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# Biobehavioral Relationships and Health Related Quality of Life in Persons with End Stage Renal Disease on Hemodialysis

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**Biobehavioral Relationships and Health Related Quality of Life in  
Persons with End Stage Renal Disease on Hemodialysis**

by

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A dissertation research report submitted in partial fulfillment of the requirements  
for the degree of Doctor of Philosophy at Virginia Commonwealth University.

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## **Abstract**

Biobehavioral Relationships and Health Related Quality of Life in Persons

with End Stage Renal Disease on Hemodialysis

By Avis K. Allen, PhD, RN

Director: Nancy L. McCain, DSN, RN, FAAN, Professor

A dissertation submitted in partial fulfillment of the requirements for the degree of

Doctor of Philosophy at Virginia Commonwealth University

Virginia Commonwealth University, 2011

The study of immune status and biobehavioral measures is limited in professional nursing. The purpose of the pre-pilot study was to describe levels of cytokines prior to, during, and after dialysis, examine changes in cytokine levels from immediate pre-dialysis to immediate post-dialysis, and to compare cytokine patterns prior to and after dialysis.

A within subject descriptive study was conducted as part of a larger pilot study to describe levels of cytokines prior to, during, and after dialysis, examine changes in cytokine levels from immediate pre-dialysis to immediate post-dialysis, and to compare cytokine patterns prior to and after dialysis. Serum cytokine samples were collected pre-dialysis and every 30 minutes during the dialysis treatment and immediately post-dialysis from a convenience sample of 10 patients. Mean age of subjects was 53.5 years and 60% were African American. The sample was equally divided between female and male. Statistical analysis using a nonparametric



paired difference test showed that only MIP-1 $\beta$  showed a significant increase from pre-dialysis to post-dialysis. Based on the results of this study, a second descriptive study was conducted.

The purpose of the second study was to examine the relationships among disease related factors, perceived stress, depressive symptoms, immune indicators, and HRQOL among patients requiring hemodialysis for ESRD using a PNI framework. Using a descriptive design, participants completed the Perceived Stress Scale (PSS), the Center for Epidemiologic Studies Depression Scale (CES-D), and one quality of life measure, the Functional Assessment of Cancer Therapy-General scale (FACT-G), during the first hour of the dialysis treatment. In addition, blood samples were collected immediately prior to dialysis for cytokine measurement and demographic information was collected from the medical record.

The sample included 75 adults with ESRD requiring dialysis who consented and were enrolled in the study. Regression analysis showed significant correlations among the psychosocial variables ( $p = <0.0001$ ,  $r = 0.65$ ). Negative correlations were found between perceived stress and health-related quality of life ( $p = 0.024$ ) and depressive symptoms with health-related quality of life ( $p = 0.0003$ ). MIP-1  $\beta$  was the only cytokine significantly (and positively) correlated with health-related quality of life ( $p = 0.0419$ ). Principal component analysis of the cytokine data revealed three factors. A three-factor solution described the cytokine data; Factors 1 and 3 represented a pro-inflammatory response and Factor 2 represented a mixture of pro-inflammatory and anti-inflammatory responses. There was a significant correlation between Factor 1 and depressive symptoms ( $p = 0.0069$ ). Significant differences in the distributions of Factors 2 and 3 were associated with the presence of cardiovascular disease (CVD) (Chi-square = 4.0,  $df = 1$ ,  $p = 0.047$ ), (Chi-square = 4.1,  $df = 1$ ,  $p = 0.043$ ), respectively, and Factor 3 with hypertension (HTN) (Chi-square = 7.6,  $df = 1$ ,  $p = 0.006$ ). However no

relationships were found between the cytokine factors and QOL, PSS, and other variables.

Findings suggest that there are relationships among psychosocial variables and possibly

biological interactions that may affect perceptions of health-related quality of life among persons

with ESRD on hemodialysis.

## CHAPTER 1: Overview

End Stage Renal Disease (ESRD) is a chronic disease that creates both physical and psychological stressors (Kring & Crane, 2005; Tsay, Lee, & Lee, 2005). Factors associated with renal failure, the accumulation of uremic toxins, and the dialysis treatment itself can produce a chronic inflammatory state in patients on hemodialysis (Piroddi et al., 2007). Heart rate and blood pressure, natural killer cell activity, and the concentration of some lymphocytes increase during acute stress (Glaser & Kiecolt-Glaser, 2005), assisting the body to cope with the stressor. Physiologic measures normally return to equilibrium or allostasis over time. However, in ESRD return to equilibrium is inhibited, leading to an internal state of chronic stress (Cukor, Cohen, Peterson & Kimmel, 2007). Chronic stress can lead to disorders of the body (McEwen, 2008). In dialysis patients elevated pro-inflammatory cytokine levels, particularly IL-6 and C-reactive protein (CRP) have been implicated in vascular disease events and mortality (Cazzavillan, et al., 2007; Lentine, Parsonnet, Taylor, Wrone, & Lafayette, 2006), as well as malnutrition (Ibrahim & Salamony, 2008; Koo, et al., 2003). Psychological changes have been connected to cytokine levels as well, resulting in depression and decreased quality of life (Dervisoglu, Kir, Kalender, Eraldemir, & Caglayan, 2007). Snaedal et al. (2009) reported finding a correlation between comorbidity and IL-6, supporting the theory that IL-6 is a strong predictor of cardiovascular disease. Studies measuring cytokine levels during hemodialysis have reported conflicting results and few studies examined large numbers of cytokines. However, elevated levels of cytokines have been reported in hemodialysis patients (Cazzavillan, et al., 2007; Ibrahim & Salamony, 2008; Sertic et al., 2007). There have been no known studies that measured a full panel of cytokines throughout the dialysis treatment.

Perceived stress, immune functioning, depressive symptoms, and disease-related factors can affect the health-related quality of life (HRQOL) of patients on hemodialysis. Health-related quality of life (HRQOL) remains lower and mortality rates remain higher for patients with ESRD than for the general population. Research indicates that hemodialysis patients with lower HRQOL were at higher risk of hospitalization and death (Mapes et al., 2003). Depression is the most common psychological problem reported by hemodialysis patients (Lopes et al., 2004) and has been linked with various health problems, including cardiovascular disease and malnutrition-inflammation complex (Cukor, Cohen, Peterson, & Kimmel, 2007; Ibrahim & Salamony, 2008; Koo et al., 2003). Stressors negatively affect the HRQOL of patients and can lead to depression and increased morbidity and mortality (Kimmel & Peterson, 2006; Ye et al., 2008).

ESRD changes the immune system in ways that are not completely understood. In summary, there appear to be correlations between perceived stress, immune functioning, depressive symptoms, and HRQOL, but the nature of such relationships is not well documented. All of these factors contribute to long-term outcomes for patients with ESRD. With mortality rates of greater than 20%, increased understanding of these relationships is important in order to develop biobehavioral interventions to improve outcomes. Psychoneuroimmunology (PNI) is the study of the interaction of the central nervous system (CNS), endocrine system, and immune system (Yang & Glaser, 2002). The PNI framework explains the physical and psychobehavioral interactions that affect the immune system (McCain, Gray, Walter, & Robins, 2005). For example, behavioral factors are believed to moderate the immune system through neuroendocrine system changes. PNI is a comprehensive model incorporating individual, environmental, physiological and spiritual factors and effectively grounds both qualitative and quantitative methods.

A within-subject descriptive study was conducted as part of a larger pilot study to describe levels of cytokines prior to, during, and after dialysis, examine changes in cytokine levels from immediate pre-dialysis to immediate post-dialysis, and to compare cytokine patterns prior to and after dialysis. Serum cytokine samples were collected pre-dialysis and every 30 minutes during the dialysis treatment and immediately post-dialysis from a convenience sample of 10 patients. Mean age of participants was 53.5 years and 60% were African American. The sample was equally divided between females and males. Statistical analysis using a nonparametric paired difference test showed that only MIP-1 $\beta$  significantly increased from pre-dialysis to post-dialysis.

The purpose of the second study was to examine the relationships among disease-related factors, perceived stress, depressive symptoms, immune indicators, and HRQOL among patients requiring hemodialysis for ESRD using a PNI framework. The study utilized a cross-sectional design to investigate factors potentially associated with the stress of undergoing hemodialysis. Few studies have addressed these factors measured simultaneously and viewed from an integrated, holistic perspective.

The sample was predominantly Black (75.7%) and male (65%) with a mean age of 53.9 (range 23-83). Mean time that participants had been on dialysis was 3.0 years with a range of less than 1 month to 20.8 years. Most had been diagnosed with hypertension (85%) and diabetes (59%). Mean levels of perceived stress were 15.9 ( $SD = 8.0$ ), levels of depressive symptoms were 16.2 ( $SD = 12.7$ ), and levels of HRQL were 68.1 ( $SD = 14.2$ ). Regression analysis showed significant correlations among the psychosocial variables ( $p = <0.0001$ ,  $r = 0.65$ ). Negative correlations were found between perceived stress and health-related quality of life ( $p = 0.024$ ) and depressive symptoms with health-related quality of life ( $p = 0.0003$ ). MIP-1 $\beta$  was the only cytokine significantly (and positively) correlated with health-related quality of life ( $p = 0.0419$ ). Principal component analysis of the log-transformed cytokine data

revealed three factors: Factors 1 and 3 represented a pro-inflammatory cytokine pattern and Factor 2 represented a mixture of pro-inflammatory and anti-inflammatory cytokines. A one-way analysis of variance (ANOVA) revealed a significant correlation ( $p = 0.0069$ ) between Factor 1 and depressive symptoms. Significant differences in the distributions of Factors 2 and 3 were associated with the presence of cardiovascular disease (CVD) (Chi-square = 4.0,  $df = 1$ ,  $p = 0.047$ ), (Chi-square = 4.1,  $df = 1$ ,  $p = 0.043$ ), respectively, and Factor 3 with hypertension (HTN) (Chi-square = 7.6,  $df = 1$ ,  $p = 0.006$ ). However no relationships were found between the cytokine factors and QOL, PSS, and other variables. Study findings suggest that there are relationships among psychosocial variables and possibly biological interactions that may affect persons with ESRD on hemodialysis perceptions' of health-related quality of life. Further studies with larger sample could provide direction for evaluating the relationship between stress, depressive symptoms, immune functioning and HRQOL. Larger studies could provide guidance toward interventions to improve HRQOL for patients on hemodialysis for ESRD.

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## **CHAPTER 2: Cytokine Patterns during Hemodialysis**

### **Abstract**

The study of immune status and biobehavioral measures is limited in professional nursing. The purpose of the pre-pilot study was to describe levels of cytokines prior to, during, and after dialysis, examine changes in cytokine levels from immediate pre-dialysis to immediate post-dialysis, and to compare cytokine patterns prior to and after dialysis.

A within subject descriptive study was conducted as part of a larger pilot study to describe levels of cytokines prior to, during, and after dialysis, examine changes in cytokine levels from immediate pre-dialysis to immediate post-dialysis, and to compare cytokine patterns prior to and after dialysis. Serum cytokine samples were collected pre-dialysis and every 30 minutes during the dialysis treatment and immediately post-dialysis from a convenience sample of 10 patients. Mean age of subjects was 53.5 years and 60% were African American. The sample was equally divided between female and male. Statistical analysis using a nonparametric paired difference test showed that only MIP-1 $\beta$  showed a significant increase from pre-dialysis to post-dialysis.

## **Cytokine Patterns during Hemodialysis**

End Stage Renal Disease (ESRD) is a chronic disease that creates both physical and psychological stressors including fatigue, muscle cramps, hypotension, diet and fluid restrictions, and physical limitations (Gurklis & Menke, 1995; Tsay, Lee, & Lee, 2005; Welch & Austin, 2001). Factors associated with renal failure and the accumulation of uremic toxins and factors associated with the dialysis treatment itself can produce a chronic inflammatory state in dialysis patients. The kidneys help regulate pro-inflammatory and pro-oxidant factors through clearance, however the dialysis procedure does not completely replace the functions of the kidney (Piroddi et al., 2007). Furthermore, impaired lymphocyte function is a result of both the uremic state and dialysis therapy. Lymphocyte subsets and monocytes change into pro-inflammatory phenotypes, resulting in an overproduction of cytokines. Elevated levels of IL-6, in particular are associated with cardiovascular disease, malnutrition and muscle wasting in ESRD patients (Piroddi et al., 2007). Dialysis-dependent factors associated with inflammation include bioincompatibility of the dialyzer, exposure to bacterial contamination due to dialysis fluid contamination, and use of drugs such as iron and erythropoietin.

### **Cytokines in End-Stage Renal Disease**

Research studies about cytokine patterns during hemodialysis treatment have primarily focused on investigating the relationship between complement activation and dialyzer membranes. Dialyzer membranes have been shown to activate the complement system, particularly the early membranes made with bioincompatible materials such as cuprophan (Andreoli et al., 2007; Grooteman et al., 1995; Lee, Hakim, and Fearon, 1984; Lonnemann, Koch, Shaldon, and Dinarello, 1988; Varela et al., 2001). Lonnemann et al. (1988) hypothesized that monocytes adhering to the membrane were exposed to endotoxins and C5a from dialysate,

inducing IL-1 production, causing a response similar to an acute phase response. Sertic et al. (2007) reported that levels of IL-6, IL-8, IL-10, TNF- $\alpha$ , IL-1 $\beta$ , and MCP-1 were significantly higher in chronic hemodialysis patients compared to healthy control subjects.

Varela et al. (2001) investigated circulating levels of IL-1 $\beta$ , IL-2, C3a and C5a before and after, and at 15, 30, and 50 minutes during a dialysis treatment with one of three randomly assigned dialyzers. Levels of IL-1 $\beta$  increased from before to after dialysis in all three groups but varied in the amount of increase seen, suggesting that IL-1 $\beta$  was a good marker for measuring dialyzer incompatibility. However, Grooteman, et al. (1995) in a dialyzer comparison study, reported that IL-1 $\beta$  and IL-6 were not detected at all but they found a slight decrease in leukocytes, particularly CD8+ cells.

Lee, Hakim, and Fearon (1984) measured complement activation comparing new and reused dialyzers with cellulosic membranes and new dialyzers with PMMA membranes. Activation of the complement system was evaluated by comparing the expression of C3b receptor on neutrophils predialysis, and at timed intervals of 10, 20, 60, and 120 minutes after the start of the dialysis treatment. The authors reported increased expression of C3b receptor by neutrophils and generation of increased C3a with the cellulosic dialysis membrane, both new and reused versus modest increases with the Polymethylmethacrylate (PMMA) membrane. However, this was a very small sample with 4 patients in each arm of the study.

Grooteman, et al. (1995) compared the biocompatibility of dialyzers with cellulose-triacetate (CTA) and polysulphon (PS) membranes. Blood samples were taken at 7.5, 15, 30, and 180 minutes after dialysis began and biocompatibility was measured by analysis for leukocytes, lymphocyte subpopulations, C3a, C5a, IL-1 $\beta$ , IL-6, and TNF $\alpha$ . Results showed a decrease in lymphocytes during the first 15 minutes of treatment for both membranes but were significantly

greater with the CTA membrane. In a similarly designed study, Andreoli et al. (2007) compared a dialyzer with cellulosic membrane with a dialyzer with a synthetic membrane (polysulfone) in a crossover design. The aim of the study was to compare the effect of each type of membrane on apoptosis, cytokine serum levels, polymorphonuclear cells (PMN), complement activation and synthesis by peripheral blood mononuclear cells (PBMC) Baseline blood samples were drawn predialysis at the beginning of the study and at the end of the trial period with each dialyzer. Blood samples were analyzed for PMN, CRP, C3a and terminal complement complex (TCC), TNF- $\alpha$ , and IL-10. They found no differences in complement activation between membranes.

Caglar et al. (2002) investigated the dialysis procedure itself as a source of inflammation in hemodialysis patients. Inflammation was assessed in hemodialysis patients during a treatment by drawing samples for CRP, IL-6, albumin FSR, and fibrinogen FSR from 2 hours before the treatment, through the treatment and 2 hours after the treatment. Findings included increased albumin FSR and fibrinogen FSR throughout the dialysis treatment and continued increase in fibrinogen FSR during the 2-hour post-dialysis period. Albumin FSR decreased slightly during the 2 hour post-dialysis period. A modest increase in IL-6 was seen throughout the dialysis treatment but a greater increase was seen from end of treatment to 2-hours post-treatment. The authors reported a weak correlation between change in the fibrinogen FSR level and the extent of change in IL-6.

Snaedal et al. (2009) investigated the relationship between comorbidities and inflammation, measuring CRP, IL-6, IL-10, and TNF- $\alpha$  from hemodialysis patients over a 12-week period in a group of 254 chronic hemodialysis patients in Sweden. The authors identified the following comorbidities in their study population: malignancy, ischemic heart disease, peripheral/cerebral vascular disease, congestive heart failure, diabetes mellitus, and systemic

collagen disease. CRP was found to be highly variable within patients but the authors reported a correlation between comorbidities and increased levels of CRP and IL-6. No significant correlations with IL-10 and TNF- $\alpha$  were found.

Tarakcioglu, Erbagci, Usalan, Deveci & Kocabas (2003) compared cytokine levels pre and post dialysis. The authors reported a significant decrease in IL-8 from predialysis to postdialysis but found no change in IL-1 $\beta$ , sIL-2R, IL-6, and TNF- $\alpha$ . In contrast, Raj et al. (2007) analyzed blood samples drawn from eight hemodialysis patients pre- and post-dialysis. IL-6, CRP and TNF- $\alpha$  results were reported in this study. IL-6 levels increased significantly but not CRP or TNF- $\alpha$ .

In summary, studies have reported conflicting results in changes in pre/post or intra cytokines. Increases in IL-6 were reported in two studies, two reported increases in IL-1, and increases in TNF- $\alpha$ , IL-2, and IL-8 were separately reported in three studies. Few studies examined large numbers of cytokines and a variety of methods were used to measure cytokines. . Past research has focused primarily on how dialyzer membranes affect specific cytokines and studies have reported varying results. Comparisons are difficult because different cytokines were measured in each study and conflicting results are reported for those studies that did include the same cytokines. In addition, many advancements have been made in the technology used in the care of patients with ESRD. The bulk of prior research has been conducted with bioincompatible membranes, particularly cupraphan. Dialyzer membranes have advanced to much more biocompatible materials. Therefore, it is important to reexamine cytokine changes in dialysis as possible contributors to an inflammatory state.

Table 1. Summary of Findings in the Literature Related to Changes in Cytokines During Hemodialysis Treatments

First Author/Date	Method	Medium	Cytokine increased
Lee/1984	Radioimmunoassay	Serum	C3a
Lonnemann/1988	Radioimmunoassay	In vitro with MNC	IL-1
Grooteman/1995	Immunoassay	Serum	TNF $\alpha$
Varela/2001	Elisha	Serum	IL-1 IL-2
Caglar/2002	Elisha	Serum	IL-6
Tarakcioglu/2003	Immunoassay	Serum	IL-8
Raj/2007	Elisha	Serum	IL-6

### Study Purpose

To date, no studies have been found that describe cytokine patterns throughout the entire dialysis treatment. Most studies have measured limited, selected cytokines before and after dialysis. Given the paucity of published information on cytokine patterns during hemodialysis, this study was undertaken to (1) describe levels of cytokines prior to, during, and after dialysis; (2) examine changes in cytokine levels from immediate pre-dialysis to immediate post-dialysis; and (3) compare cytokine patterns prior to and after dialysis.

### Design and Methods

This within-subject descriptive study was conducted in the Acute Dialysis Clinic (ADC) within an academic medical center as part of a larger pilot study to determine the optimal time in the dialysis treatment period to collect blood samples for measurement of cytokine levels. Participants were screened and consented during dialysis and data were collected on their subsequent dialysis day. The dialyzer used in the treatments was a Gambro Polyflux L dialyzer, a low-flux dialyzer with a polymix membrane, a biocompatible material. Ten adult patients ( $\geq 21$

years) admitted to the ADC who are able to give informed consent and who understood and spoke English were eligible for the study. Participants were consented by the nurse manager of the ADC and assigned an arbitrary subject code. A trained RN research assistant collected 2 ml of blood from subjects' existing indwelling catheters immediately pre-dialysis, every 30 minutes during dialysis, and immediately post-dialysis for a total of 9 sample collections for each subject. Plasma samples were cryopreserved and batch- analyzed by highly experienced personnel using a Bio-Plex® (Bio-Rad, Inc.) system.

### ***Laboratory Procedures***

A Bio-Plex® multiplex suspension array system in the Center for Biobehavioral Clinical Research (P20 NR008988), VCU School of Nursing, was used by highly experienced personnel to simultaneously measure plasma levels of 17 cytokines across the dialysis period for each subject. Bio-Rad's Human 17-Plex® bead array panel was used to measure levels of IL-1 $\beta$ , IL-2, IL-4, IL-5, IL-6, IL-7, IL-8, IL-10, IL-12, IL-13, IL-17, granulocyte-colony stimulating factor (G-CSF), granulocyte macrophage colony stimulating factor (GM-CSF), IFN- $\gamma$ , monocytes chemoattractant protein-1 (MCP-1), macrophage inflammatory protein-1 beta (MIP-1 $\beta$ ), and TNF- $\alpha$  at each of the 9 study timepoints.

### **Data Analysis**

Descriptive statistics including means, standard deviations, medians, minimum and maximum values were computed for each cytokine at each of the 9 measurement time points during dialysis. Individual patterns in cytokine were examined graphically over the study period and normality for each measure assessed. In addition, overall mean, or for non-normal data, median values were plotted to examine group values over time. Random effects mixed models were used to describe the pattern of change for each cytokine over time. These analytic models are advantageous because they incorporate the dependencies between the repeated measures



within each subject over time. The change in cytokine values was described through the slope of the fitted model to ascertain whether cytokines generally increase or decrease across dialysis.

Further, immediately post-dialysis cytokine levels were compared to the pre-dialysis values for each cytokine measure. Contrasts created from the random effects model estimated and tested the change from pre- to post-dialysis. Analyses were completed using SAS v9.1 and assumed  $\alpha = 0.05$  for statistical significance.

## Results

### Sample

Mean age of subjects was 53.5 with a range of 36-66 years and 60% were African American, 40% Caucasian, and one subject of Hispanic ethnicity. Subjects were equally divided between females and males. Eight of the 10 subjects had a history of hypertension (HTN) and 3 had been diagnosed with diabetes mellitus (DM). In addition, 3 had a history of cardiovascular disease. One subject had a history of Hepatitis C and had a hip wound at the time of the study.

Log values for each cytokine were used in analysis. Most of the values for IL-10 were below the limit of detection, thus IL-10 was not included in the panel for analysis. Further, one subject was removed from the group analyses because the biomarker values were so much higher for this individual in comparison to the other subjects. Thus, analyses were conducted for 9 subjects.

Examined individually, only IL-4 and MIP-1 $\beta$  levels changed significantly over the dialysis period. In average log values, there was a significant decrease of 0.05 in IL-4 ( $p = 0.036$ ), and a significant increase of 0.08 in MIP1 $\beta$  ( $p = 0.015$ ) *every 30 minutes* over the course of dialysis. Levels of G-CSF decreased an average of 0.05 every 30 minutes over dialysis and this change approached significance ( $p = 0.054$ ).

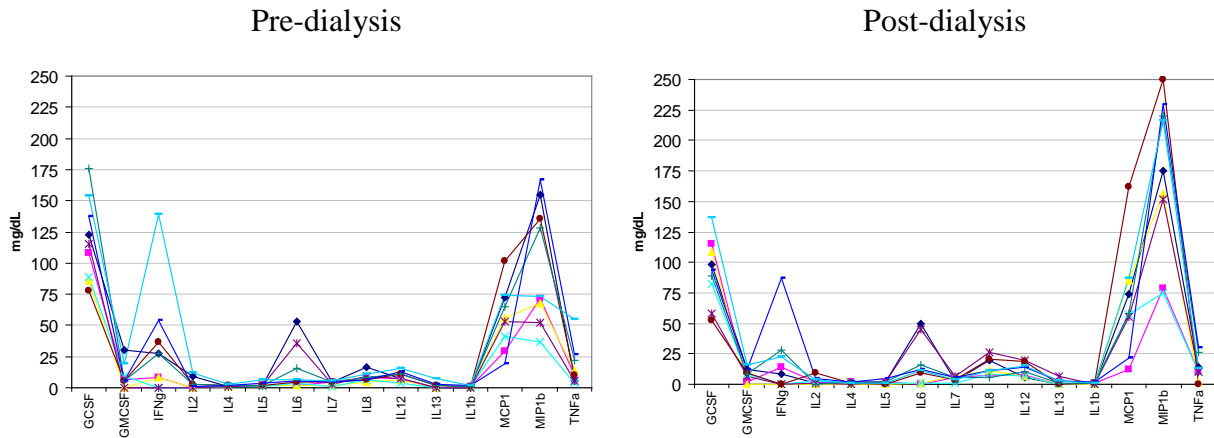
Paired differences were computed to compare biomarker values from pre-dialysis to post-dialysis (instead of observing the trend over the course of dialysis). Due to the small sample size and non-normality of the markers, a nonparametric paired difference test was conducted. Only MIP-1 $\beta$  had a significant increase of 88.6 pg/ml from the initiation to completion of dialysis. G-CSF exhibited a marginally significant decrease with a *p*-value of 0.055 (Table 1).

Table 2. Differences in Cytokine Levels: Pre- vs. Post-dialysis

	Mean Difference	Median	SD	<i>p</i> -value
GCSF	-25.80	-23.93	33.43	0.0547
GMCSF	-0.73	0.00	7.73	0.8433
IFN $\gamma$	-15.88	0.00	42.16	0.3125
IL2	-0.36	1.1	4.97	0.98
IL4	-0.39	0.00	0.85	0.3125
IL5	-0.87	0.00	2.06	0.3125
IL6	1.77	0.66	4.58	0.3594
IL7	0.87	0.34	2.37	0.5469
IL8	4.83	2.82	6.87	0.0742
IL12	2.43	0.76	4.43	0.1953
IL13	0.07	0.00	2.92	0.9063
IL1b	-0.11	0.00	0.52	0.6875
MCP1	11.23	2.23	22.64	0.2031
MIP1 $\beta$	96.67	88.61	93.89	0.0039*
TNF $\alpha$	-4.16	4.01	15.84	0.7422

When graphed using individual profile plots (Figure 1) cytokine patterns appear fairly similar, with the same cytokines spiking at the beginning and the end of dialysis; however, there are some noticeable differences in the magnitude of the observed values in these individuals. There are overall increases in values for MIP-1 $\beta$  and MCP-1 from pre- to post-dialysis, while the magnitude of values decline for G-CSF and IFN $\gamma$ , although fewer individuals have larger values of IFN $\gamma$ . All individuals experienced increases in values of IL-8 and MIP-1 $\beta$ . Values of IL-2, IL-4, IL-5 and IL-1 $\beta$  remained low at both the beginning and end of dialysis.

Figure 1. Cytokine Patterns Pre- and Post-dialysis



\* MIP1b value plotted at 250mg/dL is rescaled from actual value of 455.63mg/dL

### Discussion

Previous research in the hemodialysis population has focused primarily on investigating the effect of different dialyzer membranes on selected pro-inflammatory cytokines. Recent research has demonstrated that labeling cytokines as either pro-inflammatory or anti-inflammatory may not be accurate because the various cytokines have interdependent and pleiotropic effects. Cytokine activity may be influenced by many factors such as the nature of the target cells, growth and activation state of the cells, and concentrations (Navarro-Gonzalez & Mora-Fernandez, 2008; Xing & Wang, 2000). Many cytokines also have multiple functions and those functions may be shared by other cytokines, possibly creating synergistic effects on cells. Additionally, methods of analyzing cytokines have improved in the interim since many of these studies were completed, with current methods being much more sensitive as well as reliable and accurate. Inconsistent results have been reported in past research. CRP has been used extensively to measure inflammatory response but CRP is highly variable within patients (Snaedal et al., 2009). IL-1, IL-2, IL-6, and TNF- $\alpha$  have been measured pre-dialysis and post-dialysis with varying results.

Levels of IL-10 were not detectable in this study and were not included in the analysis, in contrast to the findings of Sertic et al. (2007). Significant changes were seen in IL-4 and MIP-1 $\beta$  over the course of dialysis and the changes in G-CSF approached significance. When values were compared pre-dialysis to post-dialysis, only MIP-1 $\beta$  showed a significant increase.

Our first purpose was to describe patterns of cytokines during dialysis. There was little change in most cytokines over the course of the hemodialysis treatment with the exception of IL-4, and MIP-1 $\beta$ . The decrease in IL-4, an anti-inflammatory cytokine due to its ability to suppress pro-inflammatory cytokines and chemokines (Dinarello, 2000) may have had an effect on MIP-1 $\beta$ , a chemokine that increased over the course of dialysis. Removal of certain cytokines by some dialyzers with adsorption properties has been documented in some studies (Randoux et al., 2001), possibly explaining the decrease in IL-4.

Our second purpose was to examine changes in cytokines from immediately pre-dialysis to immediately post-dialysis. Only MIP-1 $\beta$  increased significantly from pre-dialysis to post-dialysis. MIP-1 $\beta$  has been shown to stimulate atherosclerosis in hypertensive patients and proposed as an independent predictor for stroke and cardiovascular disease in this patient population (Tatara, Ohishi, Yamamoto, et al., 2009). It was of interest that IL-6 did not change significantly from pre-dialysis to post-dialysis. Increased IL-6 has been linked with cardiovascular disease in patients with ESRD (Piroddi, Depunzio, Calabrese, et al., 2007), but perhaps previous findings expressed less sensitive or accurate levels of IL-6. Since the authors did not have a control group, IL-6 levels may have been chronically elevated. A comparison of IL6 with nondialysis patients might provide further insight. Further, a focus on singular cytokines is likely to be less informative than the view of patterns among cytokines.

In examining the third research purpose, the patterns of cytokines pre- vs. post-dialysis were not found to be appreciably different. As seen in Figure 1, the post-dialysis spikes in MIP-1 $\beta$  and MCP-1 were slightly higher than at pre-dialysis, but the patterns per se did not differ. Based on our findings, cytokines may be drawn at any point during the dialysis treatment. This is in contrast to the results of other studies cited here (see Table 1).

The steady increase in MIP-1 $\beta$  throughout the hemodialysis treatment was very interesting. Results here contrast with previous studies performed across the dialysis treatment. Improvements in dialysis technology and sensitivity of instruments measuring cytokine levels may explain some of the differences. Improvements in dialyzer materials to more biocompatible materials could also explain some of the differences. Patient characteristics and comorbidities may also have been a contributing factor. However, more research is needed to determine if results can be replicated and to investigate causes of this phenomenon.

This was a small study in an urban group of patients with results that conflict with prior studies. Without a control group it is not possible to know if predialysis levels were more elevated or depressed at baseline. Time on dialysis, prior transplant status, medication, demographics, and patient characteristics are other variables that could have affected the cytokine levels of this group of subjects. Further research is needed to investigate cytokine patterns in a larger study to learn more about this phenomenon.

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## CHAPTER 3: VCU IRB Submission and Approval

IRB Number: \_\_\_\_\_

### DO NOT DELETE SECTIONS OF THIS FORM

#### Section 1: Principal Investigator and Other VCU Lead Project Personnel

##### 1. Principal Investigator: List Name as it exists in the Human Resource System (HRS)

**Note:** SEE GUIDANCE ON WHO CAN SERVE AS PI AT

[http://www.research.vcu.edu/irb/wpp/flash/wpp\\_guide.htm#IX-1.htm](http://www.research.vcu.edu/irb/wpp/flash/wpp_guide.htm#IX-1.htm) (EFFECTIVE DATE 4-15-06)

NAME (LAST, FIRST, MI): \_\_\_\_\_ MCCAIN, NANCY, DSN, RN, FAAN, PROFESSOR VCU SCHOOL OF NURSING

PI TITLE AND DEGREES: \_\_\_\_\_ DSN, RN, FAAN

VCU DEPARTMENT: \_\_\_\_\_ NURSING

VCU BOX # (MUST PROVIDE 6-  
DIGIT #): \_\_\_\_\_

Phone/Pager/Fax #'s: \_\_\_\_\_

VCUEmail: \_\_\_\_\_

##### 2. VCU LEAD PROJECT PERSONNEL: LIST NAMES AS THEY EXIST IN THE HUMAN RESOURCE SYSTEM (HRS)

If the PI cannot be contacted, these persons may be contacted by the IRB. Within the Research Synopsis, you will have the opportunity to list all key project personnel.

##### **SUB/CO-INVESTIGATOR:**

Name (Last, First, MI),

Degrees: \_\_\_\_\_

Department: \_\_\_\_\_

Phone/Pager/Fax #'s: \_\_\_\_\_

Email: \_\_\_\_\_

##### **MEDICALLY RESPONSIBLE INVESTIGATOR (if applicable):**

Name (Last, First, MI),

Degrees: \_\_\_\_\_

Department: \_\_\_\_\_

Phone/Pager/Fax #'s: \_\_\_\_\_

Email: \_\_\_\_\_

##### **RESEARCH COORDINATOR (if applicable):**

Name (Last, First, MI),

Degrees: \_\_\_\_\_

Department: \_\_\_\_\_

Phone/Pager/Fax #'s: \_\_\_\_\_

Email: \_\_\_\_\_

**TRAINEE (Postdoctoral Scholar, Fellow or Resident) (if applicable):**

Name (Last, First, MI),

Degrees: \_\_\_\_\_

Department: \_\_\_\_\_

Phone/Pager/Fax #'s: \_\_\_\_\_

Email: \_\_\_\_\_

**STUDENT (if applicable):**

Name (Last, First, MI),

Avis K. Allen, RN, MSN

Degrees: \_\_\_\_\_

Department: \_\_\_\_\_

Nursing

Phone/Pager/Fax #'s: \_\_\_\_\_

804 828-5899/4760/804 828-1979

Email: \_\_\_\_\_

AALLEN@MCVH-VCU.EDU

**Section 2: Type of Submission**

**RESEARCH PROJECT**

**HUMANITARIAN USE DEVICE**

See guidance at [http://www.research.vcu.edu/irb/wpp/flash/wpp\\_guide.htm#XVI-2.htm](http://www.research.vcu.edu/irb/wpp/flash/wpp_guide.htm#XVI-2.htm)

**TREATMENT USE OF INVESTIGATIONAL DRUG/DEVICE**

See guidance at [http://www.research.vcu.edu/irb/wpp/flash/wpp\\_guide.htm#XVI-5.htm](http://www.research.vcu.edu/irb/wpp/flash/wpp_guide.htm#XVI-5.htm)

### SECTION 3: TYPE OF REVIEW

#### REVIEW TYPE REQUESTED (check one):

FULL BOARD REVIEW

**NOTE:** Industry-sponsored research **MUST** be submitted to Western IRB (WIRB) for review. See instructions available at <http://www.research.vcu.edu/forms/wirb.htm>

EXPEDITED REVIEW

\* EXPEDITED CATEGORIES: 2,5,7

\* Identify the expedited category or categories in which your research falls (See Expedited Review Guidance at <http://www.research.vcu.edu/irb/reviewtypes.htm>)

EXEMPT REVIEW

\* EXEMPT CATEGORIES: \_\_\_\_\_

\* Identify the exempt category or categories in which your research falls (See Exempt Request Guidance at <http://www.research.vcu.edu/irb/reviewtypes.htm>)

### Section 4: Project Information

#### 1. PROJECT TYPE (check one):

BIOMEDICAL

Research involving medical interventions and/or FDA-regulated products

**SOCIAL-BEHAVIORAL (check one):**

Social or behavioral research that does **NOT** involve medical interventions or FDA-regulated products

SOCIAL-BEHAVIORAL QUALITATIVE

SOCIAL-BEHAVIORAL

QUANTITATIVE

SOCIAL-BEHAVIORAL QUALITATIVE

&

QUANTITATIVE

#### 2. Title of Protocol Submission:

BIOBEHAVIOR RELATIONSHIPS IN PERSONS ON HEMODIALYSIS

3. ARE THERE ANY IRB-approved protocols associated WITH THIS SUBMISSION?

Yes

No

If yes, PLEASE LIST THE ASSOCIATED VCU IRB PROTOCOL #'S:

NOTE: IF THIS SUBMISSION IS ASSOCIATED WITH OTHER NEW PROJECTS SUBMITTED TO THE IRB BUT NOT YET APPROVED), PLEASE ATTACH A COVER MEMO TO YOUR SUBMISSION NOTING RELATED PROJECTS.

4. IS THIS A Trainee or Student project IN WHICH ACTIVITIES WILL BE CARRIED OUT BY THAT INDIVIDUAL UNDER YOUR SUPERVISION?

Yes

No

## Section 5: Sponsor Data

1. DOES THE RESEARCH PROJECT INVOLVE A **Direct Federal Award** MADE TO VCU (OR A RESEARCH FUNDING PROPOSAL FOR SUCH)?  Yes  No

2. HAVE YOU SUBMITTED A RELATED RESEARCH FUNDING PROPOSAL(S) TO THE VCU OFFICE OF SPONSORED PROGRAMS (OSP)?  Yes  No

If Yes, YOU MUST PROVIDE THE **PT/PD #** FOR EACH RELATED PROPOSAL (**REGARDLESS OF THE FUNDING SOURCE**):

(1)

(2)

(3)

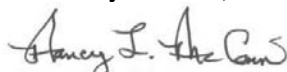
**NOTE:** Federal regulations require IRB approval of **NEW**, **RESUBMISSION**, or **COMPETING CONTINUATION** FEDERAL RESEARCH FUNDING PROPOSALS. If there is a new, resubmission, or competing continuation VCU federal research funding proposal associated with this research project, you must include a copy of your ENTIRE proposal (exclusive of appendices) and OSP Internal Approval Form with this submission. [Also see Section 10, Question 18] Failure to do so may delay your research award start date. Other sponsors also may require IRB approval of research proposals. It is the investigator's responsibility to determine whether this review is needed. If the sponsor does not require IRB approval of research proposals, **DO NOT** submit them to the IRB for review. If you have questions about whether your sponsor requires IRB approval of your research funding proposal, please contact OSP.

## SECTION 6: STATEMENTS OF COMPLIANCE

### PRINCIPAL INVESTIGATOR STATEMENT OF COMPLIANCE:

I understand and accept responsibility for ensuring the safety and welfare of all human subjects who participate in the proposed research project. I certify that all key project personnel, including myself, sub/co-investigators, research coordinators, trainees, and students have completed the VCU required training on human subjects protection. I agree to a continuing exchange of information with the VCU IRB including the requirements to (i) obtain IRB approval before making non-emergency changes/revisions to the project, except where necessary to eliminate apparent immediate hazards to subjects or others, (ii) provide progress reports to the VCU IRB at their request (and at least annually), and (iii) report promptly to the IRB all unanticipated problems and serious adverse events involving risk to human subjects (in accordance with required reporting timelines by the IRB).

SIGNATURE OF INVESTIGATOR:



DATE OF

6/1/ 2010

SIGNATURE:

### TRAINEE OR STUDENT INVESTIGATOR STATEMENT OF COMPLIANCE (IF APPLICABLE):

This is a student or trainee project, which will potentially be presented outside the classroom and/or published. I understand that I may not proceed with the research without first receiving a formal written letter of approval from the VCU IRB. I certify that I have completed the VCU required training on human subjects protection.

SIGNATURE OF TRAINEE OR STUDENT:

DATE OF

SIGNATURE:

### DEPARTMENT/DIVISION CHAIRPERSON OR DEAN STATEMENT OF COMPLIANCE\*see NOTE:

I certify that the research project referenced in this document (check one of the following):

Has been subjected to scrutiny within a VCU Committee (i.e., Massey Cancer Center Protocol Review, General Clinical Research Center [GCRC]) or sponsor study group (i.e., NIH or other agency with appropriate scientific expertise) and found to be scientifically acceptable.

Has been subjected to scrutiny by my designee or me according to criteria that include the following, as applicable: appropriate power and sample size, currency of literature review, and relevance of hypothesis or research question and found to be scientifically acceptable.

PRINT NAME, DEGREES, TITLE OF \_\_\_\_\_ D. Patricia Gray, RN, PhD  
DEPARTMENT/DIVISION CHAIRPERSON OR DEAN: \_\_\_\_\_ Chair, Department of Adult Health and Nursing Systems

SIGNATURE OF DEPARTMENT/ DIVISION \_\_\_\_\_ DATE OF  
CHAIRPERSON OR DEAN: \_\_\_\_\_ SIGNATURE: \_\_\_\_\_

**\*NOTE:** Department/Division Chairperson cannot sign if he/she is a co-investigator on the project. In these instances, a Dean's signature is required. If a designee is signing the Statement of Compliance, his/her name, degrees, and title should be listed.

### Section 7: Project Detail

ANSWER ALL OF THE FOLLOWING QUESTIONS (by marking the appropriate box to the right):

**1. Will DRUG(S) be administered in this project?** If YES, supply the following information  YES  NO  
(attach a separate sheet if necessary):

**DRUG**  
**NAME(S):** \_\_\_\_\_

If drug is INVESTIGATIONAL or involves an IND, please complete the following:

**IND #:** \_\_\_\_\_ **HELD BY (check one):**  SPONSOR  INVESTIGATOR  N/A

- If IND is held by the SPONSOR, provide copy of the INVESTIGATOR'S BROCHURE and the SPONSOR'S PROTOCOL
- If IND is held by the INVESTIGATOR, provide copy of the IND APPLICATION submitted to the FDA and safety information
- Attach copy of FDA FORM 1572

**2. Will BIOLOGIC(S) be used in this project?** If YES, supply the following information:  YES  NO

**BIOLOGIC NAME(S):** \_\_\_\_\_

**3. Are you evaluating MARKETED MEDICAL DEVICE(S) (including 510k devices) in this project?** If YES, supply the following information:  YES  NO

**DEVICE**  
**NAME(S):** \_\_\_\_\_

**NAME OF**  
**MANUFACTURER:** \_\_\_\_\_

**NOTE:** In addition, provide any supporting documentation regarding LEVEL OF RISK (SIGNIFICANT vs. NON-SIGNIFICANT RISK)

**4. Are you evaluating INVESTIGATIONAL MEDICAL DEVICE(S) or a NEW USE FOR MARKETED MEDICAL DEVICE(S) in this project?** If YES, supply the following information:  YES  NO

**DEVICE**  
**NAME(S):** \_\_\_\_\_

**NAME OF**  
**MANUFACTURER:** \_\_\_\_\_

**IDE #:** \_\_\_\_\_ **HELD BY (check one):**  SPONSOR  INVESTIGATOR  N/A

- If IDE is held by the SPONSOR, provide a copy of the INVESTIGATOR'S BROCHURE and the SPONSOR'S PROTOCOL
- If IDE is held by the INVESTIGATOR, provide a copy of the IDE APPLICATION submitted to the FDA

**NOTE:** In addition, provide any supporting documentation regarding LEVEL OF RISK (SIGNIFICANT vs. NON-SIGNIFICANT risk)

**5-A. Does this project involve the use of any procedure(s) that will expose the research subject to IONIZING RADIATION?**

- YES (Proceed to 5-B)  NO (Proceed to Question 6)

**5-B. If all of these procedures are for the direct clinical benefit of the research subject/patient, check YES. If any of these procedures are of research interest only and will not affect the clinical management of the research subject, check NO.**

- YES (no further information required)  NO (Proceed to 5-C)

**5-C. RADIATION SAFETY COMMITTEE (RSC) approval is required if you answered NO to item 5-B. Do you have RSC approval for this project?**

- YES (Attach copy of RSC Approval Letter)  NO (Contact the Radiation Safety Section at 828-9131 for approval information)

**NOTE:** See also <http://www.vcu.edu/oehs/radiation/humanuseguide.pdf>

**6-A. Does this project involve the use of RECOMBINANT DNA, BIO-HAZARDOUS SUBSTANCES including pathogenic or potentially pathogenic viruses and bacteria (e.g., Adenovirus, HIV, Hepatitis B), CARCINOGENS OR ACUTE CARCINOGENS, MUTAGENS, TERATOGENS, ACUTE TOXINS, OR SELECT AGENT MATERIALS?**

YES (Proceed to 6-B)

NO (Proceed to Question 7)

**6-B. INSTITUTIONAL BIOSAFETY COMMITTEE (IBC) approval is required if you answered YES to this question. Do you have IBC approval for this project?**

YES (Attach copy of IBC Approval Letter)

NO (Contact CHEMICAL AND BIOLOGICAL SAFETY OFFICE at 828-4866 for approval information)

**NOTE:** See also <http://www.vcu.edu/oehs/chemical/>

**7. Does this project involve GENE THERAPY?**

YES

NO

**8-A. Does this study involve cancer patients, their families, or their health care providers?**

YES \*

NO

**8-B. Is this a Cancer Prevention Study?**

YES \*

NO

\* If YES TO 8-A OR 8-B, the research project must be reviewed and approved by the MASSEY CANCER CENTER PROTOCOL REVIEW AND MONITORING SYSTEM before IRB Review, and a copy of the approval letter provided. For information, see <http://www.massey.vcu.edu/research/?pid=2013> or call the PRMS Coordinator at 628-1924.

**9. Will this project be conducted in the GENERAL CLINICAL RESEARCH CENTER (GCRC)?**

YES \*

NO

\* If YES, please review information for investigators available at <http://www.vcuhealth.org/crc/>

**10. Is your project: (1) involving human subject activities conducted by Navy and Marine Corps personnel; (2) involving naval military personnel and Department of Navy (DoN) employees as research subjects; (3) supported by naval activities through any agreement (e.g., contract, grant cooperative agreement, development agreement [CRADSs], or other arrangement), regardless of the source of funding, funding appropriation, nature of support, performance site, or security classification; or (4) using DoN property, facilities or assets?**

YES \*

NO

\* If YES, you must ensure that your project meets the additional Department of Defense (DoD)-Department of the Navy (DoN) requirements for human subject protection. Guidance on additional requirements can be found at <http://www.research.vcu.edu/irb/wpp/flash/XVII-12.htm>

**11. Will this project be conducted in a VCUHS patient care area or involve VCUHS patients?**

YES

NO

**12. Will the VCU/VCUHS INVESTIGATIONAL DRUG PHARMACY be utilized (required for all in-patient projects)?**

YES

NO \*

If NO, your research synopsis must describe detailed, appropriate drug storage and dispensing plans. For information regarding the INVESTIGATIONAL DRUG PHARMACY, call 828-7901.

**13. Do you plan to involve NON-VCU INSTITUTIONS (i.e., institutions [or employees or agents of the institutions] that are not under the authority of VCU or VCU Health Systems and are located within the United States or a United States territory) in your research project?**

YES \*

NO

\* If YES, you must follow guidance at [http://www.research.vcu.edu/irb/wpp/flash/wpp\\_guide.htm#XVII-6.htm](http://www.research.vcu.edu/irb/wpp/flash/wpp_guide.htm#XVII-6.htm)

**14. Do you plan to involve FOREIGN RESEARCH SITES (i.e., institution or non-institutional**

YES \*

NO

setting)?

\* If YES, you must follow guidance at [http://www.research.vcu.edu/irb/wpp/flash/wpp\\_guide.htm#XVII-11.htm](http://www.research.vcu.edu/irb/wpp/flash/wpp_guide.htm#XVII-11.htm)

**15. Do you plan to involve INDEPENDENT INVESTIGATORS (i.e., individuals who are not representatives of VCU or any other institution or facility) in your research project?**  YES \*  NO

\* If YES, you must follow guidance at [http://www.research.vcu.edu/irb/wpp/flash/wpp\\_guide.htm#XVII-15.htm](http://www.research.vcu.edu/irb/wpp/flash/wpp_guide.htm#XVII-15.htm)

**16. Does this project involve the creation of a HUMAN SUBJECTS REGISTRY (registries are sometimes called repositories, data sets, data banks, tissue or specimen banks) as an instrument for the conduct of research?**  YES \*  NO

\* If YES, you must follow guidance at [http://www.research.vcu.edu/irb/wpp/flash/wpp\\_guide.htm#XVII-4.htm](http://www.research.vcu.edu/irb/wpp/flash/wpp_guide.htm#XVII-4.htm)

**17. Does this project involve GENETIC TESTING, that is, testing human tissue samples for heritable characteristics or storing human tissue samples for possible future such testing?**  YES \*  NO

\* If YES, you must follow guidance at [http://www.research.vcu.edu/irb/wpp/flash/wpp\\_guide.htm#XVII-5.htm](http://www.research.vcu.edu/irb/wpp/flash/wpp_guide.htm#XVII-5.htm)

## Section 8: Research Subject Information

### VULNERABLE SUBJECTS:

Consider your criteria for inclusion or exclusion of any subpopulation, review the following information, and identify research categories (as appropriate).

**BOX 1: CHILDREN:** If you plan to allow for the inclusion of data on subjects who are children, you must indicate the inclusion of their data and identify a research category or categories below.

**NOTE:** In Virginia, children are those under the age of 18 and not emancipated.

**Do you plan to allow for the inclusion of data on subjects who are children?**  YES \*  NO

\* If YES, identify the research category or categories below.

- Research not involving greater than minimal risk (45 CFR 46.404) – **[NOTE:** see definition of minimal risk below]
- Research involving greater than minimal risk but presenting the prospect of direct benefit to individual subjects (45.CFR 46.405)
- Research involving greater than minimal risk and no prospect of direct benefit to individual subjects, but likely to yield generalizable knowledge about the subject's disorder or condition. (45.CFR 46.406)<sup>1</sup>
- Research not otherwise approvable which presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children. (45.CFR 46.407)<sup>1</sup>

**MINIMAL RISK** means that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.

<sup>1</sup> Categories 406 and 407 REQUIRE BOTH parents to provide permission for the child's participation unless one is deceased, unknown, incompetent, or only one parent has legal responsibility for care and custody. The IRB may determine that permission of both parents is required for categories 404 or 405.

**NOTE:** If you plan to allow for the inclusion of data on subjects who are children, you must include the VCU IRB CHILDREN-SUBJECT FORM with your submission if you are requesting an expedited or full board review. The form is available at <http://www.research.vcu.edu/forms/vcuirb.htm>



**BOX 2: PREGNANT WOMEN, HUMAN FETUSES, AND NEONATES:** If you plan to allow for the inclusion of data on subjects who are pregnant women, human fetuses, or neonates as subjects, you must indicate inclusion of their data and identify a research category or categories below.

**Do you plan to allow for the inclusion of data on subjects who are PREGNANT WOMEN, HUMAN FETUSES, or NEONATES as subjects?**  YES \*  NO

\* If YES, identify the research category or categories below.

- Research involving pregnant women or fetuses [PW-HF-N (45.CFR46.204)]
- Research involving neonates of uncertain viability and nonviable neonates [PW-HF-N (45.CFR46.205(a)(b)(c))]
- Research involving neonates of certain viability [PW-HF-N (45.CFR46.205(d))]
- Research involving after delivery, the placenta, the dead fetus or fetal material[PW-HF-N (45.CFR46.206)]
- Research not otherwise approvable, which presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of pregnant women, fetuses, or neonates [PW-HF-N (45.CFR.46.207)]

**NOTE:** If you plan to allow for the inclusion of data on subjects who are pregnant women, fetuses, or neonates you must include the VCU IRB PREGNANT WOMEN, FETUSES, NEONATES-SUBJECT FORM with your submission if you are requesting an expedited or full board review. The form is available at <http://www.research.vcu.edu/forms/vcuirb.htm>

**BOX 3: PRISONERS:** If you plan to allow for the inclusion of data on subjects who are, or may become, a prisoner, you must indicate that you plan to allow for inclusion of their data and identify a research category below. **NOTE: If an enrolled research subject becomes incarcerated (or otherwise meets the definition of prisoner) during the course of an IRB approved project, the PI must immediately notify the IRB and amend the protocol to allow for the inclusion of prisoners and the continuation of that subject.** If this should occur, you must follow the VCU IRB PRISONER-SUBJECT GUIDANCE and include the VCU IRB PRISONER-SUBJECT FORM with your submission to the IRB. The guidance and form are available at <http://www.research.vcu.edu/forms/vcuirb.htm>

**Do you plan to allow for the inclusion of data on subjects who are, or may become a PRISONER?**  YES \*  NO

\* If YES, identify the research category below.

- Research involving study of the possible causes, effects, and processes of incarceration, and of criminal behavior, provided that the project presents no more than minimal risk and no more than inconvenience to the subjects (45.CFR 46.306(a)(2)(i)) – [**NOTE:** see definition of minimal risk below]
- Research involving study of prisons as institutional structures or of prisoners as incarcerated persons, provided that the project presents no more than minimal risk and no more than inconvenience to the subjects (45.CFR 46.306(a)(2)(ii)) – [**NOTE:** see definition of minimal risk below]
- Research on conditions particularly affecting prisoners as a class (for example, vaccine trials and other research on hepatitis which is much more prevalent in prisons than elsewhere; and research on social and psychological problems such as alcoholism, drug addiction, and sexual assaults) provided that the project may proceed only after the Secretary (through OHRP) has consulted with appropriate experts including experts in penology, medicine, and ethics, and published notice, in the Federal Register, of his intent to approve such research (45.CFR 46.306(a)(2)(iii))
- Research on practices, both innovative and accepted, which have the intent and reasonable probability of improving the health or well-being of the subject. In cases in which those studies require the assignment of prisoners in a manner consistent with projects approved by the IRB to control groups which may not benefit from the research, the project may proceed only after the Secretary (through OHRP) has consulted with appropriate experts including experts in penology, medicine, and ethics, and published notice, in the Federal Register, of his

intent to approve such research (45.CFR 46.306(a)(2)(iv))

- Research defined as public health research that focuses on a particular condition or disease in order to (i) describe its prevalence or incidence by identifying all cases, including prisoner cases, or (ii) study potential risk factor associations, where the human subjects may include prisoners in the project population but not exclusively as a target group, provided that the project presents no more than minimal risk and no more than inconvenience to the subjects (Epidemiological Waiver Request)

**MINIMAL RISK AS IT PERTAINS TO THE PRISONER POPULATION** means that the probability and magnitude of physical or psychological harm that is normally encountered in the daily lives or in the routine medical, dental, or psychological examination of healthy persons.

**NOTE: If you plan to allow for the inclusion of data on subjects who are, or may become, prisoners, you must follow the VCU IRB PRISONER-SUBJECT GUIDANCE and include the VCU IRB PRISONER-SUBJECT FORM with your submission. The guidance and form are available at <http://www.research.vcu.edu/forms/vcuirb.htm>**

**SUBJECT ENROLLMENT PLAN:**

**Anticipated # OF SUBJECTS** (if this is a multi-center project, list only subjects under this IRB approval): 75

Is this a **MULTI-CENTER PROJECT?**  YES  NO

If YES, please provide:

**(1) # OF SITES:**

**(2) # OF SUBJECTS ACROSS ALL SITES:**

**CONSENT DOCUMENTATION:** (Mark the type of consent process/documentation planned):

- Since this project is being submitted for EXEMPT REVIEW, it does not include informed consent/assent documents.
- STANDARD CONSENT FORM:** A copy of the proposed consent form(s) is attached to this submission.
- CONSENT FORM FOR PRISONER SUBJECTS:** A copy of the proposed consent form for prisoners is attached to this submission.
- WAIVER OF SOME OR ALL ELEMENTS OF CONSENT OR PARENTAL PERMISSION: NOTE:** Waiver is not allowed for FDA-regulated research unless it meets FDA requirements for Waiver of Consent for Emergency Research (see below). A request is being made to waive the requirement to obtain prospective informed consent from subjects or permission from parents. Your research synopsis should explain why: (1) the research involves no more than minimal risk to the subjects, (2) the waiver or alteration will not adversely affect the rights and welfare of the subjects, (3) the research could not practicably be carried out without the waiver or alteration; **AND** (4) whether or not subjects will be debriefed after their participation. Guidance is available at [http://www.research.vcu.edu/irb/wpp/flash/wpp\\_guide.htm#XI-1.htm](http://www.research.vcu.edu/irb/wpp/flash/wpp_guide.htm#XI-1.htm).
- WAIVER OF DOCUMENTATION OF CONSENT, PARENTAL PERMISSION:**  
A request is being made to waive documentation of consent. The IRB may waive this requirement if it finds either: (1) that the only record linking the subject and the research would be the consent document and the principal risk would be potential harm resulting from a breach of confidentiality. Subjects will be asked whether they want documentation linking them with the research, and each subject's wishes will govern; or (2) that the research presents no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside of the research context. Your research synopsis should include a justification for waiver based on one of these two elements and include a description of the information that will be provided to participants. If you are proposing to use a verbal consent statement, the proposed consent script should be attached

to this submission. Guidance is available at [http://www.research.vcu.edu/irb/wpp/flash/wpp\\_guide.htm#XI-2.htm](http://www.research.vcu.edu/irb/wpp/flash/wpp_guide.htm#XI-2.htm)

- ASSENT FORM:** A copy of the assent form for children or decisionally-impaired persons is attached to this submission. Guidance is available at [http://www.research.vcu.edu/irb/wpp/flash/wpp\\_guide.htm#XV-2.htm](http://www.research.vcu.edu/irb/wpp/flash/wpp_guide.htm#XV-2.htm). and [http://www.research.vcu.edu/irb/wpp/flash/wpp\\_guide.htm#XVII-7.htm](http://www.research.vcu.edu/irb/wpp/flash/wpp_guide.htm#XVII-7.htm).
- WAIVER OF ASSENT:** A request is being made to waive the requirement to obtain prospective assent from children age 7 or higher, or decisionally-impaired persons. Your research synopsis should explain (1) why some or all of the individuals age 7 or higher, or decisionally-impaired will not be capable of providing assent based on their developmental status or impact of illness; (2) the research holds out a prospect of direct benefit not available outside of the research; **AND/OR** (3) [a] the research involves no more than minimal risk to the subjects, [b] the waiver or alteration will not adversely affect the rights and welfare of the subjects, [c] the research could not practicably be carried out without the waiver or alteration; **AND** [d] whether or not subjects will be debriefed after their participation. Guidance is available at [http://www.research.vcu.edu/irb/wpp/flash/wpp\\_guide.htm#XV-2.htm](http://www.research.vcu.edu/irb/wpp/flash/wpp_guide.htm#XV-2.htm).
- Waiver of Consent for Emergency Research:** Guidance is available at [http://www.research.vcu.edu/irb/wpp/flash/wpp\\_guide.htm#XVII-16.htm](http://www.research.vcu.edu/irb/wpp/flash/wpp_guide.htm#XVII-16.htm).

## Section 9: VCU Research Plan

You must use the VCU Research Plan Template that can be found at <http://www.research.vcu.edu/forms/vcuirb.htm>. Use of this template is required to provide your VCU Research Plan to the IRB. Your responses should be written in terms for the non-scientist to understand. If a detailed research protocol (e.g., sponsor's protocol) exists, you may reference that protocol. **NOTE: If that protocol does not address all of the issues outlined in each Section Heading, you must address the remaining issues in this Plan. It is NOT acceptable to reference a research funding proposal.**

## VCU RESEARCH PLAN TEMPLATE

Use of this template is required to provide your VCU Research Plan to the IRB. Your responses should be written in terms for the non-scientist to understand. If a detailed research protocol (e.g., sponsor's protocol) exists, you may reference that protocol. **NOTE: If that protocol does not address all of the issues outlined in each Section Heading, you must address the remaining issues in this Plan. It is NOT acceptable to reference a research funding proposal.**

**ALL Sections of the Human Subjects Instructions must be completed with the exception of the Section entitled "Special Consent Provisions."** Complete that Section if applicable. When other Sections are not applicable, list the Section Heading and indicate "N/A."

**NOTE: The Research Plan is required with ALL submissions and MUST follow the template, and include version number or date, and page numbers.**

### **DO NOT DELETE SECTION HEADINGS OR THE INSTRUCTIONS.**

#### **I. TITLE**

BIOBEHAVIORAL RELATIONSHIPS IN PERSONS ON HEMODIALYSIS

#### **II. STAFFING**

**A. In the table below (add additional rows as needed), indicate: (1) key project personnel including the principal investigator and individuals from other institutions, (2) their qualifications, and (3) a brief description of their responsibilities.**

NAME OF INDIVIDUAL	QUALIFICATIONS	RESPONSIBILITIES
Nancy L. McCain	DSN, RN, FAAN, Professor VCU School of Nursing	PI
Avis Allen	RN, MSN, CNN, NE-BC	Co-investigator/PhD Candidate

**B. Describe the process that you will use to ensure that all persons assisting with the research are adequately informed about the protocol and their research-related duties and functions.**

Prior to the beginning of the study, information sessions will be held for all persons involved in the research study. All persons involved in the research will be required to attend to inform them of the research protocol and their responsibilities.

#### **III. CONFLICT OF INTEREST**

**Describe how the principal investigator and sub/co-investigators might benefit from the subject's participation in this project or completion of the project in general. Do not describe (1) academic recognition such as publications or (2) grant or contract based support of VCU salary commensurate with the professional effort required for the conduct of the project**

No benefit beyond academic recognition.

#### IV. RESOURCES

Briefly describe the resources committed to this project including: (1) time available to conduct and complete the research, (2) facilities where you will conduct the research, (3 availability of medical or psychological resources that participants might require as a consequence of the research (if applicable), and (4) financial support.

THE CO-INVESTIGATOR HAS ADEQUATE TIME ALLOCATED TO COMPLETE THE RESEARCH AND APPROVAL HAS BEEN OBTAINED FOR THE USE OF THE ACUTE DIALYSIS UNIT AT VCUHS AND THE RAI DIALYSIS UNIT. MINIMAL RISK OF HARM IS ANTICIPATED AS A RESULT OF THE STUDY.

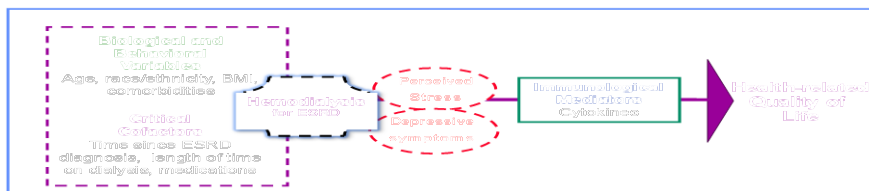
#### V. HYPOTHESIS

Briefly state the problem, background, importance of the research, and goals of the proposed project.

Chronic kidney disease has become a public health issue in the United States with rising incidence and prevalence, escalating costs and increased morbidity and mortality. All current treatments for renal failure involve many losses and stressors. Chronic stress may further compromise the already weakened immune system of patients with end stage renal disease (ESRD) on hemodialysis. There appear to be correlations between immune functioning, health-related quality of life (HRQOL), depression, and time on dialysis, but the nature of such relationships has not been fully explored using current methods and a complete panel of cytokine levels.

Psychoneuroimmunology (PNI) is the study of the interaction of the central nervous system (CNS), endocrine system, and immune system (Yang & Glaser, 2002). This multidirectional communication has an impact on the response to stressful events. The PNI framework explains the physical and psychobehavioral interactions that affect the immune system (McCain, Gray, Walter, & Robins, 2005). For example, behavioral factors are believed to moderate the immune system through neuroendocrine system changes. PNI is a comprehensive model incorporating individual, environmental, physiological, and spiritual factors that effectively guide this study. No previous studies have been found that use the PNI model to investigate relationships among the variables of interest in the ESRD population. The purpose of this study is to examine the relationships of perceived stress, depressive symptoms, and immune status to health related quality of life (HRQOL) among patients requiring hemodialysis for ESRD. Possible contributing factors to be evaluated include time on dialysis and comorbidities. Figure 1 depicts the proposed relationships among the biological and behavioral variables as well as proposed cofactors. Fundamentally, we propose that ESRD and chronic hemodialysis are stressful events resulting in biological and behavioral interactions, ultimately altering perception of health-related quality of life.

Figure 1. Conceptual Framework



## VI. SPECIFIC AIMS

EXAMINE CORRELATIONS BETWEEN IMMUNE STATUS AS INDICATED BY CYTOKINE LEVELS, PERCEIVED STRESS, AND DEPRESSIVE SYMPTOMS WITH HEALTH RELATED QUALITY OF LIFE AMONG 75 INDIVIDUALS ON HEMODIALYSIS FOR ESRD.

## VII. BACKGROUND AND SIGNIFICANCE

**Include information regarding pre-clinical and early human studies. Attach appropriate citations.**

The patient with renal failure lives with many chronic stressors, both physical and psychosocial. Products of stress such as peptides and steroid hormones are metabolized by the kidney, leading to high circulating levels in the patient with renal disease, resulting in a biochemically-induced chronic stress response (Cukor et al., 2007). One of the outcomes of chronic stress is suppressed cellular immunity (McEwen, 2007). Thus, chronic stress generated by living with a serious illness may compromise the immune system.

Sertic et al. (2007) reported that levels of IL-6, IL-8, IL-10, TNF $\alpha$ , IL-1 $\beta$ , and MCP-1 were significantly higher in chronic hemodialysis patients compared to healthy control subjects. In dialysis patients elevated proinflammatory cytokine levels, particularly IL-6 and C-reactive protein (CRP), have been implicated in vascular disease events and mortality (Cazzavillan, et al., 2007; Lentine, Parsonnet, Taylor, Wrone, & Lafayette, 2006), as well as malnutrition (Ibrahim & Salamony, 2008; Koo, et al., 2003). Psychological changes, including depression and decreased quality of life, have been connected to inflammatory cytokine changes as well (Dervisoglu, Kir, Kalender, Eraldemir, & Caglayan, 2008).

HRQOL remains lower and mortality rates remain higher for patients with ESRD than for the general population. Many factors can influence the patient's quality of life, including clinical aspects of the disease, side effects of the treatment, culture, behavior, values, and relationships with others (Kimmel, 2002; Mapes et al., 2004). Ginieri-Coccosis, Theofilou, Synodinou, Tomaras, and Soldatos (2009) reported that patients undergoing dialysis for more than 4 years had lower quality of life than those who had recently started hemodialysis. Hemodialysis patients have consistently been shown to have a lower quality of life than patients on other forms of renal replacement therapy.

Depression and depressive symptoms are the most common psychological problem reported by hemodialysis patients (Lopes et al., 2004). Depressive symptoms have been linked with various health problems, including cardiovascular disease and malnutrition-inflammation complex (Cukor, Cohen, Peterson, & Kimmel, 2007; Ibrahim & Salamony, 2008; Koo et al., 2003). Higher levels of anxiety and depressive symptoms have been linked to increased hospitalization and mortality in ESRD patients ((Kimmel & Peterson, 2005; Ye et al., 2008).

Stress is the stimulus that precipitates a response in the brain to activate physiological systems in the body. Stress activates the sympathetic-adrenal-medullary (SAM) axis and the hypothalamic-pituitary-adrenal (HPA) axis, releasing pituitary and adrenal hormones that have the potential to dysregulate immune function (Glaser & Kiecolt-Glaser, 2005). Thus chronic stress generated by living with a serious illness may compromise the immune system. Elevated levels of cortisol may dysregulate cytokine mediation of the immune system, resulting in inhibited inflammatory responses (McCain et al., 2005).

Possible contributing factors are length of time on dialysis and comorbidities. Researchers have reported conflicting results related to correlations between time on dialysis and severity of stress. Yeh and Chou (2007) reported that stress related to fluid and food restrictions and role ambiguity declined with time on dialysis, while Logan, Pellatier-Hibbert, and Hodgins (2006) reported that time on dialysis didn't affect appraisal of stressors. Using a grounded theory approach to study the experience of renal failure and treatment with hemodialysis, Gregory, Way, Hutchinson, Barrett, and Parfrey (1998) found that meanings are constantly being redefined in response to the environment and changing health status, with stressors changing over time as well. No clear patterns have been identified, with some patients experiencing periods of varying

stress levels.

Many hemodialysis patients have one or more common comorbidities that add to their illness burden such as diabetes mellitus (DM), hypertension (HTN), cardiovascular disease, connective tissue disorders, liver diseases, acquired immune deficiency syndrome (AIDS), and peripheral vascular disease (PVD) (Beddhu et al., 2000; Snaedal et al., 2009). Beddhu et al. found strong correlations between comorbidity scores and hospitalization and mortality in a study of patients on hemodialysis and peritoneal dialysis. Further, Snaedal et al. found more inflammatory activity in patients with congestive heart failure and peripheral vascular disease. Certainly such comorbidities must be addressed as cofactors affecting PNI-related associations.

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## VIII. PRELIMINARY PROGRESS/DATA REPORT

If available.

N/A

## IX. RESEARCH METHOD AND DESIGN

**Include a brief description of the project design including the setting in which the research will be conducted and procedures. If applicable, include a description of procedures being performed already for diagnostic or treatment purposes.**

This study will utilize a cross-sectional design to investigate factors potentially associated with health-related quality of life in patients undergoing hemodialysis. The study will be conducted in the Acute Dialysis Unit (ADU) on the fourth floor of the Gateway Building at VCUHS and the Renal Advantage, Inc (RAI) dialysis unit at 2521 Mechanicsville Turnpike, Richmond, VA 23223, a facility in which VCUHS routinely refers outpatients on dialysis.

A total of 75 patients who have been diagnosed with end stage renal disease requiring dialysis, and who are over 21 years of age, understand and speak English and are competent to consent will be included. Exclusion criteria include active infection/febrile illness or AIDS, diagnosis of cancer, currently on immunosuppressive drugs, or having active psychosis. Participants will be screened and consented during one of their hemodialysis treatments by the co-investigator and assigned a subject code. Variables of interest include cytokine patterns, stress, HRQOL, and depressive symptoms. During the next hemodialysis treatment, the co-investigator will collect 2 ml. plasma from the dialysis access device immediately prior to initiation of dialysis for the measurement of cytokines. Stress will be measured by the Perceived Stress Scale (PSS), a 10-item self-report scale developed to measure "the degree to which situations in one's life are appraised as stressful" (Cohen, Kamarck, & Mermelstein, 1983, p. 385). HRQOL will be measured by the Functional Assessment of Cancer Therapy-General (FACT-G) scale developed by Cella et al. (1993). It was initially developed to measure general cancer quality of life but has now been expanded into the Functional Assessment of Chronic Illness Therapy (FACIT) Measurement System (formerly the FACT System), a collection of questionnaires designed for use with other chronic disease populations ([www.facit.org](http://www.facit.org)). The FACT-G (Version 4) is a 27-item self-report scale that includes subscales for physical, functional, social/family, and emotional well-being. Depressive symptoms will be measured by the Center for



Epidemiological Studies-Depression scale (CES-D), a 20-item self-report designed to measure depressive symptoms in the past 7 days. The co-investigator will administer the scales during the first hour of the treatment.

#### **X. PLAN FOR CONTROL OF INVESTIGATIONAL DRUGS (If the VCUHS Investigational Drug Pharmacy is not used), DEVICES, AND BIOLOGICS**

Describe your plans for the control of investigational products including: (1) how you will maintain records of the product's delivery to the trial site, the inventory at the site, the use by each subject, and the return to the sponsor or alternative disposition of unused product(s); (2) plan for storing the investigational product(s) as specified by the sponsor (if any) and in accordance with applicable regulatory requirements; (3) plan for ensuring that the investigational product(s) are used only in accordance with the approved protocol; and (4) how you will ensure that each subject understands the correct use of the investigational product(s) (if applicable) and check that each subject is following the instructions properly (on an ongoing basis).

N/A

#### **XI. DATA ANALYSIS PLAN**

For investigator-initiated studies.

Descriptive statistics will be computed for demographic information and clinical factors including body mass index (BMI), length of time on dialysis, time since diagnosis of chronic renal failure (CRF), and comorbidities. Regression analysis will be used to determine the relationships of perceived stress, depressive symptoms, and immune status to HRQOL.

#### **XII. DATA AND SAFETY MONITORING**

- If the research involves greater than minimal risk and there is no provision made for data and safety monitoring by any sponsor, include a data and safety-monitoring plan that is suitable for the level of risk to be faced by subjects and the nature of the research involved.
- If the research involves greater than minimal risk, and there is a provision made for data and safety monitoring by any sponsor, describe the sponsor's plan.
- If you are serving as a Sponsor-Investigator, identify the Contract Research Organization (CRO) that you will be using and describe the provisions made for data and safety monitoring by the CRO. Guidance on additional requirements for Sponsor-Investigators is available at [http://www.research.vcu.edu/irb/wpp/flash/wpp\\_guide.htm#X-2.htm](http://www.research.vcu.edu/irb/wpp/flash/wpp_guide.htm#X-2.htm)

This study is non-interventional and involves minimal risk.

#### **XIII. MULTI-CENTER STUDIES**

If VCU is the lead site in a multi-center project or the VCU PI is the lead investigator in a multi-center project, describe the plan for management of information that may be relevant to the protection of subjects, such as reporting of unexpected problems, project modifications, and interim results.

N/A

#### **XIV. INVOLVEMENT OF NON-VCU INSTITUTIONS/SITES (DOMESTIC AND FOREIGN)**

1. Provide the following information for each non-VCU institution/site (domestic and foreign) that has agreed to participate:
  - Name of institution/site

- Contact information for institution/site

Renal Advantage Inc.  
Dr. Todd Gehr

2. For each institution, indicate whether or not it is “engaged” in the research (see OHRP’s guidance on “Engagement of Institutions in Research” at <http://www.hhs.gov/ohrp/humansubjects/assurance/engage.htm>.)

Not engaged

3. Provide a description of each institution’s role (whether engaged or not) in the human subjects research, adequacy of the facility (in order to ensure human subject safety in the case of an unanticipated emergency), responsibilities of its agents/employees, and oversight that you will be providing in order to ensure adequate and ongoing protection of the human subjects. You should only identify institutions that have agreed to participate. If additional institutions agree to participate at a later time, they must be added by amendment to the protocol.

Renal Advantage, Inc. (RAI) is a chronic dialysis unit that provides routine outpatient hemodialysis to patients with ESRD. The staff will be providing the usual care only to patients. Patients are followed by a Nephrologist assigned to them and an RN is always assigned to oversee patient care during the treatment. Informed consent, questionnaire data, and blood specimens will be obtained by the nurse researcher.

4. For each institution that is “engaged” provide an OHRP Federalwide Assurance (FWA) # if: (1) the research is not exempt, AND (2) the research involves a DIRECT FEDERAL award made to VCU (or application for such).

**NOTE:** Additional guidance at [http://www.research.vcu.edu/irb/wpp/flash/wpp\\_guide.htm#XVII-6.htm](http://www.research.vcu.edu/irb/wpp/flash/wpp_guide.htm#XVII-6.htm), and [http://www.research.vcu.edu/irb/wpp/flash/wpp\\_guide.htm#XVII-11.htm](http://www.research.vcu.edu/irb/wpp/flash/wpp_guide.htm#XVII-11.htm).

N/A

#### XV. INVOLVEMENT OF INDEPENDENT INVESTIGATORS

**INDEPENDENT INVESTIGATOR:** an individual who is acting independently and not acting as an agent or employee of any institution or facility while carrying out his or her duties in the research protocol. Additional guidance at [http://www.research.vcu.edu/irb/wpp/flash/wpp\\_guide.htm#XVII-15.htm](http://www.research.vcu.edu/irb/wpp/flash/wpp_guide.htm#XVII-15.htm).

**ENGAGEMENT IN RESEARCH:** An independent investigator becomes "engaged" in human subjects research when he/she (i) intervenes or interacts with living individuals for research purposes; or (ii) obtains individually identifiable private information for research purposes [45 CFR 46.102(d)-(f)]. See OHRP’s guidance on “Engagement of Institutions in Research” at <http://www.hhs.gov/ohrp/humansubjects/assurance/engage.htm>.

1. Provide a list of independent investigators.

2. For each independent investigator indicate whether or not he/she is “engaged” or “not engaged” in the research

3. For each independent investigator who is “engaged”: (1) describe his/her role with human subjects/identifiable

**human data, AND (2) describe YOUR oversight of his/her involvement.**

N/A

**NOTE:** If an independent investigator is “engaged,” and the research is (1) not exempt AND (2) involves a DIRECT FEDERAL award made to VCU (or application for such), the independent investigator must sign a formal written agreement with VCU certifying terms for the protection of human subjects. For an agreement to be approved: (1) the PI must directly supervise all of the research activities, (2) agreement must follow the ORSP template, (3) IRB must agree to the involvement of the independent investigator, AND (4) agreement must be in effect prior to final IRB approval.

**XVI. HUMAN SUBJECTS INSTRUCTIONS (Be sure to use the sub-headings under A-I)**

**ALL sections of the Human Subjects Instructions must be completed with the exception of the section entitled “Special Consent Provisions.” Complete that section if applicable.**

**A. DESCRIPTION**

**Provide a detailed description of the proposed involvement of human subjects or their private identifiable data in the work.**

Subjects will be screened and consent obtained during a regularly scheduled dialysis treatment and will participate in the study on their next dialysis day. Subjects will be approached after dialysis has been initiated and they are comfortably settled into the dialysis treatment. Comorbidities, clinical factors and time on dialysis will be collected from patient records. All patients are routinely assessed by the nurse assigned to the patient for physical and mental stability prior to each dialysis session. Immediately prior to the start of dialysis 2 ml. of blood will be drawn from the dialysis access. Comorbidities to be ascertained include diabetes mellitus (DM), hypertension (HTN), cardiovascular disease, connective tissue disorders, liver diseases, hepatitis B virus (HBV) and hepatitis C virus (HCV) and peripheral vascular disease (PVD). Subjects will complete the PSS, FACT-G, and CES-D during the first hour of the dialysis treatment.

**B. SUBJECT POPULATION**

**Describe the subject population in terms of sex, race, ethnicity, age, etc., and your access to the population that will allow recruitment of the necessary number of participants. Identify the criteria for inclusion or exclusion of any subpopulation and include a justification for any exclusion. Explain the rationale for the involvement of special cases of subjects, such as children, pregnant women, human fetuses, neonates, prisoners or others who are likely to be vulnerable. If you plan to allow for the enrollment of Wards of the State (or any other agency, institution, or entity), you must specifically request their inclusion and follow guidance on Wards and Emancipated Minors in the VCU IRB Written Policies and Procedures (specifically WPP#: XV-3) available at [http://www.research.vcu.edu/irb/wpp/flash/wpp\\_guide.htm#XV-3.htm](http://www.research.vcu.edu/irb/wpp/flash/wpp_guide.htm#XV-3.htm).**

Patients treated in the Acute Dialysis Unit (ADU) at VCUHS are 93.8% African American with 56.3% male. Most of the patients are within the 45-64 year age range with 43.8% aged 45-54 and 31.3% aged 55-64. The co-investigator is the Nurse Manager of the ADU and has access to this population. Application to access the patients at the Renal Advantage, Inc. (RAI) unit has been obtained and will be completed following IRB approval. Patients who have been diagnosed with end stage renal disease requiring dialysis and who are over 21 years of age and competent to consent will be included. Patients with active infections or AIDS, diagnosis of cancer, currently on immunosuppressive drugs, or who have active psychosis will be excluded.

**C. RESEARCH MATERIAL**

**Identify the sources of research material obtained from individually identifiable living human subjects in the form of specimens, records, or data. Indicate whether the material or data will be obtained specifically for research purposes or whether use will be made of existing specimens, records, or data.**

Length of time on dialysis, length of time since diagnosis of CRF, clinical data, and comorbidity data will be collected from the patient record and used for research purposes only. Participants will complete self-report instruments (PSS, FACT-G, and CES-D) and blood will be collected from the dialysis access for research purposes only. All study data will be assigned an arbitrary code number and then all identifying information will be removed from the data record and attached to the consent form. Consent forms with identifying information will be filed in an undisclosed location under lock and key and available only to the PI and co-investigator Allen.

#### **D. RECRUITMENT PLAN**

**Describe in detail your plans for the recruitment of subjects including: (1) how potential subjects will be identified (e.g., school personnel, health care professionals, etc), (2) how you will get the names and contact information for potential subjects, and (3) who will make initial contact with these individuals (if relevant) and how that contact will be done. If you plan to involve special cases of subjects, such as children, pregnant women, human fetuses, neonates, prisoners or others who are likely to be vulnerable, describe any special recruitment procedures for these populations.**

Co-investigator Avis Allen will identify potential subjects in the ADU at VCUHS and will make the initial contact during the routine dialysis treatment, provide the initial screening, and obtain consent. The charge nurse at the RAI unit will be the contact person to identify potential subjects. Initial contact then will be made by the co-investigator and she will provide the initial screening, and obtain consent.

#### **E. POTENTIAL RISKS**

**Describe potential risks whether physical, psychological, social, legal, or other and assess their likelihood and seriousness. Where appropriate, describe alternative treatments and procedures that might be advantageous to the subjects.**

No treatments are included in this study. It is possible but very unlikely that the self-report measures may be distressing for the subjects. The investigators are highly skilled in potentially emotional interactions. In the event of signs of distress, a referral will be made to appropriate health care practitioners. Blood will be drawn but will be limited to a 2 ml. sample taken during the routine start of the hemodialysis treatment. No peripheral venipuncture will be required.

#### **F. RISK REDUCTION**

**Describe the procedures for protecting against or minimizing potential risk. Where appropriate, discuss provisions for ensuring necessary medical or professional intervention in the event of adverse events to the subjects. Also, where appropriate, describe the provisions for monitoring the data collected to ensure the safety of subjects.**

All subjects are assessed for orientation and physical ability by a registered nurse experienced in dialysis care prior to each treatment as part of their routine care. This assessment will be used to determine their ability to participate in the study. Blood samples will be drawn in a sterile manner from the dialysis vascular access by the highly skilled and experienced co-investigator. In the event of signs of distress or a score exceeding 16 on the CES-D, a referral will be made to the social worker for the dialysis unit. All study data will be de-identified.

#### **G. ADDITIONAL SAFEGUARDS IF ANY PARTICIPANTS WILL BE VULNERABLE**

**Describe any additional safeguards to protect the rights and welfare of participants if you plan to involve special cases of subjects, such as children, pregnant women, human fetuses, neonates, prisoners or others who are likely to be vulnerable. Safeguards to protect the rights and welfare of participants might relate to Inclusion/Exclusion Criteria: (“Adults with moderate to severe cognitive impairment will be excluded.” “Children must have diabetes. No normal controls who are children will be used.”) Consent: (“Participants must have an adult care giver who agrees to the participant taking part in the research and will make sure the participant complies with research procedures.” “Adults must be able to assent. Any dissent by the participant will end the research procedures.”)**

**Benefit: (“Individuals who have not shown benefit to this type of drug in the past will be excluded.”).**

N/A

#### **H. CONFIDENTIALITY**

**Describe how the confidentiality of data collected as part of this project will be protected including pre-screening data (e.g., physical controls on the data; access controls to the data; coding of data; legal controls, such as a Federal Certificate of Confidentiality; statistical methods; or reporting methods).**

All data will be assigned an arbitrary code number and consent forms with identifying information will be stored in a locked file cabinet in an undisclosed location with access only by the PI and co-investigator. The arbitrary codes will be verified and kept by the PI throughout the study. Completed paper instruments will be stored in a locked file cabinet in the VCU School of Nursing. Data will be entered into a database that is password protected with the password known only to the study investigators. Error checks will be routinely done and the database reconciled. No identifying information will be entered into the database.

#### **I. PRIVACY**

**Describe how the privacy interests of subjects will be protected where privacy refers to persons and their interests in controlling access to themselves, and assess their likely effectiveness. Identify what steps you will take for subjects to be comfortable: (1) in the research setting and (2) with the information being sought and the way it is sought.**

During the data collection, patients will be comfortably seated in the dialysis recliner (RAI unit) or bed (VCUHS Acute Unit) during their regular dialysis treatment. They will be receiving their usual care. Care will be taken to ensure that fully informed consent is obtained from all subjects.

#### **J. RISK/BENEFIT**

**Discuss why the risks to subjects are reasonable in relation to the anticipated benefits to subjects and in relation to the importance of the knowledge that may reasonably be expected to result. If a test article (investigational new drug, device, or biologic) is involved, name the test article and supply the FDA approval letter.**

There are no interventions in this study proposal, thus there is minimal risk and no adverse events are expected. Subjects will have no direct benefits except the possible altruistic reward of contributing to research that may have future benefits for patients on hemodialysis.

#### **K. COMPENSATION PLAN**

**Compensation for subjects (if applicable) should be described, including possible total compensation, any proposed bonus, and any proposed reductions or penalties for not completing the project.**

N/A

#### **L. CONSENT ISSUES**

##### **1. CONSENT PROCESS**

**Indicate who will be asked to provide consent/assent, who will obtain consent/assent, what language (e.g., English, Spanish) will be used by those obtaining consent/assent, where and when will consent/assent be obtained, what steps**

will be taken to minimize the possibility of coercion or undue influence, and how much time will subjects be afforded to make a decision to participate.

Patients receiving hemodialysis at the ADU and RAI unit will be screened and consent will be obtained by co-investigator Avis Allen, Nurse Manager of the ADU. Consent will be in English and will be obtained at the ADU and RAI unit during the patient's scheduled dialysis visit. Subjects will be informed that agreeing or declining to participate will not affect their care, and they will have 48 hours to discuss their participation with family members or significant others prior to study participation.

## 2. SPECIAL CONSENT PROVISIONS

If some or all subjects will be cognitively impaired, or have language/hearing difficulties, describe how capacity for consent will be determined. Please consider using the VCU Informed Consent Evaluation Instrument available at <http://www.research.vcu.edu/irb/guidance.htm>. If you anticipate the need to obtain informed consent from legally authorized representatives (LARs), please describe how you will identify an appropriate representative and ensure that their consent is obtained. Guidance on LAR is available at [http://www.research.vcu.edu/irb/wpp/flash/wpp\\_guide.htm#XI-3.htm](http://www.research.vcu.edu/irb/wpp/flash/wpp_guide.htm#XI-3.htm).

Patients with cognitive impairment or who do not speak English will not be eligible to participate.

3. If request is being made to **WAIVE SOME OR ALL ELEMENTS OF INFORMED CONSENT FROM SUBJECTS OR PERMISSION FROM PARENTS**, explain why: (1) the research involves no more than minimal risk to the subjects, (2) the waiver or alteration will not adversely affect the rights and welfare of the subjects, (3) the research could not practicably be carried out without the waiver or alteration; AND (4) whether or not subjects will be debriefed after their participation. Guidance is available at [http://www.research.vcu.edu/irb/wpp/flash/wpp\\_guide.htm#XI-1.htm](http://www.research.vcu.edu/irb/wpp/flash/wpp_guide.htm#XI-1.htm). **NOTE:** Waiver is not allowed for FDA-regulated research unless it meets FDA requirements for Waiver of Consent for Emergency Research (see below).

N/A

4. If request is being made to **WAIVE DOCUMENTATION OF CONSENT**, provide a justification for waiver based on one of the following two elements AND include a description of the information that will be provided to participants: (1) the only record linking the subject and the research would be the consent document and the principal risk would be potential harm resulting from a breach of confidentiality. Subject will be asked whether they want documentation linking them with the research, and each subject's wishes will govern; or (2) the research presents no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside of the research context. Guidance is available at [http://www.research.vcu.edu/irb/wpp/flash/wpp\\_guide.htm#XI-2.htm](http://www.research.vcu.edu/irb/wpp/flash/wpp_guide.htm#XI-2.htm)

N/A

5. If applicable, explain the **ASSENT PROCESS** for children or decisionally impaired subjects. Describe the procedures, if any, for re-consenting children upon attainment of adulthood. Describe procedures, if any, for consenting subjects who are no longer decisionally impaired. Guidance is available at [http://www.research.vcu.edu/irb/wpp/flash/wpp\\_guide.htm#XV-2.htm](http://www.research.vcu.edu/irb/wpp/flash/wpp_guide.htm#XV-2.htm) and [http://www.research.vcu.edu/irb/wpp/flash/wpp\\_guide.htm#XVII-7.htm](http://www.research.vcu.edu/irb/wpp/flash/wpp_guide.htm#XVII-7.htm).

N/A

6. If request is being made to **WAIVE THE REQUIREMENT TO OBTAIN ASSENT** from children age 7 or higher, or decisionally impaired subjects, explain why: (1) why some or all of the individuals age 7 or higher will not be

capable of providing assent based on their developmental status or impact of illness; (2) the research holds out a prospect of direct benefit not available outside of the research; AND/OR (3) [a] the research involves no more than minimal risk to the subjects, [b] the waiver or alteration will not adversely affect the rights and welfare of the subjects, [c] the research could not practicably be carried out without the waiver or alteration; AND [d] whether or not subjects will be debriefed after their participation. Guidance is available at [http://www.research.vcu.edu/irb/wpp/flash/wpp\\_guide.htm#XV-2.htm](http://www.research.vcu.edu/irb/wpp/flash/wpp_guide.htm#XV-2.htm)

N/A

7. If request is being made to waive consent for emergency research, see guidance at [http://www.research.vcu.edu/irb/wpp/flash/wpp\\_guide.htm#XVII-16.htm](http://www.research.vcu.edu/irb/wpp/flash/wpp_guide.htm#XVII-16.htm).

N/A

8. If applicable, address the following issues related to **GENETIC TESTING**:

**a. FUTURE CONTACT CONCERNING FURTHER GENETIC TESTING RESEARCH**

Describe the circumstances under which the subject might be contacted in the future concerning further participation in this or related genetic testing research.

N/A

**b. FUTURE CONTACT CONCERNING GENETIC TESTING RESULTS**

If planned or possible future genetic testing results are unlikely to have clinical implications, then a statement that the results will not be made available to subjects may be appropriate. If results might be of clinical significance, then describe the circumstances and procedures by which subjects would receive results. Describe how subjects might access genetic counseling for assistance in understanding the implications of genetic testing results, and whether this might involve costs to subjects. Investigators should be aware that federal regulations, in general, require that testing results used in clinical management must have been obtained in a CLIA-certified laboratory.

N/A

**c. WITHDRAWAL OF GENETIC TESTING CONSENT**

Describe whether and how subjects might, in the future, request to have test results and/or samples withdrawn in order to prevent further analysis, reporting, and/or testing.

N/A

**d. GENETIC TESTING INVOLVING CHILDREN OR DECISIONALLY IMPAIRED SUBJECTS**

Describe procedures, if any, for consenting children upon the attainment of adulthood. Describe procedures, if any, for consenting subjects who are no longer decisionally impaired.

N/A

**e. CONFIDENTIALITY**

Describe the extent to which genetic testing results will remain confidential and special precautions, if any, to protect confidentiality.

N/A

BIOBEHAVIORAL RELATIONSHIPS IN PERSONS ON HEMODIALYSIS

SCREENING FORM

Date: \_\_\_\_\_

1. Age 21 or older
  - a. Yes
  - b. No
  
2. Understand and speak English
  - a. Yes
  - b. No
  
3. Capable of giving informed consent
  - a. Yes
  - b. No
  
4. Acute infection/febrile illness
  - a. Yes
  - b. No
  
5. HIV infection
  - a. Yes
  - b. No
  
6. Cancer diagnosis and/or treatment within 5 years (exclusion of non-melanoma skin cancer within last 6 months)
  - a. Yes
  - b. No
  
7. Taking immunosuppressive medications currently or within the past month
  - a. Yes
  - b. No
  
8. Diagnosis of psychotic disorder
  - a. Yes
  - b. No
  
9. Transplant status
  - a. Currently on transplant list
  - b. Not on transplant list
  - c. Prior transplant

SCREENED IN: \_\_\_\_\_ NO \_\_\_\_\_ YES → **ID#** \_\_\_\_\_



McCain/Allen

**Demographic Form**

Date:  /  /

1. Participant's date of birth:     
*m m d d y y*

2. What is your ethnicity?

Hispanic or Latino

Not-hispanic or Latino

3. What is your race?

American Indian/Alaska Native

Asian

Black or African-American

Native Hawaiian or Other Pacific Islander

White

More than one race

4. Time on dialysis:    
*Yr. Mo.*

5. Date of first dialysis treatment:     
*m m d d y y*

6. Last KT/V:

7. BMI:

8. Dialysis access:

Fistula

Graft

Catheter

9. Comorbidities:

Diabetes Mellitus

Liver Diseases

Hypertension

Hepatitis B

Cardiovascular Disease

Hepatitis C

Connective Tissue Disorder

Peripheral Vascular Disease

10. Smoking history:

Do you smoke?

No

Yes

How long has it been since you quit smoking  
(please indicate days, months or years)?

--	--

\_\_\_\_\_

Not applicable

How many packs do you smoke per day?

--	--

Not applicable

11. Do you drink alcohol?

No

Yes

If yes, how much?

12. Do you use recreational drugs (such as marijuana, prescription drugs for relaxation)?

No

Yes

If yes, how much/how often? \_\_\_\_\_

Which substances? \_\_\_\_\_

13. Do you use prescription medications?

No

Yes \_\_\_\_\_

14. Do you use over-the-counter (OTC) medications?

No

Yes (please check all that apply)

Vitamins

Supplements

Other (please list) \_\_\_\_\_

15. What is your highest level of education?

Started high school

Completed high school

Started technical training

Completed technical training

Started college

Completed college

Started post-college

Completed post-college

16. Blood pressure: 

--	--	--

 / 

--	--	--

Pulse 

--	--	--

**McCain/Allen  
Perceived Stress Scale**

Date   /   /

**Directions :** The questions below ask you about your feelings and thoughts **during the LAST MONTH** . Please fill in the corresponding bubble that best describes how often you felt or thought like the statement. There is no right or wrong answer.

**In the last MONTH, how often have you...**

	Never	Almost never	Sometimes	Fairly often	Very often
<b>1. Been upset because of something that happened unexpectedly.</b>	(0)	(1)	(2)	(3)	(4)
<b>2. Felt that you were unable to control the important things in your life.</b>	(0)	(1)	(2)	(3)	(4)
<b>3. Felt nervous and "stressed".</b>	(0)	(1)	(2)	(3)	(4)
<b>4. Felt confident about your ability to handle your personal problems.</b>	(0)	(1)	(2)	(3)	(4)
<b>5. Felt that things were going your way.</b>	(0)	(1)	(2)	(3)	(4)
<b>6. Found that you could not cope with all the things that you had to do.</b>	(0)	(1)	(2)	(3)	(4)
<b>7. Been able to control irritations in your life.</b>	(0)	(1)	(2)	(3)	(4)
<b>8. Felt that you were on top of things.</b>	(0)	(1)	(2)	(3)	(4)
<b>9. Been angered because of things that happened that were outside of your control.</b>	(0)	(1)	(2)	(3)	(4)
<b>10. Felt difficulties were piling up so high that you could not overcome them.</b>	(0)	(1)	(2)	(3)	(4)

**BIOBEHAVIORAL RELATIONSHIPS IN PERSONS ON HEMODIALYSIS**  
**McCain/Allen**

**Subject ID**

**CES-D**

**Date**   /   /

Directions: Below are feelings some people have. Please fill in the corresponding bubble that best fits **how much you have had each feeling during the past week**. If you have not had this feeling at all then fill in the bubble for "less than one day each week or none". There are no right or wrong answers.

	Less than 1 day each week or none	1-2 days per week	3-4 days per week	Most of the time
1. I was bothered by things that usually don't bother me.	<input type="radio"/> 0	<input type="radio"/> 1	<input type="radio"/> 2	<input type="radio"/> 3
2. I did not feel like eating; my appetite was poor.	<input type="radio"/> 0	<input type="radio"/> 1	<input type="radio"/> 2	<input type="radio"/> 3
3. I felt that I could not shake off the blues even with help from my family or friends.	<input type="radio"/> 0	<input type="radio"/> 1	<input type="radio"/> 2	<input type="radio"/> 3
4. I felt that I was just as good as other people.	<input type="radio"/> 0	<input type="radio"/> 1	<input type="radio"/> 2	<input type="radio"/> 3
5. I had trouble keeping my mind on what I was doing.	<input type="radio"/> 0	<input type="radio"/> 1	<input type="radio"/> 2	<input type="radio"/> 3
6. I felt depressed.	<input type="radio"/> 0	<input type="radio"/> 1	<input type="radio"/> 2	<input type="radio"/> 3
7. I felt that everything I did was an effort.	<input type="radio"/> 0	<input type="radio"/> 1	<input type="radio"/> 2	<input type="radio"/> 3
8. I felt hopeful about the future.	<input type="radio"/> 0	<input type="radio"/> 1	<input type="radio"/> 2	<input type="radio"/> 3
9. I thought my life had been a failure.	<input type="radio"/> 0	<input type="radio"/> 1	<input type="radio"/> 2	<input type="radio"/> 3
10. I felt fearful.	<input type="radio"/> 0	<input type="radio"/> 1	<input type="radio"/> 2	<input type="radio"/> 3
11. My sleep was restless.	<input type="radio"/> 0	<input type="radio"/> 1	<input type="radio"/> 2	<input type="radio"/> 3
12. I was happy.	<input type="radio"/> 0	<input type="radio"/> 1	<input type="radio"/> 2	<input type="radio"/> 3
13. I talked less than usual.	<input type="radio"/> 0	<input type="radio"/> 1	<input type="radio"/> 2	<input type="radio"/> 3

	<b>Less than 1 day each week or none</b>	<b>1-2 days per week</b>	<b>3-4 days per week</b>	<b>Most of the time</b>
<b>14. I felt lonely.</b>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
<b>15. People were unfriendly.</b>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
<b>16. I enjoyed life.</b>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
<b>17. I had crying spells.</b>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
<b>18. I felt sad.</b>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
<b>19. I felt that people disliked me.</b>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
<b>20. I could not get "going".</b>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

**McCain/Allen  
FACT-G (Version 4)**

Date   /   /

Below is a list of statements that other people with your illness have said are important. By filling in one (1) circle per line, please indicate how true each statement has been for you during the past 7 days.

**PHYSICAL WELL-BEING**

		Not at all	A little bit	Some what	Quite a bit	Very much
GP1	I have lack of energy.....	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
GP2	I have nausea.....	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
GP3	Because of my physical condition, I have trouble meeting the needs of my family.....	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
GP4	I have pain.....	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
GP5	I am bothered by side effects of treatment.....	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
GP6	I feel ill.....	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
GP7	I am forced to spend time in bed.....	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

**SOCIAL/FAMILY WELL-BEING**

		Not at all	A little bit	Some what	Quite a bit	Very much
GS1	I feel close to my friends.....	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
GS2	I get emotional support from my family.....	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
GS3	I get support from my friends.....	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
GS4	My family has accepted my illness.....	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
GS5	I am satisfied with family communication about my illness.....	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
GS6	I feel close to my partner (or the person who is my main support).....	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Q1	<i>Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer, please check this box <input type="checkbox"/> and go to the next section.</i>					
GS7	I am satisfied with my sex life.....	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

### EMOTIONAL WELL-BEING

		Not at all	A little bit	Some what	Quite a bit	Very much
GE1	I feel sad.....	0	1	2	3	4
GE2	I am satisfied with how I am coping with my illness.....	0	1	2	3	4
GE3	I am losing hope in the fight against my illness.....	0	1	2	3	4
GE4	I feel nervous.....	0	1	2	3	4
GE5	I worry about dying.....	0	1	2	3	4
GE6	I worry that my condition will get worse.....	0	1	2	3	4

### FUNCTIONAL WELL-BEING

		Not at all	A little bit	Some what	Quite a bit	Very much
GF1	I am able to work (include work at home).....	0	1	2	3	4
GF2	My work (include work at home) is fulfilling.....	0	1	2	3	4
GF3	I am able to enjoy life.....	0	1	2	3	4
GF4	I have accepted my illness.....	0	1	2	3	4
GF5	I am sleeping well.....	0	1	2	3	4
GF6	I am enjoying the things I usually do for fun.....	0	1	2	3	4
GF7	I am content with the quality of my life right now.....	0	1	2	3	4

# VCU Memo

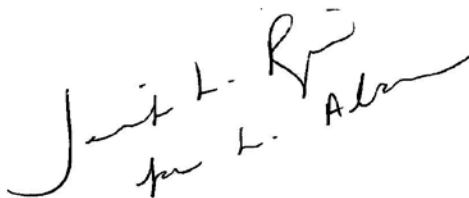
V i r g i n i a C o m m o n w e a l t h U n i v e r s i t y

Office of Research Subjects Protection  
BioTechnology Research Park  
BioTech One, 800 E. Leigh Street, #114  
P.O. Box 980568  
Richmond, Virginia 23298-0568  
(804) 828-3992  
(804) 827-1448 (fax)

DATE: July 7, 2010

TO: Nancy L. McCain, DSN, RN, FAAN  
School of Nursing  
Box 980567

FROM: Lisa M. Abrams, PhD  
Chairperson, VCU IRB Panel B  
Box 980568



RE: **VCU IRB #: HM13056**  
**Title: Biobehavior Relationships in Persons on Hemodialysis**

On July 7, 2010, the following research study was approved by expedited review according to 45 CFR 46.110 Categories 2, 5, and 7. The approval reflects the revisions received in the Office of Research Subjects Protection on July 2, 2010. This approval includes the following items reviewed by this Panel:

**RESEARCH APPLICATION/PROPOSAL:** None

**PROTOCOL (Research Plan):** Biobehavior Relationships in Persons on Hemodialysis, received 6/22/10, version 1, dated 6/3/10

- FACT-G (Version 4), received 6/22/10, version 1, dated 6/21/10
- Perceived Stress Scale, received 6/22/10, version 1, dated 6/21/10
- CES-D, received 6/22/10, version 1, dated 6/21/10

**CONSENT/ASSENT (attached):**

- Research Subject Information and Consent Form, received 7/2/10, version 1, dated 5/27/10, 4 pages

**ADDITIONAL DOCUMENTS:** None

**This approval expires on June 30, 2011.** Federal Regulations/VCU Policy and Procedures require continuing review prior to continuation of approval past that date. Continuing Review report forms will be mailed to you prior to the scheduled review.

The Primary Reviewer assigned to your research study is Lou Usry, RN. If you have any questions, please contact Ms. Usry at [lusry@mcvh-vcu.edu](mailto:lusry@mcvh-vcu.edu) and 828-9229; or you may contact Jennifer Rice, IRB Coordinator, VCU Office of Research Subjects Protection, at [jlrice@vcu.edu](mailto:jlrice@vcu.edu) and 828-3992.

*[Attachment – Conditions of Approval]*



### ***Conditions of Approval:***

In order to comply with federal regulations, industry standards, and the terms of this approval, the investigator must (*as applicable*):

1. Conduct the research as described in and required by the Protocol.
2. Obtain informed consent from all subjects without coercion or undue influence, and provide the potential subject sufficient opportunity to consider whether or not to participate (unless Waiver of Consent is specifically approved or research is exempt).
3. Document informed consent using only the most recently dated consent form bearing the VCU IRB "APPROVED" stamp (unless Waiver of Consent is specifically approved).
4. Provide non-English speaking patients with a translation of the approved Consent Form in the research participant's first language. The Panel must approve the translated version.
5. Obtain prior approval from VCU IRB before implementing any changes whatsoever in the approved protocol or consent form, unless such changes are necessary to protect the safety of human research participants (e.g., permanent/temporary change of PI, addition of performance/collaborative sites, request to include newly incarcerated participants or participants that are wards of the state, addition/deletion of participant groups, etc.). Any departure from these approved documents must be reported to the VCU IRB immediately as an Unanticipated Problem (see #7).
6. Monitor all problems (anticipated and unanticipated) associated with risk to research participants or others.
7. Report Unanticipated Problems (UPs), including protocol deviations, following the VCU IRB requirements and timelines detailed in VCU IRB WPP VIII-7:
8. Obtain prior approval from the VCU IRB before use of any advertisement or other material for recruitment of research participants.
9. Promptly report and/or respond to all inquiries by the VCU IRB concerning the conduct of the approved research when so requested.
10. All protocols that administer acute medical treatment to human research participants must have an emergency preparedness plan. Please refer to VCU guidance on <http://www.research.vcu.edu/irb/guidance.htm>.
11. The VCU IRBs operate under the regulatory authorities as described within:
  - a) U.S. Department of Health and Human Services Title 45 CFR 46, Subparts A, B, C, and D (for all research, regardless of source of funding) and related guidance documents.
  - b) U.S. Food and Drug Administration Chapter I of Title 21 CFR 50 and 56 (for FDA regulated research only) and related guidance documents.
  - c) Commonwealth of Virginia Code of Virginia 32.1 Chapter 5.1 Human Research (for all research).

[010507]

## RESEARCH SUBJECT INFORMATION AND CONSENT FORM

**TITLE:** Biobehavioral Relationships in Persons on Hemodialysis

**VCU IRB NO.:** HM13056

**SPONSOR:**

This consent form may contain words that you do not understand. Please ask the study staff to explain any words that you do not clearly understand. You may take home an unsigned copy of this consent form to think about or discuss with family or friends before making your decision.

### PURPOSE OF THE STUDY

The purpose of this study is to find out if there are connections between your stress related to being on hemodialysis, your mood, and immune system function that may influence your quality of life. You have been invited to participate in this study because you receive hemodialysis.

### DESCRIPTION OF THE STUDY AND YOUR INVOLVEMENT

If you decide to be in this research study, you will be asked to sign this consent form after you have had all your questions answered and understand what will happen to you.

You are one of 75 patients who are being invited to participate in this study. The study will take place during one dialysis session. Less than one-half teaspoon of blood will be collected from your dialysis access to measure the status of your immune system (cytokines) before you begin dialysis. During the first hour of dialysis you will be asked to complete three questionnaires. This will take about 15 minutes. Other measures of your health status will be obtained from your medical chart including how long you have been on dialysis, your age, and other medical diagnostic information.

### RISKS AND DISCOMFORTS

The blood samples will be collected from your dialysis access so there will be no additional discomfort from a needle stick. Less than one-half teaspoon of blood will be collected using sterile procedures so there will be no health risk for you. You may tire from completing the questionnaires but this should pose no discomfort and you may rest as needed while completing the questionnaires.

### BENEFITS TO YOU AND OTHERS

There will not be any direct benefit to you from this study, but the information we learn from people in this study may help other dialysis patients in the future.

### COSTS

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There are no costs for participating in this study other than the time you will spend filling out questionnaires. This will take place during your regular dialysis session so no additional time will be required at the dialysis unit.

### **ALTERNATIVES**

The alternative is not to participate in this study.

### **CONFIDENTIALITY**

Potentially identifiable information about you will consist of information from your medical record. The study information is being collected for research purposes only. Your data will be tracked by an assigned ID number, not your name or other personally identifying information, and stored separately from your medical records in a locked research area. All personal identifying information will be kept in password protected files. Your signed consent and identifying information will be kept in a locked file cabinet with your questionnaires for 12 months after the study ends and will be destroyed at that time. Access to all data will be limited to study personnel. A data safety monitoring plan is established.

We will not tell anyone the answers you give us; however, information from the study and information from your medical record and the consent form signed by you may be looked at or copied for research or legal purposes by Virginia Commonwealth University.

What we find from this study may be presented at meetings or published in papers, but your name will not ever be used in these presentations or papers and no individual will be identifiable in these reports.

### **IF AN INJURY HAPPENS**

Virginia Commonwealth University and the VCU Health System do not have a plan to give long-term care or money if you are injured because you are in the study.

If you are injured because of being in this study, tell the study staff right away. The study staff will arrange for short-term emergency care or referral if it is needed.

Bills for treatment may be sent to you or your insurance. Your insurance may or may not pay for taking care of injuries that happen because of being in this study.

### **VOLUNTARY PARTICIPATION AND WITHDRAWAL**

You do not have to participate in this study. If you choose to participate, you may stop at any time without any penalty. You may also choose not to answer particular questions that are asked in the study. Your decision to withdraw will involve no penalty or loss of care, service or benefits to which you are otherwise entitled from this service provider.

Your participation in this study may be stopped at any time by the study staff without your consent. The reasons for this might include:

- the study staff thinks it necessary for your health or safety;

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- you have not followed study instructions; or
- administrative reasons require your withdrawal.

### QUESTIONS

In the future, you may have questions about your participation in this study. If you have any questions, complaints, or concerns about the research, contact:

Nancy L. McCain, RN, DSN, FAAN  
Professor of Nursing, VCU School of Nursing  
1100 E. Leigh Street  
Richmond, VA 23298-0567  
Telephone: 804-828-3444

OR

Avis Allen  
Nurse Manager Dialysis/Vascular Access, VCU Health System  
1200 East Marshall St.  
Richmond, VA 23298  
Telephone: 804 828-5899

If you have any questions about your rights as a participant in this study, you may contact:

Office for Research  
Virginia Commonwealth University  
800 East Leigh Street, Suite 113  
P.O. Box 980568  
Richmond, VA 23298  
Telephone: 804-827-2157

You may also contact this number for general questions, concerns or complaints about the research. Please call this number if you cannot reach the research team or wish to talk to someone else. Additional information about participation in research studies can be found at <http://www.research.vcu.edu/irb/volunteers.htm>

### CONSENT

I have been given the chance to read this consent form. I understand the information about this study. Questions that I wanted to ask about the study have been answered. My signature says that I am willing to participate in this study. I will receive a copy of the consent form once I have agreed to participate.

[5-27-10 v1]

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**APPROVED**

7-7-10/Lu/JR

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Participant name printed

Participant signature

Date

---

Name of Person Conducting Informed Consent  
Discussion / Witness  
(Printed)

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Signature of Person Conducting Informed Consent  
Discussion / Witness

Date

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Principal Investigator Signature (if different from above)

Date

## **CHAPTER 4: Biobehavioral Relationships and Health Related Quality of Life in Persons with End Stage Renal Disease on Hemodialysis**

### **Abstract**

Health-related quality of life (HRQOL) is lower and mortality rates are higher for patients with end stage renal disease (ESRD) than for the general population. However, the relationships among perceived stress, immune functioning, depression, disease-related factors, and health-related quality of life have not been fully explored in this population. The purpose of this study was to examine the relationships among perceived stress, immune indicators, depressive symptoms, disease-related factors and HRQOL among patients requiring hemodialysis for ESRD.

The sample included 75 adults with ESRD requiring dialysis who consented and were enrolled in the study. Exclusion criteria included acute infections, human immunodeficiency virus infection (HIV), cancer, current use of immunosuppressive drugs, or active psychosis. Blood for cytokine analyses was drawn from the dialysis access port immediately prior to the start of dialysis. Participants completed a demographic questionnaire and the three psychosocial measures: the Perceived Stress Scale (PSS), the Center for Epidemiologic Studies Depression Scale (CES-D), and a quality of life measure, the Functional Assessment of Cancer Therapy-General scale (FACT-G), during the first hour of the dialysis treatment.

The sample was predominantly African American (75.7%) and male (65%) with a mean age of 53.9 years (range 23-83). Mean time that participants had been on dialysis was 3.0 years with a range of less than 1 month to 20.8 years. Most participants had been diagnosed with hypertension (85%) and diabetes (59%). Mean levels of perceived stress were 15.9 ( $SD = 8.0$ ),

levels of depressive symptoms were 16.2 ( $SD = 12.7$ ), and levels of HRQOL were 68.1 ( $SD = 14.2$ ). Multiple regression models were constructed with log-transformed cytokine data. Negative correlations were found between perceived stress and HRQOL ( $p = 0.0240-0.0287$ ) and depressive symptoms with health-related quality of life ( $p = 0.0007- <.0001$ ). MIP-1  $\beta$  was the only cytokine significantly (and positively) correlated with HRQOL ( $p = 0.0034-0.0068$ ).

Principal component analysis of the cytokine data revealed three factors: Factors 1 and 3 represented a pro-inflammatory cytokines and Factor 2 represented a mixture of pro-inflammatory and anti-inflammatory cytokines. There was a significant correlation between Factor 1 and depressive symptoms ( $p = 0.0069$ ). Significant differences in the distributions of Factors 2 and 3 were associated with the presence of cardiovascular disease (Chi-square = 4.0,  $df = 1$ ,  $p = 0.047$ ), (Chi-square = 4.1,  $df = 1$ ,  $p = 0.043$ ), respectively, and Factor 3 with hypertension (Chi-square = 7.6,  $df = 1$ ,  $p = 0.006$ ). However, no relationships were found between the cytokine factors and HRQOL, PSS, or other variables. Findings suggest that there are relationships among psychosocial variables and possibly biological interactions that may affect perceptions of HRQOL among persons with ESRD on hemodialysis.

## **Biobehavioral Relationships and Health Related Quality of Life in**

### **Persons with End Stage Renal Disease on Hemodialysis**

Over 350,000 persons in the United States with End Stage Renal Disease (ESRD) must have thrice weekly in-center hemodialysis sessions to maintain their kidney function. In-center dialysis is time intensive and physically and financially burdensome to ESRD patients. In addition to dialysis, patients with ESRD live with changes in diet, fluid restrictions, weakness and pain, loss of income, perceptions of stress, and role changes within the family (Kimmel, 2002; Kring & Crane, 2009; Mapes et al., 2004). Hence, it is not surprising that hemodialysis patients have consistently been shown to have a lower quality of life than patients on other forms of renal replacement therapy. Decreased quality of life in dialysis patients has been shown to be linked with increased risk of death (Mapes et al., 2004). However, little research has examined the relationships of psychosocial and immune measures that may be associated with health related quality of life (HRQOL) in persons with ESRD on hemodialysis.

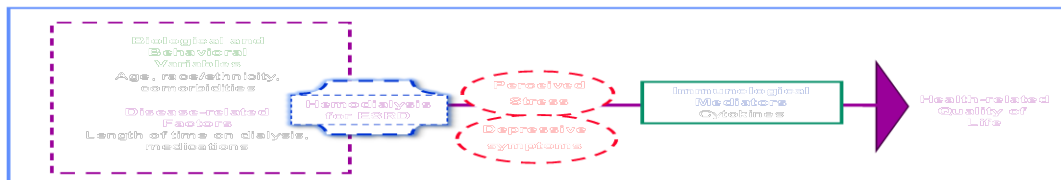
The psychoneuroimmunology (PNI) model provides an appropriate framework for the examination of the biological and behavioral factors affecting HRQOL in persons with ESRD on hemodialysis. PNI is the study of the interaction of the central nervous system (CNS), endocrine system, and immune system (Yang & Glaser, 2002). This multidirectional communication has an impact on the response to stressful events. The PNI framework explains the physical and psychosocial interactions related to stress that affect the immune system (McCain, Gray, Walter, & Robins, 2005). Psychosocial and behavioral factors are believed to moderate the immune system through neuroendocrine system changes. Psychosocial variables of interest in this study included perceived stress, depressive symptoms, and HRQOL. Disease-related factors included comorbidities, time on dialysis, and medications. No previous studies are known to have used the



PNI model to investigate relationships among these variables in the ESRD population.

Fundamentally, we propose that hemodialysis for ESRD is stressful, resulting in biological and behavioral interactions, ultimately affecting perceptions of health-related quality of life. Figure 1 depicts the proposed relationships among the variables in this study. Stress and depressive symptoms are key moderating variables in this PNI-based model.

Figure 1. Relationships among Study Variables



## Stress

Stress is the stimulus that precipitates a response in the brain to activate physiological adaptive systems. The sympathetic-adrenal-medullary (SAM) axis and the hypothalamic-pituitary-adrenal (HPA) axis are activated, releasing pituitary and adrenal hormones that have the potential to dysregulate immune function (Glaser & Kiecolt-Glaser, 2005). Products of stress such as peptides and steroid hormones are metabolized by the kidney, leading to high circulating levels in the patient with renal disease, resulting in a biochemically-induced chronic stress response (Cukor et al., 2007). One of the outcomes of chronic stress is suppressed cellular immunity (McEwen, 2007). Thus, chronic stress generated by living with a serious illness such as renal failure may further compromise the immune system in patients with ESRD. Stress has also been associated with both depression and decreased quality of life.

## **Depression**

Depression is the most common psychological problem reported by hemodialysis patients (Lopes et al., 2004) and has been associated with decreased quality of life (Dogan, Eryonucu, Sayarlioglu & Agargun, (2005). Depression has been linked with various health problems, including cardiovascular disease and malnutrition-inflammation complex (Cukor, Cohen, Peterson, & Kimmel, 2007; Ibrahim & Salamony, 2008; Koo et al., 2003). Lopes et al. (2004) used the short version of the Center for Epidemiological Studies-Depression Scale (CES-D) to assess depressive symptoms in hemodialysis patients and found that 48% of dialysis patients had a score >10, indicating probable depression (Lopes et al., 2004). Higher levels of anxiety and depression have been linked to increased hospitalization and mortality in ESRD patients (Kimmel & Peterson, 2005; Ye et al., 2008). Depression has also been linked to changes in immune function in the general population as well as patients on hemodialysis for ESRD (Hung et al., 2011; Ranjit et al., 2007).

## **Immune Factors**

Immune factors such as cytokines may be associated with increased cardiovascular disease, malnutrition, and decreased quality of life in patients on hemodialysis. Sertic et al. (2007) reported that levels of interleukin (IL)-6, IL-8, IL-4, IL-10, tumor necrosis factor-alpha (TNF- $\alpha$ ), IL-1 $\alpha$ , IL-1 $\beta$ , and monocyte chemotactic protein-1 (MCP-1) were significantly higher in chronic hemodialysis patients compared to healthy control subjects. In dialysis patients elevated pro-inflammatory cytokine levels, particularly IL-6, and C-reactive protein (CRP) have been implicated in vascular disease events and mortality (Cazzavillan, et al., 2007; Lentine, Parsonnet, Taylor, Wrone, & Lafayette, 2006) as well as malnutrition (Ibrahim & Salamony, 2008; Koo et al., 2003). Psychological changes, including depression and decreased quality of

life, have been associated with inflammatory cytokine changes as well (Dervisoglu, Kir, Kalender, Eraldemir, & Caglayan, 2008). Many common comorbidities associated with ESRD, such as diabetes and hypertension have also been implicated in immune status changes.

### **Disease-related Factors**

Disease-related factors may add to the burden of living with ESRD. Many hemodialysis patients have one or more common comorbidities that add to their illness burden, including diabetes mellitus (DM), hypertension (HTN), cardiovascular disease (CVD), connective tissue disorders, liver diseases (including hepatitis B and C), acquired immune deficiency syndrome (AIDS), and peripheral vascular disease (PVD) (Beddhu et al., 2000; Snaedal et al., 2009). Reflecting the ongoing burden of hemodialysis, one study found that patients undergoing hemodialysis for more than four years had lower quality of life than those who had recently started hemodialysis (Ginieri-Coccosis, Theofilou, Synodinou, Tomaras, and Soldatos, 2009). Beddhu et al. (2000) found strong correlations between comorbidity scores and hospitalization and mortality in a study of patients on hemodialysis and peritoneal dialysis. Further, Snaedal et al. (2009) found associations between inflammatory activity and congestive heart failure and peripheral vascular disease. Certainly such comorbidities must be considered as critical cofactors in a PNI-framework when examining factors related to HRQOL.

Treatment for ESRD is experienced through the filter of psychosocial and disease-related factors, influencing and interacting with the immune response. This interaction ultimately affects HRQOL. Multiple studies have investigated the association between select variables and HRQOL (e.g., Dervisoglu, Kir, Kalender, Eraldemir, & Caglayan, 2008; Dogan, Eryonucu, Sayarlioglu, & Agargun, 2005; Tossani, Cassano, & Fava, 2005), but no known studies have explored correlations among all of the variables and HRQOL using a PNI model. Therefore, the

purpose of this study was to examine the relationships among disease-related factors, perceived stress, depressive symptoms, immune indicators, and HRQOL among patients requiring hemodialysis for ESRD using a PNI-based framework.

## **Methods**

### **Participants, Procedures and Setting**

Participants were recruited from a two sites: a community dialysis unit and a hospital-based dialysis unit in an urban city in the Southeast. The study was approved by the Institutional Review Board of the university and the Research Board of the chronic dialysis facility. Informed consent was obtained from all participants. All patients 21 years of age or older diagnosed with ESRD requiring dialysis and competent to consent were eligible for inclusion. Exclusion criteria included acute infections or AIDS, diagnosis of cancer, currently on immunosuppressive drugs, or diagnosed with active psychosis. Potential participants were identified by the charge nurses in the dialysis units and then screened and consented by the investigator during a regular dialysis treatment session. Data on comorbidities, pertinent clinical factors (such as medications), and time on dialysis were collected from patient records. Immediately prior to the start of dialysis, 2 ml of blood for cytokine analysis was drawn from the dialysis access. Participants completed a demographic questionnaire and the three psychosocial measures (Perceived Stress Scale, Functional Assessment of Cancer Therapy-General, and Center for Epidemiological Studies-Depression scale) during the first hour of the dialysis treatment.

### **Measures**

**Cytokines.** Plasma levels of 17 cytokines were measured using a Bio-Plex® multiplex suspension array system with BioRad Human 17-Plex® magnetic bead array kits. The cytokines included in the array were IL-1 $\beta$ , IL-2, IL-4, IL-5, IL-6, IL-7, IL-8, IL-10, IL-12, IL-13, IL-17,

granulocyte-colony stimulating factor (G-CSF), granulocyte macrophage colony stimulating factor (GM-CSF), interferon-gamma (IFN- $\gamma$ ), monocyte chemotactic protein-1 (MCP-1), macrophage inflammatory protein-1 beta (MIP-1 $\beta$ ), and TNF- $\alpha$ . This panel measures analyte values in the range of 1.4  $\approx$  95,000 pg/ml, with high precision (intra-assay CV 5%-15%, inter-assay CV 5%-11%, observed vs. expected  $R^2 > 0.95$ ) and sensitivity (limit of detection = 0.6-6.4 pg/ml)(Bio-Plex Pro Tech Note 5803, 2009).

**Psychosocial Measures.** Psychosocial variables measured in this study were perceived stress, depressive symptoms, and HRQOL. Perceived stress was measured by the Perceived Stress Scale (PSS), a 10-item self-report scale developed to measure “the degree to which situations in one’s life are appraised as stressful” (Cohen, Kamarck, & Mermelstein, 1983, p. 385). Questions are designed to capture the extent to which respondents feel their lives are unpredictable, uncontrollable, and overloading. The 10 items are rated on a 5-point Likert scale, from 0 for never to 4 for very often. A higher score indicates higher levels of perceived stress. Chronbach’s alpha was reported to be 0.84-0.86 from a large sample of the general population (Cohen et al., 1983). Schwarz and Dunphy (2003) reported a Chronbach’s alpha of 0.87 in a study of perceived stress in caregivers of family members with heart failure.

Depressive symptoms were measured by the Center for Epidemiological Studies-Depression scale (CES-D), a 20-item self-report designed to measure depressive symptoms in the past 7 days. Items are scored from 0 to 3 points with higher scores indicating greater depressive symptoms. The CES-D has been found to be a valid and reliable instrument for assessing depressive symptoms in the general population with estimates of internal consistency ranging from 0.84-0.90 (Radloff, 1977).

Health related quality of life was measured by the Functional Assessment of Cancer Therapy-General (FACT-G) scale developed by Cella et al. (1993). It was initially developed to measure quality of life in persons with cancer but has now been expanded into the Functional Assessment of Chronic Illness Therapy (FACIT) Measurement System (formerly the FACT System), a collection of questionnaires designed for use with other chronic disease populations ([www.facit.org](http://www.facit.org)). The FACT-G (Version 4) is a 27-item self-report scale that includes subscales for physical, functional, social/family, and emotional well-being. Participants are asked to respond to statements as they apply in the last 7 days. Item scores range from 0 (not at all) to 4 (very much) with higher scale scores indicating better function. Internal consistency coefficients range from 0.63 to 0.89 for the subscales and 0.89 for the total score (Webster, Odom, Peterman, Lent, & Cella, 1999).

**Biological and Disease-related Factors.** Data on comorbidities including diabetes mellitus, hypertension, cardiovascular disease, connective tissue disorders, liver diseases (including hepatitis B and C), and peripheral vascular disease were obtained from medical record review. Medication profiles were also retrieved from the medical record. Time on dialysis was measured from the ESRD Medical Evidence Report, a form completed by the nephrologist for Medicare entitlement reports.

### **Analytic Approaches**

JMP® 9.0.0 (SAS Institute, Inc., Cary, NC) was used for statistical analysis. Descriptive statistics were computed for demographic information, length of time on dialysis, and comorbidities. Chronbach's alpha was calculated for the PSS, FACT-G, and CES-D. Cytokine data were logarithmically transformed because the original data were strongly skewed, then descriptive statistics were computed on the log-transformed data. The log-transformed cytokine

data were subjected to factor analysis and principal component analysis. Then relationships between the identified components and HRQOL were examined. Multiple regression models were constructed to examine the relationships of time on dialysis, cytokines, comorbidities, perceived stress, and depressive symptoms with HRQOL. Statistical significance was set at  $\alpha = 0.05$ . Each participant was assigned an arbitrary code number and no identifying information was entered into the database. Data were entered into a database that was password protected with the password known only to the study investigators. Error checks were routinely done and the database reconciled.

## **Results**

Seventy-five participants were enrolled in the study. A total of 134 candidates were screened, 36 were excluded and 23 declined to participate. Exclusions were predominantly due to acute infections or current steroid treatment. The sample was predominantly Black (75.7%) and male (65%) with a mean age of 53.9 (range 23-83) and over half (65%) had started or completed high school. Mean time on dialysis was 3.0 years with a range of less than 1 month to over 20 years (20.8) years. Most participants also had been diagnosed with hypertension (85%) and diabetes (59%). A majority of participants were taking anti-hypertensive medications (78.4%), erythropoietin stimulating hormone drugs (71.6%), iron (51.4%), and/or cardiovascular drugs (47.3%). The sample is similar in age and comorbidities to the national demographics for ESRD patients on hemodialysis, but the proportion of African Americans and males in this study sample was much higher than the national average (USRDS, 2009). The mean for the PSS was 15.9 ( $SD = 8.0$ ), indicating a moderate level of stress in the sample (Cohen & Williamson, 1988). The mean for the CES-D was 16.2 ( $SD = 12.7$ ), indicating a relatively high level of depressive symptoms overall (Radloff, 1977). The mean for the FACT-G was 68.1 ( $SD = 14.2$ ), lower than

the mean of 80.1 found in normative studies (Webster, Cella, & Yost, 2003). Means on the FACT-G subscales also were below normative data (Webster, Cella, & Yost, 2003), with the exception of the Social/Family Well-being subscale. The Physical Well-Being subscale mean was 18.7 (normative mean = 22.7), 20.1 (normative mean = 19.1) for the Social/Family Well-Being subscale, 14.9 (normative mean = 19.9) for the Emotional Well-Being subscale, and 14.4 (normative mean = 18.5) for the Functional Well-Being subscale. Table 1 displays the means for the psychosocial data. All three psychosocial measures showed good reliability in this study, with a Chronbach's alpha for the PSS of 0.83, 0.90 for the CES-D, and 0.89 for the FACT-G.

*Table 1. Sample Scores and Normative Data for Psychosocial Measures*

<b>Measure</b>	<b>Sample Mean (SD)</b>	<b>Normative Mean (SD)</b>
PSS	15.9 (8.0)	13.0 (6.5)
CES-D	16.2 (12.7)	----
FACT-G	68.1 (14.2)	80.1 (18.1)
Physical Well-being	18.7 (6.02)	22.7 (5.4)
Social/Family Well-being	20.1 (6.40)	19.1 (6.8)
Emotional Well-being	14.9 (3.12)	19.9 (4.8)
Functional Well-being	14.4 (6.33)	18.5 (6.8)

Actual distributions of the non-transformed cytokine levels are reported in Table 2 in pg/ml as measured by the BioRad 17-plex. Medians for the cytokine levels ranged from 0.1 pg/ml for IL-2 and IL-17 to 153.6 pg/ml for MIP-1 $\beta$ , and standard deviations ranged from 8.09 pg/ml for IL-4 to 592.11 pg/ml for TNF- $\alpha$ . The cytokine data were not normally distributed and therefore were log-transformed for subsequent analyses. Each cytokine was first examined in a regression model using only PSS and CES-D as covariates. However the cytokines, with the



exception of MIP-1 $\beta$ , were not significantly related to HRQOL. In order to determine if there were cytokine patterns that might correlate with HRQOL, a principal component analysis of the cytokines was completed, with a varimax rotation to maintain independence of the factors.

Table 2. Cytokine Levels (pg/ml)

<b>Cytokine</b>	<b>Mean</b>	<b>Median</b>	<b>SD</b>
IL-1 $\beta$	3.80	1.09	17.67
IL-2	31.63	0.1	191.58
IL-4	2.68	0.94	8.09
IL-5	9.77	1.91	54.36
IL-6	39.71	8.75	149.46
IL-7	17.81	5.68	59.06
IL-8	28.42	19.84	29.08
IL-10	34.34	1.71	220.20
IL-12	40.21	2.88	204.47
IL-13	9.21	0.52	37.84
IL-17	39.37	0.1	201.16
G-CSF	85.62	48.06	99.14
GM-CSF	149.38	83.05	383.80
IFN- $\gamma$	181.49	41.56	84.62
MCP-1	95.11	81.93	70.67
MIP-1 $\beta$	168.56	153.59	67.69
TNF- $\alpha$	87.37	8.79	592.11

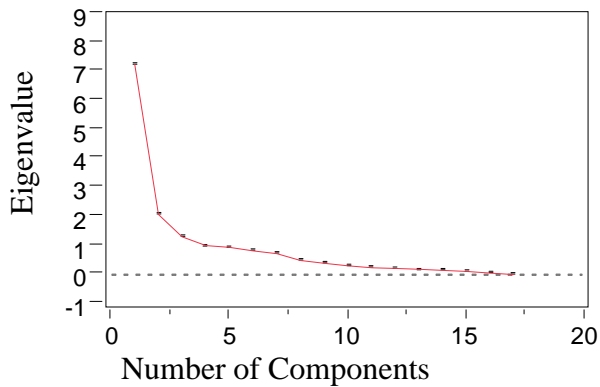
The principal component analysis of cytokine data revealed three factors (Table 3). Inspection of the screeplot (Figure 2) revealed a break after the third factor and the three components explaining 63% of the variance were retained for further analysis. The first factor represented a primarily pro-inflammatory response (IL-1 $\beta$ , IFN- $\gamma$ , TNF- $\alpha$ , IL-4, and G-CSF) and accounted for 32% of variance. The second factor represented a balance of pro-inflammatory and anti-inflammatory cytokines (IL-2, IL-7, IL-10, IL-12, IL-13, and IL-17) and accounted for 23% of variance. The third factor also represented a pro-inflammatory response (IL-2, IL-6, IL-8,

MCP-1, and MIP-1 $\beta$ ) and accounted for 17% of variance. Correlations were found between immune factor patterns and hypertension and cardiovascular disease. Stenvinkel et al. (1999) and Lentine, Parsonnet, Taylor, Wron, and Lafayette (2006) reported similar correlations between markers for inflammation and atherosclerotic vascular disease in ESRD. There were significant, albeit low, correlations between Factor 1 and depressive symptoms ( $r = 0.1, p = 0.01$ ) and significant differences in the distributions on Factor 2 by the presence of CVD (Chi-square = 4.0,  $df = 1, p = 0.047$ ), Factor 3 and CVD (Chi-square = 4.1,  $df = 1, p = 0.043$ ), and Factor 3 and HTN (Chi-square = 7.6,  $df = 1, p = 0.006$ ). However, no relationships were found between the cytokine factors and other disease-related factors (connective tissue disorder, liver disease, and/or peripheral vascular disease), perceived stress, or HRQOL.

Table 3. Factor Loadings for Log-transformed Cytokine Data

Cytokine	Factor 1	Factor 2	Factor 3
IL-1 $\beta$	<b>0.82</b>	0.22	0.17
IL-2	0.14	<b>0.56</b>	0.54
IL-4	<b>0.92</b>	0.20	0.10
IL-5	0.45	<b>0.72</b>	<0
IL-6	0.45	0.17	<b>0.64</b>
IL-7	0.39	<b>0.75</b>	-0.20
IL-8	0.14	0.06	<b>0.72</b>
IL-10	0.12	<b>0.68</b>	0.32
IL-12	0.29	<b>0.77</b>	0.23
IL-13	0.19	<b>0.61</b>	0.45
IL-17	0.23	<b>0.56</b>	0.47
G-CSF	<b>0.55</b>	0.27	-0.20
GM-CSF	0.20	0.17	-0.10
IFN- $\gamma$	<b>0.84</b>	0.25	0.32
MCP-1	0.12	0.06	<b>0.75</b>
MIP-1 $\beta$	-0.10	0.10	<b>0.53</b>
TNF- $\alpha$	<b>0.75</b>	0.42	0.15

Figure 2. Scree Plot for Cytokine Factors



Multiple regression models were constructed with log-transformed cytokine data (Table 4). Model 1 included covariates of time on dialysis, diabetes, hypertension, perceived stress, depressive symptoms, and cytokine Factors 1, 2, and 3. After controlling for time on dialysis and the comorbidities of diabetes, hypertension and cardiovascular disease, HRQOL was found to be significantly related with perceived stress ( $p = 0.0264$ ) and depressive symptoms ( $p = 0.0007$ ). Average HRQOL increased with increased perceived stress and depressive symptoms. In regression models with individual cytokines, MIP-1 $\beta$  was found to be the only cytokine significantly related with HRQOL. Since MIP-1 $\beta$  loaded onto Factor 3 in the principal component analysis, an alternate model was constructed to include this individual cytokine rather than Factor 3.

Model 2 included covariates of time on dialysis, diabetes, hypertension, perceived stress, depressive symptoms, cytokine Factors 1 and 2, and MIP-1 $\beta$ . Controlling for time on dialysis and the comorbidities of diabetes, hypertension, cardiovascular disease, and Factors 1 and 2, a significant relationship was found between perceived stress ( $p = 0.0237$ ), depressive symptoms ( $p = <.0001$ ), and MIP-1 $\beta$  ( $p = 0.0034$ ) and HRQOL. Finding no significant relationships between comorbidities and length of time on dialysis with HRQOL, these variables were

excluded and a third model was run with perceived stress, depressive symptoms, Factors 1 and 2 and MIP-1 $\beta$ . After controlling for Factors 1 and 2, significant correlations remained between HRQOL and perceived stress ( $p = 0.0287$ ), depressive symptoms ( $p = <.0001$ ), and MIP-1 $\beta$  ( $p = 0.0068$ ). Model assumptions were examined for appropriateness of model fit, and the variance inflation factor for all models was  $<5$ , indicating no multicollinearity in the models.

Table 4. Multiple Regression Modeling Results for Biobehavioral Measures and HRQOL

Term	Sum of Squares			F- Ratio			p-Value		
	Model 1	Model 2	Model 3	Model 1	Model 2	Model 3	Model 1	Model 2	Model 3
TOD	40.03	160.41		0.38	1.73		0.54	0.19	
DM	6.46	83.71		0.06	0.90		0.81	0.35	
HTN	11.71	143.03		0.11	1.54		0.74	0.22	
CVD	210.41	198.54		1.98	2.14		0.16	0.15	
PSS	548.72	497.94	466.57	5.17	5.37	5.00	0.03*	0.02*	0.03*
CES-D	1367.20	1710.78	1620.24	12.89	18.46	17.35	0.0007 $\dagger$	<.0001 $\ddagger$	<.0001 $\ddagger$
Factor 1	57.17	124.56	94.22	0.54	1.34	1.01	0.47	0.25	0.32
Factor 2	233.86	173.12	127.48	2.20	1.87	1.37	0.14	0.18	0.25
Factor 3	24.48			0.23			0.63		
MIP-1 $\beta$		857.22	727.78		9.25	7.79		0.0034 $\dagger$	0.0068 $\dagger$

TOD = time on dialysis; DM = diabetes mellitus; HTN = hypertension; CVD = cardiovascular disease; PSS = Perceived Stress Score; CES-D = Center for Epidemiologic Studies Depression Scale.

\* $p < 0.05$ ,  $\dagger p < 0.01$ ,  $\ddagger p < 0.0001$

### Discussion

ESRD is a chronic disease with multiple physical and psychological stressors (Yeh & Chou, 2007) and long-term stress has been shown to lead to dysregulation of immune responses (Yang & Glaser, 2002). In the PNI model biological and behavioral variables and cofactors result in biological and behavioral interactions that may alter HRQOL.

Factor analysis of the cytokine data suggests that pro-inflammatory cytokines have correlations with cardiovascular disease and hypertension in patients with ESRD on hemodialysis. Atherosclerosis is a pro-inflammatory disorder and increased secretion of pro-

inflammatory cytokines, including MIP-1 $\beta$ , has been linked to atherosclerosis in prior studies in the general population (Cagnin et al., 2009; Cha et al., 2000). A larger sample size for the number of variables evaluated in this study may reveal stronger associations between immune function and health-related quality of life. Although no significant relationships were found for age, race, or comorbidities with HRQOL, this study suggests that there are behavioral and possibly biological interactions that are associated with patients' perceptions of HRQOL.

Study participants reported somewhat higher stress levels (15.9,  $SD = 8.0$ ) than normative data (mean = 13.02,  $SD = 6.35$ ) reported by Cohen and Williamson (1988). Likewise, the mean for the CES-D was 16.2 ( $SD = 12.7$ ), slightly above the cutoff of 16 for depressive symptoms. These results are consistent with a large international study that reported an overall rate of 43% depressive symptoms in patients on hemodialysis (Lopes et al., 2004). Regression analysis showed that depressive symptoms, stress levels, and MIP-1 $\beta$  were significantly related to HRQOL. The mean for the FACT-G in this sample was 68.1 ( $SD = 14.1$ ), lower than the mean of 80.1 found in the general population (Webster, Cella, & Yost, 2003). This finding is similar to findings from other studies investigating quality of life in dialysis patients (Ginieri, Theofilou, Synodinou, Tomaras, and Soldatos, 2008; Walters et al., 2002) but, unlike previous studies, no significant differences were found between time on dialysis or comorbidities and HRQOL in the current study.

Both stress and depressive symptoms were negatively related to HRQOL while MIP-1 $\beta$  was positively correlated with HRQOL. Irwin and Miller (2007) suggested that cytokines may alter information processing in the brain, increasing vulnerability to negative affect. In turn, processing stress in a more negative way may contribute to a decrease in perceived quality of life. Sample means in this study were lower for IL-1, IL-2, and TNF- $\alpha$  and higher for IL-6 and

IFN $\gamma$  than those reported in normative studies (Kokkonen et al., 2010). Additionally, there was a significant correlation between a pro-inflammatory cytokine pattern (Factor 1) and depressive symptoms. Prior studies have found correlations between pro-inflammatory cytokines, particularly IL-6, and depression (Hung et al., 2010; Irwin & Miller, 2007). Lower levels of MIP-1 $\beta$  have been correlated with major depressive disorder. The MIP-1 $\beta$  relationship with quality of life scores was marginal in the context of inflated error for multiple testing effects. Thus, biological data are entirely exploratory in nature and must be further examined in future studies with larger sample sizes.

### **Implications**

The mean for depression scores in this study indicates clinical depression when compared with the normative data, yet few patients had been prescribed anti-depressive medications. The strong correlation with HRQOL and pro-inflammatory cytokines indicates that recognizing and addressing depression in patients on hemodialysis could be an important intervention to improve the health of these patients. In addition, further research is needed to better understand the ways that immune status affects depression or depression affects immune status.

Cardiovascular disease is the leading cause of mortality and morbidity for patients with ESRD (Amann, Ritz, Adamczak, & Ritz, 2003). Improving outcomes and extending survival in patients on hemodialysis is an important goal for providers. The links between pro-inflammatory cytokines and cardiovascular disease need further investigation to determine the mechanisms involved and ultimately to design interventions to improve outcomes.

Patients on hemodialysis experience physical and psychological stress from many factors in their lives. Further research to find interventions to help patients deal with stress could influence their HRQOL.

In conclusion, research suggests that stress and depression influence immune function in other populations and, given the poor outcomes for dialysis patients, it is important to understand the complex biobehavioral interactions that may be involved with this population. The PNI framework provides a structure to further investigate these phenomena. Although the findings in the current study are limited by the small convenience sample, this study provides important confirmation about the elevated levels of perceived stress and depressive symptoms and decreased quality of life in patients with ESRD on hemodialysis.

### **Limitations**

This study was conducted in an urban area in the Southeast, with a much higher percentage of African American males than the national hemodialysis population, so findings are not necessarily representative of the population of persons with ESRD on hemodialysis. In addition, the sample size may not have been large enough to detect meaningful correlations among the variables. HRQOL is a complex concept and other variables not measured may affect it. Additionally, some vascular access devices for hemodialysis are more susceptible to infection, leading to more inflammation; hence, access type might be an important variable to include in future analyses. Future studies should continue to explore the complex interactions among psychosocial factors, immune phenomena, and quality of life, as well as longer-term health-related outcomes.

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