Clinical Trial Protocol

Trial Title:	Albumin levels, inflammation and nutrition in chronic hemodialysis patients treated with medium cut-off or high-flux membranes: A cohort study.
Trial Number:	RCS2022-002
Product Name:	NA
IND No:	NA
Indication:	Chronic hemodialysis in prevalent patients with stage 5 chronic kidney disease
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	Date
Original protocol:	28 February 2023

SYNOPSIS

Sponsor:
Baxter Healthcare
Corporation One Baxter
Parkway Deerfield, Illinois
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USA

Product name:
Not applicable

Trial title:
Albumin levels, inflammation and nutrition in chronic hemodialysis patients treated with medium cut-off or high-flux membranes: A cohort study.

Trial number:
RCS2022-002

Primary endpoint:

- To establish the effect of serum albumin levels, as well as markers of inflammation and malnutrition on outcomes such as mortality/survival, non-fatal cardiovascular events, hospitalization and hospital days in hemodialysis patients treated with medium cut-off (MCO) or high-flux (HF HD) membranes.

Secondary endpoints:

- To describe the demographic and clinical characteristics of both cohorts (MCO and HF HD).
- To estimate and compare the hospital days, the incidence of mortality and hospitalization in the cohorts studied.
- To compare the cumulative hospitalization time during study participation between patients receiving MCO and those receiving HF HD.
- To compare the time to death event between patients receiving MCO and those receiving HF HD.
- To compare the frequency of non-fatal cardiovascular events in both cohorts.
- To estimate the association between serum albumin levels and outcomes (mortality, non-fatal cardiovascular events, hospitalization events and days of hospital stay), controlling for the effect of third variables such as PEW, MIS, hs CRP, type of dialyzer.

Exploratory objectives:

- To describe the use and type of nutritional supplements in the cohorts evaluated.

Trial design:
Retrospective cohort study conducted between September 1, 2017 and November 30, 2017 (inception period) with up to 4-year follow-up within the cohort. A criterion for admission to the cohort is to be a prevalent patient on chronic hemodialysis (HD) (i.e., being on chronic HD for 90 days or more), treated with high-flux (HF HD) or medium cut-off (MCO) dialyzers.

Trial population:

The population of the trial is composed of prevalent patients on HD (those with 90 days or more on hemodialysis (HD) therapy) from 12 renal clinics of the Baxter Renal Care Services network in seven cities in Colombia.

Inclusion criteria:

- Patients over 18 years of age.
- Patients diagnosed with chronic kidney disease (CKD) in renal failure, with more than 90 days in chronic hemodialysis.
- Receiving HD at least 3 times per week and with a minimum duration of 4 hours per session.
- Being treated in one of the 12 renal clinics of the Baxter Renal Care Services (BRCS) network included in the study, in the cities of Bucaramanga, Barranquilla, Medellín, Bogotá, Ibague, Armenia, Cali.
- Being covered by one of the following health insurers: Nueva EPS, Compensar, Comparta, Comfenalco Valle and Mutualser.

Exclusion criteria:

- Pregnant women.
- Patients whose clinical history does not have sufficient information to establish their nutritional diagnosis.
- Having a high comorbidity, measured as a Charlson comorbidity index > 8 and patients who are not expected to survive more than 6 months.
- Metastatic disease.

Discontinuation criterial

Patients will be followed within the study from their enrollment in the cohort until they die, are censored or reach the end of follow-up, which will be up to four years after enrollment in the cohort.

The causes of censoring are transplantation, change of dialysis provider, loss to follow-up, discontinuation of dialysis therapy, recovery of residual renal function, switch to peritoneal dialysis (PD) or change of dialyzer (i.e., change of the original dialyzer within the cohort, HF HD to MCO or vice versa).

Test product and mode of administration:
Not applicable

Product reference and mode of administration:
Not applicable

Duration of intervention: 4 years

Primary efficacy assessment:
Primary outcomes:

- Incidence of hospitalization events (per patient-year)
- Length of hospital stay (hospital days per patient-year)

- Mortality
- Survival at 4 years

Primary safety assessment:
Not applicable

Secondary efficacy assessment:
Secondary outcomes:
- Non-fatal cardiovascular events

Exploratory assessments:

- Use of oral nutritional supplements.

Statistical method:

Further details of the statistical methods defined for this study will be provided in the study's statistical analysis plan (SAP). The purpose of the SAP is to elaborate the statistical methods outlined in the protocol and to describe the analysis conventions to guide the statistical programming work. Any changes to the analyses described below will be documented in the SAP.

Missing data and the mechanism by which they occur will be evaluated: MCAR (Missing completely at random), MAR (Missing at random) and MNAR (Missing not at random), according to this evaluation, the data imputation procedures will be defined, suitable for each case.

Determination of sample size:
Based on the availability of the assembled cohorts of 1098 patients, 564 in MCO Theranova® dialyzer cohort and 534 in conventional HF-HD dialyzer cohort, this provides 90% power considering an IRR of 0.82 for all-cause hospitalization and a significance level of 0.05 (26).

Type of analysis:

Descriptive statistics: Categorical variables will be summarized using absolute and relative frequencies. For continuous variables, means (standard deviation) will be used when the distribution is normal, and medians (interquartile range) when the above assumption is not met. Given the cohort design, incidence rates for outcomes related to time to event will be calculated as frequency estimators. The frequency or magnitude estimators related to the different outcomes will be presented along with their 95% confidence intervals.

Bi-variate analysis: To identify imbalances in baseline characteristics between cohorts, as well as to assess the trend over time of continuous variables and differences between groups (MCO vs HF HD) adjusting for baseline differences, a longitudinal analysis of covariance will be conducted.

To analyze the effect of low albumin levels when compared to normal levels on the outcomes of mortality, hospitalization, and hospital stays, in patients from the baseline cohorts, adjusting for individual characteristics of comorbidities, demographics, and the type of dialyzer, a directed acyclic causal diagram (DAG) will be performed to identify potential confounding variables required for adjustment.

Association analysis: In order to evaluate the association between serum albumin levels in repeated

measurements during follow-up, and the outcomes of death, non-fatal cardiovascular events, hospitalization events and days of hospital stay in the presence of third variables such as PEW, MIS, hs CRP and the type of dialyzer used (MCO or HF HD), a set of statistical methods will be used including:

a) A Cox regression analysis for time to death or hospitalization (extended Cox) in the presence of time-varying covariates (e.g., serum albumin, PEW, MIS, hs CRP, etc.) was performed.

b) A linear mixed model for longitudinal data may allow us to model the association between repeated albumin measurements and the proposed outcomes in the presence of other variables that also vary over time. The model comprises the combination of fixed models to determine the effect of baseline explanatory variables (e.g. type of dialyzer, history of diabetes, comorbidities, etc.), and a random model that allows us to include variables that change over time such as serum albumin levels, hs CRP, MIS, PEW, residual renal function (RRF), etc.)

c) G methods for longitudinal data, which allow estimation of the causal effect of a time-varying exposure (albumin levels) in the presence of time-varying confounding variables (hs CRP, MIS, PEW, RRF, etc.). These methods can be more robust than traditional regression-based methods. Parametric G-formula and inverse probability of treatment weighted estimation with marginal structural models will be used, as recommended by Hernan M et al (27,28,29)

Given that the public health crisis due to the COVID-19 pandemic occurred during the follow-up, identifying variables will be generated for the diagnosis of this pathology and hospitalisation, for covid and covid deaths. A Fine-gray regression model will be used to adjust for competing risks such as covid-19, time to death, or hospitalisation (30).

Interim analysis:
No interim analysis is planned for this study.

Date of approval of the original protocol: February 28 of 2023

Prepared in: Microsoft Word 2010

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LIST OF ABBREVIATIONS AND DEFINITIONS

MCO	Medium Cut-Off membrane
HF	High-Flux
HD	Hemodialysis
PEW	Protein-Energy Wasting
MIS	Malnutrition Inflammation Score
hs CRP	High-sensitivity C-reactive protein
CKD	Chronic kidney disease
BRCS	Baxter Renal Care Services
PD	Peritoneal Dialysis
SAP	Statistical Analysis Plan
IPTW	Inverse Probability Treatment Weighting
RRF	Residual Renal Function
kDa	Kilodaltons
FLC	Free Light Chain
κ	Kappa
λ	Lambda
HCO	Limit (*cut-off*) of effective porosity
IL-6	Interleukin-6
TNFα	Tumor Necrosis Factor Alpha
Mo2	Monocytes
QB	Blood pump flow rate
AE	Adverse Event
COREXH	Spanish acronym for Expanded Hemodialysis Registry in Colombia
REC	Research Ethics Committee
QD	Dialysate flow rate
BP	Blood Pressure
BUN	Blood Urea Nitrogen
Kt/V	A dimensionless number used to quantify the adequacy of hemodialysis treatment.
LDL	Low Density Lipoprotein
HDL	High Density Lipoprotein
UF	Ultrafiltration
Kg	Kilogram
PLR	Platelet-Lymphocyte Ratio
iPTH	Intact Parathyroid Hormone
TIBC	Total Iron Binding Capacity
BMI	Body Mass Index

DAG	Causal Directed Acyclic Graph
CI	Confidence Interval
CIOMS	Council for International Organizations of Medical Sciences Standards
SOP	Standard Operating Procedure
EMR	Electronic Medical Record
DD	Device Deficiencies
DRAE	Device-Related Adverse Event
DSI	Dialysis Symptom Index
INVIMA	Colombia's National Food and Drug Monitoring Institute *(Instituto Nacional de Vigilancia de Medicamento y Alimentos)*
RRT	Renal Replacement Therapy

1. INTRODUCTION

1.1. Background

The scientific and technological development of chronic hemodialysis (HD) as a renal replacement therapy has seen transcendental improvements in the last 50 years. Despite advances, state-of-the-art HD programs only achieve a suboptimal replacement of renal function and continue to be a partial substitute for native kidney function in the treatment of patients with renal failure in chronic kidney disease (CKD). In this population, a complex syndrome develops that brings together pathologies associated with fluid retention and various uremic toxins that are not efficiently eliminated by commonly used dialysis membranes, which are considered very effective in the clearance of low molecular weight molecules. This is made explicit by the fact that patients in chronic HD programs continue to present high morbidity and mortality. However, the improvements of this half-century journey are largely associated with improved clearance of medium molecular size molecules (1). A healthy glomerulus filters molecules up to 65 kDa molecular weight, whereas current high-flux (HF) membranes usually have molecular weight limits between 10 and 20 kDa (2). There are two main groups of toxins that are not adequately removed by HF membranes: larger medium-weight molecules and protein-bound toxins. As for the medium-weight molecules, it is their molecular weight (0.5 - 65 kDa) that limits their removal by conventional dialysis membranes; similarly, protein-bound uremic toxins are usually low molecular weight solutes, but their binding to large serum proteins limits their removal by dialysis.

Consequently, retention of these toxins in chronic HD causes, among other things, adverse biological outcomes such as altered immune response, chronic inflammation and endothelial damage (3).

The removal of larger molecular weight solutes is mainly determined by the ratio between the molecular weight of the solute and the effective porosity (exclusion limit or *cut-off*) of the dialysis membrane. In contrast to small solutes, increasing blood and/or dialysate flow rates beyond standard ranges has a limited effect on the clearance of large solutes, although

the application of convection (convective flux) can significantly increase the clearance of large solutes.

Many of the current synthetic HD membranes are less effective than glomerular membrane in that they do not adequately remove higher molecular weight toxins (4). In previous decades, membrane technological innovation focused mainly on improving the biocompatibility profile. Now, the development of bio-engineering has allowed the production of membranes with enhanced clearance of uremic toxins (5). Several molecules (larger than 200 kDa) have been identified as toxic molecules, such as the free light chains (FLC) Kappa (κ) and Lambda (λ) (all in the medium-high molecular weight range), which are above the clearance capacity of classical high-flux membranes, since they have a molecular radius larger than that of membrane pores (6).

Current dialysis membranes are not uniform in terms of pore size. This non-uniformity results in the removal of larger solutes than those for which the membranes were designed. With high cut-off (HCO) membranes, this "tail effect" can result in the loss of proteins such as albumin. Because of the above, efforts have been made to produce membranes with a narrow pore size distribution in order to maintain a very steep screening curve (close values of retention onset and cut-off) to allow removal of retention molecules in the medium-high molecular weight range without loss of albumin or with only marginal loss (6,7).

The concept of providing enhanced removal of protein-bound uremic toxins and medium molecular weight molecules means that HD based on this type of medium cut-off (MCO) membranes, generally referred to as expanded hemodialysis (HDx), increases (expands) the membrane clearance capabilities, constituting an important therapeutic step that has yielded positive results in some efficacy studies aimed at assessing inflammation and clearance of middle molecules (8).

At least 30% of patients on dialysis show signs of chronic inflammation. In patients with CKD and low residual renal function, the half-life of cytokines is increased (9,10). Hemodialysis with low or high-flux (HF) membranes does not sufficiently remove these

proteins that are in the 15-45 kDa molecular weight range (3). This may be one of the main reasons for increased serum levels of interleukin-6 (IL-6) or TNF-α in dialysis patients, followed by increased hepatic production of C-reactive protein (CRP) and altered monocyte subpopulation. A pilot, randomized, double-blind, crossover study in 19 patients selected for the presence of systemic inflammation on HD was conducted to describe the effect of high-cut membranes (6 sessions - 2 weeks) on soluble inflammatory markers and monocyte (Mo2) subpopulations. Compared to HD treatment with HF membrane, the use of high cut-off membranes demonstrated a significant decrease in albumin levels (13.19% with respect to pretreatment levels) or, in other words, for every 5 hours of hemodialysis treatment with high cut-off membranes, an average of 9 g of albumin (1.5 g/hour) was lost to dialysate, although no patient required nutritional supplementation. In this study, although the ability of these membranes to remove significant amounts of proinflammatory cytokines was confirmed, there was no decrease in inflammatory markers or Mo2 monocytes prior to dialysis (11, 12, 13).

Medium cut-off (MCO) dialyzers use a new class of membrane designed to increase the removal of molecules in the middle weight range by HD, and are intended for routine use in patients with chronic replacement of renal function with maintenance HD. Two randomized, open-label, crossover studies were recently conducted with 4 groups that differed from each other in treatment time (4 vs. 4-5 hours) and blood (QB) flow rate (300 ± 20 vs. 400 ± 50 ml/min), in 39 patients to evaluate the performance of 3 membrane prototypes (MCO Theranova®, MCO BB and CC) differing from each other in pore size, compared to high volume HD and hemodiafiltration (HDF) with HF dialyzers. Of particular interest was the clearance of middle molecules, including κ and λ FLC (7). The most relevant results were: compared with HD HF or high-volume HDF, FLC clearance (both κ and λ) was significantly higher with MCO HD (Theranova®). Albumin loss per session with any of the 3 MCO membrane prototypes was between 2.2-7.7 g, values that are not clinically significant. (8).

In a randomized, crossover clinical trial conducted by Zickler et al. (2017) in 48 patients comparing HF dialyzers with MCO dialyzers, it was observed that in the latter group there

was a slight reduction in albumin at 4 weeks, which then normalized at 8 weeks; therefore, it was concluded that, after 12 weeks of treatment, MCO dialyzers were well tolerated, without a negative profile, in relation to the frequency of adverse events (AEs) related to the device studied (14).

The Theranova® medium cut-off dialyzer (MCO) combines and enhances the therapeutic principles of permeability, selectivity, controlled retention and internal filtration in a single dialysis membrane. The term expanded HD (HDx) has been proposed to define a treatment in which diffusion and convection are conveniently combined inside a hollow fiber dialyzer equipped with a medium cut-off membrane (6). The Theranova® dialyzer allows the MCO to remove larger middle molecules. Theranova® is a single-use hollow fiber dialyzer with enhanced removal of large middle molecules up to 45 kDa, while selectively retaining essential proteins such as albumin. (6).

A recent systematic review with meta-analysis found that medium cut-off membranes show better clearance of middle-molecule type uremic toxins (15); the effect of medium cut-off dialyzers versus high-flux dialyzers on serum albumin levels varies between randomized and observational studies (15), so more studies will be required to evaluate in more detail this new type of dialyzers. On the other hand, another recent meta-analysis (16) shows that to date there is no evidence of risk or harm with the use of medium cut-off dialyzers.

In addition to the above evidence, a recent study in a group of 20 patients showed a slight but statistically significant reduction in serum albumin levels of -0.45 g/dL in patients managed with medium cut-off membranes at 3-month follow-up (17), although no adverse events related to the use of these novel dialyzers or to this decrease in albumin levels were observed.

The issue of serum albumin levels as a risk marker in the chronic dialysis population has deserved much attention, since hypoalbuminemia has emerged as a risk marker in both HD and PD patient populations. In this regard, a cohort study of over 130,000 patients showed that in HD patients, the risk for all causes of mortality was progressively higher for each category of albumin below 4.0 g/dL. (18).

Similarly, a study involving nearly 58,000 patients on maintenance hemodialysis found that, with an approach that takes into account time-varying albumin levels, hypoalbuminemia predicts all-cause mortality as well as mortality from cardiovascular causes (19), which would imply that clinical efforts should be made to achieve serum albumin levels greater than 3.8 g/dL in these populations.

Recently, a narrative review of the literature addressed the problem of serum albumin levels related to the use of new medium cut-off membranes in maintenance hemodialysis (20), where it is highlighted that excessive albumin loss is a theoretical concern with the chronic use of dialyzers more permeable to middle molecules (medium cut-off). At this time there are no head-to-head studies that evaluate the effect of medium cut-off dialyzers compared to high-flux dialyzers on hard outcomes such as survival, safety and quality of life, adjusting for the effect of nutritional variables and micro-inflammation (20).

One of the theoretical problems that arise when evaluating serum albumin levels as a risk factor for mortality and other outcomes in a given population is that, as is well known, albumin is a negative acute-phase protein, i.e., its concentration decreases during inflammatory processes of different order (21).

Specifically, the presence of hypoalbuminemia has been frequently documented in patients with chronic kidney disease in renal failure. Albumin levels in the dialysis population may have been reduced by a decrease in the rate of albumin synthesis, or, on the other hand, also by external losses such as those secondary to the use of dialyzers for HD or through the peritoneal dialysis membrane (22). The decrease in albumin synthesis may be the result of a reduced protein intake, the inflammatory response or a combination of these processes.

In addition to the above, a systematic review of the literature with meta-analysis of HD patients found an inverse relationship between albumin levels and all-cause and cardiovascular mortality. Furthermore, a weak but significant relationship was found between C-reactive protein levels and all-cause mortality (23), highlighting the potential for adverse outcomes of malnutrition and infection/inflammation.

Regardless of the fact that hypoalbuminemia has been documented as a risk factor for mortality in dialysis, there is a hypothesis that the underlying cause of hypoalbuminemia is the true cause of morbidity and mortality, rather than hypoalbuminemia itself (22). In this sense, there is evidence that suggests that inflammation, alone or together with malnutrition, plays a significant role in the genesis of hypoalbuminemia in hemodialysis patients (22). In this order of ideas, when attempting to elucidate the association between albumin levels and outcomes such as mortality in dialysis, it is very important to evaluate the effect that "third variables" -such as inflammatory or malnutrition markers- have on the association evaluated.

Moreover, a challenge of statistical analysis in the task of establishing associations between survival and the presence of risk factors is that the latter are not fixed over time but frequently vary (as occurs with serum albumin levels). The latter type of variables is called time-dependent or covariate time-dependent risk factors (24). This type of analysis can be done with Cox models for time-dependent variables (Cox extended model).

However, in the context of chronic hemodialysis, many exposures vary over time in their relationship to a given outcome; and also, the value of a given exposure may depend on external factors that also affect the outcome. This phenomenon is known in epidemiology as confounding (25). Additionally, a time-varying confounding phenomenon occurs when confounders have values that change over time (as would be the case for markers of inflammation and malnutrition). In addition, a time-varying confounder may in turn be affected by a past exposure (e.g., the use of a type of dialyzer for hemodialysis) (25). Some methods have been used to adjust for time-varying confounding variables that are affected by past exposures; these include the inverse probability of the weighted treatment, the parametric g-formula and the G-estimation (25).

The recent availability of medium cut-off dialyzers (MCO) has generated hypotheses about their safety, the role of these membranes in the development of hypoalbuminemia in hemodialysis, and the possible association between albumin levels and outcomes such as survival/mortality, hospitalizations and quality of life, in light of third variables that

may affect this association. Given the scarcity of longitudinal follow-up data over a sufficient period of time (more than two years) for this new class of membranes (MCO) compared to high-flux dialyzers, especially with regard to "strong" clinical outcomes such as survival/mortality, the incidence of non-fatal cardiovascular events or the frequency of hospitalization events, the present study is pertinent.

1.2. Statement of the problem

Many of the current synthetic HD membranes are less effective than glomerular membrane in that they do not adequately remove higher molecular weight toxins (4). In previous decades, membrane technological innovation focused mainly on improving the biocompatibility profile. Now, the development of bio-engineering has allowed the production of membranes with enhanced clearance of uremic toxins (5). Several molecules (larger than 200 kDa) have been identified as toxic molecules, such as the free light chains (FLC) Kappa (κ) and Lambda (λ), all in the medium-high molecular weight range, which are above the clearance capacity of classical high-flux membranes, since they have a molecular radius larger than that of membrane pores (6).

The concept of providing enhanced removal of protein-bound uremic toxins and medium molecular weight molecules means that HD based on this type of medium cut-off membrane (MCO), generally referred to as expanded hemodialysis (HDx), increases (expands) the membrane clearance capabilities, constituting an important therapeutic step with which positive results have been obtained in some efficacy studies, aimed at evaluating inflammation, and the clearance of middle molecules (8).

Data from longitudinal studies on differences in clinical outcomes such as survival, cardiovascular events or hospitalization associated with the use of MCO dialyzers versus HF dialyzers are scarce.

This study aims to establish the role of serum albumin levels, as well as markers of inflammation and malnutrition on outcomes such as mortality, non-fatal cardiovascular

events, hospitalization and hospital days in hemodialysis patients treated with medium cut-off (MCO) or high-flux (HF HD) membranes.

1.3. Research question

What is the role of serum albumin levels, as well as markers of inflammation and malnutrition on outcomes such as mortality, non-fatal cardiovascular events, hospitalization and hospital days in hemodialysis patients treated with medium-cut-off (MCO) or high-flux (HF HD) membranes?

1.4. Primary endpoint

To establish the effect of serum albumin levels, as well as markers of inflammation and malnutrition on outcomes such as mortality/survival, non-fatal cardiovascular events, hospitalization and hospital days in hemodialysis patients treated with medium cut-off (MCO) or high-flux (HF HD) membranes.

1.5. Specific endpoints

1. To describe the demographic and clinical characteristics of both cohorts (MCO and HF HD).
2. To estimate and compare the days of hospital stay, the incidence of mortality and hospitalization in the cohorts studied.
3. To compare the cumulative hospitalization time during study participation between patients receiving MCO and those receiving HF HD.
4. To compare the time to death event between patients receiving MCO and those receiving HF HD.
5. To compare the frequency of non-fatal cardiovascular events in both cohorts.
6. To estimate the association between serum albumin levels and outcomes (mortality, non-fatal cardiovascular events, hospitalization events and days of hospital stay), controlling for the effect of third variables such as PEW, MIS, hs CRP and dialyzer type.

1.6. Exploratory endpoints

1. To describe the use and type of nutritional supplements in the cohorts evaluated.

2. INVESTIGATIONAL PLAN

2.1. Overall trial design and plan

This is a retrospective cohort study including prevalent HD patients treated with MCO compared to patients with the same characteristics treated with conventional HF HD. Patients included in the Expanded Hemodialysis Registry in Colombian (or COREXH, by its Spanish acronym) will participate in cohort 1. Cohort 2 will include patients selected from the same 12 renal clinics in the Baxter Renal Care Services network in Colombia, who met the same criteria for participation in the COREXH study and who were treated during the same time period, but who were given conventional HD with high-flux (HF HD) dialyzers. The inception phase of the cohorts was between September 1, 2017 and November 30, 2017. Retrospective data will then be taken from patients who during this inception period met all of the inclusion criteria and none of the exclusion criteria of this protocol. After cohort assembly, clinical information on each patient will be collected longitudinally over time for up to a maximum of four (4) years. The present trial does not contemplate any intervention for the patient, since it is a descriptive and retrospective study.

2.2. Rationale for trial design

Hemodialysis is a procedure that removes various electrolytes, toxins and excess fluid from the patient's general circulation when these cannot be excreted normally due to chronic impairment of renal function. Dialyzers with MCO membranes are capable of removing higher molecular weight toxins such as cytokines, myoglobin and FLC. Any increase in the clearance of these substances could improve inflammation and nutritional

status, correlating with symptom improvement. This suggests that patients treated with MCO dialyzers may have better clinical outcomes.

Data from longitudinal studies with sufficient follow-up time on clinical outcomes of importance to patients and health systems, such as survival, cardiovascular events or hospitalization associated with the use of MCO dialyzers versus HF dialyzers, are scarce.

This study aims to evaluate the effectiveness of HDx with MCO dialyzers, based on real data from a group of prevalent chronic HD patients from the Baxter Renal Care Services network of renal clinic in Colombia, and to compare the outcomes of this MCO cohort with a HF HD cohort in terms of incidence of hospitalization events, days of hospitalization, incidence of non-fatal cardiovascular events, and patient survival.

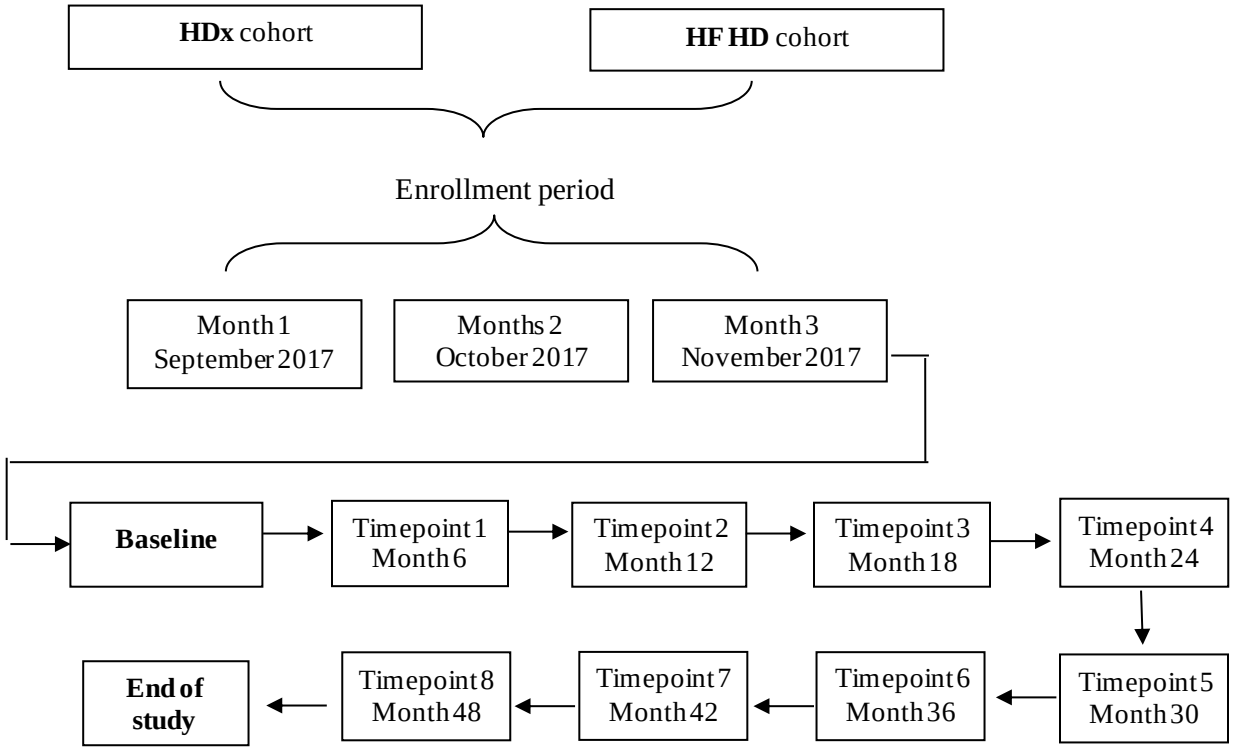
In the context of the use in maintenance HD of MCO dialyzers, it is of great importance to analyze the effect of albumin levels over time and their relationship with the proposed outcomes, adjusting for the effect that third variables that also vary over time (such as PEW, MIS, hs CRP among others) could have on these causal relationships evaluated.

2.3. Trial duration and dates

This is a retrospective, observational, cohort study. Baseline study data will be collected from the first HD session after enrollment in the study, with follow-up according to the protocol. See **Figure 1**

Data will be collected for a period of up to four (4) years for each enrolled subject, primarily at baseline and every six months. Each patient will participate in the study for a maximum period of time of four (4) years.

Figure 1 Trial outline



3. SELECTION OF STUDY POPULATION

3.1. Study population

Prevalent HD patients will be enrolled in two cohorts and followed for up to four (4) years.

- Cohort 1 (MCO cohort): Patients who received MCO treatment using Theranova® dialyzers. These patients were enrolled in the original COREXH registry between September 1, 2017 and November 30, 2017. Patients who received MCO treatment with the Theranova® dialyzer at least 3 times per week with a minimum of 4 hours/session duration were enrolled.
- Cohort 2 (HF HD cohort): Patients from the same clinics and with the same follow-up times as Cohort 1, who received treatment with conventional HD with a high-flux (HF HD) dialyzer. Those patients with a high comorbidity index who were not expected to survive 6 months based on their clinical notes will be excluded from Cohort 2 in order to match the exclusion criteria for patients with a life expectancy of less than six months as determined by their treating physician in Cohort 1 of the COREXH registry.

3.2. Inclusion criteria

In order to be enrolled in this study, each subject must meet the following inclusion criteria:

- Patients over 18 years of age.
- Patients diagnosed with chronic kidney disease (CKD) in renal failure with more than 90 days in chronic hemodialysis.
- Receiving HD at least 3 times per week and with a minimum duration of 4 hours per session.
- Being treated in one of the 12 renal clinics of the Baxter Renal Care Services (BRCS) network included in the study, in the cities of Bucaramanga, Barranquilla, Medellín, Bogotá, Ibague, Armenia, Cali.

- Being covered by one of the following health insurers: Nueva EPS, Compensar, Comparta, Comfenalco Valle and Mutualser

3.3. Exclusion criteria

Subjects meeting any of the following exclusion criteria will be excluded from the study:

- Pregnant women.
- Patients whose clinical history does not have sufficient information to establish their nutritional diagnosis.
- Having a high comorbidity, measured as a Charlson comorbidity index > 8 and patients who are not expected to survive more than 6 months.
- Metastatic disease

4. TRIAL TREATMENT

4.1. Enrollment and patient number assignment

Enrollment in the study will begin only after the investigator has received written approval for the study from an independent research ethics committee.

Given the retrospective and observational nature of this study, informed consent forms will not be used; the habeas data form will be used as authorization to use patient data for research purposes. This study protocol will be submitted to an independent research ethics committee (REC) for ethical evaluation.

Patients will be considered enrolled in the study when it has been determined that they meet all of the inclusion criteria and none of the exclusion criteria. All enrolled patients will be assigned a subject number. These consist of 8 digits and begin with the 4-digit core number followed by a dash and the 4-digit subject identification record number (e.g., 0054-0001). Subject numbers will be assigned in chronological order as subjects are registered.

4.2. Treatments to be administered

No intervention is performed on the subjects in this study; it is an observational and retrospective study.

4.3. Patient selection and treatment timing

Subjects at least 18 years of age who have been in a chronic HD program for more than ninety (90) days at the start of the cohort, with an HD session duration of at least 4 hours, and with a frequency of at least 3 times per week, can participate in this study. In addition, they should be expected to have a potential survival of at least 6 months.

The duration of the HD session in each subject will vary depending on their prescription, as determined by their treating physician. Subject data will be collected for a period of up to 48 months (4 years) from the start of the cohorts.

At the start of the cohorts, eligible patients had either been enrolled in the COREXH study and prescribed an MCO dialyzer or remained on treatment with an HF dialyzer. HD treatment details will be recorded by electronic data transfer from the Versia® electronic medical record.

It is important to mention that the initial prescription of MCO or HF HD was driven by the availability of the new technology (MCO) and not by clinical or other criteria at the time of allocation.

4.4. Restrictions

4.4.1. Prior to therapy

There are no specific restrictions regarding previous medical treatments. Details of concomitant medication and prescription of dialysis treatment will be collected.

4.4.2. Patient activity restrictions

Not applicable

4.5. Packaging and labeling

Not applicable given the retrospective nature of this study.

4.6. Storage and accountability

Not applicable given the retrospective nature of this study.

5. TRIAL PROCEDURES

5.1. Informed consent

Informed consent will not be obtained in this retrospective cohort study since there is no risk to the patient. The patient has already consented to the use of the information for observational research purposes in the Baxter Renal Care Services habeas data form.

5.2. Discontinuation criteria

Patients will be followed within the study from their enrollment in the cohort until they die, are censored or reach the end of follow-up, which will be up to four years after enrollment in the cohort.

The causes of censoring are transplantation, change of dialysis provider, loss to follow-up, discontinuation of dialysis therapy, recovery of residual renal function, switch to peritoneal dialysis (PD) or change of dialyzer (i.e., change of the original dialyzer within the cohort, HF HD to MCO or vice versa).).

5.3. Trial data capture

Patients who meet all the inclusion criteria and none of the exclusion criteria will be included in the study. The source for data extraction and verification will be the Versia® electronic medical record.

Enrolled patients will be assigned an identification number. Versia® electronic medical record data will be exported for analysis in csv format.

5.3.1. Description of variables

Details are presented in the **Appendix 1 and Appendix 2:**

- **Demographic variables:** Patient's study ID number, clinic ID, age, gender, city, insurer, ethnicity, etc.
- **Medical history variables:** Cause of CKD, previous diagnosis of hypertension, previous diagnosis of diabetes, previous diagnosis of cardiovascular disease, Charlson index adapted to CKD, diuresis (ml/day), date of initiation of chronic renal replacement therapy (RRT), and dialysis vintage time.
- **Concomitant medication:** Type of oral nutritional supplements.
- **Hemodialysis variables:** HD session duration, number of sessions per week, blood flow (Qb), dialysate flow (Qd), ultrafiltration, dry weight, type of vascular access, type of anticoagulation of the extracorporeal circuit, pre- and post-dialysis systolic blood pressure (BP), pre- and post-dialysis diastolic blood pressure (BP).
- **Laboratory variables:** Frequency of measurements is in accordance with BRCS Colombia clinical practice standards: Hemoglobin, platelets, lymphocytes, platelet/lymphocyte ratio potassium, calcium, phosphorus, albumin, blood urea nitrogen (BUN), pre- and post- urea, single pool Kt/V, ferritin, iron, transferrin saturation percentage, total iron binding capacity (TIBC), intact parathyroid hormone (iPTH), total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, triglycerides, high-sensitivity C-reactive protein (hs CRP).
- **Nutritional assessment variables:** Malnutrition-inflammation score (MIS), protein energy wasting (PEW) score, categorized PEW, nutritional assessment, body mass index (BMI), Karnofsky functional status scale, hydration status and hydration score.
- **Outcome variables:** Hospitalization, dates of hospitalization (admission and discharge dates), days of hospitalization, diagnosis of hospitalization, cardiovascular events, non-fatal cardiovascular events, death, date of death, diagnosis of death, grouped cause of death, diagnosis of Covid-19, date of diagnosis of Covid-19, hospitalization due to Covid-19 and death due to Covid-19.

5.4. Primary assessment

5.4.1. Primary efficacy assessment

- Incidence of hospitalization events (per patient-year)
- Length of hospital stay (hospital days per patient-year)
- Mortality
- Survival at 4 years

5.4.2. Primary safety assessment

Not applicable

5.5. Secondary assessment

5.5.1. Secondary efficacy assessment

- Non-fatal major cardiovascular events

5.5.2. Secondary safety assessment

Not applicable

5.6. Exploratory assessment

- Use and type of oral nutritional supplements.

5.7. Adverse event assessment

Due to the retrospective (historical) nature of this study, reporting and follow-up of adverse events is not applicable.

5.8. Safety reporting

Not applicable.

5.9. Removal of patients from the trial

This is a retrospective, observational cohort study.

Subjects may be removed from the statistical analysis if they had 13 or more consecutive HD sessions with a different dialyzer than the original one used in the inception of the cohort.

Subjects may be removed from the statistical analysis if they were hospitalized for thirty (30) days or more without guarantees about the dialysis treatment received by the patient.

In this retrospective study the investigators will conduct a longitudinal follow-up of all outcomes for up to four (4) years from the date of enrollment (September 1, 2017 through November 30, 2017), i.e., follow-up for the last patient will end no later than November 30, 2021.

Since this is a registry with real life data, absences from dialysis treatment do not imply a violation of the protocol. However, absence from dialysis treatment should be recorded observing the usual management of absenteeism in HD, as established in the Baxter Renal Care Services Colombia processes. Delivery of more than 13 consecutive dialysis sessions without the original dialyzer prescribed will be a cause for suspension in either cohort.

5.10. Other trial procedures

Not applicable.

5.11. Appropriateness of measurements

The effectiveness measures performed conform to standards and are appropriate for the study population and indication under study.

6. CLINICAL TRIAL ACTIVITIES

6.1. Schedule of evaluations and procedures

All assessments in this observational study will be conducted in accordance with **Appendix 1**, the instructions for which are listed below.

6.2. Screening period

- Each potential study subject should undergo a process to verify eligibility (see Inclusion criteria and exclusion in Sections 4.2 and 4.3**)**
- Data for the above variables will be collected as described in Section 5.3.1.

6.3. Duration of study (4-year follow-up)

- Subjects receiving scheduled HD according to MCO or HD AF treatment prescriptions will be observed retrospectively, as described in Sections 5.2 and 5.3.
- Data related to the HD treatment session will be captured, as described in Section 5.3.1.

7. QUALITY CONTROL AND QUALITY ASSURANCE

Baxter Renal Care Services (BRCS) - Colombia is responsible for implementing and maintaining quality assurance and quality control systems with written standard operating procedures to ensure that data is generated, documented and reported in accordance with protocol and applicable regulatory requirements. Quality control will be applied to all stages of data handling to ensure reliability and correct processing. BRCS is responsible for obtaining agreement from all parties involved to ensure direct access to all study related sites, source documents and reports for the purpose of monitoring and auditing. All arrangements made with the investigator/institution must be made in writing.

In this trial, data quality assurance will be performed by designated research data quality management personnel. If an investigator is contacted by any regulatory authority

regarding an audit of this or any other trial, the investigator should contact the principal investigator and the study medical monitor immediately.

8. PLANNED STATISTICAL METHODS

8.1. General considerations

Further details of the planned statistical methods will be provided in the study's statistical analysis plan (SAP). **Appendix 10.** The purpose of the SAP is to elaborate the statistical methods outlined in the protocol and to describe the analysis conventions to guide the statistical programming work. Any changes to the analyses described below will be documented in the SAP.

Missing data and the mechanism by which they occur will be evaluated: MCAR (Missing completely at random), MAR (Missing at random) and MNAR (Missing not at random), according to this evaluation, the data imputation procedures will be defined. suitable for each case.

8.2. Determination of sample size

Based on the availability of the assembled cohorts of 1098 patients, 564 in OMS in the Theranova® dialyzer cohort and 534 in conventional HD in the AF dialyzer cohort. This provides 90% power considering an IRR of 0.82 for all-cause hospitalization and a significance level of 0.05 (26). In addition, considering the use of the IPTW approach and given a prevalence of 0.5 exposure to dialyzer, with an expected number of 800 hospitalization events and a Hazard Ratio of 1.25 for hospitalization at 2-year follow-up, additional 1000 patients (500 per exposure group) to achieve an effect size of at least 0.8.

8.3. Types of analysis

Descriptive statistics: Categorical variables will be summarized using absolute and relative frequencies. For continuous variables, means (standard deviation) will be used when the distribution is normal, and medians (interquartile range) when the above

assumption is not met. Given the cohort design, incidence rates for time-to-event outcomes will be calculated as frequency estimators. The frequency or magnitude estimators related to the different outcomes will be presented together with their 95% confidence intervals.

Bi-variate analysis: To identify imbalances in baseline characteristics between cohorts, standardized mean differences will be calculated. To assess both changes over time and differences between groups (MCO vs HF HD) adjusting for baseline differences, a longitudinal analysis of covariance will be performed.

To analyze the effect of low albumin levels when compared to normal levels on the outcomes of mortality, hospitalization, and hospital stays, in patients from the baseline cohorts, adjusting for individual characteristics of comorbidities, demographics, and the type of dialyzer, a directed acyclic causal diagram (DAG) will be performed to identify potential confounding variables required for adjustment.

Figure 2. Directed acyclic causal diagram for the causal relationship between albumin and mortality, hospitalization, and non-fatal cardiovascular events.

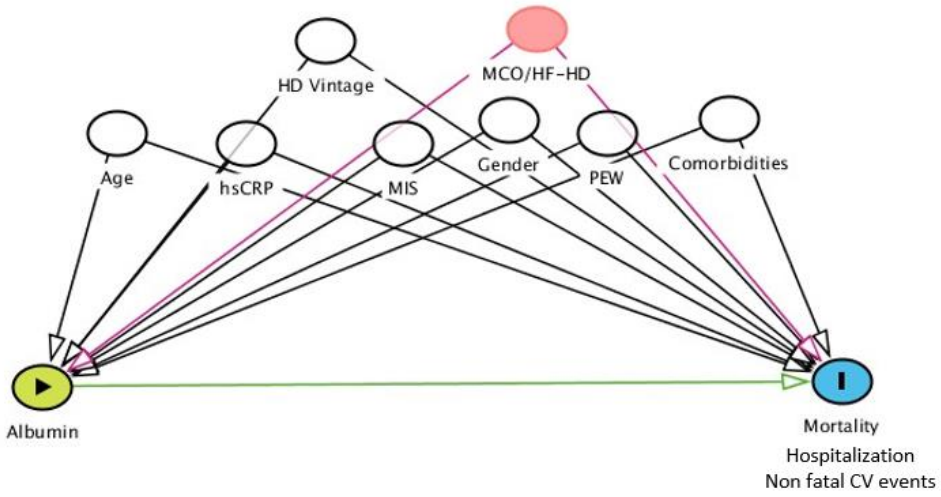
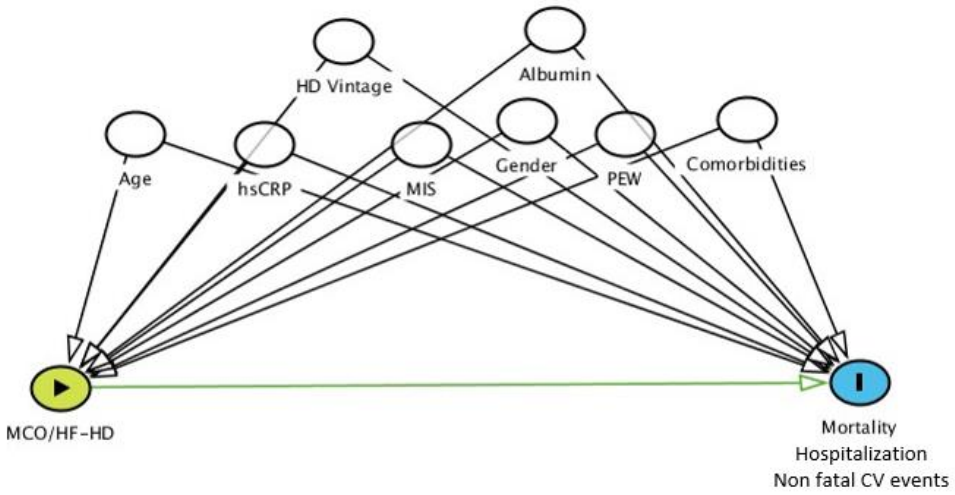


Figure 3. Directed acyclic causal diagram for the causal relationship between the type of dialyzer and mortality, hospitalization, and non-fatal cardiovascular events.



Association analysis:

In order to evaluate the association between serum albumin levels in repeated measurements during follow-up, and the outcomes of death, non-fatal cardiovascular events, hospitalization events and days of hospital stay in the presence of third variables such as PEW, MIS, hs CRP and the type of dialyzer used (MCO or HF HD), a set of statistical methods will be used including:

a) A Cox regression analysis for variables that change over time (extended Cox) for time to death, or hospitalization in the presence of covariates (serum albumin, PEW, MIS, hs CRP, etc.).

b) A linear mixed model for longitudinal data may allow us to model the association between repeated albumin measurements and the proposed outcomes in the presence of other variables that also vary over time. The model comprises the combination of fixed

models to determine the effect of baseline explanatory variables (e.g. type of dialyzer, history of diabetes, comorbidities, etc.), and a random model that allows us to include variables that change over time such as serum albumin levels, hs CRP, MIS, PEW, residual renal function, etc.)

c) G methods for longitudinal data, which allow estimation of the causal effect of a time-varying exposure (albumin levels) in the presence of time-varying confounding variables (hs CRP, MIS, PEW, RRF, etc.) see **Figure 2.** These methods can be more robust than traditional regression-based methods. Parametric G-formula and inverse probability of treatment weighted estimation with marginal structural models will be used, as recommended by Hernan M et al. (27,28,29)

Given that during the follow-up the public health crisis due to the COVID-19 pandemic occurred, identifying variables will be generated for the diagnosis of this pathology and hospitalization, due to covid and covid deaths. A Fine-gray regression model will be performed to adjust for competing risks such as covid 19, for time to death, or hospitalization (30).

Statistical analysis of the data will be performed using Stata Release 16 software (StataCorp LP, College Station, TX, U.S.A.) .

9. ADMINISTRATIVE ISSUES

9.1. Investigators and trial administrative structure

The administrative structure is described in **Table 1.** Ultimately, the principal investigator is responsible for conducting all aspects of the study; in turn, the local investigator is responsible for conducting the clinical trial activities at a given center.

Table 1. Administrative structure of the trial

Principal investigator:	Dr. Juan Carlos Mario Castillo. MD.
Sponsor:	Dr. Ángela Rivera F., MD. Global Medical Leader, Baxter Renal Care Centers
Medical monitor:	Dr. Mauricio Sanabria A. MD. MSc.
Project manager:	Dr. Jorge Fernández, MD.
Clinical trial data manager:	Jasmín Vesga Gualdrón RN. MSc.
Statistical analysis:	Universidad Nacional de Colombia – Universidad de la Sabana Colombia
Medical writer:	Dr. Mauricio Sanabria A. MD. MSc.

9.2. Research ethics committee (REC) approval (REC)

The responsible research ethics committee (REC) should be constituted in accordance with the applicable local and national requirements of each participating location. The sponsor or its designee will require documentation indicating all names and titles of the site's REC members. If any REC members are directly involved in this trial, written notification of their abstention from voting must also be obtained.

Sponsor or its designee will provide relevant documents for Investigators to submit to their respective REC for protocol review and approval. Before subjects may be enrolled into the study, the investigator requires a copy of the site's written REC approval of the protocol, informed consent form, informed assent form (if applicable) and all other subject information and/or recruitment material. The REC approval should reference the trial by exact protocol title, version number and date; identify versions of other documents reviewed; and indicate the date of approval. The investigator will prepare all required written progress reports to his/her REC in a timely manner and obtain all required written approvals (at least annually in all cases) for continued participation in the study

The investigator will immediately report to their REC any unanticipated problems associated with the study intervention that involve risks to patients or others, whether found at their site or provided by Baxter as a Safety reporting.

Sites must comply with all requirements set forth by their respective REC. The investigator will immediately notify his/her REC of any planned protocol amendment and will not implement any protocol amendment until the REC has provided written approval or a favorable written opinion on the amendment.

9.3. Ethical conduct of the trial

Since this is an observational investigation, in which the HD procedure is not modified in any aspect, the present study is considered to be without risk to the patient. Given the observational and retrospective characteristics of this study, the use of the informed consent procedure will not be considered, since the patient's authorization is found in the habeas data form for research purposes as consent for the use of his or her data for the study. Obviously, this concept is subject to the decision of the research ethics committee that will evaluate and monitor this study.

The investigators undertake to conduct this study in accordance with the principles of the Declaration of Helsinki and good clinical practice, such as the standards of the Council for International Organizations of Medical Sciences (CIOMS). In accordance with Colombian Resolution 8430 of 1993, this clinical study is classified as without risk. The identity of the research subjects will be protected. All data entered in the study databases will be handled with strict confidentiality. A REC will evaluate and supervise this study.

9.4. Patient information and consent

The investigators will not begin the trial until they have received written approval, or a favorable opinion, of the protocol from the REC. It is considered that this study does not require written informed consent.

9.5. Confidentiality

The investigator will ensure that the confidentiality of research subjects is maintained. Subject medical information obtained for the purposes of this study is confidential and is prohibited from disclosure to third parties, with the exception of representatives of health

authorities, representatives of the sponsor, or the REC responsible for approving and overseeing the study. Subjects will not be identified by name or medical record number on any documents or materials submitted to the sponsor or its representatives or during verbal communications. Subjects will be identified only by an identification number assigned by the protocol.

To help maintain patient confidentiality, each patient will be assigned a unique patient identification number. In addition, only the site investigator and designated site personnel will have access to patient identification information. All data will be compiled to construct a dataset comprising unique patient identification numbers in lieu of specific patient identifying data; all study datasets will be password-protected and will remain de-identified. While there is always a risk of loss of privacy when participating in a research program, all reasonable efforts will be made to ensure the confidentiality of patient data. Under no circumstances will patient identifying information be shared or disclosed with a third party for promotional uses. As stated above, the patient should be informed that Baxter Renal Care Services and its representatives will use his or her personal data related to the study in accordance with the laws of the country or local REC data protection guidelines.

9.6. Trial monitoring

The sponsor's team or designee will monitor study data on-site and remotely as part of safety management and clinical oversight. Full details of the monitoring will be specified in a standard operating procedure.

9.7. Trial records

All records will be kept confidential. The subject's personal information, including name and sensitive data, will not be disclosed at any time and will remains de-identified. Clinical data will not be disclosed to anyone except the sponsor or designee or government agencies, if necessary. In all cases, precautions must be taken to ensure subject confidentiality. Identification numbers will be used to identify subjects on study-related

documents. Enrolled patients will be assigned an identification number. Data from the Versia® electronic medical record will be exported for analysis in csv format, and a computing audit will be performed to verify the consistency of the information with the source document, prior to the start of the statistical analysis.

9.8. Data management plan

Given the observational and retrospective nature of this study, all data will come from the Versia® electronic medical record data source. A dedicated research team from Baxter Renal Care Services will be responsible for data extraction from the source documents and electronic data capture according to the standard operating procedures (SOP) defined for the study. The research team will also perform data quality assurance procedures to ensure the reliability and validity of the information.

9.9. Access to source documentation

In its observational and retrospective nature, the study may be evaluated by the sponsor's internal auditors or designee and/or government inspectors, who will be allowed access to source documents, the Versia® electronic medical record system and other trial records.

9.10. Data generation and analysis

Data management will be performed by the Baxter Renal Care Services' research team or designee.

Methodological support and statistical analysis will be provided externally by experts from Universidad Nacional de Colombia and Universidad de la Sabana.

Unless otherwise indicated, all analyses will be performed using statistical software Stata Release 16. College Station, TX: StataCorp LLC, all rights reserved.

9.11. Data archive

Given the observational and retrospective nature of this study, source documents originate from the Versia® EMR (Electronic Medical Record). The institution will archive the study databases in printed or electronic form in accordance with the applicable regulatory requirements stipulated in resolution 839 of 2017 and in no case will it keep them for less than 15 years. Upon expiration of any regulatory requirement to retain such data or 2 years after the date of revocation or expiration of the clinical trial agreement, whichever is later, the sponsor will direct that such data be turned over to it for destruction, or be archived by the institution for a standard storage fee for a period of time to be designated by the sponsor, and the institution will comply with such orders of the sponsor. If the principal investigator withdraws from the study (e.g., by transfer or retirement), the records will be transferred to a mutually agreed upon designee (e.g., another principal investigator). Baxter will be notified in writing of such a transfer. All study documentation and de-identified databases will be stored in an encrypted computer space dedicated for this purpose in the Baxter cloud, where only designated persons such as: Baxter clinical study data manager and data engineer will have access.

In the event that third parties designated within the study have access to the databases (i.e., epidemiologists/statisticians), they will be required to submit a report of data destruction, which must be done at the time of generating the database closure report.

9.12. Financial disclosure

The financial aspects of the trial will be documented in an agreement between the sponsor and the research teams.

9.13. Publication and disclosure policy

Any information shared by the sponsor regarding this trial, including this protocol, is considered proprietary information and should be kept confidential.

The data generated by this clinical trial are the property of the sponsor. These data may be used by the sponsor, now and in the future, for presentation or publication at the sponsor's discretion and/or for submission to regulatory agencies. In addition, the sponsor reserves the right of prior review and approval of the data from this trial relative to the possible release of proprietary information to any publication or for any submission.

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Appendix 1. Schedule of events

Variables	Baseline	Measurement every 6 months (6, 12, 18, 24, 30, 36, 42 & 48)
Demographics: (Patient identification in the study, clinic identification, age, sex, ethnicity, city, insurer).	X	
Medical history: (Cause of CKD, previous diagnosis of hypertension, previous diagnosis of diabetes, previous diagnosis of cardiovascular disease, Charlson index adapted to CKD, diuresis (ml/day), date of initiation of chronic renal replacement therapy (RRT), and dialysis vintage time).	X	
Concomitant medication: Oral nutritional supplements.	X	X
Hemodialysis parameters: Qb, Qd, UF, time, dialyzer used, anticoagulation of extracorporeal circuit for hemodialysis type and dose, Pre- and post-dialysis systolic blood pressure, Pre- and post-dialysis diastolic blood pressure, vascular access.	X	
Laboratory parameters: Hb, albumin, platelets, lymphocytes, potassium, calcium, phosphorus, BUN pre- and post-dialysis, ferritin, iron, % transferrin saturation, TIBC, iPTH, high sensitivity PCR (hs PCR), kt/v, total cholesterol, high density lipoprotein (HDL) cholesterol, low density lipoprotein (LDL) cholesterol, triglycerides.	X	X
Nutritional assessment: Malnutrition-Inflammation Score (MIS), Protein Energy Wasting (PEW) score, categorized PEW, BMI, hydration status, hydration score and Karnosfky	X	X
Event variables**: Hospitalization, dates of hospitalization (admission and discharge dates), days of hospitalization, diagnosis of hospitalization, cardiovascular events, non-fatal cardiovascular events, death, date of death, diagnosis of death, grouped cause of death, covid-19 diagnosis, date of covid-19 ,		X**

***** Outcome event variables will be recorded chronologically according to occurrence.***

Appendix 2. Specification of variables

Demographic variables

Variable	Definition	Type of variable	Scale	Categories	Source
TIMEPOINT	A point in time	Qualitative	Polytomous	1 = Screening 2 = Reference 3 = 6 months 4 = 12 months 5 = 18 months 6 = 24 months	Versia®
IDSUBJECT	Number assigned to patient to protect his/her identity and ensure confidentiality of information	Quantitative	Discrete	None Format 0001-0001	Versia®
IDSITE	Number assigned to each renal clinic	Quantitative	Discrete	None Format CO0054	Versia®
CITY	City where the renal unit is located	Qualitative	Discrete	None Open text	Versia®
INSURER	Name of patient's insurer at study entry	Qualitative	Discrete	None Open text	Versia®
AGE	Lifetime at study entry	Quantitative	Continuous	Years	Versia®
SEX	Patient's gender	Quantitative	Dichotomous	1= Male 2= Female	Versia®
ETHNICITY	Ethnicity recorded at study entry	Qualitative	Polytomous	1= Native 2= Afro-American 3= Mestizo	Versia®

Medical history variables

Variable	Definition	Type of variable	Scale	Categories	Source
DATERRT	Date chronic renal replacement therapy was received for the first time	Date	dd/mm/yyyy	None	Versia®
VINTAGE RRT	Dialysis vintage time at study entry	Quantitative	Continuous	Years	Versia®
ETIOLOGYCKD	Cause of chronic kidney disease	Qualitative	Polytomous	1= Hypertension 2= Diabetes mellitus 3= Autoimmune glomerular disease 4=Obstructive 5= Polycystic disease 6= Unknown 7= Other	Versia®
HYPERTENSION	History of hypertension at study entry	Qualitative	Dichotomous	1 = Yes 0 = No	Versia®
DIABETES	History of diabetes mellitus at study entry	Qualitative	Dichotomous	1 = Yes 0 = No	Versia®
CARDIOVASCULAR	Diagnosis of cardiovascular disease at study entry	Qualitative	Dichotomous	1 = Yes 0 = No	Versia®
CHARLSON	Score obtained by applying the Charlson comorbidity index adapted to CKD at study entry	Quantitative	Dichotomous	None	Versia®
KARNOSFSKY	Karnofsky functional scale at study entry	Quantitative	Dichotomous	None	Versia®
URINE	Diuresis mL/day	Qualitative	Polytomous	1= < 100 ml/day 2= 100 to 400 ml/day 3= >400 ml/day	Versia®

Hemodialysis treatment variables

Variable	Definition	Type of variable	Scale	Categories	Source
DURATIOHD	Duration of the weekly HD sessions received by a patient recorded at the beginning of the trial	Quantitative	Continuous	Hours	Versia®
DIALYZER	Name of dialyzer (sic) used for hemodialysis treatment. Recorded at the beginning of the trial	Qualitative	Nominal	None	Versia®
QD	Dialysate flow rate during the hemodialysis session. Recorded at the beginning of the trial	Quantitative	Discrete	mL/min	Versia®
QB	Blood pump flow rate during the hemodialysis session. Recorded at the beginning of the trial	Quantitative	Discrete	mL/min	Versia®
UF	Volume extracted from the patient during the hemodialysis session. Recorded at the beginning of the trial	Quantitative	Discrete	L	Versia®
ACCESSTYPE	Vascular access used in the hemodialysis session. Recorded at the beginning of the trial	Qualitative	Polytomous	1= Temporary catheter 2= Tunneled catheter 3= Native AVF 4= AV graft	Versia®
ANTICOAGULANT	Medication used for anticoagulation of the extracorporeal circuit for hemodialysis. Recorded at the beginning of the trial	Qualitative	Polytomous	1= Heparin 2= Low molecular weight heparin 3= Not used	Versia®

ANTICOAGDOSE	Total dose of medication used for anticoagulation of the extracorporeal circuit for hemodialysis. Recorded at the beginning of the trial	Quantitative	Discrete	UI or mcg	Versia®
PRESB	Systolic blood pressure prior to dialysis. Recorded at baseline and every six months, during follow-up	Quantitative	Continuous	mmHg	Versia®
POSTSB	Systolic blood pressure after dialysis. Recorded at baseline and every six months, during follow-up	Quantitative	Continuous	mmHg	Versia®
PREDB	Diastolic blood pressure prior to dialysis. Recorded at baseline and every six months, during follow-up	Quantitative	Continuous	mmHg	Versia®
POSTDB	Diastolic blood pressure after dialysis. Recorded at baseline and every six months, during follow-up	Quantitative	Continuous	mmHg	Versia®

Laboratory parameters variables

Variable	Definition	Type of variable	Scale	Categories	Source
ALBUMIN	Plasma albumin levels prior to dialysis, recorded at baseline and at each trial visit	Quantitative	Continuous	g/dL	Versia®

PTHI	Plasma PTHI levels prior to dialysis, recorded at baseline and at each trial visit	Quantitative	Continuous	pg/mL	Versia®
PHOSPHORUS	Plasma phosphorus levels prior to dialysis, recorded at baseline and at each trial visit	Quantitative	Continuous	mg/dL	Versia®
CALCIUM	Total serum calcium recorded at baseline and at each trial visit	Quantitative	Continuous	mg/dL	Versia®
POTASSIUM	Serum potassium levels recorded at baseline and at each trial visit	Quantitative	Continuous	mEq/L	Versia®
HEMOGLOBIN	Plasma hemoglobin levels recorded at baseline and at each trial visit	Quantitative	Continuous	g/dL	Versia®
PLATELETS	Platelet levels recorded at baseline and at each trial visit	Quantitative	Continuous	$X10^9$/L	Versia®
LYMPHOCYTES	Lymphocytes count recorded at baseline and at each trial visit	Quantitative	Continuous	$X10^9$/L	Versia®
IRON	Plasma iron levels recorded at baseline and at each trial visit	Quantitative	Continuous	mcg/dL	Versia®
FERRITIN	Plasma ferritin levels recorded at baseline and at each trial visit	Quantitative	Continuous	ng/mL	Versia®
TSAT	Transferrin saturation recorded at baseline and at each trial visit	Quantitative	Continuous	%	Versia®
TIBC	Total iron binding capacity recorded at baseline and at each trial visit	Quantitative	Continuous	ug/dL	Versia®
HSCRP	High sensitivity C reactive protein recorded at baseline and at each trial visit	Quantitative	Continuous	mg/L	Versia®

PREBUN	BUN prior to dialysis recorded at baseline and at each trial visit	Quantitative	Continuous	mg/dL	Versia®
POSTBUN	BUN after dialysis recorded at baseline and at each trial visit	Quantitative	Continuous	mg/dL	Versia®
KTV	Single pool Kt/V recorded at baseline and at each trial visit	Quantitative	Continuous	None	Versia®
CHOLESTEROL	Total cholesterol recorded at baseline and at each 12-month and 24-month visit	Quantitative	Continuous	mg/dL	Versia®
HDL	High-density lipoprotein cholesterol (HDL) recorded at baseline and at each 12-month and 24-month visit	Quantitative	Continuous	mg/dL	Versia®
LDL	Low-density lipoprotein cholesterol (LDL) recorded at baseline and at each 12-month and 24-month visit	Quantitative	Continuous	mg/dL	Versia®
TRIGLYCERIDES	Triglycerides recorded at baseline and at each 12-month and 24-month visit	Quantitative	Continuous	mg/dL	Versia®

Medication variables

Variable	Definition	Type of variable	Scale	Categories	Source
NUTRITIONAL	The patient is prescribed monthly nutritional supplements	Qualitative	Dichotomous	1 = Yes 0 = No	Versia®
TYPE	Type of nutritional supplement	Qualitative	Polytomous	1=Complete formula 2=Complete, specialized formula 3=Modular formula	Versia®

Nutritional variables

Name	Definition	Type of variable	Scale	Categories	Source
BMI	Patient's body mass index at the time of admission to the trial and during each follow-up visit	Quantitative	Continuous	kg/m^2	Versia®
CATEGORIZED_BMI	Categorized body mass index	Qualitative	Polytomous	1= Underweight (<18.5) 2 = Normal weight (18.5 – 24.9) 3 = Overweight (25.0 – 29.9) 4= Obese (>=30)	BMI
PEW	Total score on the Protein-Energy Wasting Scale recorded at baseline and at each trial visit	Quantitative	Continuous	None	Versia®
CATEGORY_PEW	Protein-Energy Wasting Scale category	Qualitative	Dichotomous	0=No wasting (0-2) 1=Wasting (>=3)	PEW
SCORE_MAL_INF	Total score on the Malnutrition Inflammation Scale recorded at baseline and at each trial visit	Quantitative	Continuous	None	Versia®
HYDRATION	State of hydration with presence of symptoms of extracellular fluid excretion	Qualitative	Polytomous	0= No signs and symptoms 1=Edema below the knees 2= Edema above the knees	Versia®
KARNOSFSKY	Karnofsky Functional Scale at baseline and every six months	Quantitative	Dichotomous	None	Versia®
NUTRIT_ASSESS	Nutritional assessment combining PEW status plus BMI, at baseline and every six months	Qualitative	Nominal	Text (e.g.; Overweight with wasting)	Versia®

Hospitalization variables

Variable	Definition	Type of variable	Scale	Categories	Source
HOSPITAL	Occurrence of hospitalization event	Qualitative	Dichotomous	1 = Yes 0 = No	Versia®
HOSPITALDX	Principal diagnosis for cause of hospitalization	Qualitative	Nominal	ICD 10 diagnosis	Versia®
MAJOR_CARDIOEVENT	Diagnosis (ICD-10) of a new cardiovascular event (Please, see Appendix 3 ICD-10)	Qualitative	Dichotomous	1=Yes 0=No	Versia®
FATALCARDIO	Fatal major cardiovascular event	Qualitative	Dichotomous	1=Yes 0=No	Versia®
COVIDEVENT	Hospitalization due to COVID-19 diagnosis	Qualitative	Dichotomous	1=Yes 0=No	Versia®
STARTHOSPDATE	Date of hospital admission	Date	dd/mm/yyyy	None	Versia®
ENDHOSPDATE	Date of hospital discharge	Date	dd/mm/yyyy	None	Versia®
DAYSTAYDAY	Difference between admission date and discharge date	Quantitative	Discrete	Days	Versia®

Mortality variables

Variable	Definition	Type of variable	Scale	Categories	Source
DEATH	Death during follow-up in the trial	Qualitative	Dichotomous	1 = Yes 0 = No	Versia®
DEATHXD	Diagnosis (ICD-10) of death	Qualitative	Nominal	ICD 10 diagnosis	Versia®

DEATHREASON	Causes of death grouped	Qualitative	Polytomous	1=Cancer 2= Cardiovascular 3=Infectious 4=Metabolic 5=Respiratory 6 = COVID 7=Other 8= Unknown	Versia®
DEATHRELAT	Dialysis-related death	Qualitative	Dichotomous	1 = Yes 0 = No	Versia®
DEATHDATE	Date of death	Date	dd/mm/yyyy	None	Versia®

End of follow-up variables

Variables	Definition	Type of variable	Scale	Categories	Source
ENDFOLLOWUP	Reason for termination of cohort follow-up.	Qualitative	Polytomous	1= Death 2= Loss to follow-up 3= Change of healthcare provider/insurer 4= Recovery of renal function 5= Discontinuation of treatment 6= Kidney transplant 7= Dialyzer change 8= Switched to PD 9= End of study	Versia®
DATEEND	Date of completion of cohort follow-up	Date	dd/mm/yyyy	None	Versia®

Appendix 3. Major cardiovascular events

ICD 10	Ischemic cardiomyopathy
I20X	Angina pectoris
I20.1	Angina pectoris with documented spasm
I20.8	OTHER FORMS OF ANGINA PECTORIS
I20.9	Angina pectoris, unspecified
I20.0	Unstable angina
I25.5	Ischemic cardiomyopathy
I25.6	SILENT MYOCARDIAL ISCHEMIA
I25.8	OTHER FORMS OF CHRONIC ISCHEMIC HEART DISEASE
I25.9	Chronic ischemic heart disease, unspecified
I24.0	ACUTE CORONARY THROMBOSIS NOT RESULTING IN MYOCARDIAL INFACTION
I24.9	Acute ischemic heart disease, unspecified
I25.X	Chronic ischemic heart disease

ICD 10	Cerebrovascular
I61.0	INTRACEREBRAL HEMORRHAGE IN HEMISPHERE, SUBCORTICAL
I61.1	INTRACEREBRAL HEMORRHAGE IN HEMISPHERE, CORTICAL
I61.2	INTRACEREBRAL HEMORRHAGE IN HEMOSPHERE, UNSPECIFIED
I61.3	INTRACEREBRAL HEMORRHAGE IN BRAIN STEM
I61.4	INTRACEREBRAL HEMORRHAGE IN CEREBELLUM
I61.5	INTRACEREBRAL HEMORRHAGE, INTRAVENTRICULAR
I61.6	INTRACEREBRAL HEMORRHAGE, MULTIPLE LOCALIZED
I61.8	OTHER INTRACEREBRAL HEMORRHAGE
I61.9	INTRACEREBRAL HEMORRHAGE, UNSPECIFIED
I62.9	(NON TRAUMATIC) INTRACRANIAL HEMORRHAGE, UNSPECIFIED
I63.0	CEREBRAL INFARCTION DUE TO THROMBOSIS OF PRECEREBRAL ARTERIES
I63.1	CEREBRAL INFARCTION DUE TO EMBOLISM OF PRECEREBRAL ARTERIES

ICD 10	Congestive Heart Failure
I11.0	HYPERTENSIVE HEART DISEASE WITH (CONGESTIVE) HEART FAILURE
I13.0	HYPERTENSIVE HEART AND KIDNEY DISEASE WITH (CONGESTIVE) HEART FAILURE
I13.2	HYPERTENSIVE HEART AND KIDNEY DISEASE WITH (CONGESTIVE) HEART FAILURE AND CHRONIC KIDNEY DISEASE
I50.0	CONGESTIVE HEART FAILURE
I50.1	LEFT VENTRICULAR FAILURE
I50.9	HEART FAILURE, UNSPECIFIED
I50.X	HEART FAILURE

I21.X	Acute myocardial infarction
I21.9	Acute myocardial infarction, unspecified
I21.2	Transmural myocardial infarction of other sites
I25.2	Old myocardial infarction
I21.4	Acute subendocardial myocardial infarction
I22.X	Subsequent myocardial infarction
I22.0	Subsequent myocardial infarction of anterior wall
I22.1	Subsequent myocardial infarction of inferior wall
I22.8	Subsequent myocardial infarction of other sites
I22.9	Subsequent myocardial infarction of unspecified site
I21.0	Transmural myocardial infarction of anterior wall
I21.1	Transmural myocardial infarction of inferior wall
I21.3	Transmural myocardial infarction of unspecified site
I23.0	HEMOPERICARDIUM AS CURRENT COMPLICATION FOLLOWING ACUTE MYOCARDIAL INFARCTION
I23.1	ATRIAL SEPTAL DEFECT AS CURRENT COMPLICATION FOLLOWING ACUTE MYOCARDIAL INFARCTION

I63.2 (I67.3 N. del T.)	PROGRESSIVE VASCULAR LEUKOENCEPHALOPATHY/ Cerebral infarction due to unspecified occlusion or stenosis of precerebral arteries
I63.3	CEREBRAL INFARCTION DUE TO THROMBOSIS OF CEREBRAL ARTERIES
I63.4	CEREBRAL INFARCTION DUE TO EMBOLISM OF CEREBRAL ARTERIES
I63.5	CEREBRAL INFARCTION DUE TO UNSPECIFIED OCCLUSION OR STENOSIS OF CEREBRAL ARTERIES
I63.8	OTHER CEREBRAL INFARCTION
I63.9	CEREBRAL INFARCTION, UNSPECIFIED
I64.X	STROKE, NOT SPECIFIED AS HEMORRHAGE OR INFARCTION
I67.8	OTHER SPECIFIED CEREBROVASCULAR DISEASES
I67.9	CEREBROVASCULAR DISEASE, UNSPECIFIED
I68.8	OTHER CEREBROVASCULAR DISORDERS IN DISEASES CLASSIFIED ELSEWHERE
I69.1	SEQUELAE OF INTRACEREBRAL HEMORRHAGE
I69.2	SEQUELAE OF OTHER NONTRAUMATIC INTRACRANEAL HEMORRHAGE
I69.3	SEQUELAE OF CEREBRAL INFARCTION
I69.4	SEQUELAE OF STROKE, NOT SPECIFIED AS HEMORRHAGE OR INFARCTION
I69.8	SEQUELAE OF OTHER AND UNSPECIFIED CEREBROVASCULAR DISEASES

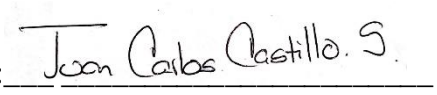
I23.2	VENTRICULAR SEPTAL DEFECT AS CURRENT COMPLICATION FOLLOWING ACUTE MYOCARDIAL INFARCTION	G45.0	VERTEBRO-BASILAR ARTERY SYNDROME
I23.3	RUPTURE OF CARDIAC WALL WITHOUT HEMOPERICARDIUM AS CURRENT COMPLICATION FOLLOWING ACUTE MYOCARDIAL INFARCTION	G45.1	CAROTID ARTERY SYNDROME (HEMISPHERIC)
I23.4	RUPTURE OF CHORDAE TENDINEAE AS CURRENT COMPLICATION FOLLOWING ACUTE MYOCARDIAL INFARCTION	G45.2	MULTIPLE AND BILATERAL PRECEREBRAL ARTERY SYNDROMES
I23.5	RUPTURE OF PAPILLARY MUSCLE AS CURRENT COMPLICATION FOLLOWING ACUTE MYOCARDIAL INFARCTION	G46.0	MIDDLE CEREBRAL ARTERY SYNDROME (I66.0†)
I23.6	THROMBOSIS OF ATRIUM, AURICULAR APPENDAGE AND VENTRICLE AS CURRENT COMPLICATIONS FOLLOWING ACUTE MYOCARDIAL INFARCTION	G46.1	ANTERIOR CEREBRAL ARTERY SYNDROME (I66.1†)
I23.8	OTHER CURRENT COMPLICATIONS FOLLOWING ACUTE MYOCARDIUM INFARCTION	G46.2	POSTERIOR CEREBRAL ARTERY SYNDROME (I66.2†)
I23.X	CERTAIN CURRENT COMPLICATIONS FOLLOWING ACUTE MYOCARDIAL INFARCTION	G46.3	BRAIN STEM STROKE SYNDROME (I60-I67†)
I24.0	CORONARY THROMBOSIS NOT RESULTING IN MYOCARDIAL INFARCTION	G46.4	CEREBELLAR STROKE SYNDROME (I60-I67†)
I24.1	DRESSLER'S SYNDROME	G46.5	PURE MOTOR LACUNAR SYNDROME (I60-I67†)
I24.8	OTHER FORMS OF ACUTE ISCHEMIC HEART DISEASE	G46.6	PURE SENSORY LACUNAR SYNDROME (I60-I67†)
I24.9	ACUTE ISCHEMIC HEART DISEASE, UNSPECIFIED	G46.7	OTHER LACUNAR SYNDROMES (I60-I67†)
I24.X	OTHER ACUTE ISCHEMIC HEART DISEASES	G46.8	OTHER VASCULAR SYNDROMES OF BRAIN IN CEREBROVASCULAR DISEASES (I60-I67†)

Appendix 4. Signature of the principal investigator

Study Title: Albumin levels, inflammation and nutrition in chronic hemodialysis patients treated with medium cut-off or high-flux membranes: A cohort study.

Study Number: RCS2023-001
Final Date: 28 february 2023

I have read the protocol described above. I agree to comply with all applicable regulations and to conduct the study as described in the protocol

Signature:  Date: **28-feb-2023**

Dr. Juan Carlos Castillo, MD.

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BRCS Agencia Soacha
CR 7 No. 47-35, Bogotá D.C. Colombia
Cell Phone No.: +57 3204867219
E-mail: juan_castillo@baxter.com

Appendix 5. Participating institutions

Renal Clinic	Location	Address	Investigator
BRCS Instituto Nacional del Riñón	Bogotá D.C	Calle 78#23-40	Dr. David Camargo, MD.
BRCS Agencia Cardioinfantil	Bogotá D.C	Carrera 14ª#163ª-98	Dr. Anthony Martínez. MD.
BRCS Agencia San Rafael	Bogotá D.C	Carrera 8 n° 17-44 sur entrada 3 piso 1 Barrio Sociego	Dr. Juan Carlos Mario Castillo
BRCS Agencia la Calleja	Bogotá D.C	Calle 127 bis #19-25 Piso 5	Dr. Sylvia Quiñónez, MD.
BRCS Sucursal Barranquilla	Barranquilla	Calle 47 # 16-167	Dr. Mario David Munevar, MD.
BRCS Sucursal Bucaramanga	Bucaramanga	Transversal 93 # 34-99 local SS10-A-B-C-D Centro Comercial el Cacique	Dr. Edward Martínez, MD.
BRCS Servicios de Terapia Renal del Valle	Cali	Calle 45N # 4N -32 la Flora	Dr. María Paz Dazzarola, MD.
BRCS Sucursal Medellín	Medellín	Carrera 57 #44ª-10	Dr. Alvaro del Castillo.
BRCS Servicios de Terapia Renal SAS	Cali	Calle 5A #42-10	Dr. Rafael Alberto Gómez, MD.
BRCS Sucursal Armenia	Armenia	Carrera 6 No. 3-180 Centro Comercial Calima Local 1-14	Dr. Rafael Alberto Gómez, MD..
Unidad Renal del Tolima S.A.S	Ibague	FLC 31 N° 4D-36 Barrio Cádiz	Dr. María Paz Dazzarola, MD.

Appendix 6. Name of principal investigator and co-investigators

Principal investigator: Dr. Juan Carlos Mario Castillo, MD.

Co-investigators: Anthony Martinez
David Camargo
Sylvia Quiñonez
Mario David Munevar Barrera
Edward Alberto Martinez
Rafael Alberto Gómez Acevedo
Maria Paz Dazzarola Morales
Alvaro del Castillo

Appendix 7. Clinical Trial Budget

ITEMS	COL. PESOS
Feasibility study, design and development of the protocol	$50,000,000
Investigator meetings (hotel expenses - travel)	$60,000,000
Training and certification in good clinical practices	$18,000,000
Research Ethics Committee Costs or IRB	$6,000,000
Study data quality monitoring activities	$30,000,000
Database design and assembly	$60,000,000
Quality assurance and database monitoring	$50,000,000
Database access support activities	$15,000,000
Statistical analysis Report and SAP	$80,000,000
Database de-identification activities	$15,000,000
Clinical Study Report	$15,000,000
Manuscript writing and publication	$30,000,000
Project administration	$25,000,000
Educational activities research team	$24,000,000
Miscellaneous Expenses	$47,800,000
Total, Budget	**$525,800,000**

Appendix 8. Trial Schedule

Activities	Month 1	Month 2	Month 3	Month 4	Month 5	Month 6	Month 7	Month 8	Month 9	Month 10
Protocol development	X	X								
Submission and approval of the protocol to the FCI Research Ethics Committee			X							
Database development				X	X	X				
Statistical analysis							X	X		
Outcomes report creation							X	X		
Writing of scientific paper									X	
Submission of scientific paper for publication										X

Appendix 9. Habeas Data Document

AUTHORIZATION FOR DATA COLLECTION AND PROCESSING
PATIENTS
RTS S.A.S. (Tax Identification Number 805.011.262-0)

In compliance with Law 1581 of 2012, Decree 1377 of 2013 and other applicable regulations regarding the protection of personal data in Colombia, the PATIENT declares that:

a He/she has been informed that RTS and the HPI[1] that are part of its network will treat his/her personal data under the terms of the General Policy for the Treatment of Personal Data.

b He/she will provide all the personal data necessary for the fulfillment of the obligations under this contract. The PATIENT undertakes to provide true data and is aware of the labor, criminal and civil liabilities arising from misrepresentation or omission of these data.

c He/she has been informed that the requested data may include sensitive information (such as health data and biometric data) and that he/she is not obliged to authorize the processing of such data, which would also be used for the purposes described above.

d All personal data provided are true and he/she has not omitted or altered any information.

e He/she has been informed of his/her rights to know, update, rectify and delete his/her personal data, as well as the procedure to request access, correction, update or deletion, through the following contact point: Email: habeasdata@baxter.com, web page http://rcs.baxter.com/es or by written communication to the following addresses: Bogotá: Transversal 23 No. 97-73, Piso 6; Cali: Calle 36 No. 2C-22 Planta 3; Telephones (2) 4447241, Customer service line: 018000-939595.

The PATIENT authorizes RTS to:

f To process your personal data in accordance with the terms of the RTS General Personal Data Processing Policy.

g The processing, collection, storage, use, circulation, deletion, updating, transmission and/or national and international transfer of the data provided, even to countries that do not guarantee the same level of protection as Law 1581 of 2012.

1 Healthcare Providing Institutions (IPS *or Instituciones Prestadoras de Servicios*) that make up the RTS S.A.S. network include:

- Instituto Nacional del Riñón Ltda. in liquidation
- Servicio de Terapia Renal S.A.S
- Unidad Renal del Tolima S.A.S.

Authorization to process personal data RTS Rev. 2022 Page 1

h The following purposes: (i) comply with obligations arising from a current or future legal relationship with you; (ii) comply with health obligations and other legal obligations; (iii) provide guidance on medical treatments, nutrition and psychology, therapies and quality of life; (iv) follow up on adherence to your treatment; (v) provide training and/or education on your treatment; (vi) provide advice on the application of medications; (vii) administer medications in your home by nurses with extensive experience; (viii) handle pharmacovigilance reports; (ix) manage your complaints, concerns and/or suggestions; (x) deliver medications; (xi) fulfill statistical and scientific purposes; (xii) provide information for clinical studies; and (xiii) in general, for any other purpose arising from the nature of the legal relationship, including educational and training purposes related to **RTS** therapies and service provision.

i By virtue of the foregoing, I authorize to be contacted via email messages, WhatsApp, telephone or phone calls, or any other means known or to be known.

This authorization shall remain in force until it is revoked based on the provisions of the legislation.

Full Name: _____
I.D. Number: _____
Place and Date: _____
Signature: _____

PRIVACY NOTICE
PATIENTS
RTS S.A.S.

RTS S.A.S (hereinafter "RTS"), a company identified with NIT 805.011.262-0 with registered address at Calle 36 No. 2c - 22 Cali, and the HPI[2] that are part of its network of services in accordance with the provisions of Law 1581 of 2012, Decree 1377 of 2013, and other applicable regulations regarding the protection of personal data in Colombia, hereby provides you with information regarding the processing of your personal data. Please read this privacy notice carefully.

1. Information on the processing of your personal data

RTS may use your personal data to: (i) comply with obligations arising from a current or future legal relationship with you; (ii) comply with health obligations and other legal obligations; (iii) provide guidance on medical treatments, nutrition and psychology, therapies and quality of life; (iv) follow up on adherence to your treatment; (v) provide training and/or education on your treatment; (vi) provide advice on the application of medications; (vii) administer medications in your home by nurses with extensive experience; (viii) handle pharmacovigilance reports; (ix) manage your complaints, concerns and/or suggestions; (x) deliver medications; (xi) fulfill statistical and scientific purposes; (xii) provide information for clinical studies; and (xiii) in general, for any other purpose arising from the nature of the legal relationship, including educational and training purposes related to **RTS** therapies and service provision.

2. About your rights

In accordance with Colombian personal data protection regulations, as the owner of the data, you are entitled to exercise your rights of access, authorization, revocation, modification, rectification and cancellation of your personal data. Likewise, you have the right to limit the use or disclosure of your personal data and revoke consent at the time you so decide, provided that data processing is not necessary to fulfill the contractual or legal obligations arising from our relationship.

3. The above rights may be exercised with a request, under the terms set forth in Title V of Law 1581 of 2012, submitted to the Compliance Officer, located at Calle 36 No. 2C -22, in Santiago de Cali, phone (2) 444-7000 Email: habeasdata@baxter.com, web page http://rcs.baxter.com/es or by written communication to the following addresses: Bogotá: Transversal 23 No. 97-73, Piso 6; Cali: Calle 36 No. 2C-22 Planta 3; Telephones (2) 4447241, Customer service line: 018000-939595.

4. Sensitive data

As part of its activities, RTS may require sensitive data such as your health information, which will be treated in accordance with the principles set forth by law. As the owner of data, you have no obligation whatsoever to provide any of your information to us. Nevertheless, you should be aware that some formalities and procedures will require the processing of personal data.

5. Privacy Policy

You can access our privacy policy at: www.rtscentrosdecuidadorenal.com

1 Healthcare Providing Institutions (IPS *or Instituciones Prestadoras de Servicios*) that make up the RTS S.A.S. network include:

- Instituto Nacional del Riñón Ltda. in liquidation
- Servicio de Terapia Renal S.A.S
- Unidad Renal del Tolima S.A.S.

Appendix 10. Statistical Analysis Plan (SAP)