1. Title

A randomized, open-label, controlled trial to evaluate efficacy and safety of a highly selective semipermeable membrane (AN-69 Oxiris) in comparison with a semi selective semipermeable membrane (standard AN-69) in COVID-19 associated acute kidney injury: oXAKI-COV study.

2. Number and version

V1.04, October 17th, 2020

3. Type of research

Randomized controlled trial
2-group design
Follow-up study
Prospective
Interventional
Multicentric
Open-label

4. Research group
5. Participating institutions

INCMNSZ. Research study workplace and place of treatment administration.

6. Financial support: neither grants nor payment for researches.
7. Abstract

Title: Randomized, open-label, controlled trial to evaluate efficacy and safety of a highly selective semipermeable membrane (AN69-Oxiris) in comparison with a selective semipermeable membrane (standard AN69) in COVID-19 associated acute kidney injury: oXAKI-COV study

Rationale: Acute kidney injury (AKI) in critically ill mechanically ventilated patients with COVID-19 disease, is present in up to 30% of this group and more than 50% of them will need renal replacement therapy in the form of continuous renal replacement therapy (CRRT). Acute kidney injury in this context seems to be a marker of multiorgan dysfunction and it produces increased mortality in this population. There is a vast amount of mechanisms that lead to AKI in critically ill patients with COVID-19; however, the cytokine storm could be the strongest mechanism implicated in AKI development in individuals with continuous renal replacement therapy requirements. Therefore, blocking or reducing the cytokine storm is thought to be a therapeutic target.

Highly selective semipermeable membranes (AN69-Oxiris) have been shown able to adsorb endotoxins and to eliminate inflammatory cytokines, thus representing a valuable therapeutic option in this infection.

Objective: Change in norepinephrine requirement by at least 0.1 micrograms / kg / min to maintain similar MAP after initiation of CRRT with Oxiris membrane compared to standard AN69 membrane. MAP measurements will be performed hourly and norepinephrine requirement will be recorded at that time.

Study design: Randomized,open-label, controlled trial in critically ill patients with suspected or confirmed COVID-19 disease, AKI, and criteria for continuous renal replacement therapy initiation admitted in any of the two participating institutions. Patients meeting inclusion criteria will be randomized to receive CRRT with AN69-Oxiris membrane or standard AN69 membrane during a 72h period.

8. Literature review

On March 11th, 2020 the World Health Organization declared the new coronavirus disease (COVID-19) as a global pandemic. In México, approximately 35% of COVID-19 positive patients require hospital admission and 4.4% do it in the intensive care unit. Acute kidney injury (AKI) in mild to moderate COVID-19 disease seems to be infrequent; in contrast, critically ill patients or those with a severe disease develop AKI in up to 30% of the cases and nearly half of them will need renal replacement therapy in the form of continuous renal replacement therapy (CRRT). AKI in this context seems to be a marker of multiorgan dysfunction and it produces increased mortality in this population.

Multiple mechanisms of AKI in COVID-19 disease have been proposed: direct injury into podocytes and proximal convoluted tubule cells, organ-organ interactions (lung-kidney axis), and cytokine storm. Of them, the severe cytokine-induced injury seems to be the strongest mechanism participating in AKI in this group of severely ill patients with CRRT need thus representing a valuable therapeutic option.

Lately, extracorporeal blood purification therapies have been proposed as a therapeutic tool for cytokine removal in patients with sepsis (prototype of cytokine storm model). Therefore, new membranes with hemoadsorption capacity have been developed and are now commercially available. The first group of membranes used for patients with sepsis and inflammatory systemic response syndrome was high cut-off semipermeable membranes (HCO) followed by non-selective adsorbent membranes, semi selective semipermeable membranes (AN69), and last highly selective semipermeable (especially those with endotoxin and cytokine adsorption, such as AN69-Oxiris). Although these membranes were designed to improve inflammation, they can also be used as a regular filter in CRTT in patients with AKI. These products can be purchased in our country and internationally but there is scant evidence supporting its efficacy to improve clinical outcomes in patients with overt sepsis.

Highly selective semipermeable membranes (AN69-Oxiris) possess a great capacity for endotoxin adsorption and cytokine removal (interleukin 6 [IL-6], tumor necrosis factor-alfa [TNF-α], C reactive protein [CRP] , and interleukin 1b), representing a valuable therapeutic option in septic shock; these findings have been tested mainly in experimental models. There are human-based studies with non-representative statistical samples in which these membranes appear to improve severity scores without any impact in mortality. This membrane has been used in some regions around the world during the COVID-19 pandemic; recently, Ma et al published two severe COVID-19 patients who were treated with AN69-Oxiris resulting in decreased levels of inflammatory markers (ie, CRP and IL-6) and better lymphocyte counts. However, there is uncertainty in the clinical benefit of those changes.

Given the lack of specific drugs or vaccine targeted for COVID-19 and, taking into account the pathophysiologic basis that supports the use of extracorporeal blood purification therapies to reduce the cytokine storm in COVID-19 infected patients with AKI requiring CRRT, the use of

these membranes could be of clinical utility in the disease. Here our group presents a randomized, open-label, controlled trial to evaluate efficacy and safety of a highly selective semipermeable membrane (AN69-Oxiris) in comparison with a semi selective semipermeable membrane (standard AN69) in COVID-19 associated acute kidney injury.

9. Hypothesis

Research question: In critically ill patients with COVID-19 disease and AKI requiring CRRT, is the AN69-Oxiris membrane of greater benefit to sustain MAP a lower vasopressor dose in comparison with a conventional AN69 standard membrane, after 72 hours of treatment?

Alternative hypothesis: The use of the AN69-Oxiris membrane will decrease vasopressor requirement in at least 0.1 micrograms/kilogram/minute to sustain a stable MAP in contrast with the usage of AN69 standard membrane, in critically ill patients with COVID-19 and AKI requiring CRRT after 72 h of treatment.

10. Goals

Primary goal: Change in norepinephrine requirement by at least 0.1 micrograms / kg / min to maintain similar MAP after initiation of CRRT with Oxiris membrane compared to standard AN69 membrane. MAP measurements will be performed hourly and norepinephrine requirement will be recorded at that time.

Exploratory goals:

- Effectiveness of the AN69-Oxiris membrane in reducing interleukin serum levels (IL 6, IL 10, and TNF alpha).

Serum will be taken every 8 hours for its measurement by ELISA method.

- To establish the safety (the same risk infection and bleeding) of using the AN69- Oxiris membrane in patients with AKI and COVID-19 infection who require CRRT.

Gross bleeding events (gastrointestinal or urinary) as well as catheter-associated infection events (criteria according to IDSA) will be recorded.

- Length of stay in UCI among patients who used AN69-Oxiris membrane in compared to the use of a conventional membrane (standard AN-69) in critically ill patients with COVID-19 associated AKI and CRRT requirement.
- To investigate the effect of AN69-Oxiris in reducing 28-day mortality in contrast compared with the effect of a conventional membrane in this population.

11. Methods

Study design: A randomized, multicentric, open-label, controlled trial

Study population: Critically ill patients on mechanical ventilation with AKI and CRRT requirements admitted with COVID-19 disease in any of the two participant institutions.

Participating institutions: INCMNSZ , INER

Timing: October 02th, 2020 to December 30th, 2021.

Interventions: patients meeting inclusion criteria and accepting to participate in this study with informed consent (or legal representative via phone call giving the pandemic lockdown), will be randomized to be treated with CRRT using the AN-69 Oxiris membrane or standard AN-69

membrane (Figure 1). Randomization will be performed on the day of admission using online software (EPIDAT 4.2). The intervention will be sustained during 72 continuous hours.
Patients will be randomized to use one of the following membranes (Figure 1):

CRRT using the AN69 Oxiris membrane (intervention group)

CRRT using the standard AN69 membrane (control group)

***Given the pandemic lockdown, informed consents for hemodialysis treatment have been collected by phone call. The study protocol and therapeutic options will be presented to the next of kin; in case of approval for study entry, the date and hour will be registered and a formal appointment for signing the informed consent will be scheduled.

Monitoring of interventions

- Blood samples will be drawn, every 8 hours during the 72 hours of treatment, to measure cytokine serum levels (IL-6,IL-10,TNF alfa).
- All renal replacement therapy prescriptions (control and intervention group) will be standardized as follows:

o Vascular access: 12 French,double-lumen, a high-flux catheter placed into the internal jugular vein or femoral vein (either right or left-sided)

o The dose of CRRT will be set at 30ml/kg/h, using ideal body weight.

o CRRT modality: Continuous veno-venous hemodiafiltration

o Anticoagulation: Regional citrate anticoagulation will be used (Gambro Prismocitrate 18/2-citrate 18 mmol/L). The goal level of ionized calcium in the circuit will be 0.2-0.4 mmol/L. Initial citrate dose will be determined according to the processed blood volume, maintaining a blood flow of 150mL/min, in close relation to a citrate dose of 2.5-5mmolL. Calculations to determine initial citrate dose will be performed using AdequatorÒ mobile application, which is widely available and validated for its use. An intravenous calcium infusion will be used to counteract the citrate effect, via a 17.4% calcium gluconate solution to sustain ionized serum calcium between 1.1-1.29 mmol/L in the arterial line.

o The Post-dilution substitution fluid rate will be set at 150mL/h.

o The dialysate flow rate will be determined as the remaining fluid obtained using the following formula:

§ Dialysate= Total effluent dose – (citrate infusion rate + post-dilution substitution fluid rate+ ultrafiltration rate)

o The ultrafiltration rate will initiate at 100mL/hour the first 4 hours and adjusted in according to the patient clinical status and attending physician judgment.

o Prismasate B/22 (K+ 4, zero-calcium) will be used as a substitution and dialysate fluid.

- Citrate-based anticoagulation monitoring and dosing will be performed using blood gas analysis of samples drawn from both the circuit and patients, according to institutional protocols previously used (described in supplemental material 1).
- Serum electrolytes will be tracked and adjusted using the institutional protocol, which is described in detail in the supplemental material.
- CRRT membrane will be replaced every 24 hours, regardless of the group.
- CRRT treatments will be performed using Prismaflex or PrismaX machines.

- Effluent delivered dose will be examined using pre-filter BUN and post-filter BUN, according to KDIGO guidelines for acute kidney injury.

Interventions and treatments unrelated to renal support therapies.

- Every patient enrolled in the trial will receive the standard of care according to the attending physician criteria and institutional protocol established in the participant centers.
- In case the patient is receiving antibiotics, the doses administered will remain unadjusted during the 72h period of the study.
- Norepinephrine will be the first-line vasopressor used to maintain MAP between 65-70 mmHg.

11. Methods/ to describe resources used

- AN69 hemofilter: it is a semi-selective, semipermeable membrane with a moderate to low cytokine adsorption capacity, but does not remove endotoxins. This membrane is made of polyacrylonitrile (AN69) with a polyethyleneimine treatment.
- AN69-Oxitis hemofilter: It is a highly selective, semipermeable membrane with enhanced capacity for endotoxin and cytokine adsorption. The aforementioned properties are possible given the larger adsorption surface added to the AN69 standard membrane and the presence of a heparin coating that decreases its thrombogenicity and increases its adsorption capacity.

12. Outcomes

Outcomes:

-Primary outcome: to establish the superiority of treatment with the AN69-Oxiris membrane to sustain a similar MAP with a lower requirement of norepinephrine (at least 0.1 micrograms/ kg/min) after 72 hours of treatment initiation, in patients with COVID-19 associated AKI requiring CRRT, compared to the usage of a standard AN69 membrane.

-Secondary outcomes:

- To evaluate the effectiveness of the AN69-Oxiris membrane in reducing interleukin serum levels (IL 6, IL 10, and TNF alpha).
- To demonstrate the advantage of the AN69-Oxiris membrane in decreasing 28-day mortality from the start of CRRT.
- To establish the safety of using the AN69-Oxiris membrane in patients with AKI and COVID-19 infection who require CRRT.
- To examine the efficacy of the AN69-Oxiris membrane in reducing the length of ICU stay compared to the use of a conventional membrane (standard AN-69) in critically ill patients with COVID-19 associated AKI and CRRT requirement.

Variables:

Acute kidney injury. Elevation in serum creatinine or decrease in the urinary output according to what is established in the KDIGO guidelines.

Mean arterial pressure. MAP is considered as the perfusion pressure for organs and, a value greater than 60 mmHg is adequate to maintain perfused the organs of an average person. The mean arterial pressure will be registered, either obtained through a peripheral arterial line (calculated from the area under the curve of the arterial pressure graph) or the non-invasive monitor using the oscillometric method.

Furosemide stress test: This term refers to a furosemide bolus of 1 mg/kg (ideal body weight) with subsequent measurement of urine output after 2 hours. It is considered negative when the urine output during this interval is less than 200 ml.

Safety variables:
* Clotting of the circuit: it is defined as the presence of clots in the circuit lines and/or filter, which condition rise in the transmembrane, pre-filter, or post-filter pressures, warranting a change of the filter.
* Allergic reaction: the sudden presence of erythema or rash at any time after starting CRRT treatment.
* Access bleeding: the occurrence of continuous bleeding at the vascular access insertion site any time after the start of CRRT treatment.
* Catheter-related bloodstream infection: the presence of any microorganism in blood cultures drawn from catheter´s lumen.

13. Sample size
The main outcome considered for this study is the mean dose of norepinephrine at 72 hours after CRRT initiation. Previous studies consider that a difference of at least 0.10 micrograms/kg/min without changes in the MAP, in the intervention group compared to the control group, is a meaningful difference to detect.

Standard deviation for norepinephrine: 0.10 micrograms/kg/min.
Type of test: Two-tailed, with a confidence level of 95% and a statistical power of 80%. Solving the following equation to calculate the sample size using the comparison of 2 means method; a total of 34 patients, 17 within each group, is required. If a 10% loss is assumed, the final sample size will be 36 individuals, 18 in the intervention group (AN69 Oxiris membrane), and 18 in the control group (standard AN69 membrane).

14. Inclusion criteria
1. Patients aged ≥ 18 years old.
2. A diagnosis of a confirmed, defined by a positive rt-PCR for SARS CoV-2, or suspected COVID-19 disease, with suggestive findings on a chest CT scan.
3. Patients on mechanical ventilation.
4. The presence of an informed consent signed by the next of kin.

5. Patients with KDIGO AKI stage 2: defined by a rise in creatinine 2-2.9 times baseline and/or a urinary output less than 0.5 ml/kg/hr for 12 hours, with failure after a furosemide stress test.
6. The use of vasopressor, any dose.
7. Complete medical history and complete laboratories.

15. Exclusion criteria
1. Chronic kidney disease KDIGO stage 4, 5, or 5D.
2. Next of kin unwilling or patient unwilling to participate.
3. Patients with a life expectancy of fewer than 72 hours according to the attending physician criteria.
4. Patients older than 75 years.
5. Patients with SOFA > 11.
6. Patients with severe liver failure.

16. Statistical analysis
Descriptive statistics will be used with measures of central tendency and dispersion of the data according to their distribution. The distribution of the variables will be analyzed with the Kolmogorov-Smirnov "Z" test. For categorical variables, frequencies and percentages will be used. For continuous variables with normal distribution, the mean and standard deviation will be shown. In contrast, the median and interquartile range will be used for continuous variables with an abnormal distribution.
The Student's t-test will be used to compare continuous variables between the two groups, in case of a normal distribution. The Mann-Whitney U-test will be performed for groups with an abnormal distribution. The analysis of data inside the same group at different time intervals (baseline vs 72 h) will be carried out using the Student's t-test, Wilcoxon sum of ranks, or McNemar's test, as appropriate.

Multivariate analysis for mortality will be performed using Cox proportional hazards, adjusted for the baseline SOFA score. Statistical analysis and graphs will be obtained using SPSS 19.0 software (Chicago, IL) and Graphpad Prism 5 software (San Diego, Ca), respectively. A p-value <0.05 will be considered significant. An intention-to-treat analysis will be pursued.

17. Groups
Group allocation for the AN-69 Oxiris membrane or the standard AN-69 membrane will be done by randomization before starting each CRRT treatment. This process will be performed through Epidat 4.2 software by one of the researchers from the Instituto Nacional de Ciencias Médicas y Nutrición, Salvador Zubirán.

18. Recruitment
All patients who meet inclusion criteria and without the presence of exclusion criteria, requiring CRRT due to AKI and COVID-19 disease, will be included. At the Instituto Nacional de Ciencias Médicas y Nutrición, Salvador Zubirán, the capacity for critically ill patients with invasive mechanical ventilation is of 44 beds.

At the Instituto Nacional de Enfermedades Respiratorias, the ICU possesses a capacity of 16 beds with invasive mechanical ventilation.
In these two areas where the recruitment will take place.
Thirty-six patients will be included. The number of participants from each institute will vary and it will depend on the subjects fulfilling the inclusion criteria. Each Institute is expected to contribute 50% of the total required subjects.

19. Follow-up variables
-Laboratory tests obtained from the electronic medical records during the hospital admission.
-Time on mechanical ventilation.
-Time and dose of vasopressor.
-Length of ICU-stay.
-Days of hospital stay.
-Recovery of kidney function (defined as dialysis-free at 28, 60, and 90 days after discharge).

20. Samples
Serum samples from included patients will be stored, labeled, and frozen at -70 °. After the recruitment period, the samples will be thawed for the measurement of serum interleukins.
These samples will be used only for the determination of the aforementioned markers and will be discarded after 3 years of study initiation.

References

1. Information from the website of the Ministry of Health, Mexico. 2020 Apr 14.
2. Ronco C, Reis T., Kidney involvement in COVID-19 and rationale for extracorporeal therapies. *Nat Rev Nephrol. 2020 Apr 9.*
3. Guan WJ, Ni ZY, Hu Y, et al., Clinical characteristics of coronavirus disease 2019 in China. *N Engl J Med. 2020 Feb 28.*
4. Ronco C, Reis T, De Rosa S., Coronavirus Epidemic and Extracorporeal Therapies in Intensive Care: si vis pacem para bellum. *Blood Purif. 2020 Mar 13:1-4.*
5. Bellomo R, Cass A, Cole L, Finfer S, Gallagher M, Lo S, et al. Intensity of continuous renal-replacement therapy in critically ill patients. *N Engl J Med. 2009;361:1627–38*.
6. Morgera S, Haase M, Kuss T, Vargas-Hein O, Zuckermann-Becker H, Melzer C, et al. Pilot study on the effects of high cutoff hemofiltration on the need for norepinephrine in septic patients with acute renal failure. *Crit Care Med. 2006;34(8):2099–104*.
7. Yumoto M, Nishida O, Moriyama K, Shimomura Y, Nakamura T, Kuriyama N, et al. In vitro evaluation of high mobility group box 1 protein removal with various membranes for continuous hemofiltration. *Ther Apher Dial. 2011;15(4):385-93*.
8. Thomas M, Moriyama K, Ledebo I. AN69: Evolution of the world's first high permeability membrane. *Contrib Nephrol. 2011;173:119–29*.
9. Cruz DN, Perazella MA, Bellomo R, de Cal M, Polanco N, Corradi V, et al. Effectiveness of polymyxin B-immobilized fiber column in sepsis: a systematic review. *Crit Care. 2007;11:R47*.
10. Rimmelé T, Assadi A, Cattenoz M, Desebbe O, Lambert C, Boselli E, et al. High-volume haemofiltration with a new haemofiltration membrane having enhanced adsorption properties in septic pigs. *Nephrol Dial Transplant. 2009;24:421–7*.
11. Ma J, Xia P, Zhou Y, Liu Z, Zhou X, Wang J, Li T, Yan X, Chen L, Zhang S, Qin Y Li X. Potential effect of blood purification therapy in reducing cytokine storm as a late complication of critically ill COVID-19. Clinical Immunology. 2020; 214
12. Shum HP, Chan KC, Kwan MC, Yan WW. Application of endotoxin and cytokine adsorption haemofilter in septic acute kidney injury due to Gram-negative bacterial infection. *Hong Kong Med J. 2013;19:491–7.*

INFORMED CONSENT

A RANDOMIZED, OPEN-LABEL, CONTROLLED TRIAL TO EVALUATE EFFICACY AND SAFETY OF A HIGHLY SELECTIVE SEMIPERMEABLE MEMBRANE (AN-69 OXIRIS) IN COMPARISON WITH A SEMI SELECTIVE SEMIPERMEABLE MEMBRANE (STANDARD AN-69) IN COVID-19 ASSOCIATED ACUTE KIDNEY INJURY: OXAKI-COV STUDY.

V 1.0: MAY 13TH, 2020

Principal Investigador: Olynka Vega Vega M.D.
Address: Vasco de Quiroga No 15, Colonia Belisario Domínguez Sección XVI, Delegación Tlalpan, México, D.F
Phone number: 5554870900 ext. 5606, mobile 5548039428
Participant investigators: Ricardo Correa Rotter, Guillermo Domínguez Cherit, Mauricio Arvizu Hernández, Carlos Torruco Sotelo, Noemí Del Toro and Adrián E. Caballero-Islas.

Sponsor: Departamento de Nefrología y Metabolismo Mineral, INCMNSZ, Subdirección de Medicina Crítica, INCMNSZ y Departamento de Enfermedades Infecciosas, INER.

Sponsor's address: Vasco de Quiroga No 15 Col. Belisario Domínguez, Sección XVI. Zip 14080.Tlalpan,Ciudad de México, México

Date and version of informed consent: Version 1; October 1th,2020.

INTRODUCTION:
The present document is an invitation to participate in a research study in our institution. Please take the necessary time to read this document and to ask the investigator any potential doubts.
To grant your support, you have the right to choose whether your family member will participate or not. The investigator must broadly explain the benefits and risk of becoming part of this project, without any pressure. **You will have all time you need to think, either personally or by consulting whoever you want, before deciding to participate.**

In order to make a truly informed decision about whether or not you agree to become part of this study, you must have the appropriate knowledge regarding potential risks and benefits for you or your family member. The present document will give you detailed information about this research study, the same information you can discuss with whoever you want, for example, a family member, your attending physician, the principal investigator, or any member of the research team. Once you have read and understood this information, your family member will be invited to become part of the project and if you agree, without any pressure or intimidation, you will be asked to give your authorization and sing this informed consent.

The present informed consent attains all requirements established in the regulation of the general health law on health research, the declaration of Helsinki, and the good clinical practices issued by the National Bioethics.

At the end of this document, you will be able to understand the following aspects:

I. Rationale and goals of this research.
II. Procedures used and their respective purpose, including realizing that they represent experimental procedures.
III. Potential risks and harms.
IV. Potential benefit from treatment.
V. Alternative procedures that might be beneficial for you.
VI. Full guarantee to receive answers to questions and clarify any doubts about the procedures, risks, benefits, and other matters related to the investigation.
VII. Complete freedom you have to withdraw your consent at any time ant to stop participating in this research, without affecting your care and treatment at our institution.
VIII. Safety from being particularly identified and that confidentiality about your information will be kept private.
IX. Full investigator commitment of providing you updated information that could be obtained during the study, even when this information could influence in your willingness to stay in the project.
X. Medical treatment availability and compensation which you are legally granted, in case of the occurrence of harms directly associated with the study.

You can ask for more time to think about it or take it home before making your final decision.

INVITATION TO PARTICIPATE AS A STUDY SUBJECT AND PROJECT DESCRIPTION.

Dear Mr./Mrs. and/or next of kin. _____

The "Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán (INCMNSZ)", through this research group, invites you or your family member to participate as a study subject in this project with the following objective: to prove the utility of a new hemodialysis filter with a clearing capacity of inflammatory molecules, which have been shown to have a detrimental role in patients with SARS CoV2 infection.
The total duration of this study will be **fourteen months (October 2020 to December 2021).**
Your family member participation will last three days, during his/her intensive care unit stay, and these days will be the first three days since the start of renal replacement therapy (hemodialysis).
The approximate number of patients will be of **36 individuals.**
Your family member is invited to participate in this study given he/she is hospitalized in the intensive care unit, with a SARS CoV2 severe infection, he/she is intubated and has developed acute kidney injury with the need of continuous renal replacement therapy initiation (continuous hemodialysis). The treatment is given by physicians from our institution and all necessary measures are being taken to improve his/her condition. With this study, our group is looking forward to reducing inflammatory molecules with a new hemodialysis filter to improve the outcomes of your family member.

PROCEDURES PERFORMED DURING THE STUDY
The participation in this research consists of the following:

(1) Your family member will be assigned to any of the two groups of study, both of them will receive continuous hemodialysis but each using a different filter: one group will receive hemodialysis with a conventional filter (control group), and the other group will be

hemodialyzed with a new filter (intervention group).

(2) ***Once continuous hemodialysis is initiated, a blood sample will be drawn every eight hours (approximately 4 mL) during the first three days of renal replacement therapy initiation.***

(3) ***Allow us to keep and freeze blood samples. Once the study is completed, we will process these samples to measure some serum levels of inflammatory markers***

(4) ***Give your permission to look into the electronic medical records in order to collect information about your family member's medical condition.***

Participating in this research has no cost.

No additional medical procedures will be performed other than those indicated by your treating physicians.

Participants' responsibilities include **allowing the use and analysis of blood samples, drawn during the study, by the study group.**

HARMS AND RISKS:

There is a risk associated during the blood sampling given a venous puncture, which is considered negligible. In most of the cases, the blood sample will be drawn via a lumen of the central venous catheter, thus reducing the risk or pain associated with a puncture.

Information regarding personal identity and medical records will not be disclosed at any moment. Confidentiality will be kept by codifying each sample.

POTENTIAL BENEFITS:

The following protocol is intended to evaluate a cutting-edge hemodialysis filter in critically ill patients infected with SARS CoV2 virus. Nowadays there is plenty of studies trying to find a useful treatment in this group of patients.

Thanks to your valuable family member participation, following patients with acute kidney injury may benefit from this new treatment.

ECONOMIC ASPECTS: there is no cost in participating in this research.

REWARDS: *there will be no rewards from becoming part of the study, given the negligible risk of participating in it.*

ALTERNATIVES FROM PARTICIPATING: *your family member's involvement in this research is voluntary. You can choose not to engage in it.*

POTENTIAL COMMERCIAL PRODUCTS DERIVED FROM RESEARCH: none.

ACTIONS TO FOLLOW AFTER STUDY COMPLETION: you can ask for study conclusions to Olynka Vega MD (principal investigator) from INCNMNSZ (phone 54870900 ext. 5606 o mobile. 5548039428). Research is a long and complex process so final results could take months to be obtained.

PARTICIPATION AND STUDY WITHDRAWAL:

You have to remember that your family member's enrollment is **VOLUNTARY**. If you decide not to enroll, the relationship with the institution (INCMNSZ) and your right to receive medical care or any service will not be affected. If you decide to participate, you have the choice to withdraw your consent and to interrupt your participation at any moment you want without affecting your medical care at INCMNSZ.

The following steps should be taken if you decide to terminate your participation: **none**.

CONFIDENTIALITY AND PERSONAL INFORMATION MANAGEMENT

Neither the name of your family member nor yours will be used in any of the public reports of the study. All information obtained from the electronic medical records will not have any personal information and it will be codified with a serial number to avoid any possibility from identification.

Codes identifying the information obtained from the medical records will only be available to main investigators, who are forced by law not to disclose the identity of your family member. Only investigators will have access to them. Other people in the research (inspectors or auditors) could have access to participants' information.
Even when there is a possibility that your privacy could be affected as a result of your participation in this research, your confidentiality will be protected as required by law, by assigning codes to your information. The code is an ID number which does not include personal data. No information about your family member will be shared without your consent, except:

- If it is necessary to protect your rights and wellbeing (for example, if there is harm and require emergency treatment); or:
- If it is required by law.

If you decided to withdraw from the study, you could ask for the elimination of all your information from the study. Every collection of data forms will be stored with the same confidentiality measures, and only the main investigators will have access to data that includes the name of the participant. If it is your will, you should contact Olynka Vega MD (principal investigator) from INCMNSZ (phone tel. 54870900 ext. 5606 o mobile. 5548039428) and express your decision in writing.

The Ethics Committee from INCMNSZ approved the performance of this research. This committee is the responsible for review, approval, and supervision of all research studies in our institution. In the future, if we identify information that can be important for your health, we will ask the Ethics Committee for Research the best way to disclose this information to you and your attending physician. Additionally, we will ask for authorization to contact you, if necessary, to request potentially relevant information for the development of this research.
Scientific data obtained as a result of this study could be used in medical publications or presentations. Your name and other personal information will be removed before using data.
If you decide, your attending physician will be informed regarding your enrollment in the study.

CONTACT WITH INVESTIGATORS:
If you have any doubts about the research, you can contact Olynka Vega MD (principal investigator) from INCMNSZ (phone tel. 54870900 ext. 5606 o mobile. 5548039428).
If you have any doubts regarding your rights as a study subject, you can contact Arturo Galindo Fraga MD, President of the Ethics Committee for Research at INCMNSZ. (Phone. 54870900 ext. 6109).

STATEMENT OF INFORMED CONSENT

I have carefully read this informed consent, have asked all questions I had and all of them have been successfully answered. To participate in this research, I agree with all of the following aspects:
I accept participating in the study previously mentioned. The general goals of the research have been fully explained to me. I consent access to the medical records and that this information could be used with the same purpose. I agree, if necessary, to be contacted in the future if the project requires to

collect additional information or if there is any finding relevant to my/ or my family members' health.
My signature implies that I have received a duplicate of this informed consent.
Please answer the following questions:

		YES (please check)	**NO (please check)**
a.	Have you read and fully understood this informed consent in your native language?	☐	☐
b.	Have you had the opportunity to ask any questions and discuss the implications of enrolling in the study?	☐	☐
c.	Have the investigators successfully answered all your questions?	☐	☐
d.	Have you received enough information about the study and spent the necessary amount of time to make a decision?	☐	☐
e.	Do you understand that your enrollment is voluntary and that you are free to terminate your participation at any time without having to justify your decision and without this affecting your medical care or the loss of benefits to you would otherwise have law?	☐	☐
f.	Do you grant access to your medical records for this research and regulatory purposes to responsible investigators, their representatives, auditors, regulatory offices, other governmental health agencies in Mexico and potentially in other countries in which the following filter could be approved for commercial use	☐	☐
g.	Do you understand the potential risks of this study?	☐	☐
h.	Do you understand that you could not receive any reward or direct benefit from participating in this study?	☐	☐
i.	Do you understand that you are not giving up any of your legal rights to which you are otherwise entitled as a subject in a research study?	☐	☐
j.	Do you understand that the investigator physician may withdraw you from the study without your consent, either because you did not follow the study requirements or if the study physician considers that your withdrawal is medically in your best interest?	☐	☐
k.	Do you understand that this study could be suspended by the sponsor at any moment?	☐	☐
m.	Do you understand that you will receive a signed and dated original of this informed consent for your personal records?	☐	☐

Patient statement: I as a patient and/or legal representative: _____

_ declare that this is my decision to participate as a clinical research subject in the study. My participation is voluntary.

I have been informed that I can deny to participate or to finish my participation at any moment of the study without suffering any penalty or loss of benefits. If I terminate my participation, I will receive the standard medical care that I have right in the Instituto Nacional de Ciencias Médicas y Nutrición Salvador

Zubirán (INCMNSZ), and I will suffer neither detriment in my medical care nor in future research studies. I can ask for additional information about the risks or potential benefits derived from my enrollment in the study.
If I have any doubts about the research, I can contact Olynka Vega MD (principal investigator) from INCMNSZ (phone tel. 54870900 ext. 5606 o mobile. 5548039428).

I have read and understood all the information that has been given to me about my participation in the study. I have had the opportunity to discuss it and to ask questions. All my questions have been completely answered. I have understood that I will receive a signed copy of the informed consent.
I am aware that in case I have any doubts about my rights as a study subject in this research, problems, worries ,or doubts, and I want to obtain additional information or to make suggestions about the development of the study, I have the freedom to contact Arturo Galindo Fraga MD, President of the Ethics Committee for Research at INCMNSZ. (Phone. 54870900 ext. 6109).

In case of obtaining informed consent by phone:

_____/_____/____ ____:____ _____
Date Hour Name of next of kin

_____
Relationship

_____
_____
Name of healthcare worker that explained and obtained the consent Signature

Signatures:

_____ _____ _____
Name of the participant Participant's signature Date

_____
In case the participant is illiterate, place thumb fingerprint.

_____ _____ _____
Name of next of kin (if necessary) Next of kin's signature Date

_____ _____
_____
Name of the investigator explaining the consent Investigator's signature. Date

_____ _____
Name of witness 1 Wittness 1 Signature

_____ _____
Date Relationship with participant.

Address: _____

_____ _____
Name of witness 2 Wittness 2 Signature

_____ _____
Date Relationship with participant.

Address: _____

Place and Date: _____

(The following document is original and consists of 7 pages)