CLINICAL TRIAL PROTOCOL

ASSESSMENT OF THE INCREMENTAL HAEMODIALYSIS SECURITY AND EFFECTIVENESS IN INCIDENT PATIENTS

PROTOCOL CODE

Trial IHDIP

VERSION:

2nd version of March 10th 2017

SPONSOR and COORDINATOR/INVESTIGATORS:

Dr. Javier L. Deira Lorenzo
Nephrology Department
Hospital Complex from Cáceres

Dr. Miguel A. Suárez Santisteban
Nephrology Unit
Hospital Virgen del Puerto from Plasencia

This project has the endorsement of the Extremadura Health and Social Policy Council and also of the Spanish Society of Nephrology

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Índex

1. PROTOCOL SIGNATURE PAGE SIGNED BY THE COORDINATOR/INVESTIGATORS

Both Dr. Javier L. Deira Lorenzo, consultant nephrologist, Hospital Complex in Cáceres, and Dr. Miguel A. Suárez Santisteban, consultant nephrologist, Virgen del Puerto Hospital in Plasencia,

state that:

They have designed and monitored the protocol of the clinical trial entitled "Assessment of the Incremental Haemodialysis security and effectiveness in Incident Patients" with the code "IHDIP" in its 2nd version of March 10th 2017.

1. They state that ethical and legal standards along with the clinical trial will be fulfilled and the Principles of Good Clinical Practice applicable in this type of projects will also be respected.
2. They state that they accept to participate as coordinator/investigators in this clinical trial.
3. They state that they have both the material and the human resources needed to carry out the clinical trial. They claim that neither another study, nor their usual tasks will interfere.
4. They state that the collaborators proposed to carry out the clinical trial are the appropriate ones.
5. They promise that each subject will be treated and monitored according to the established protocol with the favorable ruling of the Clinical Research Ethics Committee (CREC)
6. They state that the present clinical trial takes place as a "non-commercial clinical trial: a trial carried out by the researchers with no pharmaceutical industries or healthcare products involved" as long as it contains all the characteristics under article 2, point 2e of the Spanish Royal Decree 1090/2015 of December 4th through which clinical trials with drugs, Research Ethics Committees with drugs and the Spanish Clinical Trials Register are regulated.

In Cáceres, March 20th 2017

Signed by:

Dr Javier L. Deira Lorenzo
Coordinator/investigator

Dr Miguel A. Suárez Santisteban
Coordinator/investigator

2. TRIAL SUMMARY

2.1. Title: "Assessment of the incremental haemodialysis security and effectiveness in incident patients"

2.2. Protocol code: IHDIP

2.3. Sponsor and coordinator/investigators:

Dr Javier L. Deira Lorenzo, Hospital Complex in Cáceres (Spain)
Dr Miguel A. Suárez Santisteban, Hospital Virgen del Puerto in Plasencia (Spain)

2.4. Monitor: Delos® Clinical Contract Research Organization (CRO)

2.5. Investigators and centers participating, alphabetically ordered:

1. Dr Giannina Elena García Rodríguez. Hospital Arquitecto Marcide Ferrol. (A Coruña)
2. Dr Miguel A. Suárez. Hospital Virgen del Puerto.Plasencia (Cáceres)
3. Dr Javier Deira. Hospital San Pedro de Alcántara. (Cáceres)
4. Dr Jorge Huertas. Hospital de Especialidades de las Fuerzas Armadas. Quito (Equator)
5. Dr José de la Flor. Hospital Central de la Defensa Gómez Ulla. (Madrid)
6. Dr Francisca López. Hospital Costa del Sol. Marbella (Málaga)
7. Dr Antonio Gascón. Hospital Obispo Polanco. (Teruel)
8. Dr Eduardo Torregrosa. Hospital de Manises. (Valencia)
9. Dr Jesús Grande. Hospital Virgen de la Concha. (Zamora)

2.6. Ethical committee of reference: Cáceres Clinical Research Ethics Committee (CREC)

2.7. Trial design: trial

- Type of control: controlled through a routine clinical practice procedure
- Intervention assignment procedure: randomized
- Masking level and method: open trial

2.8. Primary outcome: to assess the security, effectiveness and efficiency of the incremental haemodialysis (HD) with one session per week as a starting regimen for the renal replacement therapy (RRT). It will be compared to the patients who start RRT with the conventional HD regimen.

2.9. Specific outcomes:

1. To assess the non-inferiority in the survival in 24 months among patients who start RRT with the regimen of incremental HD therapy compared to the ones who start RRT with the standard thrice weekly therapy HD regimen.
2. To compare hospitalizations, regardless of the reasons, among patients who start RRT with the regimen of incremental HD with the ones who start RRT with the conventional HD regimen.

2.10. Secondary outcomes

1. To compare the maintenance of the residual renal function (RRF) in patients who start RRT with the incremental HD therapy with those who start RRT with the standard thrice weekly therapy HD regimen.
2. To compare anaemia control, bone and mineral metabolism as well as hypertrophic cardiomyopathy in patients who start RRT with the incremental HD therapy with the ones who start RRT with the conventional HD regimen.
3. To compare the quality of life of patients who start RRT with the incremental HD method with those who start RRT with the conventional HD regimen.

2.11. To compare the efficiency (costs) of the incremental HD therapy with the conventional HD regimen.

2.12. Studied population: patients aged 18 and over with stage 5 chronic kidney disease (CKD), who start HD as RRT with a RRF of ≥ 4 ml/min/1.73m2, measured by renal clearance of urea (KrU).

2.13. Sample size: 156 patients

2.14. Inclusion criteria:

- Adults aged >18 years, incident patients with stage 5 CKD who have chosen HD as RRT initiation.
- RRF measured by KrU ≥ 4 ml/min/1.73m2.
- Informed consent signed before starting any activity related to the trial.

2.15. Exclusion criteria:

- Unplanned HD initiation (established in point 7.4 of the protocol)
- Non incident patients, in other words, patients who were previously on RRT, either on peritoneal dialysis, or on kidney transplant.
- Active neoplasia at the moment of inclusion

- Cardiovascular disease defined as: heart failure type IV of the New York Heart Association (NYHA), unstable angina or ischemic cardiopathy which has caused any admission in hospital in the last 3 months.
- Cardiorenal syndrome
- Active inflammatory disease with immunosuppressive treatment
- Hepatorenal syndrome

2.16. Intervention groups:

- Experimental group: 76 patients who start RRT with the incremental HD regimen, starting the program with just one session per week.
- Control group: 76 patients who start RRT with the conventional HD (3 sessions per week).

2.17. Trial visits:

- Selection visit
- Baseline visit
- Monthly follow-up visit (experimental group only)
- Quarterly follow-up visit
- Annual follow-up visit
- Final follow-up visit

2.18. Trial periods:

- Recruitment period: 18 months
- Follow-up period: 24 months

2.19. Trial schedule

- Date of clinical trial authorization: first quarter of 2017
- Start of the trial: second quarter of 2017
- End of the recruitment period: third quarter of 2018
- End of the follow-up period: third quarter of 2020
- End of the trial: fourth quarter of 2020

3. VISITING SCHEDULE

	Selection Visit	Baseline visit	Monthly visit*	Quarterly visit	Annual visit	End of the follow-up visit
Inclusion and exclusion criteria	X					
Informed consent document	X					
Demographic data register		X				
Comorbidity data register		X				
CKD etiology register		X				
Hospital admission			IHD	X		X
Data concerning the technique&			IHD	X		X
Residual renal function		X	IHD	X		X
Bioimpedance		X	IHD	X		X
Acid-base and electrolytic state		X	IHD	X		X
Erythropoietic levels		X	IHD	X		X
Bone-mineral metabolism levels		X		X		X
Nutrition-inflammation levels		X		X		X
Iron levels		X		X		X
KDQOL '36 US Spanish		X		X		X
Usual treatment		X		X		X
Echocardiogram#		X			X	X

* The monthly visit and determinations marked as IHD will only be carried out for patients undergoing incremental HD.

The echocardiogram will only be carried out at the beginning, after 12 months and after 24 months.

& Regarding the data related to the technique, when there are different parameters (e.g. BP weight gain, and so on), only the values obtained in the session when analytical measurements are taken will be registered.

4. INTRODUCTION:

Assisted conventional HD in a health center is the most used treatment for stage 5D CKD in the whole world. [1] By definition it is performed in an outpatient setting 3 days a week for 3 to 5 hours. However, this treatment has an unacceptable high mortality rate (10%–20% a year). This fact has been assigned, among other things, to an insufficient depuration of uremic toxins. In order to try to improve those results, new HD techniques and programs have been proposed. They are based on an increase of the dose as well as on the number of sessions, regarding the conventional HD used.[2] Nevertheless, inconsistent results of such programs in terms of clinical benefits have been shown in recent controlled and randomized trials. [3,4] Besides, a higher number of sessions has been associated to a lower rate of vascular access success and to a more accelerated loss of the RRF due to an increased exposure of the blood to the dialyzer membrane, together with frequent episodes of low blood pressure. [6,7]

RRF contributes, among other things, to the homeostasis maintenance of the internal environment, to the endogenous production of vitamin D and erythropoietin and to the elimination of protein-bound uremic toxins which are poorly dialyzed. [8,9] Thus, the maintenance of RRF in patients who start renal replacement therapy (RRT) with HD must be a basic objective since it plays a fundamental role not only in the dialysis adequacy, but also in the quality of life and in survival. [11,12]

The National Kidney Foundation-Kidney disease Outcomes Quality Initiate (NKD KDOQI 2015)[1] guidelines set the improvement of the quality of life and the patient's survival as the final objective of the RRT. It also distinguishes between appropriate dialysis and the proper care of the patient on dialysis. For patients with a significantly high RRF, measured by a renal clearance of urea (KrU) higher than 3ml/min/1.73m2, reducing the dose of dialysis or the frequency of sessions per week is suggested. In such cases a proper target is estimated to achieve a standard Kt/V (stdKt/v) of 2.3 volumes per week, including the renal clearance and the ultrainfiltration. However, in spite of the fact that more than 50% of the patients who start RRT have a KrU higher than 3 (ml/min/1.73m2) [13], few centers follow such recommendation.

Incremental or progressive HD is an initiation regimen adapted to the patient's necessities and his/her RRF. It begins with a low frequency of dialysis which increases gradually as the diuretic level and RRF decline. [10, 14, 15]

4.1. Justification

In 2015, 134.3 patients per millions of population (p.m.p) began RRT in Spain. Such figure can be risen to 158.8 among patients over 45, 404 among patients over 65 and 436 among patients over 75 (p.m.p and year). HD is used as starting RRT in 78% of patients, peritoneal dialysis (PD) in 17% and transplant in 5%. [16]

Global mortality is maintained over the last 10 years at 8%. However, a rate of 15.5% was reached in 2015 among patients treated with HD. The breakdown by age groups was: 8.5% for 45-65 year-old patients, 15% for 65-75 year-old patients and 24% for patients > 75 years old. On the other hand, in 2015 mortality among patients undergoing PD was 9.1% and 2.4%for those undergoing an early kidney transplant. [16]

Global survival in almost 55.000 incident patients (who started RRT between 2004 and 2014) was 91% in the first year, 81% in 2 years and 57% in 5 years. The median was of 6.22 years (CI of 95%: 6.10 – 6.32). With a multivariate analysis, the relative risk for patients who began RRT with an early kidney transplant was of 0.13 (IC of 95%: 0.12 – 0.14) and of 0.91 (IC of 95%: 0.86 – 0.96) for patients who began with PD, with regard to the ones who started conventional HD. Women have a HR of 0.88 (IC of 95%: 0,85 – 0.91); meanwhile the presence of diabetes as a cause for CKD rises the HR to 1.24% (IC of 95%: 1.20 – 1.29). By age groups, for patients over 45 the HR is 2.14 (IC of 95%: 1.95 – 2.34); for patients over 65, 2.78 (IC of 95%: 2.53 – 3.75), and for patients over 75, 3.75 (IC of 95%: 3.42 – 4.12). [16]

On the other hand, it has been known for some time that it is possible to obtain an accurate dose of dialysis with 2 sessions per week as long as KrU is at least 2.5 ml/min or higher. [10, 17, 18] However, interest in this field has increased recently and several works and editorials have been published.

Kamyar Kalantar-Zadeh et al [13, 19] in the U.S.A. or José Luis Teruel and collaborators in Spain have published their important experience in incremental HD and their good results in patients who start RRT with 2 HD sessions per week. Both have shown that in countries without financial difficulties, such number of sessions preserve the RRF in incident patients and get a rate of survival similar to the one obtained with the conventional HD. [13, 18-20] Currently, some authors are thinking about the number of HD sessions with which a patient must start the renal replacement therapy (RRT) and the implication in the RRF maintenance. [10, 15, 21]

Although it seems daring, it is logical to move gradually from stage 5 NoD to stage 5HD. That is how the idea of the incremental HD emerges. The patient starts with one HD session per week and increases from one to two and from two to three while declining the diuretic and/or RRF volume.

We initiated a pilot program about incremental HD in our centers in 2012. We started with just one session per week in incident patients with large diuresis, little uremic symptomatology and/or with underdeveloped AV fistulas. In no case such method influenced its early beginning (in other words, patients did not start with more RRF in order to be able to begin with incremental HD). During this time, we have treated 40 patients (25 males and 15 females) aged at 73 ± 10, 7 (88 – 42 rank) years old. 32% of them were catheter carriers. A patient died of pneumonia (89 years old, after 22 months in incremental HD), another one decided to abandon the program for family reasons (85 years old, 2 months in incremental HD) and a third patient was transplanted from a living donor after 50 days in incremental HD. Those three patients attended one session a week. 68% were not hospital admitted (whether the admission was related or not to their treatment). Time spent before starting with two sessions (or three sessions a week) was about 222±216 days (43–876 rank). Patients suffering either glomerular or vascular etiology spent 98 days in 1 HD session per week, meanwhile patients suffering tubulointerstitial nephritis spent 376 days. During follow-up time, 1172 sessions were carried out with that strategy, compared to the 3516 that would have had to be carried out with the conventional HD pattern. When advancing to 2 sessions a week patients stay an average of 87±166 days (0–560 rank) in such regime. 459 sessions were avoided. This results in savings over 17,000€ savings per patient are saved.

Such results were communicated, in part, in the last Sociedad Española de Nefrología (Spanish Nephrology Society) Congress. In conclusion, and according to our experience and other authors' experience [23-25], incremental HD in incident patients with one session a week can be an acceptable option, which reduces the number of sessions (and also the transportations). Not only does it contribute to an improvement of the quality of life, but it also helps by cutting down costs, presenting few complications. Nevertheless, currently there are no randomized and controlled trials which support it.

Based on these data, we set the hypothesis that starting RRT with an HD incremental regimen with just one session per week can contribute to preserve RRF, maintain the continuous kidney clearance of mean molecules and solutes joined to proteins. For those reasons, in terms of survival and hospital admissions, the results will not be worse than those of conventional HD with three sessions per week.

5. OUTCOMES

5.1. Primary outcome

To assess incremental HD security, effectiveness and efficiency with one session a week as an RRT starting regimen, compared to those patients who start RRT with the conventional method.

5.2. Specific outcome:

1. To assess the non-inferiority in survival during two years among patients who start RRT with the incremental HD regimen compared to the ones who start RRT with the conventional HD.

2. To compare hospital admissions by number and days of admission and reasons among patients who start RRT with the incremental HD regimen and the ones who start RRT with the conventional HD.

5.3. Secondary outcome

1. To compare the RRF maintenance of patients who start RRT with the incremental HD regimen with regard to the ones who start RRT with conventional HD.

2. To compare the anaemia, bone-mineral metabolism and hypertrophic cardiomyopathy levels of patients who start RRT with the incremental HD regimen with regard to the ones who start RRT with conventional HD.

3. To compare the quality of life of patients who start RRT with the incremental HD regimen with regard to the ones who start RRT with conventional HD.

4. To assess RRT's efficiency (costs) in the incremental HD regimen with regard to conventional HD.

6. TRIAL DESIGN:

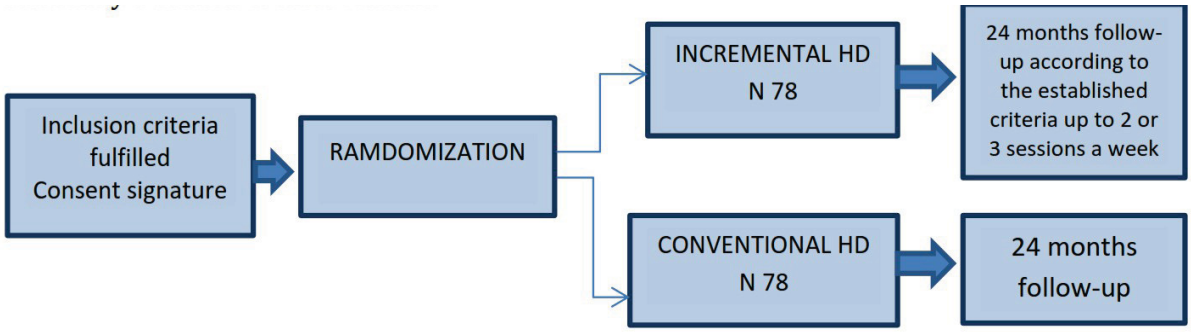
This project involves a randomized controlled trial (RCT) and opened clinical trial controlled by the usual clinical practice where the security and clinical benefits of two groups with different starting HD methods are compared: incremental HD compared to starting with conventional HD.

156 patients will be included in our trial in order to be able to obtain at least 13 events per intervention area. They will be recruited in different centers of different countries. Each patient will be assigned with an alphanumeric identification code. Such code consists of two figures which indicate the number of patient, three letters which indicate their center of inclusion, treatment area and the trial code. Thus, the first patient included in the Hospital Complex in Cáceres (Spain) would be:

- 01- CHC-cHDc or IHD - IHDIP

Once the trial has been initiated additional centers will be allowed to participate and at the same time other centers will be allowed to cease before finishing the inclusion period, e.g. due to lack of activity.

The choice of assigning the patient either to the experimental group or to the controlled one will be made by centralized randomization. Such randomization has been stratified depending on the patient's age (75 years old) and it has been made by blocks of four to keep both groups balanced. By the patient's inclusion in the electronic case report forms the system will randomly create a branch of intervention.



Patients all who start either the incremental HD regimen (experimental group) or the conventional HD (control group) will have the same baseline data. All data must be present in the patient's clinical history to be considered as source data.

During the follow-up period some analytical determinations will have different regularity in the incremental HD group and the control one, as it will be further explained in the point 10: procedures of the trial.

Once they have advanced up to 3 sessions a week, patients who begin the trial in the incremental HD branch will have the same visits and determinations than the control group. Nevertheless, they will have the same follow-up until completing 24 months than the patients in the experimental group (incremental HD).

A recruitment period of 18 months from the first patient's inclusion has been established. The expected maximum length of each patient's involvement in the trial (his/her follow-up period) will be 24 months. Besides, the expected maximum length for the whole trial from the first patient's inclusion until the last one's follow-up is 42 months. The trial will be considered as finished after the last included patient's follow-up.

The trial could be prematurely interrupted for security, scientific or administrative reasons. In that case, researchers must contact immediately every participant and act according to the given instructions.

7. ELIGIBILITY CRITERIA

Participants' choice to be included in the trial will be carried out by the main researcher of each center only once the written consent form has been signed.

7.1. Patients' recruitment procedure and materials

The first time a patient attends to the dialysis unit, inclusion and exclusion criteria will be assessed and he or she will be given the informed consent form for the trial.

7.2. Inclusion criteria

Selected patients must fulfill every of the following inclusion criteria in order to be finally included in the trial:

- Incident patients aged 18 and over with stage 5 CKD who have chosen HD as RRT initiation.
- RRF measured by KrU ≥ 4 ml/min/1.73m2
- Signature of the informed consent before starting any activity related to the trial.

7.3. Exclusion criteria:

Any selected patient who fulfills at least one of the following exclusion criteria will not be eligible to participate in the trial:

- Unplanned HD. Unplanned here means that the urine has not been collected in the 24 hours previous to the first session or that the urine was not collected in the previous 30 days.
- Patients who were in RRT (non-incident patients), in the PD method or renal transplant.
- Active neoplastic process at the moment of inclusion
- Defined cardiovascular illness: heart failure type IV (NYHA), unstable angina or ischemic cardiopathy with hospital admission in the last 3 months.
- Cardiorenal or hepatorenal syndrome
- Active inflammatory disease with immunosuppressive therapy

8. PATIENTS' INFORMATION AND CONSENT DOCUMENT

The content in the informed consent and its procurement will be carried out according to the article 29 of the Regulation (EU) nº 536/2014 of the European Parliament and of the Council of 16 April 2014.

The informed consent form shall be done in writing, dated and signed by the person who made the interview and also by the patient participating in the trial. In case the patient is not able to give his informed consent, his legal representative will do it after being properly informed. If the patient is not able to write, he/she will be able to give and register the consent by using the alternative means for such purposes in the presence of at least one impartial witness. In that case, the witness will sign and date the informed consent document. The participant or his named legal representative (in case he/she will not be able to give the informed consent) will receive a copy of the document where he/she has given informed consent. The informed consent shall be documented. The patient or his/her named legal representative will be given the appropriate time to carefully think about the decision of whether participating or not in the trial.

The researcher will be responsible of deeply informing the patient or his/her legal representative. With such information he/she will be allowed to:

- Understand the nature, objectives, benefits, implications, risks and disadvantages of the trial.
- Know his/her rights and guarantees in terms of his/her protection, particularly the right to refuse to participate and the right to leave the trial at any time without suffering any damage and without having to provide any justification.
- Know the conditions under which the trial will be carried out, including the planned duration of the participation, as well as the possible alternatives to the treatment.

In case new information may bring significant changes in the risk/benefit ratio assessment, the consent must be reviewed and updated. Participants all (including those who have already started the trial) must be informed again, they must receive a copy of the reviewed form and give their consent in order to be able to continue.

Before starting any activity related to the trial, the patient's or the legal representative's written informed consent document must be obtained.

9. INTERVENTION

9.1 Incremental haemodialysis HD

Incremental HD, also called progressive or infrequent HD, is a HD starting method adapted to each patient's individual needs. It is fundamentally influenced by RRF. The number or frequency of sessions with which the patient starts RRT (one or two HD sessions a week) is lower than the number of sessions in conventional HD (three per week). Such frequency will be increased (from one to two and from two to three) as the diuretic volume and/or RRF decline.

9.2 Starting incremental HD

Patients in incremental HD method will start HD with just one session a week. In each visit, the clinical situation will be assessed, biochemical determinations will be performed, dialysis parameter will be registered and also suitable medical tests will be run.

9.3 Criteria for progression

Once RRT has been started through incremental HD with one session a week, the frequency will be increased to two weekly sessions, only in case one the following incremental criteria is fulfilled:

- RRF, measured by KrU, declines under 4ml/min/1.73m2 and over 2.5ml/min/1.73m2
- Intersessional weight gain (weekly) which influence an ultrafiltration (UF) rate over 13ml/kg/hour. If these UF rates are necessary to achieve the dry weight, it must be objectified through bioimpedance. If these UF rates are kept for a minimum of 3 weeks, it will be considered a progression criterion.
- Clinical event that requires non-programmed HD sessions (more than one) for its resolution.

Patients who are undergoing the incremental HD method with two sessions a week will be changed to the conventional HD method (with three weekly sessions) if:

- RRF, measured by KrU, declines under 2.5 ml/min/1.73m2
- There is intersessional weight gain (weekly) which influence an ultrafiltration (UF) rate over 13ml/kg/hour. If these UF rates are necessary to achieve the dry weight, it must be objectified through bioimpedance. If these UF rates are kept for a minimum of 3 weeks, it will be considered a progression criterion.
- There is a clinical event that requires non-programmed HD sessions (more than one) for its resolution.
- An appropriate dialysis dose measured by a standard Kt/v (std Kt/V) over 2.1 is impossible to be achieved.

9.4 Control systems

As it is advised in the usual clinical practice, and especially with regard to patients with incremental HD, special attention will be paid to volume overload, hyperkalemia and metabolic acidosis.

In order to maintain a correct level of hydration, the interdialytic weight gaining and the ultrafiltration rates needed to maintain weight will be registered. Monthly bioimpedance of patients undergoing incremental HD and quarterly bioimpedance of patients undergoing conventional HD will help to dismiss a possible overhydration.

If researchers estimate it necessary, both potassium and acid-base balance levels could be monitored during the inter monthly period by researchers (e.g. with a Venous blood gases control). Such controls will not necessarily be registered, since they are part of the usual clinical practice.

10. PROCEDURES OF THE TRIAL

Methods and calendars for the assessment, register and analysis of the security and effectiveness levels will be defined hereunder.

10.1 Selection visit

During the selection visit, the required assessment to confirm whether the chosen patient can be included or not in the trial will be performed. The procedures to be performed in this visit are:

- Verification of the inclusion criteria fulfillment. The selected patient must fulfill ALL inclusion criteria previously mentioned in point 7.3 of the protocol
- Verification that exclusion criteria are not fulfilled. The eligible patientmust not fulfill ANY of the exclusion criteria previously mentioned in point 7.4 of the protocol.
- Signature of the informed consent document by the patient.

All the assessments and obtained results must be included in the clinical history, including the fact that the patient is given the informed consent document and that the patient voluntarily agrees to participate in the trial.

10.2 Baseline visit

Hereunder, all the procedures to be carried out during this visit will be described. All the assessments are common for both groups. The obtained results must be included in each patient's clinical history.

- Visit date register: this date will be considered as the starting date of the trial and it must coincide with the first HD session.
- Patient's code.
- Intervention area: conventional or incremental HD
- Demographic data register: gender and age.
- Comorbidity register:
  - Charlson comorbidity index
  - Diabetes Mellitus (yes/no)
  - Congestive heart failure, no type IV of the NYHA (yes/no)
  - Non active coronary heart disease (yes/no)

  - Peripheral vascular disease (yes/no)
  - Cerebrovascular disease (yes/no)
  - Lung disease or smoking problems (yes/no)
  - Liver disease (yes/no)
  - Other diseases (yes/no)
- CKD etiology register: EDTA codes.
- Residual renal function register: urine volume of 24 hours (in ml), urea and creatinine in the blood and urine (in mg/dl) and proteinuria in g/24h will be measured. Weight and size will be registered (in order to calculate the body surface). If the patient may not have a recent urine test (previous 30 days), he/she will be asked to bring the 24h urine for the day when the trial begins.For KrU calculation (in ml/min/1.73m2) the formula is attached the case report form (CRF).
- Bioimpedance: data regarding the urea distribution volume (in liters); both lean tissue index (LTI) and fat tissue index (FTI) measured in kg/m2 and pre and post overhydration state (in liters) will be registered. In case of not having bioimpedance, Watson formula could be used for the V calculation.
- Acid-base and electrolytic state: pH, bicarbonate and potassium levels in blood
  - will be measured and registered.
- Erythropoietic levels: haemoglobin (Hb) and the erythropoiesis-stimulating agents (ESA) dose will be measured and registered.
- Bone-mineral metabolism levels: serum PTH, phosphorus, calcium and magnesium levels (in mg/dl) will be measured and registered.
- Nutrition-inflammation levels: serum total proteins, albumin, b2 microglobulin, C-reactive protein (CRP) and transferrin levels will be measured and registered.
- Iron levels: the value of serum iron (Fe) of the transferrin saturation index (TSAT) and serum ferritin will be measured and registered.
- Quality of life survey: quality of life survey values from Kidney Disease and
  - Quality of Life (KDQOL'36 Spanish) will be registered.
- Usual treatment: drugs and their usual doses for the treatment of the problems associated to the CKD -anti-hypertensive and diuretic medicines, as well as bicarbonate, P binders, calcimimetic agents and vitamin D analogues, will be registered.
- Echocardiogram: ejection fraction (EF), left ventricular mass (LVM) and the existence or lack of pericardial effusion will be registered. It will be considered as basal echocardiogram as long as it is performed within the first 60 days.

10.3 Monthly follow-up visit

Such visit will be ONLY made to the patients who started RRT in the intervention group (incremental HD) and who monthly continue in such method of treatment. This monthly visit of assessment will be made until progression to conventional HD or until the follow-up ending (24 months) if they are still in incremental HD. One single patient could be visited up to 24 times.

Assessments and obtained results all must be written in the clinical history. All the procedures to be carried out during such visit are described hereunder:

Hospital admissions register: every hospital admission in the previous month to the date of the visit and their reasons will be registered.

Data referred to the HD technique: the following data will be registered:

- Number and date of the HD sessions.
- Vascular access: native arteriovenous fistula, tunneled or non- tunneled Central Venous Catheter (CVC) (in case more than one is registered, the number of days the patient is with each one of them will be registered)
- Dialysis effective time (in minutes)
- Dry weight (in kilos)
- Intersession weight gaining (in kilos)
- BP (on connection and disconnection)
- Urea post
- HD dose: stdKT/V (formula is attached in the case report form CRF)

Whenever there may be different levels e.g. BP levels, only the level of the visit (session) where determinations are carried out will be registered.

- Residual renal function register: 24 hours urine volume (in ml), urea and creatinine in blood and urine (in mg/dl) will be measured.
- Bioimpedance: the same data than in the baseline visit: urea distribution volume (in liters), LTI and FTI (in kg/m2) and pre and post HD overhydration state (in liters) will be measured.
- Acid-base and electrolytic state: pH, bicarbonate and potassium levels in blood will be measured and registered.
- Erythropoietic levels: Hb and ESA dose will be measured and registered.

10.4 Quarterly follow-up visit

The patients ALL who continue in the trial, regardless of the starting method or the one in which they are at that moment, will undergo the assessment in the previous point (10.3 monthly) and the following follow-up determinations will be done every three months:

- Bone-mineral metabolism levels: serum PTH, phosphorus, calcium and magnesium levels (in mg/dl) will be measured and registered.
- Nutrition-inflammation levels: serum total proteins, albumin, b2 microglobulin, CPR and transferrin levels will be measured and registered.
- Iron levels: the value of serum iron (Fe) of the Transference saturation index (TSAT) and serum ferritin will be measured and registered.
- Quality of life survey: quality of life survey values from Kidney Disease and Quality of Life (KDQOL'36 Spanish) will be registered.
- Usual treatment: drugs and their usual doses for the treatment of problems associated to the CKD -anti-hypertensive and diuretic medicines, as well as bicarbonate, P binders, calcimimetic agents and vitamin D analogues, will be measured.

10.5 Annual follow-up visit

The patients ALL who continue in the trial, regardless of the starting method or the one in which they are at that moment will undergo monthly and quarterly assessment and also:

- Echocardiogram: ejection fraction (EF), left ventricular heart mass (LVM) and the existence or not of pericardial effusion will be registered. The echocardiogram will be carried out only in the visits corresponding to months 12 and 24 of the follow- up procedure.

10.6 Final follow-up visit

The patients ALL who are in month 24 month of the trial, regardless to the starting method or the one in which they are at that particular time, will receive their final the follow-up visit. All procedures performed during such visit will be described hereunder. The assessments and obtained results will be written in each patient's clinical history.

- End of the follow-up date: the date when the follow-up is finished will be registered.
- Reason for ending the follow-up: the cause for the end of the follow-up (follow- up ending) will be registered.

- Hospital admissions register: every hospital admission and their reasons during the previous month to the date of the visit will be registered.
- Data referred to the HD technique: following data will be registered
  - Number and date of the HD sessions.
  - Vascular access: native or prosthetic arteriovenous fistula, tunneled or non-tunneled CVC. In case a patient has used more than one, the number of days the patient has been with each one of them will be registered.
  - Dialysis effective time (in minutes)
  - Dry weight (in kilos)
  - Intersession weight gaining (in kilos)
  - BP (on connection and disconnection)
  - Urea post
  - HD dose: stdKT/V

Whenever there may be different levels, only the level of the visit (session) where determinations are performed will be registered.

- Residual renal function register: 24-hours urine volume (in ml), urea and creatinine in blood and urine (in mg/dl) will be measured.
- Bioimpedance: the same data than in the baseline visit: urea distribution volume (in liters), LTI and FTI (in kg/m2) and pre and post HD overhydration state (in liters) will be measured.
- Acid-base and electrolytic state: pH, bicarbonate and potassium levels in blood
- will be measured and registered.
- Erythropoietic levels: Hb and ESAs dose will be measured and registered.
- Bone-mineral metabolism levels: serum PTH, phosphorus, calcium and magnesium levels (in mg/dl) will be measured and registered.
- Nutrition-inflammation levels: serum total proteins, albumin, b2 microglobulin,
- CPR and transferrin levels will be measured and registered.
- Iron levels: the value of serum Fe of the TSAT index and serum ferritin will be measured and registered.
- Quality of life survey: quality of life survey values from Kidney Disease and Quality of Life (KDQOL'36 Spanish) will be registered.
- Usual treatment: drugs and their usual doses for the treatment of the problems associated to the CKD -anti-hypertensive and diuretic medicines, as well as bicarbonate, P binders, calcimimetic agents and vitamin D analogues, will be registered.

Echocardiogram: EF, LVM and the existence or lack of pericardial effusion will be registered.

In case patients end the trial before fulfilling the 24 moths of follow-up (either due to death or retreat) only the date and reasons of ending, as well as hospital admissions if there has been any from the last visit will be registered in the final follow-up visit.

11. PATIENTS' REMOVAL

11.1. Removal criteria:

Patients could be moved off the trial, at any time, due to one of the following reasons:

- Kidney transplantation
- Transfer from the center and follow-up loss
- End of trial (by their own or their family decision)
- RF recovery
- Some exclusion criteria appearance during the trial
- Unwanted effects with regard to the intervention, according to the researcher's assessment, serious enough as to justify the patient will be the patient's final removal from the trial.
- Consent withdrawal
- Breach of HD sessions by the patient

11.2. Removal procedure

In such cases, the researcher must proceed with the final visit of the follow-up as it has been described in point 10.6

11.3. Patients' substitution

No replacement procedure will be carried out for those patients who prematurely withdraws the follow-up.

12. SAFETY ASSESSMENT

12.1. Safety criteria

- Survival: a follow-up time will be established in order to calculate survival rates. It will be defined as the difference in days from the date of the end of the follow-up minus the date of the baseline visit. Events will be accounted either as deaths (follow-up less than 24 months) or end of the follow-up. Removed patients from the trial due to the reasons established in the point 11.1 will be accounted as censored data.

- Hospital admissions: a form where the date of entry and discharge, as well as the cause is included in every CRF (case report form). Hospital admissions, regardless of the cause, the number and the admission days will be registered. If a patient may stay in hospital for some days of one month and some days of the next one, just one admission will be registered. The date will be the one when the patient first arrived and all the days of the hospital stay will be registered as days of the first month (e.g. if a patient is admitted on 10th March and he is discharged on 12th April: a 32 days admission in March will be registered).

  The following list will be considered as reasons for direct admissions:

  - Infections of any etiology
  - Vascular access (intervention, repair, substitution, thrombosis or bleedings)
  - Heart failure or ischemic cardiopathology
  - Gastrointestinal bleeding
  - Other reasons

12.2. Registry of unfavourable events related to the session frequency

In case there may be any contingency likely related to the less number of weekly sessions in patients who are in the intervention arm, and while they are keeping their follow-up with the incremental HD with 1-2 sessions a week, it will be registered in their clinical history. Such contingencies must be associated to either an extra or non-programmed session or to the advance of their weekly session. There is a wide range of contemplated complications e.g. a patient who needs an urgent session due to respiratory failure symptoms or hyperkalemia. The date of the contingency, a complete description, additional exploration or laboratory tests results, its seriousness, as well as its ending must be registered.

The seriousness assessment will be carried out according to the following classification. Categories are not mutually exclusive:

- Death
- Patient's life has been at risk
- Hospital admission or admission extension
- Clinically relevant

13. EFFECTIVENESS ASSESSMENT

13.1. Effectiveness criteria

In order to assess the intervention effectiveness under study (incremental HD as starting method of RRT) the following factors will be assessed:

RRF maintenance: urine 24-hour volume (in ml), glomerular filtration rate (GFR) (average residual urea and creatinine clearance) and the KrU (both in ml/min/1.73m2) will be measured in both groups in order to assess the maintenance.

- Urine volume. In each follow-up period (every 3 months) urine cc loss in 24 hours will be compared (previous visit's volume minus current volume) as well as its rate per month (lost volume divided by the period of time).
- Percentage of patients with diuresis of < 400cc and < 100cc
- GRF and KrU. In each follow-up period (every 3 months) ml/min/1.73m2 loss of both indexes (previous visit's ml/min minus current volume) will be compared. Then the rate per month (lost ml/min divided by the period of time)
- RRF maintenance time. Both mean and median time of KrU maintenance between 4 to 2.5ml/min/1.73m2 will be calculated.

Anemia control: In both groups and in every visit, the erythropoietin resistance index (ERI) will be calculated through the formula

ERI = weekly EPO (in UI)/patient's weight (in kg)/Hb (in gr/dl)

For patients who are taking darbepoetin, the proposed equivalent dose with EPOrHu is 1 mcg darbepoetin = 200 UI of EPOrHu

Bone-mineral metabolism control: in order to be assessed,

- Parathyroid hormone, serum phosphorus and calcium levels (all of them in mg/dl), as well as calcium-phosphorus product (CaxP) will be measured.

Hypertrophic cardiomyopathy control: in both groups the EF and the LVM (and its relationship with the body surface or ILVM) baseline and annual measurements will be taken.

- The cut-off point for LVH diagnosis is defined as ILVM ≥ 125g/m2, with no gender difference.
- Pericardial effusion: it will be considered as yes or no matter.

Patients' quality of life: patients' quality of life will be assessed through the Kidney Disease and Quality of Life (KDQOL'36 US Spanish) survey.

14. EFFICIENCY ASSESSMENT

14.1. Efficiency criteria

Efficiency in both branches of the trial will be totally compared at the end of the follow-up. In order to assess the intervention efficiency under study, the following factors will be taken into account:

Regardless of the HD starting method, every patient's monthly costs during the whole follow-up until the finalization, event or death will be calculated. In such monthly costs, transport, HD sessions, as well as hospital admissions will be counted following the next factors:

- HD session costs: each session is estimated to cost €201 (£170.681)
- Medical transport costs: each transportation is estimated to cost €20 (£16.98)
- Hospital admission costs: one day in hospital is estimated to cost €498 (£422.87)

Such rates are not expected to show in an actual or updated way neither the costs nor the prices paid for each of these services. Neither can they be representative costs of all the hospitals participating in the trial. We assume such differences, since our intention is not to "invoice", but to have some rates which allow us to calculate somehow which HD starting method is more or less expensive and, therefore, more or less efficient. [26]

1 Euros (€) to Pounds (£) conversions calculated on March 2017

15. STATISTICS

15.1. Sample size

The sample size was calculated based in the contrast of a null hypothesis H0: The rate between the median survival time is not under the limit of no inferiority, through a Log-Rank test for two independent samples (no-inferiority in a function of exponential survival). Assuming the following parameters:

- Inclusion period is 18 months,
- Maximum period of the follow-up is 24 months,
- Median survival time in the conventional HD group is 74 months[16].
- Median time until censure is 12 months N
- Non-inferiority limit is 4 months.
- Type I error 5%
- Type II error 20%.

We must included 76 patients for the conventional HD group and 76 in incremental HD group, totaling 152 patients in the trial.

15.2. Population to analyze

The population to analyze in this study is all patient included in the study, regardless if they finally end the 24 months of follow-up period. In other words, we will perform an intention-to-treat analysis.

15.3. Intermediate analysis

When all patients included reach 12 months of follow-up and after finished the inclusion period, we analyzed all patient outcome. This analysis will be the same at the end of the follow up.

15.4. Statistical methods

In this section we describe all statistical method we will apply to reach the trial objectives. In all statistical test we assume a type I error of a 5% and type II error of a 20%.

- Descriptive analysis: We will perform a descriptive analysis of the total population participating in the trial, as well as an analysis of each study group. All the variables registered in the baseline visit will be analyzed. Qualitative variables will be written with frequency and percentages and quantitative variables will be written with the mean, median, standard deviation and interquartile range.

For all qualitative variables of the trial, we will perform Chi-square test or statistical Pearson's test when expected cells counts will not adequate.

For all quantitative variables of the trial we will perform the Student's t-test or non-parametric Mann-Whitney test, when the sample is not fit to normal distribution.

- Survival analysis. The differences of survival time between the two arms of the trial will be evaluated by:

- Bivariate analysis. The differences between mean and median survival time between both arms of the trial through Kaplan-Meier tests will be assessed. The analysis of the differences will perform through the log-rank test.

- Multivariate analysis. We will evaluate the real contribution of trial intervention in the survival and all significant survival variables by a multivariate Cox regression model.

- Hospital admissions analysis: The difference in hospital admissions will be analyzed through two different measurement variables:

- Number of admissions analysis. The mean and median of number of admission in each trial arm will be calculated. The difference among the averages will be assessed through the Student's t-test or Mann-Whitney nonparametric test.

- Admission time analysis. The mean and median of days of all admissions of each trial arm will be calculated. The difference among the averages will be assessed through the Student's t-test or Mann-Whitney nonparametric test.

- RRF maintenance analysis. The differences between the two arms of the trial in the maintenance of FRR will be assess by three measurement variables:

- 24h urine maintenance rate. We will compare the volume of 24h urine at the end of follow up with the volume registered at baseline. Such evolution will be done through Wilcoxon test. Proportion rate of patients who keep 24h urine volume at the end of the follow-up will be assessed. Such comparison will be done through Chi-square test or Pearson's test, according to the distribution of observed proportions.

- RRF maintenance rate (IFG and KrU). RRF maintenance evolution along the follow-up with regard to the baseline one will be compared. Such evolution will be done through Wilcoxon test. Proportion of patients who maintain their residual renal function at the end of the follow-up will be compared. Such comparison will be done through Chi-square test or Pearson's test, according to the distribution of observed proportions.

- RRF maintenance time. The differences between mean and median RRF maintenance time between both arms of the trial will be assessed by Kaplan-Meier tests. The assessment of the differences will be done through the log-rank test.

- Anaemia control. Erythropoietin Resistance Index (ERI) between both arms of the treatment will be compared; and differences through Student's t-test or Mann-Whitney nonparametric test will be assessed. Such assessment will be done at the end of the treatment, 24 months and at 3, 6 12 months.

- Bone-mineral metabolism control. Serum PTH and phosphorus levels, as well as CaxP product will be compared between both branches of the treatment through Student's t-test or Mann-Whitney nonparametric.

Proportion of patients who maintain CaxP product level under 55 will be assessed. Such comparison will be done through Chi-square test or Pearson's test, according to the distribution of observed proportions.

- Specific cardiomyopathy control. For each arm of the trial, differences among ejection fraction (EF), left ventricular mass (LVM) and left ventricular mass index (LVMI) will be assessed. In order to assess the differences in the existence or not of pericardial effusion between both branches of the trial, Chi-square test or Pearson's test, according to the distribution of observed proportions, will be done.

- Life quality assessment. We compared the quality of life through the obtained punctuations of life quality survey between both arms of HD. Obtained results will be assessed through the Student's t-test or Mann-Whitney nonparametric alternative.

- Efficiency assessment: We compare the efficiency results of each arms of the trial. We will be assessed the difference by Student's t-test or Mann-Whitney nonparametric alternative.

16. QUALITY CONTROL AND QUALITY ASSURANCE

The Data Manager, the sponsor, also FundeSalud (Foundation for research and training of health professionals of Extremadura, Spain) and coordinator/investigators will perform regular controlled visits (either face-to-face or online) during the trial in order to make sure that both the protocol and Good Clinical Practices (GCP) are met. The investigator and the staff of the center where the study is taking place will allow the use of data or source documents necessary for the CREC to carry out the monitoring, the audit, the revision and for the health authorities to proceed with inspections.

Both the investigator and relevant staff must be available during the monitored visits and possible audits, and they will also devote the necessary time.

17. LEGAL AND ETHICAL ASPECTS

This trial will be performed according to the protocol, the GCP guidelines and the applicable national laws and requirements of the countries where the study is being carried out.

17.1. Type of trial:

The present trial has been categorized as low-intensity intervention clinical trial, since neither drugs nor placebos are used. Complementary procedures in diagnosis or follow-up imply a minimal risk or additional charge for the patients' security compared to that of the usual clinical practice.

Likewise, this trial is defined as a Non-commercial clinical trial, since it has been directly carried out by the researchers without the participation of the pharmaceutical industry or the healthcare product companies. The present trial involves the following characteristics:

1. The sponsor is a university, a hospital, a public scientific organization, a non-profit institution, a patient organization or an individual researcher.
2. The ownership of the data of this trial belongs to the sponsor from the first moment.
3. No agreements between the sponsor and third parties allowing them to use the data for regulatory or patent purposes are in place.
4. The design, conduct, recording and reporting of the clinical trial are under sponsor's control
5. According to these characteristics, these trials cannot be part of any development program for commercial purposes.

Both definitions are registered under article 2 of the Spanish Royal Decree 1090/2015 of 4th December, where clinical trials with drugs, Clinical Research Ethics Committee and Spanish register of clinical trials are regulated.

17.2. Publication commitment

The sponsor or the coordinator/investigators of the trial explicitly commit themselves to publish the whole information and obtained data after finishing such trial regardless of the results.

17.3. With regard to the confidentiality

Coordinator/investigators will be in charge of making sure that collaborators participating in the trial all respect the confidentiality of the patients' information, according to the GCP and the relevant legislation. The same way it will be researcher's responsibility to maintain such information so that authorities can have access to it whenever they need it. Such registers must be confidentially maintained during the time established by the legislation.

This trial will be carried out according to the current legislation and fulfilling with the orders included in the Spanish Organic Law 15/1999 dated on 13th December on Personal Data Protection and, the Spanish Royal Decree 1720/2007 dated on 21st December.

18. DATA MANAGEMENT AND RECORD-KEEPING

18.1. Case report forms

A case report form (CRF) will be completed for each patient with data taken directly from the source documents. Under no circumstances shall the CRF be taken as a source document.

Completed original CRFs are exclusively owned by the sponsor or coordinator/investigators and they will not be available to third parties under any circumstances, except for the representatives authorized by the sponsor or the competent regulatory authorities.

It is the researcher's responsibility to make sure that all CRFs are being properly fulfilled, reviewed and approved by his own signature. The researcher will be responsible for the accuracy and veracity of the registered data included in CRFs at any time.

Once the CRFs have been fulfilled, the information will be registered in an online database that will meet all the appropriate requirements for that purpose. The researcher will be responsible for properly maintaining the CRFs and the online database.

18.2. Files maintenance

The researcher will be the only responsible person for conserving all patients' identification files, signed informed consent forms, and copies of all CRFs along the period of time established by the regulation.

If the researcher moves to another working center or quits providing services for whatever reason, the trial's records could be transferred to a designated person with the sponsor's knowledge and written approval.

19. FUNDING

For this trial's development, some costs have to be born in mind. They can be divided into three different groups:

- The project's design, randomization and platform, web page or any other computer system that allows an online data collection.
- Monitoring (follow-up and data register)
- Planning and data statistical processing

Such points could be ordered to be done by a Clinical Research Support Center (CRSC) or similar Contract Research Organization (CRO).

Besides, all public options are considered funding sources, through relevant aids form for that purpose. Not only that, but also private centers which could be somehow involved in the project.

20. PUBLICATION POLICY

All unpublished information included in the trial will be considered as confidential and belongs to the Researchers. Such information includes: the clinical protocol, the trial's basic data, the CRFs, assessment methods and technical methodology. This information must not be revealed to anyone without previous consent and it must not be used for any other purposes than those of the trial.

Once the statistical analysis is completed, the obtained results will be checked and discussed by the research team. The coordinator/investigators will elaborate a final form together with the rest of collaborators. Results will be communicated to the CREC and the competent authorities.

The researchers undertake not to use or transmit any information with regard to the trial to third parties, nor to disclose and/or publish the results obtained in this trial without a previous written consent by the coordinator/investigators.

In any case, the following conditions must be respected:

1. The results of the present trial cannot be published until it has been finished.

2. The coordinator/investigators will allow the data obtained in this study to be published by magazines of recognized scientific prestige and disclosed in seminars and lectures within the medical professional field, provided that the paragraph a) above is respected and the review of the article's final draft is allowed too.

21. ABBREVIATION INDEX

BP	Blood pressure
CI:	Confidence Interval
CKD:	Chronic Kidney Disease
CREC:	Clinical Research Ethics Committee
CRF:	Case Report Form
CRO:	Clinical Contract Research Organization
CRSC:	Clinical Research Support Center
CVC:	Central Venous Catheter
EDTA:	European Dialysis and Transplant Association
EF:	Ejection fraction
EPO:	Erythropoietin
ERI:	Erythropoietin Resistance Index
FTI:	Fat Tissue Index
GCP:	Good Clinical Practices
GFR:	Glomerular Filtration Rate
Hb:	Haemoglobin
HD:	Haemodialysis
HR:	Harzard Ratio
IHD:	Incremental Haemodialysis
KrU:	Renal Clearance of Urea
LTI:	Lean Tissue Index
LVH	Left Ventricular Hypertrophy
LVM:	Left Ventricular Mass
LVMI:	Left Ventricular Mass Index
NKD	National Kidney Foundation-Kidney disease Outcomes Quality
NYHA:	New York Heart Association
PD:	Peritoneal dialysis
RF:	Renal Function
RRF:	Residual Renal Function
RRT:	Renal Replacement Therapy
UF:	Ultrafiltration

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