Title	Effect of Medium Cut-Off Hemodialysis on Protein Energy Wasting.
Acronym	EMCOPEW
NCT number	NCT05309109
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Statistical analysis plan of the EMCOPEW study

This Statistical Analysis Plan (SAP) was written according to the guidelines proposed by Yuan et al.(1) and by Gamble et al. (2) for randomized clinical trials.

1. SAP versions, dates and reasons for revision

Version #1: July 24th, 2025.

Version #2: February 09th, 2026: to account for the stop of follow-up for transplanted patients and the missing values at baseline.

2. Trial registration number

NCT05309109

3. Study title

Effect of Medium Cut-Off Hemodialysis on Protein Energy Wasting: The EMCOPEW study

4. Acronym of the study

EMCOPEW

5. SAP contributors with roles and responsibilities

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6. Background and rationale of study

In patients on maintenance hemodialysis (HD), protein energy wasting (PEW) defined as loss of muscle mass and fuel reserves of the body is frequent and associated with severe morbidity and mortality. Several factors, including inflammation, oxidative stress, metabolic disorders, loss of nutrients, diabetes, retention of middle molecule uremic toxins and dialysis procedure contribute to PEW. It has been previously reported that intensive HD treatments such as short daily and nocturnal HD may improve nutritional parameters. Moreover, post-dilution Online hemodiafiltration (OL-HDF) may also improve PEW by preserving lean body mass evaluated by bioimpedance analysis (BIA) probably through decreased inflammation, stimulation of appetite and better removal of uremic toxins. The recently developed medium cut-off dialyzer (MCO) in HD has demonstrated efficient depuration of middle uremic toxins as compared to high flux HD (HF-HD), similar to that of OL-HDF. Both MCO-HD and OL-HDF may exert beneficial effects on PEW, since they increase removal of higher weight middle molecules, which mostly encompass proteins related to inflammation and PEW in the uremic milieu.

7. Study type

This is a superiority, prospective, parallel, randomized, and multi-center clinical study.

The patient and the methodologist will be blinded to the randomization arm.

8. Objectives and related endpoints (units and calculations used to derive outcomes)

The primary objective is to evaluate the effect of HD-MCO in patients suffering from chronic end-stage renal disease, by comparing the change from baseline to 12 months follow-up in the lean tissue mass measured using BIA between the patients of the control group (HD-HF) and the patients randomized in the experimental group (HD-MCO).

The secondary objectives are to compare the following outcomes between control group versus the experimental group:

1) The change in the lean tissue mass (kg) measured using BIA between inclusion and 4 months and between inclusion and 8 months.
   The change in the fat tissue mass (kg) measured using BIA between inclusion and 4 months, between inclusion and 8 months and between inclusion and 12 months.
   The change in the bone mineral content measured using BIA between inclusion and 4 months, between inclusion and 8 months and between inclusion and 12 months.
2) The change in the muscle tissue mass (kg) measured with 3T MRI between inclusion and 12 months.
3) The change in the anthropometric measures between inclusion and 6 months and between inclusion and 12 months.
   The change in the BMI (kg/m²) between inclusion and 6 months and between inclusion and 12 months.
   The change in the nPCR between inclusion and 6 months and between inclusion and 12 months.
   nPCR = (UreaAv x 2,801) / (25,8 + 1,15 spKt/V + 56,4/ spKt/V) + 0,16.
   spKt/v
   single pool KT/V according to the Daugirdas formula:
   spKt/V = -ln((PostBUN/ PreBUN)-(0.008*t/60)) + (4-(3.5*PostBUN/PreBUN)) *
   ((PostWt-PreWt)/PostWt)
   Where UreaAv is the urea concentration in mmol/l before dialysis,
   PreBUN and PostBUN are the pre-dialysis and the post-dialysis Blood Urea Nitrogen concentration in mg/dL,
   PreWt and PostWt are the pre-dialysis weight and the post-dialysis weight in kg,
   t is the delivered treatment time in minutes.
4) The change in the hand grip strength between inclusion and 6 months and between inclusion and 12 months.
5) The change in the time of the 25-foot walk test between inclusion and 6 months and between inclusion and 12 months.
   The change in the score of the KDQOL-SF questionnaire between inclusion and 6 months and between inclusion and 12 months.
   The change in the score of the MIS questionnaire between inclusion and 6 months and between inclusion and 12 months.
6) The change in the following biomarkers between inclusion and 6 months and between inclusion and 12 months.: albumin, pre-albumin, transferrin, urea, creatinine, creatinine indices, total cholesterol, triglycerides, LDL and HDL cholesterol, hemoglobin, leucocytes, platelets, ferritin, transferrin saturation coefficient, calcium, phosphorus, PTH, 25 OH vitamin D, bicarbonate, beta2-microglobulin, KT/V, percentage reduction in urea, myoglobin and beta2-microglobulin, fibrinogen, haptoglobin, troponin, NT-BNP, IFG-1, Leptin, Myostatin, Adipokine, CRP, IL-6, TNFα, IL-8, IL-17, IL-22, IL1 alpha, IL1 beta, Interferon gamma, asymmetric dimethylarginine, homocysteine and oxidised LDL.
   The percentage reduction of urea and beta2-microglobuline will be calculated as follow: (Cpre-Cpost)/Cpre *100, where Cpre and Cpost are the pre and the post treatment concentrations, respectively.
   The post treatment concentration of beta2-microglobulin will be corrected using a single-compartment kinetic model, as follow: Cpost corrected = Cpost/(1+ΔBW/0.2xBWpost), where ΔBW is the weight lost during the session and BWpost the body weight at the end of the session.
   Creatinine indices (CI) will be determined as follows:

Cl (*mg/kg/day*) = 16.21 + 1.12 x [1 *if male*; 0 *if female*] – 0.06 x *age (year)* – 0.08 x *spKt/V urea* + 0.009 x Cr_{pre} *(µmol/l)*

7) The EPO consumption after 12 months
   The EPO resistance index defined as weight-adjusted EPO dose per week (IU/kg/week) divided by hemoglobin concentration (g/dl).
8) The change in Kidney Disease Quality of Life (KDQOL-SF) survey between inclusion and 6 months and between inclusion and 12 months.

9. Inclusion criteria

- Adult patient (≥ 18 years old).
- Patient suffering from chronic end-stage renal disease, with standard high-flux chronic hemodialysis, 3 times 4 hours a week for more than 3 months.
- Patient able to walk.
- Patient with a BMI above 20 and below 40 kg/m².
- Patients benefiting from a social security scheme or benefiting from it through a third party.
- Informed consent signed by the patient after clear and complete information about the clinical investigation.

10. Non-inclusion criteria

- Patient with an uncontrolled medical condition (e.g. psychiatric disorder) likely to interfere with participation in the study or ability to sign informed consent.
- Patients with an associated pathology (active cancer, active infectious disease or chronic inflammatory disease) which may have an excessive influence on CRP levels (CRP levels > 35 mg/L).
- Patients treated with oral or intravenous nutritional supplements.
- Patients with residual diuresis greater than 0.5 liters.
- Patients who have undergone limb amputation
- Patients allergic to polyethersulfone membranes
- Patient already participating in a clinical investigation whose main objective or secondary objectives are likely to have an impact on the main objective of this clinical investigation.
- Pregnant or breastfeeding women, women of childbearing age who do not have effective contraception (hormonal/mechanical: oral, injectable, transcutaneous, implantable, intrauterine device, or surgical: tubal ligation, hysterectomy, total oophorectomy), or having a positive pregnancy test at inclusion.
- Persons benefiting from enhanced protection, namely minors, persons deprived of their liberty by a judicial or administrative decision, adults under legal protection.

11. Exclusion criteria

We will exclude the subjects in case of consent withdrawal and objection to the use of his/her data.

12. Definition of the two compared groups

- Control group: patients with high-flux hemodialysis (HF-HD)
- Experimental group: patients with medium cut-off hemodialysis (MCO-HD)

13. Randomization details

Subjects will be randomized 1:1 ratio (VS) by minimization and stratified by vascular access, age, presence of diabetes, time since starting dialysis and gender.

14. Sample size calculation

Based on data from a pilot study, the rate of change in lean body mass after 12 months of evolution was estimated at 37±36 kg in the HD-MCO arm and -14±30 kg in the HD-HF arm. To show a difference in lean mass variation of 30 kg between the two groups, with a standard deviation equal to 36, for a first-species alpha risk of 5% bilaterally and a power of 80%, 23 patients per group are required.

15. Interim analysis (timing, person, adjustment of the significance level)

No intermediate analysis is planned.

16. Guideline for an early stop of the study

The study may be prematurely suspended in the event of unexpected adverse events necessitating review of product safety profile. On the same token, in the event of unexpected developments or new information pertaining to the product and showing that the objectives of the study of the clinical program are unlikely to be reached, the sponsor may be persuaded to prematurely suspend the study.

No statistical discontinuation criteria have been drawn up.

17. Timing of final analysis

- A 12-month inclusion period.
- A 15-month follow up of the last patient.
- A 6-month period for data analyses.

18. Timing for assessing each collected parameters

Visits	Pre inclusion	**Inclusion**	**Visit V_0**	**Visit V_1**	**Visit V_2**	**Visit V_3**	**Visit V_4**
			90 days max	4 months ±15 j	6 months ±15 j	8 months ±15 j	12 months ±15 j
Patient Information	X^R	X^R					
Inclusion/Non-inclusion criteria	X^R	X^R					
Informed consent from signature		X^R					
Demographic data		X^{S+R}					
History		X^{S+R}					
Randomization			X				
Clinical evaluation			X^{S+R}	X^{S+R}	X^{S+R}	X^{S+R}	X^{S+R}
BMI			X^{S+R}		X^{S+R}		X^{S+R}
Bio-impedance measurement			X^{S+R}	X^{S+R}		X^{S+R}	X^{S+R}
Anthropometric measurements			X^R		X^R		X^R
Grip measurement			X^R		X^R		X^R
Walk test			X^R		X^R		X^R
KDQOL-SF			X^R		X^R		X^R
MIS			X^R		X^R		X^R
Biological tests [1]			X^{S+R}		X^{S+R}		X^{S+R}
IRC treatment			X^{S+R}	X^{S+R}	X^{S+R}	X^{S+R}	X^{S+R}
MRI 3T (optional) + ß-HCG assay for women of childbearing age		X^{R*}				X^{R*}	
Adverse event gathering		X^R	X^R	X^R	X^R	X^R	X^R

[1]*Standard nutritional biological tests* (albumin, pre-albumin, transferrin, urea, creatinine, creatinine index, total cholesterol, triglycerides, LDL and HDL cholesterol, hemoglobin, leucocytes, platelets, ferritin, transferrin saturation coefficient, calcium, phosphorus, PTH, 25 OH vitamin D, bicarbonate, beta2-microglobulin, KT/V, percentage reduction in urea, myoglobin and beta2-microglobulin, fibrinogen, haptoglobin, troponin, NT-BNP, IFG-1, Leptin, Myostatin, Adipokine, CRP, IL-6, TNFα, IL-8, IL-17, IL-22, IL1 alpha, IL1 beta, Interféron gamma, asymmetric dimethylarginine, homocysteine and oxidised LDL.)

*To be carried out within 3 months of the next visit

X^S: for care

X^R: specific to clinical investigation

19. Reporting the representativity of the studied population

A flowchart will be decomposed according to the following sets. The effectives and the related differences in-between two consecutive sets will be reported. The causes of the related differences will also be listed.

- **The screened set.** The patients having signed the informed consent.
- **The intension-to-treat set (ITT).** The patients who were randomized according to their allocated group, regardless of their adherence to the entry criteria, regardless of the intervention they received, and regardless of subsequent withdrawal from intervention or deviation from the protocol.
- **The full analysis set (FAS).** The previous ITT population, excluding participants who failed to meet major entry criteria (3) and participants with no data post-randomization or with missing outcome.

20. Withdrawals and follow-up data

Patients may be withdrawn early from the clinical investigation for several reasons:

- Subject request or consent withdrawal.
- Investigator request.
- Subject lost to follow-up (patient missing a control) will be contacted by each research center to assess reasons for the loss.
- Subject death.
- Disease progression which requires discontinuation of therapy or results in inability to continue to comply with clinical investigation procedures.
- Non-compliance clinical investigation requirements.

The investigator will document the reasons for premature study discontinuation.

21. Definition of the studied population

All the analyses will be performed based on the full analysis set. If a patient withdraws consent, he/she will be asked for permission to use data obtained prior to withdrawal and to collect the primary outcome. If this is achieved, the patient will be included in the final analyses. If the patient declines, all data from that patient will be destroyed (except for safety data).

We observed informative missing data in the outcomes due to a protocol deviation involving a stop of follow-up for transplanted patients. We will be limited to a complete-case analysis and will address this limit in the discussion section.

22. Level of statistical significance (p-values, confidence intervals, one- or two-sided)

Statistical significances will be achieved for p-values lower than 5% by using two-sided alternative hypotheses and two-sided 95% confidence intervals.

23. Plan and rationale for controlling the type I error (multiplicity of tests)

We will not consider the inflation of the type I error. The level of the proof will be the higher for the principal outcome. The statistical analyses related the secondary analyses will be considered as exploratory results with a risk of false positive.

24. Sub-group analyses and/or tests of interactions

No sub-group analyses or tests of interactions are planned.

25. Description of the baseline patient characteristics

A first table will be proposed with demographic variables and other baseline characteristics will be summarized. Descriptive statistics (mean, median, standard deviation, interquartile range) will be presented for continuous variables for each treatment group and for all patients. The number and percentage of patients in each category will be presented for categorical variables for each treatment group and all patients. In addition, all relevant medical history, and protocol solicited medical history will be summarized by treatment group.

The means, the standard deviations and the number of missing values will be presented for each treatment arm and marginally for the following variables: age (years), body height (cm), body weight (kg), BMI (kg/m^2), dialysis vintage (years). The effectives, the percentages of patients in each category and the number of missing values will be presented for each treatment arm and marginally for categorical variables: gender, nephropathy history, comorbidities.

No p-value will be reported. The balance diagnostics of baseline covariates between the two arms will be achieved by estimating standardized differences (4). Unbalances will be considered for values higher than 10%.

The outcome available at baseline will also be presented.

26. Analysis of the primary outcome

A second table will be proposed to compare the outcomes of the patients of the full analysis set.

To avoid the exclusion of patients with missing values on the outcomes at baseline, multiple imputation by chained equations (MICE) will be performed *m* times. *m* will be at least equal to the percentage of incomplete cases. To combine the results from m complete data analyses, p-values will be pooled using *pool()* function from *mice* package in case of parametric test. In case of non-parametric case, the Fisher method (5) will be used to pooled the p-values.

27. Analysis of the secondary outcomes

The same strategy will be used for secondary outcomes with missing data at baseline.

For binary outcomes, the effectives, the percentages of patients in each category and the numbers of missing values will be presented for each treatment arm and marginally. Comparison between the two groups will be performed using a Chi-2 test or a Fisher test.

For the quantitative, the means, the standard deviations, and the number of missing values will be presented for each treatment arm and marginally. Comparison between the two groups will be performed using a Student test or a Mann-Whitney test.

For the quality of life questionnaire, the change of the global score will be compared between the two groups. If we find a difference, we will compare each sub-score.

Due to the very small number of MRIs performed, analyses of MRI results will not be performed.

28. Graphical presentation of treatment effects

For each outcome, the slope between inclusion and 12 months (using the available data at inclusion, 4, 6, 8 and 12 months) will be presented in both group.

29. The assumptions of the statistical methods, and alternative methods if they are false

The main assumption of the previous analyses is related to the missing data. Because we expect a very low number of missing values on the outcomes, we will perform complete case analysis. The excluded patients will be compared to the rest of the studied population to appraise the possible selection bias.

30. References

1. Yuan I, Topjian AA, Kurth CD, Kirschen MP, Ward CG, Zhang B, et al. Guide to the statistical analysis plan. Paediatr Anaesth. mars 2019;29(3):237-42.

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