KIDNEYTEXT

STATISTICAL ANALYSIS PLAN

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INTRODUCTION

The Statistical Analysis Plan (SAP) is developed to guide the main analysis of the KIDNEYTEXT trial data i.e. the analysis of the change between randomly allocated treatment (receiving dietary behaviour text messages plus usual care or usual care) and dietary behaviours as measured by adherence to renal dietary intake recommendations.

This document is based on the original study protocol and published trial design.

The SAP describes participant characteristics and outcomes that will be analysed, as well as the statistical methods that will be applied.

ROLE OF THE FUNDING SOURCE

KIDNEYTEXT was supported by National Health and Medical Research Council (NHMRC) PhD scholarship grant and NHMRC Better Evidence and Translation in Chronic Kidney Disease (BEAT-CKD) Program Grant (1092579). Funding for the trial was provided by Sydney Medical School Foundation Grant and the Centre for Transplant and Renal Research at Westmead Hospital. The study was initiated by the study investigators and was designed and conducted independently of the sponsors. This SAP was also prepared by the study investigators, entirely independently of the sponsors. Representatives of the funding sources did not have any influence on the planned analyses, nor will they have influence on the interpretation and reporting of the trial results.

BACKGROUND OF THE STUDY

Managing nutrition is critical for reducing morbidity and mortality in patients on haemodialysis but adherence to the complex dietary restrictions remains problematic. Given the complexity of dietary requirements in haemodialysis and the difficulty patients have in comprehending and integrating these requirements, text messaging offers an inexpensive and readily available way to motivate and help patients with managing their diet by providing frequent, short bursts of information over an extended period of time.

Design

KIDNEYTEXT is a six month, prospective, randomised controlled trial (ACTRN12617001084370). The aim of this study is to assess the feasibility and effectiveness of a mobile phone text message intervention to improve dietary and lifestyle behaviour in patients on haemodialysis. The results of this study will inform a larger trial. A total of 130 patients receiving haemodialysis will be randomised (stratified by geographical location) in a 2:1 ratio to KIDNEYTEXT intervention plus usual care or usual care.

The primary endpoint is feasibility. Feasibility will be measured using: dietary adherence as compared against evidence-based practice standards for protein, potassium, sodium and phosphorus; recruitment rate; drop out rate; and acceptability using semi-structured interviews to describe perspectives on participation in the trial. We hypothesise that

receiving dietary and lifestyle related text messages in addition to usual dietary care will be feasibile and result in improved dietary behaviours.

The trial design was published in BMJ Open.

Follow-up

Randomisation will occur after completion of the initial study assessment. Endpoint data will be collected at baseline, three months and six months.

Endpoint definitions

Dietary adherence: This will be measured using the 24-hour pass methodology (1) to assess dietary intake with particular focus on renal dietary components: protein, potassium, phosphorous and sodium intake compared to renal dietary guideline recommendations. Dietary intake will be assessed using a 24-hour recall, of both a dialysis day and a non-dialysis day, to ensure that we capture any differences in dietary intake on these days. Dietary assessment will be conducted within two weeks' of a participants scheduled review. Dietary intake data will be analysed using Xyris Software Foodworks version 9 Pty Ltd (using food databases AUSNUT 2011-2013, Aus Foods 2017, Aus Brands 2017). Dietary intake data will be measured at baseline, 3 months and 6 months. Adherence will be defined as meeting three of the four nutrition guidelines.

- dietary protein intake more than or equal to 1.2 grams of protein per kilogram of ideal body weight per day

- dietary potassium intake less than or equal to 1mmol of potassium per kilogram of ideal body weight per day

- dietary phosphate intake less than or equal to 1000mg phosphorus per day

– dietary sodium intake less than or equal to 2300mg sodium per day

Serum potassium: Pre-dialysis serum potassium levels will be collected at baseline, 3 months and 6 months. Blood will be collected by trained nursing staff in the dialysis units. At baseline a pre-dialysis serum potassium level will be requested. In addition, the 2 prior serum potassium levels collected as part of routine care will be obtained (i.e. 1 month and 3 months prior to study enrolment). At 3 months and 6 months a pre-dialysis potassium blood test will be requested, or if within 2 weeks of the study visit, a participants' usual blood test may be obtained. A participant will receive text messages targeting potassium control if 2 of 3 blood tests are high. A high serum potassium will be defined as ≥5.5mmol/L.

Serum phosphate: Pre-dialysis serum phosphate levels will be collected at baseline, 3 months and 6 months. Blood will be collected by trained nursing staff in the dialysis units. At baseline a pre-dialysis serum phosphate level will be requested. In addition, the 2 prior serum phosphate levels collected as part of routine care will be obtained (i.e. 1 month and 3 months prior to study enrolment). At 3 months and 6 months a pre-dialysis phosphate blood test will be requested, or if within 2 weeks of the study visit, a participants' usual blood test may be obtained. A participant will receive text messages targeting phosphate control if 2 of 3 blood tests are high. A high serum phosphate will be defined as ≥1.78mmol/L.

Interdialytic weight gains (IDWG): At baseline, 3 months and 6 months the most recent 3 interdialytic weight gain measurements will be averaged. If IDWG is not available, then the volume of ultrafiltration will be used if available. A participant will receive text messages

targeting fluid and sodium control if they have high IDWGs. An elevated IDWG will be defined as the averaged IDWG being ≥3.5% predialysis dry weight.

Patient-Generated Subjective Global Assessment (PG-SGA): Changes in nutritional status will be measured using the Patient-Generated Subjective Global Assessment tool. This will provide a global rating (A, B or C) to denote nutritional status and a numerical value (0-16) to denote the change in nutritional status within the global category with increasing numerical value denoting worsening nutritional status (e.g. A3 to A7 indicating worsening nutritional status).

Quality of life: Quality of life scores will be measured using EQ-5D-5L. This tool will be administered at baseline, 3 months and 6 months.

Dietary Quality: Dietary quality will be measured with the Australian Healthy Eating Index (HEI) that uses seven parameters to assess the quality of a person's diet. This will provide an overall score from 0-110, with higher scores indicating better dietary quality. A 5-point improvement in AHEI will be considered a significant improvement. Change in the number of serves of fruit, serves of vegetables, grams of added sugar and grams of fibre per day will also be analysed. These analyses will compare baseline, 3 months and 6 months.

Intake of renal specific dietary nutrients: The change in the intake of renal specific dietary components (protein, potassium, sodium and phosphorus) will be analysed comparing baseline, 3 months and 6 months. Dietary intake will be assessed using a 24-hour recall, of both a dialysis day and a non-dialysis day, to ensure that we are capture any differences in dietary intake on these days. Dietary assessment will be conducted within two weeks' of a participants scheduled review. Dietary intake data will be analysed using Xyris Software Foodworks version 9 Pty Ltd (using food databases AUSNUT 2011-2013, Aus Foods 2017, Aus Brands 2017).

Exploratory endpoints

Blood pressure: Pre-dialysis and post-dialysis systolic and diastolic blood pressures will be obtained at baseline and 6 months. The 3 most recent blood pressure measurements will be used.

Serum urea, bicarbonate, parathyroid hormone and albumin: Pre-dialysis serum levels will be obtained at baseline and 6 months.

Glycaemic control: In those participants who have diabetes, HbA1c levels will be obtained at baseline and 6 months. For participants who do not have a HbA1c level at initiation of the study, the last usual care level will be used.

Healthcare utilisation: Will be estimated from participant self-report diaries / calendars collected at 3 and 6 months. Utilisation will include, healthcare-related appointments, including general practitioner, specialists and allied health, and medication prescriptions from community pharmacists. Planned and unplanned hospital admissions will be obtained from hospital medical records including reasons for admission.

STATISTICAL HANDLING POLICY

The trial statistician will conduct the main analysis and he/she will blind to the randomisation.

STATISTICAL ANALYSIS

Dichotomous variables will be summarised as numbers and percentages, continuous variables will be present means and standard deviation (SD), or medians and 25th and 75th percentiles, according to their distribution. Baseline characteristics will be described for each group to assess balance in the randomisation.

The primary outcome, dietary adherence at 6 months, will be compared across the two groups with a logistic regression, adjusting for the stratification variable, site of intervention. If there are unbalanced characteristics at baseline, we will further explore the comparison between the groups, adding those characteristics as covariates to the logistic model. The short-term dietary adherence at 3 months will also be compared using the same approach. We will evaluate the proportion of dropouts associated with the intervention in each arm and explore if the dropouts are associated with baseline characteristics of the participants using a logistic regression adjusting for the stratification.

The secondary outcomes, serum potassium, serum phosphate and weight gain will be analysed longitudinally (baseline, 3 months, 6 months) with a linear mixed model. The stratification variable will be added to the model. The proportion of patients meeting the threshold levels for high potassium and high phosphate, as defined before, will be compared between the two groups using a logistic mixed model while adjusting for stratification.

All the other secondary endpoints and exploratory endpoints will be analysed with a similar methodology, using linear mixed models for continuous outcomes and logistic mixed models for dichotomous ones, while adjusting for stratification.

All the analyses will follow an intention-to-treat principle, but a sensitivity analysis will be conducted, excluding those participants who had endpoints collected outside of pre-specified protocol timeframes (i.e. more than 2 weeks after study visits).
The analysis will be conducted in R software. The significance level will be set at 0.05 level and 95% confidence intervals will be reported for all point estimates.

Economic evaluation: A trial-based evaluation will be undertaken. Costs of the intervention and control arms will be estimated separately using the health care utilisation data over a time horizon equal to trial follow-up (discounting will therefore not be required). The costs will be estimated from the perspective of the health care funder and will not include patient out of pocket costs such as co-pay. Unit costs will be assigned using aggregate values from the Pharmaceutical Benefits Scheme, Medicare Benefits Scheme and the Independent Hospital Pricing Authority. The intervention costs will include a dietitians salary for set up and maintenance with hours estimated from the trial, and provision of text messages. No infrastructure costs associated with the intervention have been identified. Trial maintenance costs will be excluded. The primary and secondary outcomes measured in the trial will be used as the basis for estimating benefits. Incremental cost effectiveness ratios (ICER) will be calculated for selected outcomes as follows:

ICER= (costs of intervention – costs of control)/(benefits of intervention – benefits of control)

Benefits will be expressed as the change in the outcome that would represent a meaningful difference. Utility values from the EqQ5D-5L will be used to calculated quality adjusted life (QALY) years for the intervention and the control and calculation of an ICER expressed as cost per QALY. Bootstrapping will be used to estimate a distribution around costs and health outcomes, and to calculate the confidence intervals around the incremental cost-effectiveness ratios. One-way and multi-way sensitivity analysis will be conducted around key variables. A cost-effectiveness acceptability curve will be plotted to provide information about the probability that the intervention is cost-effective, given willingness to pay for each additional QALY gained.

Missing data

We will not use imputation for missing endpoints. Each analysis will be performed with the available data. We will compare the baseline characteristics of patients with missing outcomes. If baseline differences are found, we will run a sensitivity analysis adjusting the comparison of the groups to the characteristics associated with the missing data.

Exploratory subgroups analysis

Treatment effects will be studied in relation to the following characteristics: sex. Age, dialysis vintage (< 1 year, 1-5 years, >5 years), dialysis location (WSLHD, SESLHD), dialysis type (in-centre, satellite, home), presence of diabetes, number of comorbidities, country of birth (Australia or other), primary language (English or other), number of dietitian consultations, text message permutations (potassium, phosphorus, sodium and fluid or none), reason for text message permutation (e.g. clinical and/or dietary indications). This

will be done by testing the interaction of the respective subgroup variable with the treatment group, in the regression model for the outcome of interest.

References

1. Raper N, Perloff B, Ingwersen L, Steinfeldt L, Anand J. An overview of USDA's Dietary Intake Data System. J Food Compost Anal. 2004;17(3):545-55.

Appendix:

Table 1: Baseline characteristics		
Characteristics	**KIDNEYTEXT (n=)**	**Control (n=)**
Sex (Male)	n/N (%)	n/N (%)
Age	Mean (SD) Median (IQR)	Mean (SD) Median (IQR)
Cause of ESRF		
Diabetes	n/N (%)	n/N (%)
Hypertension	n/N (%)	n/N (%)
Interstitial Nephritis	n/N (%)	n/N (%)
Polycystic Kidney Disease	n/N (%)	n/N (%)
Obstructive Nephropathy	n/N (%)	n/N (%)
Reflux Nephropathy	n/N (%)	n/N (%)
Autoimmune (e.g. Glomerulonephritis, IgA nephropathy, lupus)	n/N (%)	n/N (%)
Other	n/N (%)	n/N (%)
Undetermined	n/N (%)	n/N (%)
Dialysis Vintage	Mean (SD) / Median (IQR)	Mean (SD) / Median (IQR)
< 1 year	n/N (%)	n/N (%)
1-5 years	n/N (%)	n/N (%)
>5 years	n/N (%)	n/N (%)
Dialysis Location		
Western Sydney	n/N (%)	n/N (%)
South East Sydney	n/N (%)	n/N (%)
Dialysis Type		
In-centre	n/N (%)	n/N (%)
Satellite	n/N (%)	n/N (%)

Home	n/N (%)	n/N (%)
Previous RRT		
Renal transplant	n/N (%)	n/N (%)
Peritoneal Dialysis	n/N (%)	n/N (%)
Number of co-morbidities		
0-3	n/N (%)	n/N (%)
>3	n/N (%)	n/N (%)
Cultural Background		
Australia, New Zealand	n/N (%)	n/N (%)
Aboriginal, Torres Strait Island	n/N (%)	n/N (%)
Polynesian	n/N (%)	n/N (%)
European	n/N (%)	n/N (%)
North American	n/N (%)	n/N (%)
South and Central Asian	n/N (%)	n/N (%)
North-Eastern Asian	n/N (%)	n/N (%)
South-East Asian	n/N (%)	n/N (%)
Middle East, North Africa	n/N (%)	n/N (%)
Sub-saharan Africa	n/N (%)	n/N (%)
Other	n/N (%)	n/N (%)
Country of Birth		
Australia	n/N (%)	n/N (%)
Other	n/N (%)	n/N (%)
Primary language		
English	n/N (%)	n/N (%)
Other	n/N (%)	n/N (%)
Seen a dietitian	n/N (%)	n/N (%)

Table 2: Text message permutations and indications for use

	Number of participants	**Elevated dietary intake**	**Elevated clinical indicators**
None	n	-	-
Potassium	n	n/N (%)	n/N (%)
Phosphorus	n	n/N (%)	n/N (%)

Sodium and Fluid	n	n/N (%)	n/N (%)

Table 3: Adherence to renal dietary guidelines			
	KIDNEYTEXT	**Control**	**P**
Potassium			
Baseline	n/N (%)	n/N (%)	
3 months	n/N (%)	n/N (%)	
6 months	n/N (%)	n/N (%)	
Phosphorus			
Baseline	n/N (%)	n/N (%)	
3 months	n/N (%)	n/N (%)	
6 months	n/N (%)	n/N (%)	
Sodium			
Baseline	n/N (%)	n/N (%)	
3 months	n/N (%)	n/N (%)	
6 months	n/N (%)	n/N (%)	
Protein			
Baseline	n/N (%)	n/N (%)	
3 months	n/N (%)	n/N (%)	
6 months	n/N (%)	n/N (%)	
Participants meeting 3 of 4 renal dietary guidelines	n/N (%)	n/N (%)	

Table 4: Mean dietary intake			
	KIDNEYTEXT	**Control**	**P**
Potassium			
Baseline	Mean (SD) / median (IQR)	Mean (SD) / median (IQR)	
3 months	Mean (SD) / median (IQR)	Mean (SD) / median (IQR)	
6 months	Mean (SD) / median (IQR)	Mean (SD) / median (IQR)	
Phosphorus			
Baseline	Mean (SD) / median (IQR)	Mean (SD) / median (IQR)	
3 months	Mean (SD) / median (IQR)	Mean (SD) / median (IQR)	
6 months	Mean (SD) / median (IQR)	Mean (SD) / median (IQR)	

Sodium			
Baseline	Mean (SD) / median (IQR)	Mean (SD) / median (IQR)	
3 months	Mean (SD) / median (IQR)	Mean (SD) / median (IQR)	
6 months	Mean (SD) / median (IQR)	Mean (SD) / median (IQR)	
Protein			
Baseline	Mean (SD) / median (IQR)	Mean (SD) / median (IQR)	
3 months	Mean (SD) / median (IQR)	Mean (SD) / median (IQR)	
6 months	Mean (SD) / median (IQR)	Mean (SD) / median (IQR)	

Table 5: Dietary quality (Australian Healthy Eating Index)			
	KIDNEYTEXT	**Control**	**P**
Baseline			
Total score	**Mean (SD) / median (IQR)**	**Mean (SD) / median (IQR)**	
Fruit (serves/d)	Mean (SD) / median (IQR)	Mean (SD) / median (IQR)	
Vegetables (serves/d)	Mean (SD) / median (IQR)	Mean (SD) / median (IQR)	
Fibre (g/d)	Mean (SD) / median (IQR)	Mean (SD) / median (IQR)	
Added sugars (g/d)	Mean (SD) / median (IQR)	Mean (SD) / median (IQR)	
3 months			
Total score	**Mean (SD) / median (IQR)**	**Mean (SD) / median (IQR)**	
Fruit (serves/d)	Mean (SD) / median (IQR)	Mean (SD) / median (IQR)	
Vegetables (serves/d)	Mean (SD) / median (IQR)	Mean (SD) / median (IQR)	
Fibre (g/d)	Mean (SD) / median (IQR)	Mean (SD) / median (IQR)	
Added sugars (g/d)	Mean (SD) / median (IQR)	Mean (SD) / median (IQR)	
6 months			
Total score	**Mean (SD) / median (IQR)**	**Mean (SD) / median (IQR)**	
Fruit (serves/d)	Mean (SD) / median (IQR)	Mean (SD) / median (IQR)	
Vegetables (serves/d)	Mean (SD) / median (IQR)	Mean (SD) / median (IQR)	
Fibre (g/d)	Mean (SD) / median (IQR)	Mean (SD) / median (IQR)	
Added sugars (g/d)	Mean (SD) / median (IQR)	Mean (SD) / median (IQR)	
Higher scores of the AHEI indicate better dietary quality			

Table 6: Changes to clinical markers			
	KIDNEYTEXT	**Control**	**P**
Baseline			
Elevated potassium	n/N (%)	n/N (%)	
Serum potassium	Mean (SD) / median (IQR)	Mean (SD) / median (IQR)	
Elevated phosphate	n/N (%)	n/N (%)	
Serum phosphate	Mean (SD) / median (IQR)	Mean (SD) / median (IQR)	
IDWG	Mean (SD) / median (IQR)	Mean (SD) / median (IQR)	

3 months			
Elevated potassium	n/N (%)	n/N (%)	
Serum potassium	Mean (SD) / median (IQR)	Mean (SD) / median (IQR)	
Elevated phosphate	n/N (%)	n/N (%)	
Serum phosphate	Mean (SD) / median (IQR)	Mean (SD) / median (IQR)	
IDWG	Mean (SD) / median (IQR)	Mean (SD) / median (IQR)	
6 months			
Elevated potassium	n/N (%)	n/N (%)	
Serum potassium	Mean (SD) / median (IQR)	Mean (SD) / median (IQR)	
Elevated phosphate	n/N (%)	n/N (%)	
Serum phosphate	Mean (SD) / median (IQR)	Mean (SD) / median (IQR)	
IDWG	Mean (SD) / median (IQR)	Mean (SD) / median (IQR)	

Table 7: Healthcare usage			
	KIDNEYTEXT	**Control**	**P**
3 months			
Dietitian consultations	Mean (SD) / median (IQR)	Mean (SD) / median (IQR)	
Unplanned hospitalisations	Mean (SD) / median (IQR)	Mean (SD) / median (IQR)	
Kidney transplantation	Mean (SD) / median (IQR)	Mean (SD) / median (IQR)	
Death	n/N (%)	n/N (%)	
6 months			
Dietitian consultations	Mean (SD) / median (IQR)	Mean (SD) / median (IQR)	
Unplanned hospitalisations	Mean (SD) / median (IQR)	Mean (SD) / median (IQR)	
Kidney transplantation	Mean (SD) / median (IQR)	Mean (SD) / median (IQR)	
Death	n/N (%)	n/N (%)	