this study?

- Staff at all the research study sites (including this study institution)
- Personnel who provide services to you as part of this study
- Other individuals and organizations that need to use your PHI in connection with the research, including people at the sponsor and organizations that the sponsor may use to oversee or conduct the study.
- The members of the study institution's Institutional Review Board and staff of the Office of Research Compliance and Regulatory Affairs.

How will you know that your PHI is not misused?
People that receive your PHI as part of the research are generally limited in how they can use your PHI. In addition, most people who receive your PHI are also required by federal privacy laws to protect your PHI. However, some people that may receive your PHI may not be required to protect it and may share the information with others without your permission, if permitted by the laws that apply to them.

Can you change your mind?
You may choose to withdraw your permission at any time. A withdrawal of your permission to use and share your PHI would also include a withdrawal from participation in the research study. If you wish to withdraw your permission to use and share your PHI you need to notify the study doctor, listed on the first page of this document, in writing. Your request will be effective immediately and no new PHI about you will be used or shared. The only exceptions are (1) any use or sharing of PHI that has already occurred or was in process prior to you withdrawing your permission and (2) any use or sharing that is needed to maintain the integrity of the research.

Will this permission expire?
Your permission will expire at the end of the study. If the study involves the creation or maintenance of a research database repository, this authorization will not expire.

Will your other medical care be impacted?
By signing this document you agree to participate in this research study and give

permission to this study institution to use and share your PHI for the purpose of this research study. If you refuse to sign this document you will not be able to participate in the study. However, your rights concerning treatment not related to this study, payment for services, enrollment in a health plan or eligibility of benefits will not be affected.

SIGNATURES

[ ] _____ (check box and initial) I AGREE to allow my blood samples to be saved for future biomarker studies.

The research team has discussed this study with you and answered all of your questions. Like any research, the researchers cannot predict exactly what will happen. Once you have had enough time to consider whether you should participate in this research you will document your permission by signature below.

You will receive a copy of this signed document for your records.

_____
Printed Name of Research Participant

_____ _____
Signature of Research Participant or Legally Authorized Representative* Date

_____
* If signed by a legally authorized representative,
a description of such representative's authority must be provided

_____ _____
Signature of Individual Obtaining Consent Date

APPENDIX J – CRITICAL MEDICATION LIST

The following is a list of medication categories (with examples) to be acknowledged (yes/no) in the Case Report Forms if administered to the patient during the SCD-PED-01 Clinical Trial (starting at 24 hours prior to Observation until 168 hours of treatment or ICU discharge, whichever comes first. Only antibacterial use is captured during follow-up period.

ANTIBACTERIALS FOR SYSTEMIC USE

Ampicillin	Ceftazidime	Moxifloxacin
Azithromycin	Ciprofloxacin	Nafcillin
Aztreonam	Ciprofloxacin hydrochloride	Piperacillin
Bactrim (Sulfamethoxazole, Trimethoprim)	Clindamycin	Piperacillin w/tazobactam (Piperacillin, Tazobactam)
Cefadroxil	Daptomycin	Synercid (Dalfopristin,Quinupristin)
Cefalexin	Doripenem	Tigecycline
Cefazolin	Erythromycin	Tobramycin
Cefazolin sodium	Gentamicin	Vancomycin
Cefepime	Levofloxacin	
Cefepime hydrochloride	Linezolid	
Cefoxitin	Meropenem	
	Metronidazole	

ANTIMYCOTICS FOR SYSTEMIC USE

Amphotericin b, liposome	Fluconazole
Caspofungin	Micafungin

ANTITHROMBOTIC AGENTS

Acetylsalicylic acid	Clopidogrel	Enoxaparin sodium
Argatroban	Drotrecogin alfa	Heparin
Bivalirudin	Enoxaparin	Warfarin sodium

BLOOD SUBSTITUTES

Albumin	Albumin human	Blood, whole
Cryoprecipitate	Red blood cells	
Plasma	Red blood cells, leucocyte depleted	
Platelets		

VASOPRESSORS

Dobutamine	Norepinephrine	Phenylephrine hydrochloride
Dopamine	Norepinephrine bitartrate	Vasopressin
Epinephrine	Phenylephrine	
Milrinone		

APPENDIX K – CRRT PRESCRIPTION GUIDELINE and REGIONAL CITRATE ANTICOAGULATION (RCA) PROTOCOL EXAMPLE

1. **Purpose**: The purpose of the guidelines is to standardize, to the extent possible, the provision of CRRT to patients who require CRRT. While these guidelines should govern the CRRT prescription provided to most patients, there will be special circumstances (e.g. inborn errors of metabolism, exogenous toxin removal) that will require deviation from these guidelines.

2. **Modality:** CRRT will be prescribed as continuous veno-venous hemodiafiltration (CVVHDF). A total minimum small solute clearance of 2000 ml/min/1.73m^2 will be prescribed. The clearance will be divided equally between dialysis and hemofiltration as follows:
    a. 50% as dialysis fluid using Prismasate™ via the dialysis pump
    b. 50% as replacement fluid divided between pre-replacement and post-replacement as follows:
        i. 50 ml/hour as post-filter replacement fluid via the replacement fluid pump using (Prismasol™). This is necessary to prevent clotting of the deaeration chamber (50 ml/hour is the lowest allowable rate)
        ii. The remaining fluid rate (total replacement fluid rate – 50 ml/hour) pre-filter replacement fluid via the pre-blood pump (PBP) using Prismasol™.
    c. The composition of Prismasate™ and Prismasol™ should be equivalent. Any additives (e.g. potassium chloride) should be added in equivalent concentrations to both dialysis and replacement solutions.

3. **Regional citrate anticoagulation:** All CRRT circuits will receive regional citrate anticoagulation. The initial prescription and calcium level monitoring will be based on the size of patients and the presence, or lack thereof, of significant hepatic dysfunction. **REMEMBER TO ACCOUNT FOR THESE FLUIDS IN THE PATIENT REMOVAL RATE AS THESE ARE EXTERNAL TO THE CRRT MACHINE.**
    a. **Patients > 1 year of age and with normal hepatic function:**
        i. Order ACD-A™ and $CaCl_2$ (8 grams/1 liter NS) to bedside
        ii. Initial ACD-A™ rate = 1.5 x CRRT blood pump rate x min/hour (e.g., f blood pump rate is 100 ml/minute; the ACD-A™ rate is 150 ml/hour). This is to be infused at a stopcock or y-connector on access line.
        iii. Initial $CaCl_2$ rate = 0.6 x blood pump rate x min/hour (e.g., if blood pump rate is 100 ml/minute; the $CaCl_2$ rate is 60 ml/hour).
        iv. Calcium monitoring schedule
            1. Check patient total and ionized calcium prior to CRRT initiation.
            2. Check patient and system ionized calcium 5 minutes after CRRT settings at prescribed rates.
            3. Check patient and system ionized calcium 2 hours after CRRT settings at prescribed rates.
            4. Check patient and system ionized calcium every 8 hours thereafter
            5. Check patient total calcium daily
            6. Check patient and system ionized calcium one hour after any change in ACD-A™ or $CaCl_2$ rate
    b. **Desired Calcium Concentration ranges**
        i. Circuit ionized calcium = 0.25 to 0.40 mmol/L
        ii. Patient ionized calcium = 1.1 to 1.3 mmol/L (a higher level may be requested by ICU/CICU service if clinically indicated)
        iii. Patient systemic calcium = 8 to 12 mg/dL
    c. **Citrate anticoagulation management**
        i. Bedside RN to call for patient ionCa < 1 mmol/L or >1.5 mmol/L, or circuit ionCa < 0.25 mmol/L or > 0.40 mmol/L
        ii. Circuit ionCa managed with ACD-A™ rate
            1. For circuit ionCa < 0.25 mmol/L, decrease ACD-A™ 10%
            2. For circuit ionCa > 0.40 mmol/L, increase ACD-A™ 10%
        iii. Patient ionCa managed by $CaCl_2$ rate
            1. For patient ionCa < 0.9, increase $CaCl_2$ 20%
            2. For patient ionCa 0.9- 1, increase $CaCl_2$ 10%

3. For patient ion Ca 1.3-1.5, decrease $CaCl_2$ 10%
4. For patient ion Ca> 1.5, decrease $CaCl_2$ 20%

4. **Access Size: (per clinical investigator decision)**

5. **Blood pump flow rate: The minimum blood pump flow rate should be 50 ml/minute to prevent circuit clotting unless not clinically tolerated:**
   a. Neonate/Infants – 8 to12 ml/kg/minute
   b. Toddlers – 6 to 8 ml/kg/minute
   c. Older children and adolescents– 3-6 ml/kg/minute

6. **3-hour Fluid Balance Safety Limit: Limits set to prevent < 5% of blood volume error over 3 hours for smaller patients and <10% over three hours for larger patients**
   a. Patients < 30 kg – 150 ml
   b. Patients 30-50 kg – 200 ml
   c. Patients > 50 kg – 300 ml

7. **Scheduled circuit changes: Circuits should be changed no later than every 72 hours, as this is the maximum interval at which the machine has been tested by the manufacturer for accuracy. Any diversion from this recommendation must have rationale documented in the medical record. The following situations serve as examples:**
   a. The patient has a do not resuscitate or do not escalate care order that was placed on the chart while the patient is receiving CRRT.
   b. The patient is so clinically unstable that the patient will likely not tolerate stopping and restarting CRRT.

8. **Blood priming at CRRT initiation and blood return at CRRT termination**
   a. Blood priming of the CRRT circuit should be done if the extracorporeal volume of the circuit is > 10% of the patient's blood volume.
   b. Blood should not be returned to the patient at CRRT termination when circuits are blood primed unless specifically requested by the physician in a separate order.

APPENDIX L – SCD/CRRT BLOOD PRIMING PROTOCOL

Prismaflex HF1000

The blood volume for the Prismaflex HF1000 is 165 ml and for the SCD is 120 ml, leading to a total extracorporeal circuit volume (ECV) is 285 ml. Blood prime will occur if the ECV total is greater than 10% of the patient's blood volume, based on an estimate of blood volume = 70 ml/kg x patient body weight (kg) [24]. As such, there are three patient weight ranges that will dictate the need, or lack thereof for blood priming:

Patient weight (kg)	Total Blood Volume	Blood Prime Need: HF1000
>40 kg	>2800 ml	None (a)
24-40 kg	1680-2800 ml	HF1000 alone (b)
15-24 kg	1050-1680 ml	HF1000+SCD (c)

This additional circuit blood volume for the standard SCD in 24-40 kg patients can be handled with blood priming with matched blood similar to the standard practice in neonates. The situation is most commonly encountered in neonatal CRRT, where circuit ECV can represent nearly 50% of patient blood volume, yet the same principles apply for this clinical study. [25]

Renaflo HF 400, HF 700, and HF 1200

The following tables display the same breakdown of blood prime need by weight for the extracorporeal blood volume of the Renaflo HF 400, HF 700, and HF 1200.

Renaflow HF 400

Renaflo HF 400 ECV 28ml + Braun Tubing ECV 156ml + SCD ECV 120ml = 304ml Total ECV

Patient Weight (kg)	Total Blood Volume	Blood Prime Need: HF 400
>43 kg	>3010 ml	None (a)
26 – 43 kg	1820 – 3010 ml	HF400 alone (b)
15 – 26 kg	1050 – 1820 ml	HF400 + SCD (c)

Renaflow HF 700

Renaflo HF 700 ECV 53ml + Braun Tubing ECV 156ml + SCD ECV 120ml = 329ml Total ECV

Patient Weight (kg)	Total Blood Volume	Blood Prime Need: HF 700
>47 kg	>3290 ml	None (a)
30 – 50 kg	2100 – 3290 ml	HF700 alone (b)
15 – 30 kg	1050 – 2100 ml	HF700 + SCD (c)

Renaflow HF 1200

Renaflo HF1200 ECV 83ml + Braun Tubing ECV 156ml + SCD ECV 120ml = 359ml Total ECV

Patient Weight (kg)	Total Blood Volume	Blood Prime Need: HF 1200
>51 kg	>3570 ml	None (a)
34 – 51 kg	2380 – 3570 ml	HF1200 alone (b)
15 – 34 kg	1050 – 2380 ml	HF1200 + SCD (c)

Investigators should use the reference letters in the third column (i.e. a, b, or c) to determine the blood prime protocol in the text below.

a) For patients >40 kg: The blood volume for this patient population is >2800 ml, so the HF1000 plus the SCD represents <10% of the patient blood volume. Thus, for patients >40 kg:

   i. The initial and all new CRRT circuits will be not primed with blood but with crystalloid or other fluid that is the local standard of care.
   ii. For daily SCD filter changes (not associated with a CRRT circuit change), a new crystalloid primed SCD will be placed in line with the CRRT circuit without need for blood priming.
   iii. The investigator can prime with blood or other colloid if they believe it is clinically indicated.

b) For patients >24-40 kg: The blood volume for this patient population is >1680-2800 ml, thus the SCD alone represents <10% of the patient blood volume, but the ECV of the SCD and any CRRT circuit will comprise >10% of the total patient blood volume. Thus, for patients >24 kg:

   i. The initial and all new CRRT circuits will be primed with blood per the local standard of care protocol.
   ii. For initial and daily SCD filter changes (not associated with a CRRT circuit change), a new crystalloid primed SCD will be placed in line with the CRRT circuit without need for blood priming.

iii. The investigator can prime the SCD with blood or other colloid if they believe it is clinically indicated.

c) For patients 15-24 kg: The blood volume for this population is <1680 ml, thus the HF1000 + SCD ECV represents >10% for the entire range of patient weight from 15-24 kg. Thus, for patients with a weight of 15-24 kg:

i. A crystalloid primed SCD circuit will be placed in line with a crystalloid primed CRRT circuit. For the initial CRRT/SCD circuit, the entire CRRT + SCD circuit will then be primed with blood per local standard of care prior to initiating CRRT /SCD therapy with the patient. Given the relatively large blood ECV to patient size in this group, the following patient lab parameters should be achieved prior to initiating CRRT/SCD therapy to prevent severe acidosis or hypocalcemia
   a. Patient pH of at least 7.20
   b. Patient ionized calcium of at least 1.1 mmol/L

ii. Patient should be given calcium gluconate IV (at least 300 mg) at the start of CRRT/SCD therapy.
   a. An equivalent about of IV calcium can be given in a different formulation (ex. 100 mg of IV calcium chloride).

iii. Once the CRRT+SCD therapy is initiated, patient ionized calcium and pH should be obtained no later than 15 minutes after achievement of final CRRT blood flow and effluent rates.

iv. For the daily SCD circuit change, one of two options will be available:
   a. A completely new CRRT circuit can be used with the SCD circuit with a repeat of the procedure in the paragraph above
   b. A circuit to circuit prime can be performed per local standard of care whereby the blood in the previous CRRT + SCD circuit is used to prime a new CRRT + SCD circuit

APPENDIX M – PLACEMENT OF SCD IN CRRT / ECMO CIRCUIT