ACTIVE Dialysis Statistical Analysis Plan

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1 INTRODUCTION

1.1 Trial Description

The proposed study is a multi-centre, randomised, controlled trial of the effect of extended dialysis (24 hours per week or more) compared with standard dialysis (up to 18 hours per week) on quality of life measured using EQ5D, other clinical outcomes and cost utility in patients with ESKD.

Participants will be randomised to receive either of the two treatment strategies: "extended" or "standard" dialysis. Information will be collected at baseline, three, six, nine and twelve months after commencement of intervention. Data on persistence of therapy, requirement and mode of renal replacement therapy and vital status will be collected at a minimum at 24, 36 and 60 months after randomisation through the ANZDATA registry or from sites. Data on health service usage, vital status and dialysis parameters will be collected following the conclusion of the intervention period where data linkage facilities are available. Serious Adverse Events (SAE), as per protocol definition, will be collected until the conclusion of the 12 months of study intervention.

1.2 Description of Centres

Centres may recruit participants undergoing dialysis in their own home (or preparing to do so) or participants receiving dialysis in hospital or satellite centres that have the capacity to offer extended dialysis. However, the participant's dialysis setting (home or in-centre/satellite) must be determined prior to recruitment into the study.

Using the intention-to-treat (ITT) principle all participants randomised will contribute to the final study analyses. The only exception would be the case where a participant withdraws consent for participation and for the use of their data.

1.3 Duration of Subject Participation

All participants are asked to participate in the 12 month intervention phase and to attend three, six, nine and twelve month follow-up visits. Additionally, all participants are asked to participate in an observational cohort phase by providing consent to collection of data on renal replacement modality and weekly hours of haemodialysis as well as the collection of data on vital status, health and health services usage.

1.3.1 Intervention phase

Participants withdrawn from the randomised treatment for any reason (either from their own volition or on advice from their physician) will be followed up according to the study follow up schedule and analysed according to the intention-to-treat-principle providing they consent to such follow up.

The intervention period is defined as:

- Completion of 12 months from randomisation, *or*
- Participant withdraws consent for study treatment, *or*
- Participant dies, *or*
- The participant no longer requires dialysis (eg. renal transplantation), *or*
- The randomised therapy is unexpectedly no longer available to the participant (eg. unable to continue home dialysis, in-centre extended dialysis unavailable, change to a different dialysis modality).

1.4 Duration of the Study

The study duration includes at least 45 months for subject accrual and a further 12 months of participation after the last subject is enrolled.

1.5 Home Haemodialysis Training

Some centres will offer participation in the study to individuals planning to receive their dialysis therapy at home. While each participating centre will take responsibility for preparing patients to dialyse safely at home, it is expected the home training process will include the following major tasks:

- Vital signs, including BP measurement

- Setting up and tearing down the dialysis machine without assistance

- Recognizing machine problems and troubleshooting them appropriately

- Able to access dialysis vascular access consistently and independently

- Machine disinfection

- Water treatment maintenance

At the end of the training process for home HD, the study coordinator will ascertain that the participant is willing to participate in the study. After randomisation, participants will receive any additional training needed specific to the assigned home HD modality. Training may be required on the use of enuresis sensors to detect blood leaks at the needle site and fluid leaks from machines and lines as well as procedures to secure needles and lines. It is anticipated that this additional training will take approximately one to two weeks.

1.6 Data Linkage

The observational data generates hypotheses that extended hours of haemodialysis may reduce mortality as well as reduce hospitalisations and medication requirements. Data linkage offers a means of ascertaining differences in mortality and health services usage in a rigorous methodology while minimising the trial demands on participants and sites. Ethics approval for this aspect of the study is received from the data custodians.

Participants will be asked to consent to data linkage to ANZDATA (or equivalent data source in other countries) at 24, 36 and 60 months and other time points to ascertain vital status, renal replacement therapy modality and dialysis hours. The ANZDATA information will establish the durability of each intervention as well as medium-term effects of randomisation on participant survival. De-identified data only will be sent to The George Institute for International Health where it will be kept according to standard data security measures (pass-word protected secure server, etc.) In countries where data linkage is not available, sites will collect information from their medical records on vital status, renal replacement therapy modality and dialysis hours.

Data linkage to Medicare Australia data (MBS and PBS use), and to state-based hospital and emergency department admissions databases will be conducted from time to time following the conclusion of the 12 month intervention to ascertain vital status, health services utilisation and dialysis parameters. De-identified data only will be sent to The George Institute for Global Health where it will be kept according to standard data security measures (pass-word protected secure server, etc.). In order to provide power to detect differences in survival rates between the groups, we will follow the group until survival in the standard dialysis arm is 25%.

2 Study Population

2.1 Participant Recruitment

All adult patients with end-stage kidney disease who meet the inclusion and no exclusion criteria without regard for race, ethnicity or national origin will be considered eligible for this study.

2.2 Participant Inclusion Criteria

Participants are eligible for INCLUSION in the study if ALL the following criteria are met:

1. Incident or prevalent patients requiring maintenance haemodialysis therapy for ESKD
2. Aged 18 years or older
3. Undergoing dialysis for 18 hours per week or less
4. Suitable for either extended or standard dialysis in the view of the treating physician
5. Agreeable to randomisation

2.3 Participant Exclusion Criteria

Patients will be EXCLUDED from the study if, in the opinion or knowledge of the responsible clinician the following criterion is present:

1. Life expectancy of less than 6 months
2. Definite plans to undergo renal transplantation within 12 months of entry to the study
3. Inability to complete quality of life questionnaire
4. Concomitant major illness that would limit assessments and followup
5. High chance that the patient will not adhere to study treatment and follow up in the view of the treating physician.

2.4 Recruitment log

Study coordinators and investigators will keep a log of potentially eligible participants at each site. This log will collect the initials of all potentially eligible participants, but will not contain any other information that will permit the identification of any individuals. For individuals felt not to be appropriate for participation in the study by the investigator, the reason for this will be collected in the log. For individuals who are invited to participate but choose not to do so, the most important reason (from a pre-defined list) will be recorded.

3 Study Design

3.1 Aim & Hypothesis

The study seeks to determine whether a regimen of extended hours haemodialysis (>24hrs per week) improves the quality of life of dialysis patients when compared to standard dialysis treatment (<18hrs per week). In addition, the study will explore the cost-effectiveness of providing such a dialysis regimen and assess the comparative effects upon hospital admissions, blood pressure, cardiac structure and function and safety.

3.2 Study Treatments

Eligible participants will be randomly allocated to extended (≥24 hours per week) or standard (<18 hours per week) dialysis. All participants will continue with routine medical care and monitoring for all aspects of their treatment, with the provision that the duration of dialysis fits within the parameters of the group to which the individual has been randomized. Routine medical care and monitoring includes, but is not limited to, those practices outlined in the 'Routine Expected Care and Monitoring of ACTIVE Dialysis participants' document. Study

centres will be encouraged to meet minimum clearance recommendations according to local guidelines.

3.3 Power Calculations

The total proposed sample size of 200 will provide 90% power (with alpha=0.05) to detect an absolute difference of 0.10 in health related quality of life (utility or QALY weights, measured on the 0-1 scale) over 12 months between the intervention and control treated participants. The main assumption underlying the power calculations is a mean EQ-5D scores of approximately 0.70 at baseline with no change in the standard dialysis group, and an improvement of 0.10 in the extended dialysis group, with a common standard deviation (SD) of 0.22. These values were obtained from the Canadian study of long dialysis with a comparable patient population. [16]

The trial will have substantial power to detect clinically important differences in secondary endpoints based on data from the Canadian randomised pilot trial of daily long dialysis,[20] and on registry data including 90% power to detect the following differences between the intervention and control groups:

- A difference of 9.2 mmHg in systolic blood pressure change at 12 months.
- A difference in the change in LV mass index observed between baseline and 12 months of 7.7 g/m^2 (presuming 125 participants complete cardiac MRI imaging).
- A difference of 30% in the relative risk of mortality when the survival in the standard treatment arm reaches 25%.
- The trial will have power to detect a reduction in the mean annual number of days of hospitalisation from 4.0 to 2.5 days, assuming that the number of days in hospital follows an exponential distribution.[21]

3.4 Study Outcomes

Primary Outcome

The primary end-point for this study is the difference in the change in quality of life between the two groups from randomisation to the end of the intervention period as measured by the EQ-5D instrument.

Secondary Outcomes

These will include:

1) Survival and cardiovascular outcomes

    a) Cardiovascular structure

        i) Change in left ventricular mass index on magnetic resonance imaging of the heart over 12 months, reported centrally

    b) Blood pressure

        i) Systolic blood pressure evolution from baseline to end of the intervention period, taken as the average of the 2nd and 3rd of 3 measurements taken after 5 minutes rest and measured immediately prior to a dialysis session

        ii) Systolic blood pressure evolution from baseline to all follow-up visits occurring during the intervention period, taken as the average of the 2nd and 3rd of 3 measurements taken after 5 minutes rest and measured immediately prior to a dialysis session

    c) Requirement for blood pressure lowering

i) Number and dose of blood pressure lowering agents from baseline to the end of the intervention period, defined as the change from baseline to study end of 'number of maximum BP-lowering medication dose equivalents' calculated as described in Appendix 1.

ii) Number of blood pressure lowering agents from baseline to all follow-up visits occurring during the intervention period, defined as the change from baseline to study end of 'number of maximum BP-lowering medication dose equivalents' calculated as described in Appendix 1

iii) The percentage of people on no blood pressure lowering medications at study endpoint.

iv) The percentage of people on no blood pressure lowering medications at followup visits during the intervention period.

d) Clinical cardiovascular events

i) Time to the occurrence of a combined end-point consisting of new onset of documented acute myocardial infarction, stroke or death due to cardiovascular causes.

ii) Time to the occurrence of a combined end-point consisting of new onset of documented acute myocardial infarction, stroke, death due to cardiovascular causes and cardiovascular SAEs during the intervention period.

e) Survival

i) Difference in survival between the two groups at 24, 36 and 60 months and when survival in the standard treatment arm reaches 25% (This endpoint will not be reported in the primary results paper)

2) Quality of life and patient acceptability.

a) Quality of life

i) Quality of life from baseline to the follow-up visits occurring during the intervention period as measured by the EQ-5D instrument

ii) Quality of life as measured by the SF-36 two composite scores (physical-health composite and mental-health composite) measured within the KDQOL instrument from baseline to the end of the intervention period

iii) Quality of life as measured by the SF-36 two composite scores (physical-health composite and mental-health composite) measured within the KDQOL instrument from baseline to the follow-up visits occurring during the intervention period

iv) Quality of life as measured by the individual eight domains of the SF-36 as measured within the KDQOL instrument from baseline to the end of the intervention period (This endpoint will not be reported in the primary results paper)

v) Quality of life as measured by the individual eight domains of the SF-36 as measured within the KDQOL instrument from baseline to the follow-up visits occurring during the intervention period (This endpoint will not be reported in the primary results paper)

b) Patient acceptability

i) Adherence to the randomized treatment (defined according to Appendix 2) assessed at the end of the intervention period

ii) Adherence to the randomized treatment (defined according to Appendix 2) assessed as the average of the relative adherence scores at each of the intervention period follow-up visits.

    (1) Adherence to the randomized treatment defined as the percentage in each group fully compliant at the end of the intervention period

    (2) Adherence to the randomized treatment defined as the percentage in each group fully compliant at each of the intervention period follow-up visits, and

iii) Persistence of the randomized treatment (defined by relative adherence scores and by full compliance percentages) at 24, 36 and 60 months (This endpoint will not be reported in the primary results paper)

3) Changes in biochemical and haematological markers

  a) Mineral metabolism

    i) Percentage at optimal phosphate target defined as a phosphate < 1.5mmol/l AND no use of phosphate binders at the follow-up visits occurring during the intervention period.

    ii) Dose of phosphate binders (defined as number of pills) at the follow-up visits occurring during the intervention period

    iii) Number of patients on phosphate supplementation (oral or systemic including delivery via dialysate) at the follow-up visits occurring during the intervention period. (Phosphate supplementation is defined as a medication/supplement administered with the primary goal of replacing phosphate)

    Dose of phosphate binders (defined as number of pills) at the end of the intervention period compared with baseline

    iv) Number of patients on phosphate supplementation (oral or intravenous) at the end of the intervention period. (Phosphate supplementation is defined as a medication/supplement administered with the primary goal of replacing phosphate

  b) Erythropoiesis Stimulating Agent requirement

    i) Dose of erythropoiesis stimulating agents (ESA) at the follow-up visits occurring during the intervention period compared with baseline. ESA doses will be converted using the main formula in the Appendix 3. Sensitivity analyses using alternative formulae including those also provided in Appendix 3 will be performed.

    ii) Dose of erythropoiesis stimulating agents (ESA) at the end of the intervention period compared with baseline. ESA doses will be converted using the main formula in the Appendix 3. Sensitivity analyses using alternative formulae in Appendix 3 will be performed.

4) Safety outcomes

  a) survival

    i) Survival measured using proportional hazards

  b) Serious Adverse Events (SAEs)

    i) Comparison of SAEs by diagnostic group

5) Vascular Access

    i) Time to first vascular access failure defined as thrombosis or fistula revision where revision is defined as a procedure that requires a new anastomosis

    ii) Time to first vascular access intervention or failure

iii) Time to first vascular access infection

iv) Number of reported access-related AEs.

6) Hospitalisations

    i) Number of reported hospitalisations from randomisation to end of intervention period. If the number of categories are limited, a negative binomial model will be used otherwise this variable will be modelled as a continuous secondary endpoint.

    ii) Total duration of hospitalisations from randomisation to end of intervention period. (This endpoint will not be reported in the primary results paper)

4. Analysis principles

1. All analyses will be conducted on an intention-to-treat basis.
2. All randomized participants will be analysed in the group to which they were assigned regardless of protocol violations.
3. All tests are two-sided and the nominal level of alpha will be 5%.
4. P-values will not be adjusted for multiplicity. However the outcomes are clearly categorized by degree of importance (primary, main secondary and other secondary) and a limited number of subgroup analyses are pre-specified.

4.1 Trial profile

Flow of patients through the study will be displayed in a "CONSORT" diagram. We will report number of screened patients who met study inclusion criteria and number randomised into the study.

4.2 Characteristics of patients and baseline comparisons

Description of the following baseline characteristics will be presented by treatment group. Discrete variables will be summarized by frequencies and percentages. Percentages will be calculated according to the number of patients for whom data are available. Where values are missing, the denominator (which will be less than the number of patients assigned to the treatment group) will be stated in either the body or a footnote in the corresponding summary table. In some instances, additional frequencies and percentage of patients in each category will be reported as indicated in the list below. Continuous variables will be summarized by use of standard measures of central tendency and dispersion using mean and standard deviation and/or quantile points at 0.25, 0.5 and 0.75 where appropriate. Free text entries for fields collecting both categorical and free text information (eg ethnicity) will be assessed and assigned to a category if appropriate at the discretion of the Study Director.

4.3 Baseline characteristics of patients:

- Sex
- Age
- Pre-dialysis Weight
- Height
- Waist circumference
- Hip circumference
- Heart Rate
- Dialysis ideal body weight (kg)
- Ethnicity:
  Caucasian
  Aboriginal or TSI
  Maori
  Pacific islander
  Asian
  Indian
  other
- Medication
  - Number on erythropoeitic agents
  - Number on blood pressure-lowering medications

- o Number on phosphate binders
- Primary cause of Kidney disease:
  Diabetic Nephropathy
  Hypertension/ vascular Nephropathy.
  Glomerulonephritis
  Reflux Nephrology
  Polycystic Kidney Disease
  Other

- Time since most recent commencement of dialysis

- Co-morbidity:

Diabetes Mellitus – type 1, type 2, nil
Hypertension
Ischaemic heart disease
   Angina
   Acute MI
   Previous Coronary Artery Bypass
Congestive Heart Failure
   NYHA classification
Cerebrovascular Disease
Peripheral Vascular Disease
Current smoker
Former smoker
Non-smoker

- Dialysis site: home, centre (hospital and satellite)
- Dialysis in last week: number of hours/session, number of sessions/wk, number of hours/wk
- Timing of dialysis: day/night
- Access: native AVF, synthetic graft, tunnelled catheter, non-tunnelled catheter, other
- Mode of access: BH cannulation, RL cannulation, Dialysis catheter, other
- Dialysate composition: Na, K, Ca, Glc, addition of phosphate
- Dialysis parameters: blood flow rate, dialysate flow rate

Physical characteristics
- Pre-dialysis blood pressure, average of 3 if available,
- Height, weight, BMI (derived from height and ideal body weight)
- Waist
- Hip
- Waist:hip circumference
- Pre-dialysis heart rate

Achieved characteristics at end of study intervention period
- Dialysis site: home, centre (hospital and satellite)
- Dialysis in last week: number of hours/session, number of sessions/wk, number of hours/wk
- Timing of dialysis: day/night
- Access: native AVF, synthetic graft, tunnelled catheter, non tunnelled catheter, other
- Mode of access: BH cannulation, RL cannulation, Dialysis catheter, other
- Dialysate composition: Na, K, Ca, Glc, addition of phosphate:
- Dialysis parameters: blood flow rate, dialysate flow rate

4.4 Laboratory Results
Continuous variables will be summarized by use of standard measures of central tendency and dispersion using mean and standard deviation as well as quantile points at 0.25, 0.5 and 0.75 where appropriate stratified by measurement time points (baseline, 3, 6, 9 and 12 months) and by treatment group. To assess the treatment effect on laboratory variables, mixed linear model including random intercept, treatment and time (categorical) will be used.

Laboratory Measures

- Haemoglobin
- Total white blood cell count
- Platelet count
- Sodium
- Potassium
- Chloride
- Glucose
- Calcium (using corrected calcium formula)
- Phosphate
- Calcium phosphate product
- Bicarbonate
- Urea

- Small molecular clearance reported as either Urea Reduction Ratio or Kt/v
- Creatinine
- Albumin
- C-reactive protein
- Parathyroid Hormone
- Total cholesterol
- Triglycerides
- Ferritin
- Transferrin saturation
- HbA1c (if diabetic)

The corrected calcium will be calculated according to the following formula.

corrected calcium (in mmol/l) = measured calcium (in mmol/l) + ((40-albumin (g/l)) x 0.02)

5. Analysis Methods

5.1 Primary outcome

The primary endpoint will be summarised by mean (sd) and quartiles stratified by treatment group. Single imputation will be performed if the endpoint is missing: 1) if patient died before the 12 month FU then his quality of life score is 0, 2) if the patient reaches the end of the study duration before 12 months or if the quality of life score at 12 month is missing then the last available score will be used. Linear regression will be used to test the effectiveness of extended dialysis over standard dialysis (control) adjusted with the baseline score. The model will include the change - from randomisation to 12 month - in quality of life as dependent variable. The covariates will be treatment group (extended *versus* standard dialysis) and the baseline quality of life score.

Sensitivity analysis:
A sensitivity analysis will be done excluding patients who reach the 12 month follow-up but did not complete the 12 months quality of life survey.

Sub-group analysis:
The following subgroups will be considered for the primary endpoint and for the analysis of left ventricular mass index:
1. Region (China *versus* Aus NZ Canada)
2. Home or centre dialysis
3. Less or equal to 6 months *versus* more than 6 months dialysis duration at baseline

5.2 Secondary/SAEs outcomes

Summary of each secondary or safety endpoints will be provided. Continuous outcome will be summarised by their mean (SD), while binary outcome will be summarised by percentages. Survival outcome will be summarised by proportion of event by group and their median time will be reported. The intervention effect on each secondary/SAEs will be assessed depending on their nature. The Left ventricular mass index (LVMI) endpoint will include subgroup stratification. Blood pressure values are taken as the average of the 2nd and 3rd of 3 readings. Where only 2 separate readings are recorded, the second of the 2

readings will be used. Where only 1 reading is reported, it will be used. In other respects, single imputation will be performed in the same way as the primary outcome.

Continuous: All continuous secondary endpoints will be analysed as the primary using linear regression adjusted with its baseline counterpart. Change in left ventricular mass index on magnetic resonance imaging analysis will be restricted to the subgroup of participants with both baseline and 12 month measurement. Descriptive table stratified by MRI vs. no-MRI for all baseline characteristics will also be provided.

Continuous repeated measurements: All laboratory variables and secondary outcomes repeatedly measured over time such as systolic blood pressure, EQ5D quality of life evolution, KDQOL by domain and by composite score, average compliance, dose of phosphate binders and dose of erythropoiesis will be modelled using a Linear Mixed model including random intercept, randomisation and time categories. Treatment effect will be tested using their Wald type test p-value from the model. Mean and 95% CI of all continuous repeated measurement outcomes will be displayed in a graphics over time (baseline, 3, 6, 9 and 12 months) along with the p-value of the significance of the treatment effect estimated using a Mixed Linear Model adjusted with time as categorical and baseline as reference.

Binary repeated measurement: will be analysed using logistic Generalised Estimating Equation to take into account the correlation due the repeated measurement effect. The dependent variables for models will include dialysate phosphate supplementation, and blood pressure target.

Count: Count secondary endpoints such as number of reported access-related adverse events will be modelled using a negative binomial model.

Survival time: All time to event variables will be censored at the conclusion of the subjects' intervention period if the event of interested has not been observed. Survival curves and estimated median survival time will be generated according to the Kaplan-Meier method. Log-rank test will be used to assess the difference between the two survival curves by secondary endpoint.

Recurrent event: Recurrent secondary endpoints will be analysed using Andersen and Gill approach that is a generalization of a Cox proportional hazard model.

Cost and household impact, secondary QOL analyses: Cost endpoint will be analysed in a separate report.

5.3 Exploratory analyses

The FHN rank-based procedure

The FHN rank-based procedure will be performed as an exploratory analysis. Two composite outcomes will be tested, that of death and change in left ventricular mass index (LVMI), and of death and change in final physical-health composite of the SF-36 health survey (PCS) contained within the KDQOL. A rank-based procedure will be applied where patients are ranked from lowest (poorest outcome) to highest (best outcome. Participants who died during the intervention period will be ranked from lowest to highest according to survival time from randomisation. Other participants will then be ranked from least favourable change to most favourable change in LVMI (or PCS) from baseline to end of the intervention period. Participants will be censored at the conclusion of their intervention period if they survive but there is no followup LVMI (or PCS). Ranks between treatment groups will be compared with a log-rank test with calculated hazard ratios (and 95% confidence intervals) using proportional-hazards regression.

Impact of dialysis session frequency

The effect of dialysis session (3 versus more than 3 sessions per week) alone and its interaction with the intervention will be investigated for the primary endpoint and for change in LVMI. For both outcomes, the analysis will be a linear regression model adjusted with the intervention, the outcome baseline score, the dialysis session and the interaction between dialysis session and intervention.

Further analyses: Further analyses for the cohort phase of the study will be subject to a separate report when data is available.

Appendices

Appendix 1: Calculation of maximum BP-lowering medication dose equivalents

This is calculated using the US or Aus labelling indications. For each class we would allocate a number {1.0 if on maximum labelled dose, 0.5 if on half the maximum labelled dose}. We would add the total for each class. In this way we will end up with a single number that represents the blood pressure lowering load.

Appendix 2: Calculation of adherence/persistence scoring

allocated extended dialysis			allocated standard dialysis		
hrs/week		score	hrs/week		score
24 (or more)	fully adherent	1.00	24 (or more)	not adherent	0.00
23	partial adherence	0.83	23	partial adherence	0.17
22	partial adherence	0.67	22	partial adherence	0.33
21	partial adherence	0.50	21	partial adherence	0.50
20	partial adherence	0.33	20	partial adherence	0.67
19	partial adherence	0.17	19	partial adherence	0.83
18 (or less)	not adherent	0.00	18 (or less)	Fully adherent	1.00

Appendix 3: ESA conversion formula

1) "Doses of rEPO are reported in micrograms of darbepoetin per kilogram per week (μg/kg/week) with doses of erythropoietin alpha and beta converted to these units by dividing by 240 [23, 24], and methoxy polyethylene glycol-epoetin beta doses being converted by multiplying by 1.19 [25, 26]."

2) Sensitivity 330.6:1 (U epoetin alfa to 1 μ g darbepoetin alfa (Horowitz paper) – probably what FHN used but could have been 375:1)

3) Sensitivity: PBS conversions from Therapeutic Relativity sheets (separate Excel file attached)