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Patient Preferences for Longer or More Frequent In-Center Hemodialysis Regimens: A Multicenter Discrete Choice Study

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ABSTRACT

Rationale & Objective: Longer and more frequent hemodialysis sessions are associated with both benefits and harms. However, their relative importance to patients and how they influence acceptability for patients have not been quantified.

Study Design: Discrete-choice experiment in which a scenario followed by 12 treatment choice sets were presented to patients in conjunction with varying information about the clinical impact of the treatments offered.

Setting and Participants: Patients with kidney failure treated with maintenance dialysis for ≥1 year in 5 UK kidney centers.

Predictors: Length and frequency of hemodialysis sessions, and their prior reported associations with survival, quality of life, need for fluid restriction, hospitalization, and vascular access complications.

Outcomes: Selection of longer (4.5hr) or more frequent hemodialysis (4 sessions per week) regimens versus remaining on 3 sessions per week with session lengths of 4 hours.

Analytical Approach: Multinomial mixed effects logistic regression estimating the relative influence of different levels of the predictors on the selection of longer and more frequent dialysis, controlling for patient demographic characteristics.

Results: Among 183 prevalent in-centre haemodialysis patients (mean 4.7 years on dialysis, mean age of 63.7 years), 38.3% (70/183) always chose to remain on regimens of 3 sessions per week with session duration of 4 hours. Depicted associations of increasing survival and quality of life, reduced need for fluid restriction, and avoiding additional access complications were all significantly associated with choosing longer or more frequent treatment regimes. Younger age, fatigue, previous experience of vascular access complications, absence of heart failure, and shorter travel time to dialysis centers were associated with preference for 4 sessions per week. Patients expressed willingness to trade up to 2 years

of life to avoid regimens of 4 sessions per week or access complications. After applying estimated treatment benefits and harms from existing literature, the fully adjusted model revealed that 27.1% would choose longer regimens delivered 3 times per week and 34.3% would choose 4hrs 4 times per week. Analogous estimates for younger fatigued patients living near their unit were 23.5% and 62.5%, respectively.

Limitations: Estimates were based on stated preferences rather than observed behaviors. Predicted acceptance of regimens was derived from data on treatment benefits and harms largely sourced from observational studies.

Conclusions: Predicted acceptance of longer and more frequent HD regimens substantially exceeds their use in current clinical practice. These findings underscore the need for robust data on clinical effectiveness of these more intensive regimens and more extensive consideration of patient choice in the selection of dialysis regimens.

Index Terms: Longer dialysis, frequent dialysis, discrete choice experiment, health economics

Plain-Language Summary

Longer or four times a week dialysis have been associated with better outcomes, yet their use is limited and they are perceived as undesirable to patients. 184 people on dialysis completed a discrete choice questionnaire, which presented the association of these longer and more frequent treatments with longer survival, less hospitalization, better quality of life, and fewer vascular access complications. Presented with available evidence on these associations, 27.1% of patients would choose longer dialysis and 34.3% would choose four times a week dialysis, far more than is currently observed in routine practice. Better data on clinical effectiveness to guide patient choice is needed.

INTRODUCTION

Observational and clinical trial data have shown survival and quality of life advantages for more intensive haemodialysis regimens than the four hours three times a week regimens recommended by clinical practice guidelines.[1] These regimens include longer session length delivered three times a week, and four sessions a week. Despite the stated advantages, acceptance of these treatments in routine clinical practice and clinical trials suggest that underlying patient preferences and treatment burden may be factors influencing a patient's choice.[2]

Through a range of potential mechanisms more intensive dialysis regimens have potential benefits but also potential harms such as fatigue, survival, cardiovascular disease and vascular access patency which have been identified as core haemodialysis trial outcomes in consensus exercises.[3-5] Previous stated preference work has reported on the proportion of patients who might select more intensive haemodialysis regimens, but not in the presence of outcome information, which should ideally be presented as part of shared decision making, tailored to the characteristics and goals of the individual.[6,7]

By eliciting preferences to the possible benefits and harms of a treatment, the relative importance of individual trial endpoints for an intervention can be identified.[8,9] In addition to further clarity around clinically meaningful differences, the potential size of benefit required to meaningfully change acceptance of a treatment can be estimated.[10] A comprehensive understanding of patient preferences could assist in and predicting capacity requirements, and identify groups who need additional education or support when recruiting to trials or undertaking shared decisions around treatment.

Discrete choice experiments (DCEs) have been shown to accurately estimate patient preferences towards treatments, by asking patients to consider treatment options while the potential benefits and harms of the different treatment options are varied.[11] We present a DCE conducted across five centres in the United Kingdom, designed to elicit patient preferences towards longer session length as part of a three times a week dialysis schedule, four times a week haemodialysis, or remaining on the standard three times a week regimen, all delivered in-centre.[12,13] Accounting for individual patient characteristics which influence these preferences, we estimate the acceptance of these more intensive regimens in the presence of benefits and harms identified in the literature for a prevalent population and specific groups.

METHODS

This labelled DCE is reported in accordance with ISPOR Good Research Practices publications in this area.[14,15] The DCE was designed to elicit preferences towards the dialysis regimen choices of longer session length delivered three times a week, versus more frequent four times a week haemodialysis, versus remaining on three times a week haemodialysis, with the preferences dependent on four outcome-based treatment attributes (survival, hospitalisation, quality of life and vascular access complications). By asking the respondent to complete multiple choice sets, the relative importance of the attributes, their levels, the choices (dialysis regimens) and any trade-offs can be estimated. Detailed information for the discrete-choice experiment methodology applied in health care can be found elsewhere.[15] Ethical approval for the study was obtained in June 2019 (Health Research Authority IRAS reference 253384) and the participants were recruited between February 2019 and November 2019.

Participants and study perspective

The inclusion criteria for the study were prevalent in-centre haemodialysis patients who had been receiving treatment for at least one year. This ensured sufficient experience of in-centre haemodialysis to consider and relate to the scenario, and aligned with the informing studies in which the majority of patients who received these treatments had been dialysing in excess of one year. [12,13] The exclusion criteria were: an existing diagnosis of malignancy (as patients with a limited life-expectancy may not be offered these regimens, and may have their treatment shortened towards the end of life)[12] or the presence of a formal diagnosis of cognitive impairment in the medical notes, or the presence of cognitive impairment as assessed by the dialysis nursing staff or the researcher conducting the questionnaire.

The questionnaire booklet begins by asking participants to consider a scenario where they were an in-centre haemodialysis patient who after two years of treatment had developed high ultrafiltration rates and significant fatigue. In the scenario the staff at the dialysis unit hypothetically offer them longer sessions (4.5hrs) three times a week,[12] more frequent four times a week 4hr duration hemodialysis [13] or remain on the current 4hr three times a week treatment (an opt-out choice). The questionnaire then asks the participant to consider which haemodialysis regimen they would select in this scenario twelve times. With each of the twelve questions (choice sets) the associated benefits and harms (survival, hospitalisation, quality of life, fluid restriction and vascular access complications) vary in a prespecified manner to build a statistical model of the individual's preferences (Item S1)

Treatment Choices, Attributes and levels

We presented two, more-intensive regimen choices that were based on published data evaluating these treatments in the context of the increased hospitalisation and mortality associated with the long interdialytic interval intrinsic to three times a week haemodialysis schedules [16], and that were designed to be plausible and available in existing clinical practice. Attributes had all been prioritised in existing mixed methods research. In order to predict acceptance, existing evidence between attributes and the treatment regimens being offered informed attribute and level selection.[7,12,13,17,18] Each of the twelve DCE questions included a labelled description of longer, four times a week and continuing three times a week haemodialysis and the attributes associated with them for that particular DCE choice set. Table 1 shows an example of the attributes presented to the patient for the third DCE choice set, which illustrates the range of levels each attribute could take: survival (9 years, 10 years, 12 years or 14 years), quality of life (you feel the same, you feel better), fluid restriction (you can drink the same, you can drink more), hospitalisation (once a year, once every two years) and access complications (no change, more complications). All twelve DCE choice sets are presented in Item S1. In order to present absolute years of survival for the survival attribute, the survival associated with continuing on standard haemodialysis of 9 years was estimated using a parametric exponential survival model fitted on the patients with ultrafiltration rates of >10ml/kg/hr who continued to receive 3xW HD in an informing analysis.[13] This model included age, gender, comorbidities, phosphate, dialysis access and ultrafiltration rate as adjustment variables.

Instrument design and sample size

The goal of the DCE is to build a model from which the relative influence of each of the attributes, and anything pertaining to the of the treatments themselves, can be estimated. Undertaking this could involve presenting every permutation of the attributes and asking the respondent to select a treatment, however this is rarely practical. Fewer DCE questions may result in improved response efficiency (the measurement error associated with respondent inattention introduced by too many questions).[14] It is considered common practice to have between 8 and 16 DCE questions,[15] with reviews highlighting 70% of studies having 3 to 6 attributes with up to 4 attribute levels.[19] A full-choice array containing every possible permutation of the attribute levels was generated and from this a D-efficient design was identified by sampling subsets of this array. This was performed using the DCREATE command in STATA[20] resulting in a randomly ordered design with 12 DCE questions and a D-efficiency of 1.607. A sample size of 128 respondents for the 12 question DCE was estimated with the approximate formula[21] using an

alpha of 0.95, accuracy of 10% and an expected choice proportion of 20%[6]. This was doubled to 256 to allow for subgroup and interaction effects estimation.

Data collection

Research nurses and clinical trial assistants screened individuals based on the inclusion criteria then approached haemodialysis patients on the dialysis unit for consent to perform the paper questionnaire. Often the patient would complete the questionnaire while receiving dialysis and with the researcher nearby facilitating assistance when required, in line with ISPOR Good Research Practices.[14,15] Following an explanation of the decision scenario the respondent undertook a comprehension question that presented the treatments with hypothetical benefits and harms in the same format as the rest of the DCE, and asked the respondent to state which treatment has the best levels for each of the five attributes. The twelve DCE questions were then completed along with some demographic information including: the SONG-HD fatigue measure,[22] travel time to the dialysis unit, personal experience of hemodialysis access problems, if the more intensive regimens had previously been offered and a short health literacy question.[23] The researchers completed a demographic information from patients notes including comorbidities, hemodialysis schedule, dialysis access, haemoglobin and ultrafiltration volume.

Statistical Analysis

The differences in patient characteristics according to whether the patient had been previously offered more intensive dialysis were statistically assessed using independent T-tests for continuous variables and Chi-Squared tests for categorical variables.

A multinomial logistic model with random coefficients (mixed effects), with the selection of one of the treatments as the dependent (outcome) variable was used to estimate the relative influence of different levels of the attributes and description of the treatment regimens, with odds ratios (OR) reported.[24] A mixed model allows for correlated preferences (e.g. a patient having a greater preference for both longer and more frequent dialysis), and is fit on data with an observation per treatment offered (e.g. 3 observations per choice-set). Allowing the constants associated with the descriptions of the treatments to vary between respondents provided a superior fit compared to fixed values for all respondents, and the standard deviation of all random parameters were significant. The final models were estimated with 1000 Halton draws.

Patient characteristics which may influence preferences for attributes and choices were controlled for by specifying interactions between these variables in the model. All choice attributes were treated as

categorical with the demographic variables of age (<50, 50-80 & >80 years), travel time (<30 or >=30 minutes), time on renal replacement therapy (<2 years, 2-5 years, >5 years) categorised based on their distributions. The SONG HD Fatigue measure was calculated based on the sum of questions on feeling tired, lacking energy and limits on usual activities individually scored 0-3 (total score 0-9).[22] All analyses including those with interactions use the opt-out of continuing on three times a week, 4 hours as the reference. The best performing model in the presence of interactions was identified using Akaike information criterion which penalises for additional co-variates. Using the model with the best performance, trade-offs between survival and other attributes and predicted acceptance of treatments were estimated. Survival in years was treated as a continuous variable in the model, and using the STATA WTP[25] command an estimate of the number of years patients would sacrifice to improve other attributes or avoid the treatment burden associated with the more intensive regimens was calculated. Because individuals who always choose the opt-out (to stay on 3xW 4hrs) have an infinitely large choice specific constant for the opt-out alternative potentially resulting in bias, the results of the analysis are presented only in those who always chose the opt-out excluded. An analysis on all patients is reported in Table S1. Interactions between patient characteristics and choice specific constants were specified as fixed effects in all models. The probability of acceptance of the regimens was estimated using the model with the best Akaike information criterion: a systematic review which informed UK hemodialysis guidelines was updated and effect sizes for the treatment attributes associated with the different regimens extracted.[1] Applying these effect sizes to estimates of survival, quality of life, fluid restriction and access complications to informing literature and the parametric survival estimate identified values to set the attributes for each regimen. Acceptance of treatments are reported for the cohort who completed the questionnaire, and for patients with specific characteristics determined by those included in informing clinical trials[4], or clinically relevant subgroups. The attributes from the literature (largely observational), alongside more conservative estimates, informed by a reduction by one level of any attributes associated with improved outcomes, are detailed in Table 5.

RESULTS

Across five centres, 292 patients were approached, of whom 204 consented (69.9%), 196 patients returning the questionnaire and 183 completing all 12 DCE questions. The demographics were comparable to prevalent in-centre HD patients in the UK and observational studies informing the questionnaire. After reading the description of the fictional patient in the opening scenario, 40.2% (47/117) of respondents felt it sounded like them and a further 38.5% (45/117) somewhat like them.

Table 2 reports the overall demography of those completing the questionnaire, and then stratified by whether more intensive dialysis had (65/183, 35.5%) or had not been discussed (118/183, 64.5%). Overall, 24.7% and 14.8% of patients had previously been approached about longer hours and 4xW HD respectively. Patients who had been offered more intensive dialysis were statistically more likely to be younger, male, live nearer the renal centre and have had previous dialysis access complications, with a tendency to be more comorbid. Feeling that the scenario sounded like them was associated with a higher fatigue score (4.9 vs 3.1, P=0.002). 53.6% (97/181) had previously experienced vascular access problems.

23.3% (42/180) of patients incorrectly answered all five of the comprehension tests questions, which did not significantly vary with health literacy (P=0.8).

Treatment and outcome preferences

From 183 completed 12-question-DCEs resulting in 2,196 choices, longer dialysis sessions were selected in 29.3%, more frequent four times a week in 20.4% and continuing on three times a week haemodialysis in 50.3%. Increasing quality of life and survival and reduced fluid restriction with a regimen all had a clinically plausible positive influence on the selection of a more intensive regimen, while increased vascular access complications associated with a regimen reduced the likelihood of a regimen's selection (Table 3). Hospitalisation had no influence. The adjusted odds ratios (e.g. benefits and harms set to that of 3xW HD) of selection of longer hours were 0.06 (95% CI 0.02 - 0.14) and for four times a week 0.005 (95% CI 0.001 - 0.01). These adjusted values in isolation are only illustrative, as patients and clinicians consider offering or accepting these regimens in the presence of benefits and harms which are generally more preferable for the revised treatment being offered, rather than the same as the current treatment. These estimates did not significantly differ when limited to individuals who got no comprehension test questions wrong (Table S2).

Interactions between demography, experience, symptoms and choice

Patients under the age of 50 had a stronger preference for the more intensive regimens, and decreasing age was associated with significant increases in how patients valued survival advantages and fluid restrictions (Figure 1 & 2). Higher ultrafiltration rates did not modify preferences towards reduced fluid restriction (Figure 2).

Patients who had experienced a vascular access complication found both regimens more acceptable than those who had not (Figure 1). Having experienced a dialysis access complication or receiving

dialysis via a fistula rather than a catheter/line was associated with greater preference more intensive regimens. The absence of heart failure significantly increased preference for four times a week HD but diabetes and previous myocardial infarction had no influence on treatment preference, and there was no interaction between comorbidities and the attributes of survival or quality of life.

Patients who scored less than 4 on the SONG-HD Fatigue measure had very low preference towards four times a week haemodialysis, while increasing fatigue was associated with increasing preference towards quality of life improvements associated with a regimen, particularly in those scoring >7. There was no relationship between higher health literacy, Tuesday/Thursday/Saturday dialysis schedule compared to the Monday/Wednesday/Friday schedule, or the number of years treated by haemodialysis and preferences towards either more intensive regimen.

Trading survival for improvements in other attributes

The fully interacted model (Table S3) resulted in linear increases in the coefficients informing the odds ratios for increasing survival in years enabling the estimation of trade-offs between survival and the other attributes. The 38.3% (70/183) who always chose to stay on 3xW 4hrs introduced a bias in the estimates due to having an infinitely small treatment-specific odds ratio, and following their exclusion the following estimates were obtained (Table 4, model reported in Table S3): patients would sacrifice approximately 2 years of life to avoid attending four times a week or an access complication, and sacrifice more liberal fluid intake or quality of life for an additional two-thirds of a year of survival.

Projected acceptance of longer or four times a week hemodialysis

Patient characteristics, hypothesised treatment benefits and model specification influenced the proportion of patients who would choose longer dialysis three times a week, four times a week or opt to remain on their current treatment (Table 5). Based on the more optimistic treatment benefits, 29.1% would dialyse longer, 35.8% would dialyse four times a week and 35.1% remain on their current treatment, with these proportions changing to 27.1%, 34.3% and 38.6% respectively when incorporating patient characteristics in the model. More conservative benefits generally increased the percentage opting to remain on current treatment by approximately 10 percentage points. Simulating a cohort comparable to those recruited into the frequent haemodialysis network (FHN) trial, the proportion selecting four times a week dialysis was 44.6%. Elderly patients with moderate fatigue who live far from the unit would select longer and four times a week dialysis 11.0% and 22.0% of the time, while the

proportions for younger severely fatigued patients living nearer the unit were 23.5% and 62.5% respectively.

DISCUSSION

This multi-centre study used a DCE to estimate preferences towards the benefits and harms associated with longer and more frequent in-centre haemodialysis regimens. Improvements in quality of life, survival and fluid restriction were associated with selecting a more intensive regimen. Younger, more fatigued patients who were able to do their own blood pressure, pulse and temperature undergoing hemodialysis (and perhaps other dialysis-related tasks) were more likely to choose four times a week dialysis. However, longer and four times a week haemodialysis could be considered undesirable as 38.5% of patients completing the DCE did not choose them in any situation, and those who did would still sacrifice two years of additional life to avoid them. Despite this, if presented with benefits of these regimens from the literature, between half and two-thirds of patients would be willing to be treated with dialysis regimens that are 4 times per week or dialyse for longer than 4 hours three times a week.

Our findings corroborate existing research: 33.5% of US haemodialysis patients who were struggling with their fluid restriction said they would dialyse for an additional 30 minutes and 19.6% would do an additional weekly session, although the benefits associated with these regimens were not presented. Patients from the US study were generally closer to the patient phenotype described in our scenario and in whom these interventions are routinely used.[6] A study using conjoint analysis identified that 44% of sampled patients would not select daily hemodialysis irrespective of the potential health benefits, however 38.9% of patients would chose the treatment if the quality of life and survival benefits were comparable to those applied to four times a week in our study.[26] Both studies found greater acceptance in younger, less comorbid patients. The statistical and clinical significance of the attributes of survival, quality of life and avoiding vascular access complications, with the lower importance of hospitalisation, align with recent prioritisation exercises for clinical trial endpoints in haemodialysis.[18] Direct comparison of the predicted acceptance of treatments in our cohort to other studies is challenging: simulating the FHN daily trial cohort who were offered 5-6 sessions a week 37-44% of patients would select 4 times a week HD, compared to the 12% of those approached agreeing to participate in the FHN trial. A third of patients in our study had been approached about more intensive regimens and real world data suggests around 3.5% subsequently receiving four times a week dialysis and 18% receiving 4.5hrs 3xW in clinical practice.[12,13] Discrepancies between real-world use and predicted uptake could relate to observed and unobserved differences in the cohorts approached, patient interpretation of the choice scenario or the

statistical models. To tackle the long interdialytic interval, the fourth session should ideally be scheduled during this period, although some patients may wish to preserve a 2-day gap. However patients can recognise and quantify the potential survival and quality of life benefits associated with an additional session during the traditional long interdialytic interval.[27] More generally models from DCE studies have been shown to have reasonable positive predictive value for choices made in real world clinical practice[28], but the disproportionate presence of selecting the status quo exists both in this study and many others exploring decision-making.[29]

The strengths of our study include a strong underlying methodological design to elicit preferences, and the presentation of HD regimens which are currently available and for which some estimates of efficacy are known. The presented scenario resonated with 78.6% of respondents who had personal experience of haemodialysis. The modest sample size exceeding formal power calculations, and where possible estimates on subgroups were drawn from interactions, retaining the overall sample size. Weaknesses included the assessment of stated preferences and not genuine choices that the patient subsequently made, potentially over-optimistic baseline survival estimates for the scenario and that acceptance probabilities were informed by largely observational data. A quarter of patients answered all four comprehension test questions incorrectly, which may relate to questionnaire complexity or the cognitive function of the patient group.

Findings from our study raise the policy and future research issue that if patient acceptance of these treatments is as high has estimated in our study, it is even more important to obtain high quality evidence to determine their clinical effectiveness prior to more routine presentation of these regimens to patients. The difference between predicted and observed uptake of these treatments suggests there are individuals who may be willing to do more HD treatment to access benefits reported in the literature, while only a third of this cohort had actually been approached regarding the treatment options. The findings do allude to certain groups of patients who are more likely to accept these treatments, and could inform models of haemodialysis capacity. Significant increases in uptake could be offset by an incremental approach to haemodialysis dosing that would include lower frequency when starting dialysis.[30] Integral to these decisions around treatment would be the presentation of information obtained from generalisable trials of these interventions in HD patients which have been challenging to recruit or retain patients, or statistically demonstrate health benefits.[2,31,32] This person-centred shared decision would need to elicit the treatment goals of the patient as prioritised in other settings, consider if in-centre HD could deliver these and offer alternatives.[7,33] Based on the findings

from our study, there is an increasing imperative to gain high quality data on the clinical and cost-effectiveness of these treatment options to advocate for their use with decision-makers and inform patients in whom the treatments are indicated.

Supplementary Material

Item S1: Summary of the Discrete Choice Experiment Choice Sets

Table S1: Non-interacted model output with survival as a continuous variable, overall and in those did not always choose the opt-out

Table S2: Non-interacted model output in those who answer all cognition questions correctly

Table S3: Fully interacted model result

ARTICLE INFORMATION

Authors' Contributions: research idea and study design: JF & ARH; data acquisition: JF, EV, TB, PL, AD & LD; data analysis/interpretation: JF, ARH & AD; statistical analysis: JF & ARH; Each author contributed important intellectual content during manuscript drafting or revision and agrees to be personally accountable for the individual's own contributions and to ensure that questions pertaining to the accuracy or integrity of any portion of the work, even one in which the author was not directly involved, are appropriately investigated and resolved, including with documentation in the literature if appropriate.

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References

1. Ashby D, Borman N, Burton J, et al. Renal Association Clinical Practice Guideline on Haemodialysis. *BMC Nephrol.* 2019/10/17 2019;20(1):379.
2. Sergeyeva O, Gorodetskaya I, Ramos R, et al. Challenges to enrollment and randomization of the Frequent Hemodialysis Network (FHN) Daily Trial. *J Nephrol.* May-Jun 2012;25(3):302-309.
3. Garg AX, Suri RS, Eggers P, et al. Patients receiving frequent hemodialysis have better health-related quality of life compared to patients receiving conventional hemodialysis. *Kidney Int.* Mar 2017;91(3):746-754.
4. Chertow GM, Levin NW, Beck GJ, et al. In-center hemodialysis six times per week versus three times per week. *N Engl J Med.* Dec 9 2010;363(24):2287-2300.
5. Chertow GM, Levin NW, Beck GJ, et al. Long-Term Effects of Frequent In-Center Hemodialysis. *J Am Soc Nephrol.* Jun 2016;27(6):1830-1836.
6. Flythe JE, Mangione TW, Brunelli SM, Curhan GC. Patient-stated preferences regarding volume-related risk mitigation strategies for hemodialysis. *Clin J Am Soc Nephrol.* Aug 7 2014;9(8):1418-1425.
7. Morton RL, Sellars M. From Patient-Centered to Person-Centered Care for Kidney Diseases. *Clinical Journal of the American Society of Nephrology.* 2019;14(4):623-625.
8. Watson V, Carnon A, Ryan M, Cox D. Involving the public in priority setting: a case study using discrete choice experiments. *Journal of Public Health.* 2011;34(2):253-260.
9. Stamuli E, Torgerson D, Northgraves M, Ronaldson S, Cherry L. Identifying the primary outcome for a randomised controlled trial in rheumatoid arthritis: the role of a discrete choice experiment. *Journal of Foot and Ankle Research.* 2017/12/15 2017;10(1):57.
10. Terris-Prestholt F, Quaife M, Vickerman P. Parameterising User Uptake in Economic Evaluations: The role of discrete choice experiments. *Health economics.* 2016;25 Suppl 1(Suppl Suppl 1):116-123.
11. Bryan S, Gold L, Sheldon R, Buxton M. Preference measurement using conjoint methods: an empirical investigation of reliability. *Health Econ.* Jul 2000;9(5):385-395.

12. Fotheringham J, Sajjad A, Stel VS, et al. The association between longer haemodialysis treatment times and hospitalization and mortality after the two-day break in individuals receiving three times a week haemodialysis. *Nephrol Dial Transplant.* Sep 1 2019;34(9):1577-1584.

13. Fotheringham J, Latimer N, Froissart M, et al. Survival on four compared with three times per week haemodialysis in high ultrafiltration patients: an observational study. *Clinical kidney journal.* 2020;14(2):665-672.

14. Reed Johnson F, Lancsar E, Marshall D, et al. Constructing Experimental Designs for Discrete-Choice Experiments: Report of the ISPOR Conjoint Analysis Experimental Design Good Research Practices Task Force. *Value in Health.* 2013/01/01/ 2013;16(1):3-13.

15. Bridges JFP, Hauber AB, Marshall D, et al. Conjoint Analysis Applications in Health—a Checklist: A Report of the ISPOR Good Research Practices for Conjoint Analysis Task Force. *Value in Health.* 2011/06/01/ 2011;14(4):403-413.

16. Fotheringham J, Fogarty DG, El Nahas M, Campbell MJ, Farrington K. The mortality and hospitalization rates associated with the long interdialytic gap in thrice-weekly hemodialysis patients. *Kidney Int.* Sep 2015;88(3):569-575.

17. Morton RL, Tong A, Webster AC, Snelling P, Howard K. Characteristics of dialysis important to patients and family caregivers: a mixed methods approach. *Nephrology Dialysis Transplantation.* 2011;26(12):4038-4046.

18. Evangelidis N, Tong A, Manns B, et al. Developing a Set of Core Outcomes for Trials in Hemodialysis: An International Delphi Survey. *American Journal of Kidney Diseases.* 2017/10/01/ 2017;70(4):464-475.

19. Marshall D, Bridges JF, Hauber B, et al. Conjoint Analysis Applications in Health - How are Studies being Designed and Reported?: An Update on Current Practice in the Published Literature between 2005 and 2008. *The patient.* Dec 1 2010;3(4):249-256.

20. Hole A. DCREATE: Stata module to create efficient designs for discrete choice experiments. 2017.

21. Louviere JJ, Hensher DA, Swait JD. *Stated Choice Methods: Analysis and Applications.* Cambridge: Cambridge University Press; 2000.

22. Ju A, Teixeira-Pinto A, Tong A, et al. Validation of a Core Patient-Reported Outcome Measure for Fatigue in Patients Receiving Hemodialysis: The SONG-HD Fatigue Instrument. *Clin J Am Soc Nephrol.* Nov 6 2020;15(11):1614-1621.

23. Chew LD, Griffin JM, Partin MR, et al. Validation of screening questions for limited health literacy in a large VA outpatient population. *J Gen Intern Med.* May 2008;23(5):561-566.

24. Hole AR. Fitting mixed logit models by using maximum simulated likelihood. *Stata Journal.* 2007;7(3):388-401.

25. Hole AR. A comparison of approaches to estimating confidence intervals for willingness to pay measures. *Health Economics.* 2007;16(8):827-840.

26. Halpern SD, Berns JS, Israni AK. Willingness of patients to switch from conventional to daily hemodialysis: looking before we leap. *The American Journal of Medicine.* 2004/05/01/ 2004;116(9):606-612.

27. Solimano RJ, Lineen J, Naimark DMJ. Preference for Alternate-Day Versus Conventional In-Center Dialysis: A Health Utility Elicitation. *Canadian journal of kidney health and disease.* 2020;7:2054358120914426-2054358120914426.

28. Quaife M, Terris-Prestholt F, Di Tanna GL, Vickerman P. How well do discrete choice experiments predict health choices? A systematic review and meta-analysis of external validity. *The European Journal of Health Economics.* 2018/11/01 2018;19(8):1053-1066.

29. Samuelson W, Zeckhauser R. Status quo bias in decision making. *Journal of Risk and Uncertainty.* 1988/03/01 1988;1(1):7-59.

30. Obi Y, Streja E, Rhee CM, et al. Incremental Hemodialysis, Residual Kidney Function, and Mortality Risk in Incident Dialysis Patients: A Cohort Study. *Am J Kidney Dis.* Aug 2016;68(2):256-265.

31. Jardine MJ, Zuo L, Gray NA, et al. A Trial of Extending Hemodialysis Hours and Quality of Life. *Journal of the American Society of Nephrology.* June 1, 2017 2017;28(6):1898-1911.

32. Dember LM, Lacson E, Brunelli SM, et al. The TiME Trial: A Fully Embedded, Cluster-Randomized, Pragmatic Trial of Hemodialysis Session Duration. *Journal of the American Society of Nephrology.* 2019;30(5):890-903.

33. Chan CT, Blankestijn PJ, Dember LM, et al. Dialysis initiation, modality choice, access, and prescription: conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference. *Kidney Int.* Jul 2019;96(1):37-47.

Table 1 – Example of Discrete Choice Experiment choice set (number 3), and different attribute levels (14 years survival also presented in other choice sets)

Description	**Longer sessions**	**Extra Session**	**No Change**
Frequency	Three times a week	Four times a week	Three times a week
Session length	4 and a half hours	4 hours	4 hours
Information			
Survival	10 years	12 years	9 years
Quality of Life	You feel the same	You feel better	You feel the same
Fluid Restriction	You can drink the same	You can drink more	You can drink the same
Hospitalisation	once a year	once every two years	once a year
Access Complications	More complications	No change	No change
Your decision	☐	☐	☐

Table 2 – Patient Demographics

		Previously offered more intensive dialysis		
	Overall	Yes (longer and/or 4xW)	No	
	183	65/183	118/183	P
Age	63.7 (15.4)	60.1 (16.0)	65.7 (14.7)	0.009
<50	18.6% (34/183)	23.1% (15/65)	16.1% (19/118)	
50-80	67/2% (123/183)	67.7% (44/65)	66.9% (79/118)	
>80	14.2% (26/183)	9.2% (6/65)	17.0% (20/118)	
Gender	63.4% (116/183)	76.9 (50/65)	55.9 (66/118)	0.005
Ethnicity (White)	80.3% (147/183)	78.5 (51/65)	81.4 (96/118)	
Comorbidity				
Diabetes	36.6% (67/183)	41.5 (27/65)	33.9 (40/118)	0.3
Previous Myocardial Infarction	9.3% (17/183)	10.8 (7/65)	8.5 (10/118)	0.6
Heart Failure	10.4% (19/183)	15.4 (10/65)	7.6 (9/118)	0.1
Weight	83.4 (25.4)	85.3 (25.3)	82.4 (25.5)	0.8
Ultrafiltration				
Two day interval (ml/kg/hr)	6.8 (3.2)	6.6 (3.4)	6.9 (3.1)	0.3
One day interval (ml/kg/hr)	5.2 (2.8)	5.3 (2.8)	5.2 (2.9)	0.6
Haemoglobin	106.3 (19.7)	108.6 (16.2)	105.1 (21.5)	0.9
Time on Dialysis (years)	4.3 (4.2)	4.0 (3.4)	4.5 (4.6)	0.2
<2 years	30.6% (56/186)	27.7% (18/65)	32.2 (38/118)	
2-5 years	41.5% (76/186)	50.8% (33/65)	36.2 (43/118)	
>5 years	27.4% (51/186)	21.5% (14/65)	31.4 (37/118)	
Dialysis Access				0.4
AVF	72.6% (130/179)	71.9% (46/64)	73.0% (84/115)	
Dialysis Catheter	23.5% (42/179)	25.0% (16/64)	22.6% (26/115)	
Other	3.9% (7/179)	3.1% (2/64)	4.4% (5/115)	
Mon/Wed/Fri Schedule	56.1% (101/180)	65.6% (42/64)	50.9% (59/116)	0.1
SONG HD Fatigue Score	4.9 (2.5)	5.1 (2.7)	4.8 (2.4)	0.2
<4	35.0% (64/183)	33.9% (22/65)	35.6% (42/118)	
4-7	44.8% (82/183)	44.6% (29/65)	44.9% (53/118)	
>7	20.2% (37/183)	21.5% (14/65)	19.5% (23/118)	
Previous Access Complications	53.6% (97/181)	68.3% (43/63)	45.8% (54/118)	0.004
Dialysis Travel Time (minutes)	25.0 (16.4)	20.8 (14.0)	27.3 (17.2)	0.005
Inadequate Health Literacy	15.6% (28/180)	19.4% (12/50)	13.6% (16/118)	0.3

Values for categorical variables are given as percentage (number), for continuous variables, mean ± standard deviation.

Table 3 – Adjusted odds ratios from multivariable analysis for the selection of longer and more frequent dialysis, presented alongside their potential benefits and harms.

	Coefficient	Odds Ratio	P
Survival			
10 years (+1 yr)	1.01 (0.53 - 1.48)	2.73 (1.7 - 4.39)	<0.001
12 years (+2 yrs)	3.24 (2.64 - 3.84)	25.5 (13.97 - 46.55)	<0.001
14 years (+4 yrs)	3.79 (3.08 - 4.51)	44.36 (21.7 - 90.7)	<0.001
Quality of Life improved	0.4 (0.04 - 0.76)	1.49 (1.04 - 2.14)	0.03
Fluid Restriction relaxed	0.47 (0.12 - 0.83)	1.61 (1.13 - 2.28)	0.008
Hospitalisation reduced	0.11 (-0.15 - 0.38)	1.12 (0.86 - 1.46)	0.4
Access Complications increased	-2.12 (-2.63 - -1.62)	0.12 (0.07 - 0.2)	<0.001
Longer 3x Week	-2.86 (-3.75 - -1.97)	0.06 (0.02 - 0.14)	<0.001
Four times a week	-5.39 (-6.54 - -4.24)	0.005 (0.001 - 0.01)	<0.001

Multivariable adjusted coefficients and Odds ratios for dialysis regimens represent the likelihood of being selected if there were no benefits or harms compared to 3xWHD. The overall likelihood of a treatment being selected can be estimated by the sum of the coefficients for a given treatment. E.g. Four times a week resulting in +2 years survival, quality of life improved and fluid restriction relaxed: 3.24 + 0.4 + 0.47 – 5.39 = -0.02

Table 4 – Years of patient survival traded for improvements in other attributes or avoiding longer/more frequent dialysis.

	Years of survival traded	95% CI
Longer Three times a week	-1.03	-2.43 to 0.36
Four times a week	1.98	0.29 to 3.67
Quality of life	-0.65	-1.11 to -0.20
Fluid Restriction	-0.67	-1.13 to -0.20
Access Complication	2.23	1.49 to 2.97

Interpretation: Negative value – In the absence of other attributes or change in HD regimen (due to multivariable adjustment), the number of years survival a patient would give to obtain the attribute. Positive value – the number of years survival a patient would give to avoid the attribute. 70 of 183 respondents who always chose to stay on 3xWHD excluded.

Table 5 – Probability of acceptance according to patient characteristic and available evidence

		Standard Estimates			Conservative Estimates		
		3xW 4.5hrs	4xW	Opt-out	3xW 4.5hrs	4xW	Opt out
Cohort	Patient / Treatment Characteristics	Survival +1yr[12] No other benefits[31]	Survival +2yrs [13], Reduced fluid restriction[4], Improved Quality of Life[3]	No change in attributes	No change in attributes	Survival +1yr	No change in attributes
Sampled population	See Table 2, Interactions specified*	0.271 (0.254 - 0.289)	0.343 (0.324 - 0.361)	0.386 (0.370 - 0.402)	0.239 (0.219 - 0.259)	0.272 (0.256 - 0.287)	0.489 (0.470 - 0.508)
FHN Trial	Mean age 50 (SD 14), Heart Disease 20%, 39% on HD for 2-5 years, Fatigue VAS 4.7 (SD 2.2), 42.7% doing own obs, 65% live near the unit	0.259 (0.246 - 0.272)	0.446 (0.434 - 0.458)	0.295 (0.289 - 0.302)	0.233 (0.219 - 0.247)	0.371 (0.357 - 0.386)	0.396 (0.382 - 0.410)
Established, Elderly Patient	Age 82, Lives far from the unit, Moderate Fatigue	0.110 (0.073 - 0.147)	0.220 (0.207 - 0.232)	0.670 (0.645 - 0.696)	0.078 (0.038 - 0.119)	0.147 (0.139 - 0.155)	0.774 (0.742 - 0.807)
Young working age patient	Age 45, Lives near the unit, Severe Fatigue, Does own obs	0.235 (0.218 - 0.251)	0.625 (0.608 - 0.642)	0.140 (0.133 - 0.147)	0.230 (0.210 - 0.251)	0.554 (0.537 - 0.572)	0.215 (0.205 - 0.226)

***** Interactions specified: Choice specific constants and the variables age, time on dialysis, heart failure, fatigue, undertaking own observations and travel time

FIGURES

Figure 1 – Treatment specific constant interactions

Figure 2 – Attributes and interactions