ENGLISH TRANSLATION

Study protocol with statistical analysis plan

English translation of the December 2025 research proposal

OFFICIAL TITLE • ENGLISH TRANSLATION OF THE ETHICS CERTIFICATE TITLE

Evaluation of the Clinical Performance of the Robust Hemodialysis Machine and Wolfgang HD-180 Dialyzer in Patients Receiving Maintenance Hemodialysis at Bethesda Hospital Yogyakarta

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Source	Indonesian research proposal, translated into English

SOURCE VERSION

This pre-enrollment proposal includes the sample-size calculation in III.C.3 and statistical methods in III.H. The committee certificate does not identify the version it reviewed. The latest manuscript reports two sessions with the new Robust–WOLFGANG system followed by two with the established Nikkiso–Purifier system. This post-study description differs from the proposal. The translation preserves the proposal as written.

Research proposal

Evaluation of Dialysis Adequacy and Safety of Switching to a New High-Flux Polyethersulfone Hollow-Fiber Dialyzer (WOLFGANG-HD180) Compared with a Conventional Dialyzer in Patients Receiving Maintenance Hemodialysis at Bethesda Hospital Yogyakarta

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The original proposal title is translated above. Figures are rendered as descriptions of their labels and relationships. The blank case report form is typeset in English.

Abbreviations in the proposal

AL, white blood cell count; ALT, alanine transaminase; AST, aspartate transaminase; AT, platelet count; β2-M, beta-2-microglobulin; BUN, blood urea nitrogen; ER, extended release; Hb, hemoglobin; Hct, hematocrit; HD, hemodialysis; IL, interleukin; IR, immediate release; IV, intravenous; KDIGO, Kidney Disease: Improving Global Outcomes; KDOQI, Kidney Disease Outcomes Quality Initiative; LFG, glomerular filtration rate; NKF, National Kidney Foundation; PES, polyethersulfone; PGTA, end-stage kidney disease; URR, urea reduction ratio.

I. Introduction

I.A Background

End-stage kidney disease is a serious health problem that requires kidney replacement therapy. Hemodialysis is a principal treatment used to remove waste products and excess fluid (Gaudry et al., 2025). Dialysis quality and adequacy are important for survival and quality of life. Adequacy is generally assessed with Kt/V, a measure of dialysis dose based on urea clearance, and the urea reduction ratio (URR). For hemodialysis three times a week, NKF KDOQI recommends a minimum Kt/V of 1.2, approximately equivalent to a URR of 65% (Daugirdas et al., 2015). Inadequate dialysis is associated with a higher risk of uremic complications and cardiovascular mortality (Chen et al., 2023).

An important challenge is the removal of middle-molecule uremic toxins such as beta-2-microglobulin (β2M). This protein has a molecular weight of about 11.8 kDa. Healthy kidneys remove it, but it accumulates in patients on dialysis because conventional low-flux filters do not effectively clear it (Tattersall, 2007). Elevated β2M is a nontraditional risk factor for increased cardiovascular morbidity and mortality in long-term hemodialysis patients (Mumtaz et al., 2010). Chronic accumulation may cause dialysis-related amyloidosis, including carpal tunnel syndrome and bone and joint disease (Portales-Castillo et al., 2020).

The choice of dialyzer affects how efficiently dialysis removes waste. High-flux membranes have larger pores and higher permeability than low-flux membranes, which permits greater clearance of middle molecules such as β2M. Studies associate low-flux dialysis with high serum β2M concentrations. High-flux dialyzers improve β2M clearance and reduce its long-term accumulation (Mumtaz et al., 2010; Tattersall, 2007). Large observational studies have also reported lower morbidity and mortality with high-flux membranes than with low-flux membranes (Canaud et al., 2006; Leypoldt et al., 1999; Woods and Nandakumar, 2000). Improved β2M clearance might reduce long-term complications of its accumulation (El-Wakil et al., 2011).

Bethesda Hospital Yogyakarta is a private hospital serving approximately 130 maintenance hemodialysis patients. Most dialyzers used by the unit have been Fresenius products, referred to in this proposal as the previous dialyzer. A less expensive new-generation Wolfgang polyethersulfone (PES) dialyzer is now available and is claimed to offer noninferior performance. It has a hollow-fiber design with uniform radial dialysate distribution around each fiber and ultrasonically bonded caps intended to prevent blood and dialysate leakage. Product information describes high biocompatibility, improved clearance of small and medium-to-large uremic toxins, and high β2M clearance with minimal albumin loss. These features might improve Kt/V and URR and lower β2M without excessive albumin loss.

The proposed switch from Fresenius to Wolfgang at Bethesda Hospital Yogyakarta needs scientific evaluation to establish efficiency and determine whether the switch would reduce clinical benefit. This study will compare Kt/V, URR and β2M clearance before and after changing to Wolfgang. It will also examine urea, creatinine, electrolytes including sodium and potassium, calcium and albumin. Evidence on the clinical performance of the new dialyzer could inform clinical decisions and policy in the hospital dialysis unit.

I.B Research questions

General question. Is there a significant difference in dialysis adequacy and safety before and after the dialyzer is changed?

Specific questions. Do the following differ significantly before and after the change?
1. Hemodialysis adequacy measured by Kt/V and URR.
2. Serum β2-microglobulin concentration.
3. Other laboratory parameters, including albumin, electrolytes, calcium and routine blood counts.
4. Occurrence of adverse effects.

I.C Study objectives

The general objective is to assess the efficacy and safety of replacing the Fresenius dialyzer with the Wolfgang dialyzer in maintenance hemodialysis patients at Bethesda Hospital Yogyakarta.

The specific objectives are to compare the following before and after switching dialyzers: (1) Kt/V and URR, (2) serum β2M, (3) other laboratory parameters, including albumin, electrolytes, calcium and routine blood counts, and (4) occurrence of adverse effects.

I.D Originality of the study

Comparative studies of previous and new dialyzers addressing both dialysis adequacy and β2M are limited. Table 1 summarizes the prior studies and their differences from the proposed study, as described in the proposal.

Table 1. Prior studies and their relationship to the proposed research

Authors and study	Methods and findings	Difference from this study
Mumtaz et al. (2010). Beta-2 microglobulin levels in hemodialysis patients.	Cross-sectional study of 50 maintenance dialysis patients. Mean β2M was 92.6 mg/L in patients and 2 mg/L in controls. Low-flux dialyzer use was identified as a major factor associated with elevated β2M.	Observational study. Dialysis adequacy was not evaluated.
El-Wakil et al. (2011). Effect of high flux versus low flux hemodialysis on serum beta-2 microglobulin, advanced oxidation protein products and protein carbonyl.	Comparative before-and-after high-flux study in 20 chronic dialysis patients. High-flux dialysis significantly lowered serum β2M and protein carbonyl relative to low-flux dialysis and removed middle molecules more efficiently. Advanced oxidation protein products did not differ significantly between groups.	Comparison of high- and low-flux membranes in general without a brand-specific comparison. Outcomes were β2M and oxidative stress.
Locatelli et al. (2009). Effect of Membrane Permeability on Survival of Hemodialysis Patients.	Prospective randomized trial of 738 dialysis patients assigned to low- or high-flux membranes and followed for 3–7.5 years. Overall survival did not differ significantly. The proposal reports improved survival with high flux in subgroups with dialysis duration greater than 3.7 years or low albumin, and less accumulation of β2M with high flux.	Large study focused principally on long-term survival rather than dialysis adequacy measures.

I.E Expected benefits

For patients. If the Wolfgang dialyzer improves adequacy and reduces toxins such as β2M at lower cost, patients may receive more effective and efficient dialysis. Potential long-term benefits include fewer complications such as amyloidosis and cardiovascular disease, and improved survival and quality of life. Monitoring safety indicators such as albumin will help determine whether the switch harms patients.

For the institution. The study may provide a scientific basis for choosing a dialyzer. If results are favorable, Bethesda Hospital could adopt Wolfgang as its standard dialyzer to improve care and cost efficiency. The findings could contribute to accreditation or unit performance reports and demonstrate evidence-based adoption of new technology.

For scientific knowledge. The study will add evidence in nephrology and kidney replacement therapy about the efficacy and safety of a new high-flux dialyzer compared with conventional dialysis, particularly in relation to dialysis adequacy and β2M clearance. It may inform further studies and the development of improved membranes. Results may be published in a scientific journal or presented at a scientific meeting and may contribute to evidence-based care for end-stage kidney disease.

II. Literature review

II.A Hemodialysis for end-stage kidney disease

End-stage kidney disease is characterized by irreversible loss of kidney function and inadequate excretion of metabolic waste and fluid. During hemodialysis, a pump circulates blood through a dialyzer containing a semipermeable membrane. Dialysate flows on the other side. Solutes such as urea, creatinine and potassium diffuse from blood into dialysate. Ultrafiltration removes excess water across a pressure gradient. Dialysis seeks to restore internal homeostasis as closely as possible by removing uremic toxins and controlling volume and electrolytes (Gaudry et al., 2025).

Patients generally receive hemodialysis two or three times per week for approximately four to five hours per treatment, according to clinical need. Dialysis sustains life but does not restore all normal kidney functions. Chronic uremic complications, metabolic disturbances, inflammation, anemia and other problems remain despite dialysis (Daugirdas et al., 2015; Gaudry et al., 2025).

II.B Dialysis adequacy, Kt/V and URR

Adequacy refers to how effectively dialysis removes waste and fluid. The two laboratory measures most often used are Kt/V and URR (Daugirdas et al., 2015). Kt/V combines dialyzer clearance (K, L/h), dialysis duration (t, hours) and the patient's urea distribution volume (V, total body water). It expresses the fraction of that volume cleared of urea per session. The Daugirdas formula in the proposal uses predialysis and postdialysis BUN, treatment duration, body water volume and weight loss:

$$spKt/V = -\ln(R - 0.008 \times T) + (4 - 3.5 \times R) \times 0.55 \times \text{weight loss} / V$$

R is the ratio of postdialysis to predialysis BUN. V is the volume of body water. Weight loss uses the same units as V, and T is the duration of dialysis in hours. URR is the percent decrease in blood urea concentration during a session: URR = 100% × (predialysis urea − postdialysis urea) / predialysis urea. A URR of 65% corresponds approximately to a Kt/V of 1.2.

The 2015 NKF KDOQI guideline recommends a minimum single-pool Kt/V of 1.2 per session for three-times-weekly hemodialysis and a higher target (at least 1.4) to ensure adequacy. Likewise, URR should reach at least 65%, with a target above 70% (Daugirdas et al., 2015). Values below these standards are associated with higher mortality and morbidity, including malnutrition and uremic pericarditis. In observational studies, mortality fell as Kt/V rose to about 1.2–1.4, with little additional benefit possible at higher values (Chen et al., 2023).

Blood flow (Qb), dialysate flow (Qd), treatment time, dialyzer area and efficiency, the patient's distribution volume and adherence to schedule and diet influence adequacy. Predialysis and postdialysis urea may be measured every one to three months to calculate Kt/V or URR. Absence of uremic symptoms, good appetite and stable weight also indicate functional adequacy (Daugirdas et al., 2015).

II.C Low-flux and high-flux dialyzers and membranes

The dialyzer is the artificial kidney at the heart of the dialysis machine. It contains thousands of hollow fibers made of semipermeable membranes. Blood flows through the fibers and dialysate outside them, or vice versa depending on the design. Substances move across the fiber walls (Liangos and Jaber, 2013).

Dialyzers are classified by membrane material and flux or permeability. Materials discussed in the proposal include polysulfone, polyethersulfone and modified cellulose (cellulose diacetate, triacetate, polyamide and others). Synthetic membranes such as polysulfone and PES usually provoke less inflammation than older unmodified cellulose membranes. Fresenius developed a polysulfone membrane called Helikson, while Wolfgang uses PES (Samaya Medika Indonesia, 2025). Low-flux

membranes have smaller pores and lower ultrafiltration coefficients, limiting the removal of medium- to high-molecular-weight solutes. High-flux membranes have larger pores and higher coefficients and can remove middle molecules such as β2M and some larger substances. They can also be used for hemodiafiltration (HDF), which combines diffusion and convection to clear middle molecules more effectively.

Figure 1. Low-flux hemodialysis, high-flux hemodialysis and online hemodiafiltration

The original diagram (Santos et al., 2022) shows blood and dialysate flowing past opposite sides of a membrane. Low-flux HD is labeled “diffusion”. High-flux HD and online HDF are labeled “diffusion” and “convection”. The online HDF circuit also shows the addition of substitution fluid.

Dialyzer selection should reflect the patient’s condition and treatment goals. Low-flux dialysis generally removes small molecules such as urea, creatinine and potassium sufficiently but is less effective for β2M and phosphate. High-flux dialyzers are indicated for long-term dialysis patients to help prevent β2M amyloidosis. Some studies suggest a benefit in patients with high cardiovascular risk or more than five years of dialysis (Locatelli et al., 2009).

Performance measures include the mass transfer–area coefficient (KoA) for a solute such as urea, reflecting theoretical maximum clearance, and the ultrafiltration coefficient (KUF), reflecting fluid removal per unit pressure. High-flux dialyzers have high urea KoA and KUF. Clearance also depends on membrane surface area. Sizes such as 1.3, 1.6 and 2.0 m² allow matching to body size (Liangos and Jaber, 2013).

II.D Wolfgang dialyzer technology and the previous dialyzer

The proposal describes the hospital’s previous dialyzer as a low-flux polysulfone model with limited β2M clearance. It identifies the proposed new product as the high-flux WOLFGANG-HD180 PES dialyzer distributed by PT Samaya Medika, Indonesia. The proposal describes the following features on the basis of brochure information.

Uniform radial flow. Dialysate is distributed evenly around each hollow fiber, improving diffusion throughout the bundle and reducing stagnation. Ultrasonic cap bonding. An ultrasonically sealed joint is intended to prevent blood or dialysate leakage and improve safety. Dialysate inlet. A smooth, compatible port facilitates machine connection without excessive turbulence.

Membrane area and models. The HD130, HD150, HD180 and HD200 have surface areas of approximately 1.3 to 2.0 m². The proposal mentions mid-flux M models and possibly high-flux L-series models. Surface area is important when matching a dialyzer to a patient’s body surface area.

Middle molecules and albumin. The manufacturer claims improved clearance of medium-to-large molecules, particularly β2M. The PES membrane is designed to minimize albumin loss despite its larger pores. Some high-flux membranes permit small amounts of albumin to pass. The Wolfgang design seeks to balance porosity for β2M with retention of albumin.

Biocompatibility. The proposal describes PES as highly biocompatible, with minimal complement and immune-cell activation when blood contacts the membrane, potentially reducing allergic or inflammatory reactions. The brochure describes the device as having excellent biocompatibility.

Materials. The product is reported to be free of DEHP plasticizer and BPA, a feature the proposal considers important to long-term safety, particularly with repeat use. Solute clearance. In addition to β2M, the product is said to provide high urea and creatinine clearance and effective phosphate clearance. Phosphate (PO4) has a molecular weight of about 96 Da, but it is difficult to lower because of its distribution in the body. The proposal suggests that high-flux membranes may improve phosphate removal per treatment compared with low-flux membranes.

On these grounds, investigators expect Wolfgang to deliver noninferior or possibly better adequacy at a lower price than the previous Fresenius dialyzer, particularly if that dialyzer is low-flux. The main interests are urea and creatinine clearance, with improved Kt/V and URR, and β2M clearance. Potential harms include a fall in serum albumin or hematologic effects such as hemolysis and inflammatory activation. Both dialyzers will be compared in the same patients to control individual differences.

II.E Beta-2-microglobulin in dialysis patients

β2M is the light-chain protein of the MHC class I complex on the surface of all nucleated cells. It weighs approximately 11.8 kDa. Under normal conditions, it is produced continuously, filtered at the glomerulus, and broken down by kidney tubules. In end-stage kidney disease, elimination falls markedly, leading to accumulation in blood and tissues (Sedighi et al., 2014).

Without residual kidney function, serum β2M in dialysis patients may reach tens of times its normal level. Mumtaz et al. reported a mean above 90 mg/L compared with a normal concentration of about 2 mg/L. Levels are associated with dialysis duration and membrane type. Low-flux membranes remove little β2M, so it accumulates between treatments. High-flux membranes can substantially reduce β2M in a session, although some remains in poorly dialyzable compartments and postdialysis rebound occurs (Mumtaz et al., 2010).

Long-term accumulation leads to dialysis-related amyloidosis. Amyloid fibrils form in tissues, especially bones and joints. Clinical manifestations include carpal tunnel syndrome from thickening of the transverse carpal ligament, destructive arthritis in large joints such as shoulders and knees, bone cysts that may cause fractures, and deposits elsewhere. Amyloidosis usually appears after more than five to seven years of dialysis, particularly with low-flux treatment. Preventive measures include early use of high-flux membranes or hemodiafiltration to increase β2M removal. High-cutoff dialyzers with very large pores are also available to clear amyloid, although use is limited (Portales-Castillo et al., 2020).

Elevated β2M is also suspected to contribute to cardiovascular disease in dialysis patients. It is regarded as an inflammatory marker and a uremic toxin that may contribute to atherosclerosis. Higher serum concentrations correlate with higher all-cause and cardiovascular mortality in hemodialysis patients (Chazot et al., 2015). Reducing β2M is therefore of interest for prevention of amyloidosis and potential improvement in long-term cardiovascular outcomes.

β2M is usually measured by immunoassay such as ELISA or nephelometry. Normal concentrations in healthy people are approximately 0.8–2.5 mg/L. Dialysis patients may have concentrations of tens of milligrams per liter. Studies often measure predialysis β2M, when accumulation is greatest, and postdialysis β2M to estimate removal during a session. In the 30–60 minutes after dialysis, concentrations may rebound by 30–40% because of redistribution from outside the blood vessels. Longitudinal predialysis values, for example after several months on another membrane, or a specific β2M Kt/V formula are alternative measures of removal (Casino et al., 2010).

Strategies to lower β2M include high-flux dialyzers, more intensive dialysis using longer or more frequent sessions, online HDF that adds convection and may double β2M clearance relative to conventional HD, and hemoperfusion (HP) with an adsorbent column. An Indonesian study of 30 patients found no greater fall in β2M with eight weeks of HD plus HP than with HD alone. The small sample and short duration limited the study (Kurniawan, 2024). Regular HDF has been reported to lower β2M levels and amyloidosis incidence. Where HDF is unavailable, consistent use of high-flux dialyzers is a practical approach (Canaud et al., 2025).

II.F Other laboratory measures for evaluating dialysis

Other relevant measures include blood urea or BUN, creatinine, serum albumin, electrolytes, calcium and blood counts (hemoglobin, hematocrit, leukocytes and platelets). Urea, a small uremic toxin, forms the basis of Kt/V. Creatinine is a waste product of muscle metabolism removed by dialysis. Predialysis creatinine often remains high (about 8–15 mg/dL) but has relatively low toxicity. It is also used as an adequacy marker, although it is not included in Kt/V calculations (Hosten, 1990). The proposed study measures pre- and postdialysis urea and creatinine to compare removal by each dialyzer. Higher clearance should produce larger falls over a session.

Albumin is the main plasma protein and reflects nutrition and inflammation. Low albumin strongly predicts mortality in dialysis patients (Cheng et al., 2023). Here serum albumin is measured to monitor possible excessive loss through high-flux membranes. Some high-flux membranes permit about 1–3 g of albumin loss per session (Cuvelier et al., 2019). Wolfgang is designed to minimize loss. Comparing serum albumin before and after the intervention period will identify any significant decrease. If the new dialyzer is safe, albumin should be stable or should not fall significantly.

Hemodialysis corrects the hyperkalemia common in kidney failure. Predialysis potassium is often about 5–6 mEq/L and may fall to the normal range after dialysis (3–4 mEq/L), depending on the dialysate gradient. Sodium should remain relatively stable. An isonatremic dialysate with sodium of 138 mEq/L helps maintain the blood sodium concentration and prevent muscle spasms or cerebral edema (Correa et al., 2021). Sodium and potassium will be measured before and after the change of dialyzer to evaluate short-term changes. Because these small solutes diffuse through both membranes, little difference in clearance is expected. The study will nevertheless report electrolytes to assess safety, including electrolyte disturbances possibly associated with membrane malfunction.

Dialysis patients often receive dialysate containing calcium at 1.5 mmol/L or 3 mEq/L to maintain calcium balance (Garimella and Malhotra, 2019). Modality influences blood calcium: for example, HDF may remove more calcium. A change of dialyzer is expected to have little effect on calcium (McIntyre, 2008). Predialysis calcium can also inform assessment of bone and mineral status. Calcium is recorded as a secondary outcome.

An automated complete blood count measures hemoglobin, hematocrit, white blood cells and platelets. Dialysis patients often have anemia due to diminished erythropoietin and chronic blood loss. Changing the dialyzer may have little immediate effect on hemoglobin. Blood counts can help identify hemolysis and changes in blood cells. A less biocompatible dialyzer might be accompanied by leukocytosis from inflammation or thrombocytopenia from membrane adsorption (Kartikasari et al., 2020). Before-and-after blood counts are therefore important for safety.

Together these measures will assess changes in dialysis adequacy and whether the patient’s overall condition is maintained or improved, including albumin as a nutritional marker, electrolyte balance, and the absence of adverse effects.

II.G Theoretical framework

Figure 2, translated as a table. The source links the high-flux dialyzer (larger pores and greater efficiency) to end-stage kidney disease and sets out the following pathways.

Pathway in end-stage kidney disease	Downstream variables shown
Retention of small uremic molecules	Increased urea links to Kt/V and URR. Increased creatinine, increased potassium and increased phosphate are shown as additional branches. Increased phosphate links to decreased calcium.

Pathway in end-stage kidney disease	Downstream variables shown
Retention of middle-molecule uremic toxins	Increased β2-microglobulin.
Water retention	Dilution of sodium links to decreased sodium. Apparent weight gain links to Kt/V.
Loss of plasma proteins	Decreased albumin.
Impaired vitamin D activation	Impaired calcium absorption links to decreased calcium.

II.H Conceptual framework

Figure 3, translated as a table. The source distinguishes the independent variable, potential confounding variables, dependent variables and intervention.

Diagram element	Source labels and relationships
Starting group	Maintenance hemodialysis patients using the previous low-flux polysulfone dialyzer.
Intervention	Switch to a new high-flux dialyzer with a PES membrane.
Potential confounders	Vascular access, heparin dose, dialysis modalities other than HD, acute infection or active inflammatory disease.
Dependent variables	HD adequacy: Kt/V and URR. Middle-molecule clearance: serum β2M. Small-molecule clearance: BUN and creatinine. Other measures: serum albumin, sodium, potassium, total calcium and complete blood count (hemoglobin, hematocrit, leukocytes and platelets).

Chapter III. Research methods

III.A. Study design

This quasi-experimental study uses a one-group pretest–posttest design and a noninferiority approach. Outcome variables will be measured in one group of patients receiving maintenance hemodialysis (HD) before and after a change of dialyzer, with no external control group. Each participant will serve as their own control to reduce the influence of between-person variability, including differences in clinical status. The noninferiority objective is to demonstrate that the new dialyzer is no worse in clinically meaningful terms than the established dialyzer in delivering adequate dialysis.

III.B. Setting and study period

The study will take place in the outpatient hemodialysis unit of Bethesda Hospital, Yogyakarta, from the granting of ethics clearance until study completion.

III.C. Study participants

III.C.1. Population and participants

The target population comprises all patients with end-stage kidney disease (ESKD) receiving HD. The accessible population comprises patients with ESKD receiving HD at Bethesda Hospital, Yogyakarta. According to unit records, approximately 130 patients receive regular HD. This population includes adults of different ages and sexes and with different causes of kidney disease, including diabetes, hypertension and glomerulonephritis. Study participants are members of the accessible population who meet the eligibility criteria.

III.C.2. Inclusion, exclusion and withdrawal criteria

Inclusion criteria

1. ESKD with regular HD at Bethesda Hospital, Yogyakarta, for at least the preceding three months. The three-month minimum is intended to ensure that patients are established on treatment and past the early adaptation period.

2. Regular HD twice weekly. A uniform frequency is intended to reduce variation in weekly Kt/V.

3. Vascular access via an arteriovenous shunt.

4. Use of standard-dose heparin.

5. Age 18–75 years (adults).

6. Willingness to participate, documented by signed written informed consent.

Exclusion criteria

1. Dialysis modalities other than conventional HD, such as hemodiafiltration or routine additional hemoperfusion.

2. Acute infection or active inflammation during the measurement period, such as sepsis or active pneumonia. These conditions can lower albumin, raise β_2-microglobulin as an acute-phase reactant, and alter the volume of distribution.

3. A kidney transplant or switch to peritoneal dialysis scheduled in the near future.

4. Active hepatitis B.

5. Unwillingness to continue or withdrawal of consent at any point in the study.

Criteria for withdrawal after enrollment

1. Cessation of HD at Bethesda Hospital before the postintervention measurements are complete, because of transfer to another HD center or death.

2. Poor adherence resulting in incomplete pre- or postintervention data, such as repeated missed HD sessions or refusal of postintervention blood sampling.

3. A serious adverse event during the study that is suspected to be related to the intervention, such as a severe allergic reaction to the Wolfgang dialyzer. The participant will be withdrawn for safety.

III.C.3. Sampling and sample size

Consecutive eligible patients will be recruited from the population receiving maintenance HD for ESKD at Bethesda Hospital. Each eligible patient presenting for scheduled HD will be offered participation until the target is reached. Consecutive sampling was chosen because the population is confined to one hospital and to minimize selection bias.

Sample size was determined for a paired pre–post design with a one-sided noninferiority approach. Kt/V, an indicator of HD adequacy, is the primary variable for this calculation. The objective is to demonstrate that the new Wolfgang dialyzer is no worse in clinically meaningful terms than the established Fresenius dialyzer in delivering adequate dialysis. The sample size for a paired comparison uses the formula for a difference between paired means.

$$n = [(Z\alpha + Z\beta) \times SD / (\mu_1 - \mu_2)]^2$$

In the formula, n is the sample size, the standard normal values are $Z\alpha = 1.645$ and $Z\beta = 0.84$, SD denotes the standard deviation, and μ denotes a within-group mean.

The calculation assumes a one-sided significance level (α) of 0.05, power ($1 - \beta$) of 0.80, a standard deviation of 0.25 for the between-time difference in Kt/V based on the literature and similar studies, and a noninferiority margin of 0.15 for the mean difference. The margin was chosen because a Kt/V difference of less than 0.15 was considered clinically unimportant for patient outcomes. These inputs yielded a minimum of 18 participants. Allowing for 20% dropout, the proposal gives a minimum recruitment target of 23.

III.D. Study variables

1. Independent variable. Dialyzer type (established/low flux versus new/high flux).

2. Dependent variables. Dialysis adequacy will be measured by Kt/V and urea reduction ratio (URR, %). The middle-molecule clearance measure is serum β_2-microglobulin (mg/L). The small-molecule clearance measures are blood urea nitrogen (BUN, mg/dL) and creatinine (mg/dL). Secondary outcomes include serum albumin (g/dL), automated complete blood count (hemoglobin, hematocrit, white blood cell and platelet counts), serum sodium and potassium (mEq/L), and serum calcium (mg/dL). All these variables will be measured before and after the change of dialyzer. Analysis will focus on changes (Δ), the difference between pre- and postintervention values. The incidence and severity of adverse events will also be recorded, including intradialytic hypotension, muscle cramps, allergic reactions, circuit clotting, and nausea or vomiting.

3. Confounding variables. Eligibility criteria address vascular access, heparin dose, other dialysis modalities, acute infection and inflammatory disease.

III.E. Study procedures

1. Preparation. The investigators will prepare the protocol/proposal, case report form (CRF) and informed consent form. They will apply to the local medical and health research ethics committee. The study will be introduced to the Bethesda Hospital HD team, including the physician responsible for HD, nurses and management, to coordinate the work.

2. Recruitment and informed consent. Investigators will identify maintenance HD patients from unit records and contact eligible patients or meet them at a scheduled HD session. They will explain the study objectives and procedures and obtain a signed consent form from those willing to participate. Each participant will be assigned a study code, for example a numeric code, to protect confidentiality.

3. Baseline data collection. During the two weeks before the dialyzer is changed, the investigators will collect demographic and baseline data and complete a CRF for each participant. In the HD session, blood will be collected before and after treatment for BUN, creatinine, albumin, β_2-microglobulin, electrolytes, calcium and complete blood count. Blood will be sampled according to procedure, for example from the arterial and venous ports on the HD machine.

Session records will include pre- and post-HD weight, duration, ultrafiltration (UF) volume, blood flow rate (Qb), dialysate flow rate (Qd), dialyzer type and batch number, and number of prior uses if the established dialyzer is reused. Kt/V and URR will be calculated from pre- and postdialysis urea and related data, using the Daugirdas formula or software as applicable.

4. Dialyzer change. After baseline data have been collected, the HD unit will switch each study participant to the WOLFGANG-HD180 dialyzer at the HD session one week later. Other treatment parameters, including the machine, dialysate solution, Qb, Qd, treatment duration and UF target, will be kept the same as previously prescribed by the physician so that only the dialyzer differs.

5. Postintervention data. After the participant first uses the dialyzer in the following week, postintervention measurements will be collected for all variables. The same HD parameters will be recorded as for the preceding session, including pre- and post-HD weight, UF, duration, Qb, Qd, dialyzer and batch number. Kt/V and URR will be calculated and recorded for that session.

6. Monitoring and other records. Throughout the study, investigators will record intradialytic hypotension, muscle cramps, dizziness (as an indicator of tolerance), additional heparin requirements and other relevant observations. They will also record transfusions, changes in erythropoietin treatment and other interventions or events that may affect results, such as recent surgery or infection.

7. Laboratory analysis. Pre- and postdialysis samples will be sent to the laboratory. The hospital will measure urea, creatinine, electrolytes, calcium, albumin and complete blood counts. A private laboratory (Prodia) will measure β_2-microglobulin. Pre- and postdialysis β_2-microglobulin samples may be frozen and analyzed together for accuracy.

8. Data processing. CRF data will be entered into an electronic database. Change in each variable will be calculated for each participant as the postintervention value minus the preintervention value. Data will be checked for outliers and missing values. Participants who withdraw will be excluded from the final analysis.

9. Statistical analysis.

10. Report preparation.

11. Dissemination and publication.

III.F. Operational definitions

Variable	Operational definition	Scale and units
1. Dialyzer type	Dialyzer used during the HD session. Established dialyzer, RenMed LF16. New dialyzer, WOLFGANG-HD180.	Categorical (0 = established, 1 = new)
2. Kt/V	HD adequacy index calculated from urea clearance, session duration and change in body weight using the Daugirdas formula. spKt/V = −ln(R − 0.008 × T) + (4 − 3.5 × R) × 0.55 × weight loss / V.	Ratio, dimensionless
3. URR	Percentage reduction in blood urea in one HD session. URR = [(predialysis urea − postdialysis urea) / predialysis urea] × 100%.	Ratio, %
4. BUN	Serum blood urea nitrogen concentration before and after HD.	Ratio, mg/dL
5. Creatinine	Serum creatinine concentration before and after HD, representing a small uremic toxin.	Ratio, mg/dL
6. β_2-microglobulin	Serum β_2-microglobulin before dialysis (maximum accumulation) and after dialysis (to assess clearance in a single session).	Ratio, mg/L
7. Serum albumin	Albumin concentration before and after HD as an indicator of nutritional status and protein loss.	Ratio, g/dL
8. Sodium	Blood sodium concentration before and after HD.	Ratio, mEq/L
9. Potassium	Blood potassium concentration before and after HD.	Ratio, mEq/L
10. Calcium	Total serum calcium concentration before and after HD.	Ratio, mg/dL
11. Automated complete blood count	Hematology measures include hemoglobin, hematocrit, white blood cell count and platelet count.	Ratio. Hemoglobin, g/dL. Hematocrit, %. White blood cells and platelets, per µL.
12. Pre-HD weight	Body weight before HD, including excess fluid.	Ratio, kg
13. Post-HD weight	Body weight after the HD session, approaching dry weight.	Ratio, kg
14. UF volume	Fluid removed in one HD session, calculated from the difference between post- and pre-HD weight.	Ratio, L
15. HD duration	Length of each HD session, standardized in this study at 4.5 hours.	Ratio, h
16. Blood flow rate (Qb)	Rate at which blood is pumped through the dialyzer.	Ratio, mL/min
17. Dialysate flow rate (Qd)	Flow rate of the delivered dialysate.	Ratio, mL/min

III.G. Study schedule

The study is planned to run for six months.

Activity	Month(s)
Protocol and ethics clearance	1
Participant recruitment	2, 3
Collection of demographics and baseline data	2, 3
Dialyzer change (intervention) and postintervention data collection	4
Laboratory testing	4, 5
Data processing and analysis	5, 6
Report preparation for dissemination and publication	5, 6

III.H. Statistical analysis

Continuous participant characteristics will be summarized using medians or means and categorical characteristics using counts or percentages. Normality will be assessed using the Shapiro–Wilk test for sample sizes below 50 and the Kolmogorov–Smirnov test for sample sizes of 50 or more. Pre- and postintervention measurements will be compared using paired t-tests for normally distributed data or the Wilcoxon signed-rank test otherwise. In addition to absolute differences, percentage changes may be calculated for selected variables for clinical interpretation and supplementary information.

Exploratory correlations between changes in Kt/V and β_2-microglobulin will be assessed using Pearson or Spearman correlation. Differences in adverse-event proportions will be assessed using the chi-square test or Fisher’s exact test. A p value below 0.05 will be considered statistically significant. All analyses and data visualizations will be conducted using GraphPad Prism.

Participants with missing data will be excluded from analysis. Withdrawals and the reasons for withdrawal will be recorded, and withdrawn participants will be excluded from analysis.

III.I. Study costs

Table 2. Estimated study budget. Amounts are in Indonesian rupiah (Rp).

Cost item	Unit cost (Rp)	Quantity	Total (Rp)
Laboratory tests			
1. β_2-microglobulin (Prodia)	1,241,000	2 sessions × 2 measurements (before and after HD) × 25 patients = 100	124,100,000
2. BUN, creatinine, albumin, Na, K, Ca	902,000	100 (shared laboratory quantity)	90,000,000
3. Complete blood count	174,000	100 (shared laboratory quantity)	17,400,000
Consumables			

Cost item	Unit cost (Rp)	Quantity	Total (Rp)
4. EDTA Vacutainer tubes (box of 100)	80,000	1 box	80,000
Personnel			
5. Research assistant, three months	7,500,000	1 person	7,500,000
Participant incentives			
6. Transportation allowance	50,000	2 sessions × 25 participants = 50	2,500,000
7. Boxed snack	20,000	2 sessions × 25 participants = 50	1,000,000
Transport and operations			
8. Delivery of blood samples to an outside laboratory	500,000	Lump sum	500,000
Administration			
9. Ethics clearance fee	300,000	1	300,000
Total			243,380,000

III.J. Ethical considerations

The study protocol follows Good Clinical Practice and the Declaration of Helsinki and is awaiting ethics clearance from the faculty ethics committee. Participants receive a written informed consent form after a full explanation of the study objectives, procedures and risks.

References

Canaud, B., Bragg-Gresham, J., Marshall, M., Desmeules, S., Gillespie, B., Depner, T., Klassen, P., Port, F., 2006. Mortality risk for patients receiving hemodiafiltration versus hemodialysis: European results from the DOPPS. Kidney international 69, 2087–2093.

Canaud, B., Davenport, A., Morena-Carrere, M., Amico, M., Molinari, N., Cristol, J.-P., 2025. Continuous beta-2 microglobulin–based clearance highlights superiority of high-Dose HDF over high-flux HD in predicting outcomes. Sci Rep 15, 20421. https://doi.org/10.1038/s41598-025-07497-2

Casino, F.G., Pedrini, L.A., Santoro, A., Mandolfo, S., David, S., De Cristofaro, V., Teatini, U., Lomonte, C., Lopez, T., 2010. A simple approach for assessing equilibrated Kt/Vβ2-M on a routine basis. Nephrol Dial Transplant 25, 3038–3044. https://doi.org/10.1093/ndt/gfq173

Chazot, C., Kirchgessner, J., Pham, J., Vo-Van, C., Lorriaux, C., Hurot, J.-M., Zaoui, E., Grassmann, A., Jean, G., Marcelli, D., 2015. Effect of Membrane Permeability on Cardiovascular Risk Factors and β2m Plasma Levels in Patients on Long-Term Haemodialysis: A Randomised Crossover Trial. Nephron 129, 269–275. https://doi.org/10.1159/000380767

Chen, Y.-K., Chu, C.-S., Niu, S.-W., Lin, H.Y.-H., Yu, P.-H., Shen, F.-C., Chao, Y.-L., Kuo, I.-C., Hung, C.-C., Chang, J.-M., 2023. The prognostic value of URR equals that of Kt/V for all-cause mortality in Taiwan after 10-year follow-up. Sci Rep 13, 8923. https://doi.org/10.1038/s41598-023-35353-8

Cheng, T., Wang, X., Han, Y., Hao, J., Hu, H., Hao, L., 2023. The level of serum albumin is associated with renal prognosis and renal function decline in patients with chronic kidney disease. BMC Nephrol 24, 57. https://doi.org/10.1186/s12882-023-03110-8

Correa, S., Scovner, K.M., Tumlin, J.A., Roy-Chaudhury, P., Koplan, B.A., Costea, A.I., Kher, V., Williamson, D., Pokhariyal, S., McClure, C.K., Mc Causland, F.R., Charytan, D.M., 2021. Electrolyte Changes in Contemporary Hemodialysis: A Secondary Analysis of the Monitoring in Dialysis Study. Kidney360 2, 695–707. https://doi.org/10.34067/KID.0007452020

Cuvelier, C., Tintillier, M., Migali, G., Van Ende, C., Pochet, J.-M., 2019. Albumin losses during hemodiafiltration: all dialyzers are not created equal - a case report. BMC Nephrol 20, 392. https://doi.org/10.1186/s12882-019-1567-8

Daugirdas, J.T., Depner, T.A., Inrig, J., Mehrotra, R., Rocco, M.V., Suri, R.S., Weiner, D.E., Greer, N., Ishani, A., MacDonald, R., Olson, C., Rutks, I., Slinin, Y., Wilt, T.J., Rocco, M., Kramer, H., Choi, M.J., Samaniego-Picota, M., Scheel, P.J., Willis, K., Joseph, J., Brereton, L., 2015. KDOQI Clinical Practice Guideline for Hemodialysis Adequacy: 2015 Update. American Journal of Kidney Diseases 66, 884–930. https://doi.org/10.1053/j.ajkd.2015.07.015

El-Wakil, H., Abou-Zeid, A., El-Gohary, I., El-Seoud, N., El-Yazeed, M., El-Leithy, M., 2011. Effect of high flux versus low flux hemodialysis on serum beta-2 microglobulin, advanced oxidation protein products and protein carbonyl. Alexandria Journal of Medicine 47, 37–42. https://doi.org/10.1016/j.ajme.2011.04.004

Garimella, P.S., Malhotra, R., 2019. Dialysate Calcium: A Lot More Than 'Set It and Forget It.' Kidney Med 1, 238–241. https://doi.org/10.1016/j.xkme.2019.05.005

Gaudry, S., Srisawat, N., Joannidis, M., 2025. Renal replacement therapy. Intensive Care Med 51, 1514–1517. https://doi.org/10.1007/s00134-025-07987-x

Hosten, A.O., 1990. BUN and Creatinine, in: Walker, H.K., Hall, W.D., Hurst, J.W. (Eds.), Clinical Methods: The History, Physical, and Laboratory Examinations. Butterworths, Boston.

Kartikasari, N.D., Notopuro, P.B., Widodo, W., Hernaningsih, Y., 2020. Hemoglobin, Hematocrit, Leukocyte, and Platelet Changes Due To Ultrafiltrationhemodialysis in Chronic Kidney Disease Patients. INDONESIAN JOURNAL OF CLINICAL PATHOLOGY AND MEDICAL LABORATORY 26, 340–343. https://doi.org/10.24293/ijcpml.v26i3.1565

Kurniawan, W.T., 2024. Pengaruh Kombinasi Terapi Hemodialisis dan Hemoperfusi Terhadap Penurunan Kadar Beta2-Mikroglobulin pada Pasien Penyakit Ginjal Tahap Akhir yang Menjalani Hemodialisis Rutin: Multi Center Study. [Effect of combined hemodialysis and hemoperfusion on β_2-microglobulin levels in patients with end-stage kidney disease receiving maintenance hemodialysis: a multicenter study.] Universitas Gadjah Mada.

Leypoldt, J.K., Cheung, A.K., Carroll, C.E., Stannard, D.C., Pereira, B.J., Agodoa, L.Y., Port, F.K., 1999. Effect of dialysis membranes and middle molecule removal on chronic hemodialysis patient survival. American journal of kidney diseases 33, 349–355.

Liangos, O., Jaber, B.L., 2013. Dialyzer Structure and Membrane Biocompatibility, in: Azar, A.T. (Ed.), Modelling and Control of Dialysis Systems: Volume 1: Modeling Techniques of Hemodialysis Systems. Springer, Berlin, Heidelberg, pp. 427–480. https://doi.org/10.1007/978-3-642-27458-9_9

Locatelli, F., Martin-Malo, A., Hannedouche, T., Loureiro, A., Papadimitriou, M., Wizemann, V., Jacobson, S.H., Czekalski, S., Ronco, C., Vanholder, R., 2009. Effect of Membrane Permeability on Survival of Hemodialysis Patients. J Am Soc Nephrol 20, 645–654. https://doi.org/10.1681/ASN.2008060590

McIntyre, C.W., 2008. Calcium balance during hemodialysis. Semin Dial 21, 38–42. https://doi.org/10.1111/j.1525-139X.2007.00368.x

Mumtaz, A., Anees, M., Bilal, M., Ibrahim, M., 2010. Beta-2 microglobulin levels in hemodialysis patients. Saudi J Kidney Dis Transpl 21, 701–706.

Portales-Castillo, I., Yee, J., Tanaka, H., Fenves, A.Z., 2020. Beta-2 Microglobulin Amyloidosis: Past, Present, and Future. Kidney360 1, 1447–1455. https://doi.org/10.34067/KID.0004922020

Samaya Medika Indonesia, 2025. WOLFGANG Polyethersulfone Hollow Fiber Hemodialyzer.

Santos, A., Cunha, R., Stinghen, A., Souza, W., 2022. Online hemodiafiltration (HDF) versus high-flux hemodialysis (hf-HD): A review. Research Society and Development 11, 1–17. https://doi.org/10.33448/rsd-v11i4.27237

Sedighi, O., Abediankenari, S., Omranifar, B., 2014. Association Between Plasma Beta-2 Microglobulin Level and Cardiac Performance in Patients With Chronic Kidney Disease. Nephrourol Mon 7, e23563. https://doi.org/10.5812/numonthly.23563

Tattersall, J., 2007. Clearance of beta-2-microglobulin and middle molecules in haemodiafiltration. Contrib Nephrol 158, 201–209. https://doi.org/10.1159/000107251

Woods, H., Nandakumar, M., 2000. Improved outcome for haemodialysis patients treated with high-flux membranes. Nephrology Dialysis Transplantation 15, 36–42.

Appendix 1. Blank case report form

Evaluation of dialysis adequacy and the safety of switching to a new polyethersulfone hollow-fiber dialyzer (WOLFGANG-HD180) compared with a conventional dialyzer in patients receiving maintenance hemodialysis at Bethesda Hospital, Yogyakarta.

Bethesda Hospital, Yogyakarta • 2025

I. Participant information

Field	Entry
Date form completed	_____
Initials	_____
Age	_____
Study participant number	_____
Date of baseline data collection (established dialyzer)	_____
Date of postintervention data collection (new dialyzer)	_____

II. Demographic data

Field	Entry or options
II.1. Date of birth	____ / ____ / _____ (day/month/year)
II.2. Address	_____
II.3. Sex	☐ Male ☐ Female
II.4. Menstrual status (women)	☐ Menstruating ☐ Menopausal ☐ Estrogen therapy
II.5. Occupation	_____
II.6. Education	☐ Did not finish primary school ☐ Completed primary school ☐ Completed junior secondary school ☐ Completed senior secondary school ☐ Higher education

III. Baseline clinical data

III.1. Cause of kidney failure (primary diagnosis). Check one.

Option	Option
☐ E1. Primary glomerulopathy	☐ E6. Uric acid nephropathy
☐ E2. Diabetic nephropathy (diabetes mellitus)	☐ E7. Obstructive nephropathy
☐ E3. Lupus nephropathy (systemic lupus erythematosus)	☐ E8. Chronic pyelonephritis
☐ E4. Hypertensive nephropathy (hypertension)	☐ E9. Other
☐ E5. Polycystic kidney disease	☐ E10. Unknown

III.2. Comorbidities. Record each condition present and describe its timing.

Condition	Entry	Condition	Entry
Diabetes mellitus		Coronary heart disease	
Hypertension		Stroke	
Cancer		Ear, nose or throat infection	
Hepatitis B		Dental infection	
Hepatitis C		Lupus	
Cirrhosis		Joint pain	
Tuberculosis		Asthma	
Anemia		Other	

Description of timing _____

History of allergies, including drugs or vaccines _____

Use of antithrombotic drugs (antiplatelets or anticoagulants), such as aspirin, clopidogrel or warfarin. Describe type, product, formulation, dose, frequency and duration.

_____

Field	Entry or options
III.3. HD start date and duration	____ / ____ / _____ (day/month/year). Time on HD ____ years ____ months.
III.4. HD frequency	____ times/week
III.5. Vascular access	☐ AV fistula ☐ Double-lumen catheter. Site: ☐ Jugular vein ☐ Subclavian vein ☐ Femoral vein
III.6. Dry weight	____ kg
III.7. Height	____ cm

IV. Assessments and parameters. Established dialyzer session (preintervention)

Field	Entry or options
IV.1. Date of HD session	____ / ____ / _____ (day/month/year)
IV.2. Vital signs	Current blood pressure ____ mmHg. Mean systolic pressure: ☐ <120 ☐ 120–140 ☐ 140–160 ☐ >160. Pulse ____ beats/min. Temperature ____ °C.
IV.3. Dialyzer	Brand _____ Type _____ Surface area ____ m². Reuse number ____.
IV.4. HD duration	____ hours ____ minutes
IV.5. Flow rates	Qb ____ mL/min. Qd ____ mL/min.
IV.6. UF volume	Target ____ L. Achieved ____ L.
IV.7. Weight	Before HD ____ kg. After HD ____ kg.
IV.8. Blood pressure	Before HD ____ mmHg. Lowest intradialytic pressure ____ mmHg.
IV.9. Heparin	☐ Standard ☐ Mini-dose ☐ No heparin. Bolus ____ units. Continuous infusion, if applicable ____ units/hour.

IV.10. Laboratory measurements

Analyte	Before HD	After HD	Units
BUN			mg/dL
Urea			mg/dL
Creatinine			mg/dL
Sodium			mEq/L
Potassium			mEq/L
Calcium			mg/dL
Albumin			g/dL
β_2-microglobulin			mg/L
Hemoglobin			g/dL
Hematocrit			%
White blood cells			per µL
Neutrophils (count)			per µL
Neutrophils (%)			%
Lymphocytes (count)			per µL
Lymphocytes (%)			%
Platelets			per µL

IV.11. Dialysis adequacy. Kt/V _____ URR _____ %

V. Assessments and parameters. New dialyzer session (postintervention)

Field	Entry or options
V.1. Date of HD session	____ / ____ / _____ (day/month/year)
V.2. Vital signs	Current blood pressure ____ mmHg. Mean systolic pressure: □ <120 □ 120–140 □ 140–160 □ >160. Pulse ____ beats/min. Temperature ____ °C.
V.3. Dialyzer	Brand _____ Type _____ Surface area ____ m². Reuse number ____.
V.4. HD duration	____ hours ____ minutes
V.5. Flow rates	Qb ____ mL/min. Qd ____ mL/min.
V.6. UF volume	Target ____ L. Achieved ____ L.
V.7. Weight	Before HD ____ kg. After HD ____ kg.
V.8. Blood pressure	Before HD ____ mmHg. Lowest intradialytic pressure ____ mmHg.
V.9. Heparin	□ Standard □ Mini-dose □ No heparin. Bolus ____ units. Continuous infusion, if applicable ____ units/hour.

V.10. Laboratory measurements

Analyte	Before HD	After HD	Units
BUN			mg/dL
Urea			mg/dL
Creatinine			mg/dL
Sodium			mEq/L
Potassium			mEq/L
Calcium			mg/dL
Albumin			g/dL
β_2-microglobulin			mg/L
Hemoglobin			g/dL
Hematocrit			%
White blood cells			per µL
Neutrophils (count)			per µL
Neutrophils (%)			%
Lymphocytes (count)			per µL
Lymphocytes (%)			%
Platelets			per µL

V.11. Dialysis adequacy. Kt/V _____ URR _____ %