PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Impact of Incremental versus Conventional Initiation of Haemodialysis on Residual Kidney Function: Study protocol for a multicentre feasibility randomised controlled trial.
AUTHORS	KAJA KAMAL, RAJA MOHAMMED; Farrington, Ken; Wellsted, David; Sridharan, Sivakumar; Alchi, Bassam; Burton, James; Davenport, Andrew; Vilar, Enric

VERSION 1 – REVIEW

REVIEWER	Matthew Roberts Eastern Health Clinical School, Monash University, Australia
REVIEW RETURNED	10-Jan-2020

GENERAL COMMENTS	The authors present a trial protocol for a feasibility study in preparation for an RCT comparing twice weekly “incremental” haemodialysis to standard thrice weekly haemodialysis in patients new to dialysis. This is an important topic and important to try to assess with a RCT. Major comments: The authors have submitted a manuscript with references, two tables, a figure, a list of equations, and their Study Protocol (Version 1.0, 28/6/2017). It is unclear what is supplementary materials and what is not. Under “Measurement of dialysis adequacy”, there is reference to “Details of the method of measuring dialysis adequacy are provided in supplementary materials” but it is not clear if this is the Calculations document or the protocol. I wonder if the protocol could be accessed via a link to the author’s institution. It is not specifically cited so I am not sure it is needed as an online supplement. Please specifically reference what is intended as an online supplement. The primary objective relates to feasibility. Some discussion about how the feasibility outcomes would affect progression to and planning of the future study is needed. What level of “recruitability” would make the larger study feasible, and what level would cause the authors to abandon the idea of a larger study? Is there a threshold proportion of patients adhering to the protocol that would affect the feasibility of a larger study? I would also question the reliance on the Cocks and Torgerson paper in justifying the sample size of this study. Cocks and Torgerson emphasize the difference between a “pilot” study and a “feasibility” study and their recommendations are pertinent to a “pilot” study. The authors have made feasibility their primary objective and in this regard a sample size that gives an acceptable 95% confidence interval around the proportion of patients considered “recruitable” may be more relevant.

	Because eligibility is based on a very specific measure (inter-dialytic urea clearance), and because it impacts the feasibility outcomes, the screening process needs to be very clearly explained. There is a bit more detail in the protocol document than the manuscript. However, there are some aspects that are still not clear. Will all patients starting dialysis be approached and asked to perform an inter-dialytic urine collection soon after they start? This is important for the denominator for the primary outcome: will it be all patients in the dialysis unit, or just some? If just those who are "potentially eligible" (Table 1), what defines "potentially eligible"? The intention to treat principle is being maintained and this is appropriate. What are the specific triggers to switch a patient to thrice weekly? Will data be collected on the reasons patients in the Incremental arm switched to thrice weekly dialysis? This is an important feasibility outcome, and understanding the reasons for non-adherence to the protocol is important. Measuring residual kidney function in haemodialysis is not simple and the authors have published in this area. A specific section with discussion of the choice of measures of RKF for specific aspects of the study is needed. For example, eligibility for inclusion is based on the inter-dialytic urea clearance as a measure of residual kidney function. However, the European Best Practice Guidelines recommend residual kidney function be based on the mean of urea and creatinine clearance. In the data analysis section, the mean of urea and creatinine clearance (mentioned for the first time) is what will be used to calculate the rate of decline of RKF (part of the primary objectives). This appears in Table 2. I assume urea clearance is used for eligibility because calculation of dialysis dose is urea-based. Does this mean it should be used for eligibility assessment? The manuscript does not mention the fact that patients having twice weekly dialysis will have a different inter-dialytic time period to thrice weekly dialysis patients. This is mentioned in the protocol document but needs to be explained in the manuscript. This is an important practical issue that may introduce bias in the measurement of residual kidney function. A figure would be really helpful here to help visualise where in the days of the dialysis week the collection will occur. My reading of the protocol (p19 of 28) is that thrice weekly patients will undergo a 44 hour urine collection between session 1 and session 2 on weekdays, and incremental patients will undergo a 68 hour urine collection over the weekend. Although the residual kidney function is calculated in mL/min, will the longer collection introduce bias (more likely to be incomplete if over a longer time?) in this outcome, and how will this risk be addressed? The rate of decline of kidney function is a main outcome. How will this be compared using regression analysis for individual subjects? Will you compare the mean of the slopes in one group to the mean of the slopes in the other group with a t-test? Will a linear mixed model be used? Figure 1 has not come out very cleanly in the PDF document (i.e. arrow in the middle of nowhere) and could be improved. The top two boxes are essentially the same thing. It would be great to have this like a CONSORT diagram and to show on this figure the how the feasibility outcomes will be derived. For example – the numerator and denominator boxes for % screened who fulfil study criteria, the % retained, the % adhering to protocol. Minor comments:

	Please use “regimen” instead of “regime”. A “regime” pertains to a ruling system of government. Why is blood-borne virus positivity an exclusion criterion? How does HIV, HBV or HCV affect residual kidney function? Is a pregnancy test really necessary in someone with Stage 5 CKD about to start dialysis, and did you really do this?

REVIEWER	Adeel Rafi Ahmed Beaumont Hospital, Dublin, Republic of Ireland.
REVIEW RETURNED	26-Jan-2020

GENERAL COMMENTS	The study eventually aims (once the pilot project completed) to answer a valid and important question in the haemodialysis population. The issues the authors will face, as with all studies related to HD are various confounding factors that will have an effect on residual renal function and funding for recruitment if the project progresses, as was the case with the frequent haemodialysis study. 2- There is much stronger but limited data supporting longer/frequent dialysis (eg Tassin- France) and survival is not solely dependent on residual renal function preservation. 3- Related to this protocol: It is important to mention in the abstract that hospitalisation, fluid overload needing resetting dry weight and episodes of hyperkalaemia are being assessed in the study protocol to improve its relevance as the majority of readers will just focus on the abstract. 4- In the methods section:. "RKF will be measured monthly by urea clearance in both arms and converted to Std Kt/VRKF" . Residual urine volume should also be included as part of the residual kidney function marker to allow relatively easier interpretation and application to daily practice.Perhaps at initiation and then during the week of reassessment(3monthly, 6monthly etc) .Refer to the CHOICE study. 5- Overall, despite some reservation, the study protocol is setting up the base (by assessing effective size to power a multicentre RCT) to answer a pertinent clinical question.

REVIEWER	Arif Khwaja Sheffield Kidney Institute, Sheffield England
REVIEW RETURNED	03-Feb-2020

GENERAL COMMENTS	This is a very important exploratory study that aims to address a critical issue in personalising haemodialysis therapy. The methods paper is very clear and well written

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Reviewer Name

Matthew Roberts

Institution and Country

Eastern Health Clinical School, Monash University, Australia

Please state any competing interests or state ‘None declared’:
None declared.

Please leave your comments for the authors below

The authors present a trial protocol for a feasibility study in preparation for an RCT comparing twice weekly “incremental” haemodialysis to standard thrice weekly haemodialysis in patients new to dialysis. This is an important topic and important to try to assess with a RCT.

Major comments:
The authors have submitted a manuscript with references, two tables, a figure, a list of equations, and their Study Protocol (Version 1.0, 28/6/2017). It is unclear what is supplementary materials and what is not. Under “Measurement of dialysis adequacy”, there is reference to “Details of the method of measuring dialysis adequacy are provided in supplementary materials” but it is not clear if this is the Calculations document or the protocol. I wonder if the protocol could be accessed via a link to the author’s institution. It is not specifically cited so I am not sure it is needed as an online supplement. Please specifically reference what is intended as an online supplement.

->Thank you for these comments. We agree that the number of documents submitted could be confusing. To make this clearer we have incorporated Table 1 and Table 2 in the main body of the manuscript. We have also added a section “Legends to Figures”. The document titled “Measurement of dialysis adequacy”) has been labelled as “Supplementary Material”. As mentioned by the reviewer, the study protocol is not part of the part of the manuscript – and we think it would be best to withdraw this to avoid confusion. Hence the submission now consists of the amended manuscript (IncrementalHDprotocolpaper 1.35 revised_k_FINAL_highlight), Figures 1 and 2, and Supplementary Material.

The primary objective relates to feasibility. Some discussion about how the feasibility outcomes would affect progression to and planning of the future study is needed. What level of “recruitability” would make the larger study feasible, and what level would cause the authors to abandon the idea of a larger study? Is there a threshold proportion of patients adhering to the protocol that would affect the feasibility of a larger study? I would also question the reliance on the Cocks and Torgerson paper in justifying the sample size of this study. Cocks and Torgerson emphasize the difference between a “pilot” study and a “feasibility” study and their recommendations are pertinent to a “pilot” study. The authors have made feasibility their primary objective and in this regard a sample size that gives an acceptable 95% confidence interval around the proportion of patients considered “recruitable” may be more relevant.

->We thank the reviewer for raising these issues. In response we have clarified the justification of the sample size of the study, based as the reviewer suggests on the width of the 95% confidence intervals around feasibility variables. We have amended the sample size section of the methods to include the following section:

“If the definitive study were to be carried out using the same 4 centres, the available incident HD population would be around 600 annually or 1200 over a proposed 2 year recruitment period. We anticipate that 40% of these patients will meet the eligibility criteria ie 480 patients. To achieve 180 analysable patients at 6 months following randomisation we will need to recruit 50% of eligible patients assuming a retention rate of 75% over 6 months.

->This feasibility study will test these assumptions on effect size, the proportion of incident patients who can be pre-screened who are eligible to be approached for study consent, the proportion of patients approached for screening who consent, pass formal screening and undergo randomisation (recruitability), and the retention rate during the 6 months after randomisation (retainability). Sample sizes between 24 and 50 have been recommended for feasibility studies [29, 30]. Initially we chose a sample size of 50 but, because of a higher than anticipated recovery of renal function in the first few weeks of recruitment, increased this to 54. A sample of this size will enable us to estimate eligibility, recruitability, screen-failure rate and retainabililty rate to within a 95% confidence interval of +/- 11-14%. “

It is difficult to address directly the reviewer’s question “What level of “recruitability” would make the larger study feasible, and what level would cause the authors to abandon the idea of a larger study?” since the design of the study could be amended to accommodate a range deviations from the assumptions. Instead we have added a more general comment to the discussion section.
“The proposed feasibility study will test assumptions around the effect size, the eligibility, recruitability, and retainability. Deviations from the assumed values will alter the design of the definitive study eg number of centres required, eligibility criteria, primary outcome measure, sample size, and may indicate that a definitive study is non-viable. “

Because eligibility is based on a very specific measure (inter-dialytic urea clearance), and because it impacts the feasibility outcomes, the screening process needs to be very clearly explained. There is a bit more detail in the protocol document than the manuscript. However, there are some aspects that are still not clear. Will all patients starting dialysis be approached and asked to perform an inter-dialytic urine collection soon after they start? This is important for the denominator for the primary outcome: will it be all patients in the dialysis unit, or just some? If just those who are “potentially eligible” (Table 1), what defines “potentially eligible”?

To clarify the approach to recruitment, all adult patients who have commenced haemodialysis in the previous 3 months will be considered for the study. Those who potentially meet the eligibility criteria after review of medical records including the requirement for a standard of care inter-dialytic urea clearance ≥3ml/min/1.73m2 BSA (potentially eligible patients), will eligible for study screening. Those consenting for the study will undergo formal screening to include confirmation of their meeting the eligibility criteria including that inter-dialytic urea clearance ≥3ml/min/1.73m2 BSA on retesting. For the purpose of this feasibility study recruitability will defined as the proportion of potentially eligible patients who are approached consent to formal screening and randomisation and who consent to undergo this minus the small proportion who fail formal screening on the basis of an inadequate interdialytic urea clearance.

We have amended the section on Participants in the Methods section to reflect this.

The intention to treat principle is being maintained and this is appropriate. What are the specific triggers to switch a patient to thrice weekly? Will data be collected on the reasons patients in the Incremental arm switched to thrice weekly dialysis? This is an important feasibility outcome, and understanding the reasons for non-adherence to the protocol is important.

->Thank you for pointing the lack of clarity in relation to this. We have amended the section in method “Interventional Group: Incremental HD arm” to include the following.

“Clinicians will also be permitted to increase the dialysis frequency to thrice-weekly or greater if required. The main trigger for this will be failure to meet minimum adequacy targets but clinicians will have the freedom to make this transition on other clinical grounds including hyperkalaemia and fluid overload. The reasons for switching from twice to thrice weekly will be recorded. Hyperkalaemia and fluid overload are also captured as Serious Adverse Events. “

Measuring residual kidney function in haemodialysis is not simple and the authors have published in this area. A specific section with discussion of the choice of measures of RKF for specific aspects of the study is needed. For example, eligibility for inclusion is based on the inter-dialytic urea clearance as a measure of residual kidney function. However, the European Best Practice Guidelines recommend residual kidney function be based on the mean of urea and creatinine clearance. In the data analysis section, the mean of urea and creatinine clearance (mentioned for the first time) is what will be used to calculate the rate of decline of RKF (part of the primary objectives). This appears in Table 2. I assume urea clearance is used for eligibility because calculation of dialysis dose is urea-based. Does this mean it should be used for eligibility assessment?

->There are two main methods of including residual kidney function in haemodialysis prescription. The first converts residual urea clearance to an equivalent dialysis sessional clearance. The second converts sessional Kt/V to a weekly equivalent clearance. Both these allow the addition of dialysis and renal clearances. There are two variants of the second method: standard Kt/V and the Casino-Lopez Equivalent renal urea clearance (EKR). Both these are urea clearance based. The ERBP guidelines recommend use of GFR (mean of urea and creatinine clearance) in the EKR equation rather than urea clearance which was intrinsic to originally derived equation. We have used standard Kt/V which takes a more conservative view of residual kidney function since urea clearance is around 30% lower than GFR. We have included a section in the methods to explain this.

It is important to differentiate inclusion of RKF in dialysis prescription and the optimal assessment of RKF as an outcome measure. We have explained the reasons for our use of urea clearance in this setting. We have however used rate of decline of GFR as the primary outcome measure since this is generally a more standard method of measurement of kidney function. We will also assess rate of decline of urea clearance

The manuscript does not mention the fact that patients having twice weekly dialysis will have a different inter-dialytic time period to thrice weekly dialysis patients. This is mentioned in the protocol document but needs to be explained in the manuscript. This is an important practical issue that may introduce bias in the measurement of residual kidney function. A figure would be really helpful here to help visualise where in the days of the dialysis week the collection will occur. My reading of the protocol (p19 of 28) is that thrice weekly patients will undergo a 44 hour urine collection between session 1 and session 2 on weekdays, and incremental patients will undergo a 68 hour urine collection over the weekend. Although the residual kidney function is calculated in mL/min, will the longer collection introduce bias (more likely to be incomplete if over a longer time?) in this outcome, and how will this risk be addressed?

->We agree that the precise method of collecting urine and measurement of dialysis adequacy requires clarification and we have added a section titled “Measurement of dialysis adequacy” to explain this and this clarifies the longer duration of collection for those on twice weekly dialysis compared to twice weekly dialysis. We have also added figure 2 which will clarify the urine collection and blood sampling time points.

With regard to bias, we agree that there might be slight bias with patients collecting urine over longer time periods being more likely to submit an incomplete collection but this will be mitigated by the incentive to patients on twice weekly dialysis to complete a collection because an incomplete

collection may result in an increase in their dialysis intensity due to the protocol. We have explained this in this section.

The rate of decline of kidney function is a main outcome. How will this be compared using regression analysis for individual subjects? Will you compare the mean of the slopes in one group to the mean of the slopes in the other group with a t-test? Will a linear mixed model be used?

->This is correct. We will compare mean slope of groups with a t test and also use a mixed effect model which we have previously employed similarly in a retrospective analysis of patients initiated twice versus thrice weekly (Kaja Kamal, Vilar et al, NDT 2019. We have explained this as follows with reference to the model planned in the following amended paragraph under Data Analysis:

“Change in RKF will be determined using several methods. We will calculate, using linear regression analysis for individual subjects, rate of decline in GFR (mean of urea and creatinine clearance) for individual subjects and compare means of these rates between incremental and conventional HD groups with a t test if normally distributed. This effect size will be important in powering future definitive trials. Using a previously described method we will employ a mixed effects model to compare rate of decline in GFR between randomisation groups[28]. As an indicator of RKF, we will compare urine volume data between groups using similar statistical techniques to the above. We will also compare proportions of patients in the two groups who have a residual interdialytic urea clearance ≥ 2 and ≥ 3 ml/min/1.73m2 at 6 months.”

Figure 1 has not come out very cleanly in the PDF document (i.e. arrow in the middle of nowhere) and could be improved. The top two boxes are essentially the same thing. It would be great to have this like a CONSORT diagram and to show on this figure the how the feasibility outcomes will be derived. For example – the numerator and denominator boxes for % screened who fulfil study criteria, the % retained, the % adhering to protocol.

->We agree that Figure 1 is not presented very cleanly and have recreated this figure a recommended as a consort diagram with emphasis on the data that will be used to calculate eligibility, recruitability and retainability and we have labelled these in the new diagram for clarity.

Minor comments:
Please use “regimen” instead of “regime”. A “regime” pertains to a ruling system of government.

‘Regime’ meaning - a system or ordered way of doing things. Seems correct.
Regimen menaing
1. a prescribed course of medical treatment, diet, or exercise for the promotion or restoration of health.
"a regimen of one or two injections per day"
2.
ARCHAIC
a system of government.

->We agree this should be corrected and have done so throughout the manuscript.

Why is blood-borne virus positivity an exclusion criterion? How does HIV, HBV or HCV affect residual kidney function?

->These will be excluded for simplicity due to handling and transfer of blood samples for analysis of

middle molecule levels. In a definitive study it is not anticipated that we would exclude such patients.

Is a pregnancy test really necessary in someone with Stage 5 CKD about to start dialysis, and did you really do this?

->The reason for a pregnancy test in females of child bearing age is that in the circumstance of pregnancy it would be necessary to withdraw patients from the study since their dialysis regime could not follow the study protocol given recommendations for frequent dialysis in such patients. It is expected that a limited number of patients recruited will be female and of childbearing age so we do not feel this is over-burdensome for the study protocol. This is one of the measures taken to reduce chance of withdrawals prior to the primary endpoint analysis (6 month). We have commented on the reason for the pregnancy test in methods:

“Pregnancy test will be performed in females of child-bearing age to reduce chance of unexpected pregnancy occurring during the study which would require study withdrawal.”

Reviewer: 2

Reviewer Name

Adeel Rafi Ahmed

Institution and Country

Beaumont Hospital, Dublin, Republic of Ireland.

Please state any competing interests or state ‘None declared’:
None Declared

Please leave your comments for the authors below
The study eventually aims (once the pilot project completed) to answer a valid and important question in the haemodialysis population. The issues the authors will face, as with all studies related to HD are various confounding factors that will have an effect on residual renal function and funding for recruitment if the project progresses, as was the case with the frequent haemodialysis study.

2- There is much stronger but limited data supporting longer/frequent dialysis (eg Tassin- France) and survival is not solely dependent on residual renal function preservation.

->We agree that there are data supporting longer duration dialysis and to an extent more frequent dialysis from the various published Tassin datasets. However, in a recent publication from the Tassin group patients in the first year after initiating dialysis seem to experience a significant mortality of 21% (Chazot C, Deleaval P, Bernollin AL, Vo-Van C, Lorriaux C, Hurot JM, Mayor B,Jean G. Target weight gain during the first year of hemodialysis therapy is associated with patient survival. Nephron Clin Pract. 2014;126(3):128-34). Residual renal function was not measured though it was noted that 70% of patients were receiving loop diuretics at initiation, which reduced to only 15% at 12 months. This is likely to indicate loss of renal function in the majority of these patients during the first year of dialysis. It may be that this loss of residual kidney function was a factor in the early mortality in this study since residual kidney function is known to be a key predictor of survival. We completely accept that when residual function has been lost twice weekly treatments are inappropriate and that extended dialysis (increased treatment time and/or frequency) may be beneficial in some patients. Hence we do not

think that the Tassin data is in conflict with the rationale underlying our current study. For brevity though we have not commented on this in the manuscript since the focus of the manuscript is the study of lower intensity dialysis in the early period after initiating dialysis.

3- Related to this protocol: It is important to mention in the abstract that hospitalisation, fluid overload needing resetting dry weight and episodes of hyperkalaemia are being assessed in the study protocol to improve its relevance as the majority of readers will just focus on the abstract.

->We agree the abstract would be strengthened by this and have added the following sentence in the abstract:
“Safety outcomes will include hospitalisation, fluid overload episodes, hyperkalaemia events and vascular access events.”

4- In the methods section:. "RKF will be measured
monthly by urea clearance in both arms and converted to Std Kt/VRKF"
Residual urine volume should also be included as part of the residual kidney function marker to allow relatively easier interpretation and application to daily practice. Perhaps at initiation and then during the week of reassessment(3monthly, 6monthly etc) .Refer to the CHOICE study.

->Urine volume data will be available as this is required for measurement of residual kidney function and we agree it would be beneficial to report this. We will therefore compare this between groups. We have added a comment on this in the Data Analysis section:
“As an indicator of RKF, we will compare urine volume data between groups using similar statistical techniques to the above.”

5- Overall, despite some reservation, the study protocol is setting up the base (by assessing effective size to power a multicentre RCT) to answer a pertinent clinical question.

->We thank you for this comment

Reviewer: 3

Reviewer Name

Arif Khwaja

Institution and Country

Sheffield Kidney Institute, Sheffield England

Please state any competing interests or state ‘None declared’:
nil

Please leave your comments for the authors below
This is a very important exploratory study that aims to address a critical issue in personalising haemodialysis therapy. The methods paper is very clear and well written

VERSION 2 – REVIEW

REVIEWER	Matthew Roberts Eastern Health Clinical School, Monash University, Australia
REVIEW RETURNED	12-Mar-2020

GENERAL COMMENTS	The authors have addressed the comments satisfactorily and this revision is clearly presented.

REVIEWER	Adeel rafi ahmed Beaumont Hospital kidney centre Dublin, Republic of Ireland
REVIEW RETURNED	24-Mar-2020

GENERAL COMMENTS	The authors have significantly improved their manuscript since the first review with appropriate amendments.