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Randomised controlled trial of the impact of haemodiafiltration on uraemic neuropathy: FINESSE study protocol

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ABSTRACT

Introduction The majority of patients undergoing haemodialysis (HD) show evidence of uraemic neuropathy, a condition with no known disease-modifying treatments. The pathogenesis of uraemic neuropathy is poorly understood, but may be related to cumulative exposure to middle molecules or other solutes such as potassium. It is not known whether haemodiafiltration (HDF) reduces the progression of uraemic neuropathy.

Methods and analysis Filtration In the Neuropathy of End-Stage kidney disease Symptom Evolution (FINESSE) is a multicentre, randomised, open-label, blinded endpoint assessment, controlled trial designed to assess the impact of HDF versus HD on uraemic neuropathy. Maintenance HD patients will be randomised in a 1:1 ratio to receive HDF or HD with high-flux membranes for 4 years. The primary endpoint is the difference in the mean change in Total Neuropathy Score (TNS)—a measure of peripheral neuropathy combining symptoms, signs and nerve conduction velocity—over the study period. Secondary outcomes include change at annual timepoints in the TNS and the Neuropathy Symptom Score; and in morbidity, mortality and safety events.

Ethics and dissemination The FINESSE trial has been approved by the Ethics Review Committee of the Sydney South West Area Health Service (HREC/09/RPAH/268) and of Adventist HealthCare Limited (2012–027). When published in a peer-reviewed journal, it will be the largest and longest reported randomised trial aimed at reducing the incidence and severity of uraemic neuropathy. It will advance the understanding of the natural history of uraemic neuropathy and the influence of convective therapies on both neurophysiological and clinical outcomes. It will also allow refinement of current hypotheses surrounding the pathogenesis of uraemic neuropathy and, most importantly, may lead to improvements in the lives of the many patients affected by this debilitating condition.

Trial registration number ACTRN12609000615280.

Strengths and limitations of this study

- Filtration In the Neuropathy of End-Stage kidney disease Symptom Evolution will be the largest (120 participants) and longest (4 years) study of uraemic neuropathy ever undertaken.
- The primary neuropathy endpoint is assessed by a blinded assessor.
- Participants and caring staff are not blinded.
- The primary neuropathy endpoint is measured using a tool that includes symptoms, signs and nerve conduction measures.

INTRODUCTION

Worldwide, the number of people with end-stage kidney disease is expected in double by 2030 to more than 5 million,[1] with most recipients of renal replacement therapy being treated with dialysis.[2 3] In addition to higher mortality, people receiving maintenance dialysis have greater symptom burden than the general population and lower health-related quality of life (HRQOL).[4 5] A contributor to the poorer HRQOL in recipients of dialysis is uraemic neuropathy.[6]

Uraemic neuropathy is a common and progressive distal symmetrical polyneuropathy that manifests with the insidious onset of paraesthesia, pain, weakness and muscle wasting. Nerve conduction studies (NCS) are abnormal in 90%–100% of patients receiving maintenance dialysis therapy.[7] The proportion of these who are symptomatic varies widely in published studies, with rates as high as 93% in small studies,[8] although the true prevalence of symptomatic uraemic neuropathy may be closer to the 16% reported in a recent study of 225 prevalent haemodialysis (HD) patients.[9 10] The pathophysiology of the condition is poorly understood but a causal role has been suggested for middle molecular weight uraemic toxins (‘middle molecules’) and/or persistent hyperkalaemia.[9] There are conflicting reports on the impact of improved renal clearance on disease trajectory, with some reports of

benefit with increased clearance through intensive dialysis[11] or renal transplantation,[12] but others of progression or persistence despite transplantation.[9 13] There are no proven disease-modifying treatments.

Haemodiafiltration (HDF) combines the convective clearance of haemofiltration with HD resulting in enhanced clearance of small and middle molecules,[14] the most widely measured of which is β2-microglobulin.[15 16] HDF may ameliorate uraemic neuropathy by improved clearance of both middle molecules and smaller uraemic solutes. It has been associated with a reduced incidence of carpal tunnel surgery (possibly suggesting reduced β2-microglobulin amyloidosis)[17] in older reports and with improved nerve excitability measures in the modern era.[18 19]

We designed the Filtration In the Neuropathy of End-Stage kidney disease Symptom Evolution (FINESSE) trial to determine the effect of HDF compared with standard high-flux HD on the progression of uraemic neuropathy in recipients of maintenance HD therapy.

METHODS

Aim and design

FINESSE is a multicentre, prospective, randomised, open-label study with blinded endpoint assessment comparing the effect of HDF versus conventional high-flux HD on the incidence and progression of uraemic neuropathy.

Setting and participants

The study is underway at four dialysis centres (Concord Repatriation General Hospital, Royal Prince Alfred Hospital, Prince of Wales Hospital and Sydney Adventist Hospital) in metropolitan Sydney, Australia. Patients dialysing in-centre, meeting the eligibility criteria (box 1) and able to provide informed consent were invited to participate (figure 1).

Box 1 Inclusion and exclusion criteria

Inclusion criteria
1. Incident or prevalent patients requiring maintenance haemodialysis therapy for ESKD.
2. Aged 18 years or older.
3. Suitable for either HDF or standard dialysis in the view of the treating physician.
4. Agreeable to randomisation.

Exclusion criteria
1. Life expectancy less than 6 months.
2. Definite plans to undergo renal transplantation, transfer to a non-study site, transfer to peritoneal dialysis or transfer to home haemodialysis within 12 months of entry to the study.
3. Receiving HDF.
4. Unable or unwilling to complete neuropathy staging, including nerve conduction studies.

ESKD, end-stage kidney disease; HDF, haemodiafiltration.

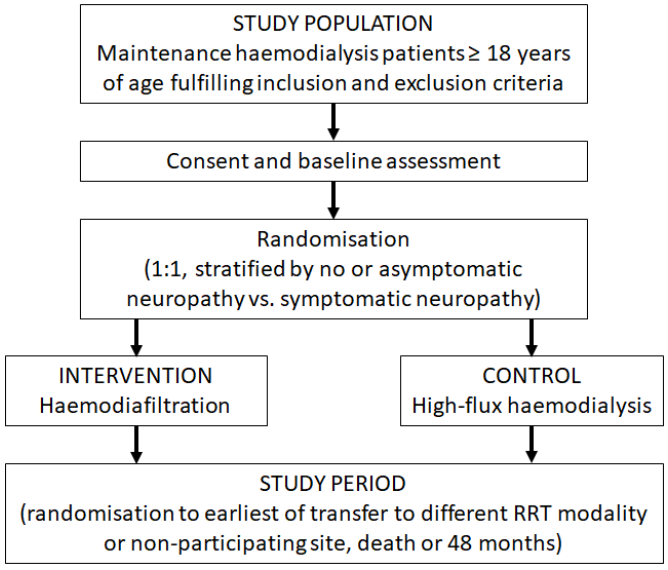

Figure 1 Filtration In the Neuropathy of End-Stage kidney disease Symptom Evolution study flow. RRT, renal replacement therapy.

Study procedures

Eligible dialysis patients at participating units who provided written informed consent proceeded to the baseline visit. The number of screened patients found to be ineligible or who did not participate and their reasons for non-participation were recorded in the site screening log. Study visits occur at 6-monthly intervals with neurological assessment annually (table 1). All participants were asked to consent to follow-up beyond the study period, by direct follow-up until 4 years after the enrolment of the final participant and, separately, via data linkage. Linkage to the Australian and New Zealand Dialysis and Transplant registry (ANZDATA) and to Medicare Australia will enable ascertainment of long-term event endpoints (table 2). While participants and treating clinicians are not blinded, endpoint assessments are undertaken by blinded assessors. Participants are trained not to reveal their allocation to the neurologist/neurophysiologist performing neurological assessment. At the conclusion of the study period, participants and their treating physicians have the option of continuing or altering their allocated treatment.

Intervention and control

Participants are allocated to HDF or standard HD using a high-flux membrane. While the mode of HDF was not prescribed, predilution HDF was initially used for all participants in the treatment arm until June 2010 when only one site had commenced recruitment. After June 2010, all participants in the treatment arm at all sites received postdilution HDF. No minimum convection volume was mandated, although after the presentation of HDF trials at the European Renal Association-European Dialysis and Transplant Association meeting in June 2011, sites were encouraged to use higher volumes as far as possible.[20] Background routine medical care includes the

Table 1 Schedule of visits

			Main study period (months)							
Timepoint	Baseline	Randomisation	6	12	18	24	30	36	42	48
Consent, demographics and dialysis history	X									
Medications, dialysis parameters, BP, laboratory tests	X		X	X	X	X	X	X	X	X
Serum banked	X		X	X	X	X	X	X	X	X
Neurological studies: NCS, TNS, NSS	X			X		X		X		X
Subgroup studies										
Nerve excitability studies	X			X		X		X		X
QOL questionnaires: EQ5D, KDQOL-SF	X		X	X	X	X	X	X	X	X
KDRL Score	X		X	X	X	X	X	X	X	X
HbA1c*	X			X		X		X		X

*Collected only in participants with known diabetes.
BP, blood pressure; EQ5D, EuroQol-5D; HbA1c, glycated haemoglobin; KDQOL-SF, Kidney Disease Quality of Life Short Form; KDRL, Kidney Disease-Related Loss; NCS, nerve conduction studies; NSS, Neuropathy Symptom Score; QOL, Quality of Life; TNS, Total Neuropathy Score.

use of a multivitamin supplement containing water-soluble vitamins (including B-group vitamins) following dialysis. The number of dialysis hours and sessions per week remain at the discretion of the treating physician.

Study duration

Participants remain in the study for 48 months or until they die, receive a renal transplant, change to peritoneal dialysis, move to a dialysis setting unable to provide both treatments or withdraw consent. Follow-up is expected to average between 30 and 36 months. Recruitment commenced in July 2009 and, due to unforeseen contractual restrictions that allowed only limited access to online HDF, was not completed until late 2013. Data locking is yet to be completed and results are anticipated in 2019.

Neuropathy assessment

The primary outcome will be assessed by modified Total Neuropathy Score (TNS). TNS is a measure of peripheral polyneuropathy, is validated in diabetic and chemotherapy-induced neuropathy[21] and, in line with the consensus statement of the American Academy of Neurology for neuropathy assessment in research, includes symptoms, signs and electrophysiological findings.[22] It combines a structured symptom questionnaire (0–8 points), neurological examination signs (0–12 points) and tibial and sural nerve sensory amplitudes on NCS (0–8 points), to provide a score of 0 to 28. Higher scores indicate more severe neuropathy and may be graded on a five-level scale (where grades 0–4 are, respectively, no, minor, moderate, moderate–severe, severe) (tables 3A, B). TNS includes sural nerve amplitude, which is among the most sensitive NCS parameters for the detection of neuropathy.[23–25] Reported TNS interexaminer reliability is high (Spearman's rho 0.966).[26] License for the TNS was provided to Professor Arun Krishnan by Professor David Cornblath and Johns Hopkins University.

An additional assessment tool, the Neuropathy Symptom Score (NSS), is included as a secondary outcome. While it only assesses the symptom domain of neuropathy, NSS is a validated measure devised for diabetic peripheral neuropathy[27] which has been used in HD populations[23] and is employed here using the modification described by Krishnan *et al*[8] (table 4). This questionnaire identifies the presence or absence of symptoms in three categories and assigns one point for each present symptom (four motor, three negative sensory and two positive sensory) with a maximum possible score of 9 points. NSS-based neuropathy stage (table 5) will also be calculated by combining the NSS score, NCS results and the presence or absence of 'disabling' neuropathic symptoms (ie, sensory abnormalities).[8 27 28]

Neuropathy assessments are undertaken by qualified neurologists and neurophysiologists under the supervision of Dr Arun Krishnan. Assessors are blinded to participant treatment allocation. Dr Krishnan will duplicate neuropathy assessments performed by each assessor for five separate patients to allow assessment of inter-rater reliability.

Study endpoints

The primary endpoint is the between-group difference in the mean change in TNS over the study period. The secondary endpoints include a variety of neurological, clinical and safety endpoints (table 2). In addition

Table 2 Study endpoints

Endpoint category	Endpoint
Primary	Difference in mean change in TNS from baseline over the study period
Secondary	
Neuropathy	Proportion with no or asymptomatic neuropathy on TNS at each annual assessment (ie, TNS 0-8)
	Proportion with no or asymptomatic neuropathy on NSS at each annual assessment (ie, Stage 0–1)
	Mean change from baseline in TNS and NSS at each annual assessment
	Mean change from baseline in sural nerve sensory amplitude at each annual assessment (mV)
Safety	Time to access failure*
	Episodes of access failure*
	Episodes of septicaemia†
	Survival at 24, 36 and 48 months
Durability	Durability of intervention at annual assessment up to 48 months
	Durability of intervention after 48 months
Long-term events‡	Surgery for carpal tunnel syndrome
	Parathyroidectomy
	Fractures requiring hospitalisation and in-hospital fractures
	First major coronary event§
	Total major cardiovascular events in composite and by category§
	Number of hospital admissions and hospitalised days
	Technique survival
	Vital status and cause of death
	Survival in each group at 60 months and when survival in the control arm reaches 25%.

*Defined as thrombosis or revision of fistula or graft.
†Defined as blood culture positive septic episode without defined source.
‡Obtained through data linkage, subsequent to the appropriate poststudy approvals.
§Defined as a composite of cardiovascular death or hospitalisation due to/including any of acute myocardial infarction, cerebrovascular event, percutaneous coronary or cerebrovascular revascularisation or surgical coronary or cerebral revascularisation.
NSS, Neuropathy Symptom Score; TNS, Total Neuropathy Score.

to designated endpoints, all participants have routine biochemical and haematological testing at regular intervals (table 1) including predialysis serum calcium, phosphate, bicarbonate, parathyroid hormone, β2-microglobulin, haemoglobin and troponin. A variety of clinical and therapeutic parameters will also be recorded including predialysis systolic blood pressure, dialysis prescription, flow rates, convection volumes and medication use (dose and regimen of phosphate binders, vitamin D analogues, cinacalcet, erythropoietin-stimulating agents and antihypertensive agents).

Participants were also asked to consent to data linkage to the ANZDATA registry and to the Medicare Benefits Schedule and the Pharmaceutical Benefits Scheme records of the Australian universal healthcare system. Data linkage will be used to ascertain vital status, technique survival, healthcare service use and the occurrence of prespecified events during an observational period following the completion of the intervention.

Randomisation

Participants were randomised in a 1:1 fashion with stratification by baseline neuropathy grade. Strata 1 was defined as TNS grade 0–1 (no or minor neuropathy) and strata 2 as TNS grade 2–4 (moderate to severe neuropathy) (tables 3b). The allocation sequence was based on blocks of 4 and generated centrally by an independent statistician who had no other involvement in the study. To ensure allocation concealment, randomisation was performed by an independent university employee based on a physically separate site with no other involvement in the study. The randomisation schedule was known only to these two individuals and to an additional independent unblinded statistician who was responsible for preparing reports for the Data Safety Monitoring Board.

Monitoring and safety

Adverse events and serious adverse events (SAE) are recorded at each study visit. An independent Data Safety Monitoring Board is performing ongoing review of predefined safety parameters and overall study conduct. The committee will autonomously review unblinded data on participant characteristics, including mortality and SAE.

Table 3A Total Neuropathy Score (TNS)

	Score				
Parameter	**0**	**1**	**2**	**3**	**4**
Sensory symptoms	None	Symptoms limited to fingers or toes	Symptoms extend to ankle or wrist	Symptoms extend to knee or elbow	Symptoms above knees or elbows, or functionally disabling
Motor symptoms	None	Slight difficulty	Moderate difficulty	Require help/assistance	Paralysis
Pin sensibility	Normal	Reduced in fingers/toes	Reduced up to wrist/ankle	Reduced up to elbow/ knee	Reduced to above elbow/ knee
Strength	Normal	Mild weakness	Moderate weakness	Severe weakness	Paralysis
Tendon reflexes	Normal	Ankle reflex reduced	Ankle reflex absent	Ankle reflex absent, others reduced	All reflexes absent
Sural amplitude*	Normal/reduced to >95% LLN	76 to 95% LLN	51 to 75% LLN	26 to 50% LLN	0 to 25% LLN
Tibial amplitude†	Normal/reduced to >95% LLN	76 to 95% LLN	51 to 75% LLN	26 to 50% LLN	0 to 25% LLN

*Lower limit of normal range for sural amplitude by age group (age range (years), amplitude (μV)): 0–20, 12 μV; 21–40, 9 μV; 41–60, 7 μV; 61–80, 6 μV.
†Lower limit of normal range for tibial amplitude: 3 mV.

Substudies

Patients who were willing and had sufficient English language ability to self-administer a questionnaire were invited to participate in HRQOL assessments. HRQOL was assessed using the EuroQol-5D-3L,[29] Kidney Disease Quality of Life Short Form V.1.3[30] and the Kidney Disease-Related Loss Score.[31]

Study power

TNS score was chosen as the primary outcome based on the recommendations of the American Academy of Neurology, which strongly emphasised the need for composite measures that incorporated symptomatic and nerve conduction assessments.[22] However, at the time of study design, no existing reports for composite score measurements in dialysis patients were available to inform study power calculations. The study was thus powered for the proportion of patients with symptomatic neuropathy as this data was available and constitutes an important secondary outcome. The expected prevalence of TNS grades in the control group was derived from published data using NSS.[7 8 23] The recruitment target of 120 participants was determined as the sample size that provided 90% power (alpha=0.05) to detect a reduction in the prevalence of moderate to severe neuropathy from 80% in the control arm to 48% in the treatment arm (absolute difference of 32%), including an allowance for 20% combined dropout and loss to follow-up (n=96 in the final analysis). In addition, we also calculated that with 90% power (with alpha=0.05) the study could detect an absolute difference of 2.56 μV in the mean response of sural nerve sensory amplitudes between the treatment groups (assuming a mean sural nerve sensory amplitude of

Table 3B Severity grade for TNS

Symptom status	Grade	Score	Descriptive terminology
Asymptomatic	0	0–1	None
	1	2–8	Minor
Symptomatic	2	9–16	Moderate
	3	17–24	Moderately severe
	4	25–28	Severe

Table 4 Modified Neuropathy Symptom Score

	Score 1 point for presence of a symptom
Symptoms of muscle weakness	
Symptoms of limb muscle weakness	Shoulder girdle and upper arm
	Hand
	Glutei and thigh
	Legs
Sensory disturbances	
Negative symptoms	Difficulty identifying objects in mouth
	Difficulty identifying objects in hands
	Unsteadiness in walking
Positive symptoms	'Numbness,' 'part of your body is asleep,' 'like having been given local anaesthetic,' 'pins and needles', 'prickling,'—at any site
	Pain—burning, deep aching, tenderness—at any location

Table 5 Neuropathy Symptom Score (NSS) stages

Stage	Definition		
	NSS score (max 9)	NCS	'Disabling' neuropathic symptoms
0 No neuropathy	<2	Normal	No
1 Asymptomatic	0	Abnormal	No
2 Symptomatic	≥2	Normal	No
	≥1	Abnormal	No
3 Disabling	≥2	Normal	Yes
	≥1	Abnormal	Yes

Adapted from Krishnan *et al*.[28]
NCS, nerve conduction studies.

5.8±3.9 µV). More recently, studies have been conducted that provide data on the TNS from an external cohort (Krishnan A, personal communication). In 49 dialysis patients, the mean TNS was 9.2±7.8 and 42% (20/48) had TNS grade 2–4 (ie, moderate to severe). Using these assumptions, FINESSE has 90% power to detect a mean difference of 5.2 in TNS between treatment arms at study end and 80% power to detect a mean difference of 4.5. A minimum clinically meaningful difference in neuropathy has been defined as a difference in lower limb motor nerve conduction velocity of 2.2 m/s,[32] or a change of 2 points in a standardised clinical examination[33]—both of which individually result in a change of 2 in TNS score.

Statistical analysis

All analyses will be performed on an intention-to-treat basis. In the primary analysis, the mean change in TNS from baseline will be analysed using a restricted maximum likelihood-based repeated measures approach. Analyses will include the fixed, categorical effects of treatment, visit and treatment-by-visit interaction, as well as the continuous, fixed covariates of baseline score and baseline score-by-visit interaction. Outside of the primary analysis, binary endpoints will be analysed using the χ^2 test to compare proportions. Mann-Whitney U test or transformations may be used when distributions are skewed or not normally distributed. Odds ratios will be estimated using logistic regression analysis. For continuous repeated measures, secondary analysis will be performed using a linear mixed model including random intercept, randomisation and time categories.

Ethics and dissemination

The study received ethical approval. The study is overseen by an independent Data Safety Monitoring Board, coordinated by the Australasian Kidney Trials Network. The FINESSE Study is registered with the Australian New Zealand Clinical Trials Registry (ACTRN12609000615280). The results are intended to be disseminated through conference presentations and publication in the peer-reviewed medical literature.

Patient and public involvement statement

The study objective was to assess the impact of two dialysis modalities in current practice on the severity of neuropathy as assessed in part by patient-reported symptoms and function. There was no direct patient or public contribution to the study design.

DISCUSSION

FINESSE is the largest and longest randomised trial aiming to test a disease-modifying intervention for uraemic neuropathy. This unique cohort of patients will provide valuable information on the natural history of uraemic neuropathy and will determine the place of HDF in its management. As the advent of online ultrapure dialysate generation has reduced the cost of delivering HDF, any benefits shown in FINESSE will be implementable with only a modest cost increment and no requirement for increase in pill burden or time on dialysis.

The primary cause of uraemic neuropathy is believed to be middle molecular weight uraemic toxins ('middle molecules', defined as uraemic toxins with a mass of 500–60 000 Da). Support for this hypothesis comes from the decline in the prevalence of β2-microglobulin amyloidosis and severe uraemic neuropathy correlating with the widespread adoption of high-flux dialysis membranes (defined by their greater clearance of middle molecules).[34] Prior to the introduction of high-flux membranes for HD, peritoneal dialysis patients had a lower prevalence of uraemic neuropathy and recent evidence suggests that peritoneal dialysis may be associated with better neurophysiological parameters than HD, differences attributed to the greater middle molecule clearance afforded by the peritoneal membrane.[35 36] In addition, residual renal function also provides increased middle molecule clearance and is inversely correlated with the presence of neurophysiological abnormalities.[37] Despite these associations, prospective evidence for the middle molecule hypothesis is scarce. Dramatic improvements were shown in an early study using a membrane highly permeable to middle molecules[35] and a recently published trial of 66 participants randomised to HD or haemoperfusion plus HD over 12 weeks reported an increase in sensory conduction velocity and an improvement in symptoms that correlated with a reduction in β2-microglobulin.[38] However, large-scale prospective dialysis trials have not included neuropathy as an outcome.

Despite a large body of circumstantial and observational evidence, no single solute in the middle molecular range has been convincingly identified as the culprit neurotoxin.[9] In response to this, an alternative hypothesis attributes a pathogenic role to persistent hyperkalaemia, which is common in HD patients and may lead to axonal loss via chronic activation of damaging calcium-dependent intracellular mechanisms. Predialysis hyperkalaemia

has been shown to cause peripheral nerve depolarisation which improves in the immediate postdialysis period.[8] Dietary potassium restriction has recently been shown to prevent deterioration in uraemic neuropathy in a small, randomised trial in patients with non-dialysis-dependent chronic kidney disease.[39] While the effect of HDF on middle molecule clearance is the most pronounced difference from conventional HD, HDF does also improve the clearance of small molecules such as potassium.[14] Thus, HDF may plausibly improve uraemic neuropathy outcomes regardless of the underlying pathophysiological mechanisms.

The natural history of uraemic neuropathy also remains incompletely understood. Subclinical disease (abnormal electrophysiological studies in the absence of symptoms) is almost universal, being present in 60%–100% of patients.[9 24] However, it is not clear what proportion of asymptomatic patients will progress to experience symptoms or whether established disease progresses in the face of adequate dialysis. Cross-sectional studies suggest that electrophysiological findings are worse in patients who have been on dialysis for a longer period, and that both clinical and electrophysiological findings increase with patient age.[24 40] The severity of uraemic neuropathy on a single assessment has been associated with mortality.[10 41] As a prospective, longitudinal study, the current trial affords the opportunity to clarify important aspects of the natural history of uraemic neuropathy, and may uncover additional modifiable and non-modifiable risk factors for disease progression.

While pilot studies have demonstrated improvement in symptoms and NCS parameters with zinc supplementation of dialysate, with vitamin B12 and with erythropoietin therapy,[42–44] there is no established disease-altering treatment for uraemic neuropathy. Moreover, even the therapeutic effect of dialysis on uraemic neuropathy is unclear. Adequate peritoneal and HD appear to be equally effective in retarding the progression of established uraemic neuropathy but neither is likely to lead to significant improvement.[45 46] Case reports suggest that improvement in symptoms and neurophysiological abnormalities can be associated with intensive HD (5–6 times per week)[47] while the association with renal transplantation is the subject of conflicting reports.[12 48] Even if intensive HD and transplantation are effective treatments, they may not be available modalities for all, especially the very frail. HDF is a modality that is more widely accessible and can be delivered with minimal, if any, increase in cost.[49]

FINESSE trial will also provide a deeper understanding of the utility of the clinical measures of uraemic neuropathy. While NCS measures are only loosely correlated with symptoms and signs of uraemic neuropathy, the multimodal TNS permits the identification of patients with the full range of symptoms, signs and electrophysiological abnormalities. However, the minimum clinically meaningful difference for TNS is not known. This study may permit a greater understanding of the meaning of this measure in accordance with the growing focus on patient-centred outcomes in clinical research.[50]

In conclusion, morbidity due to uraemic neuropathy is expected to increase in line with the increases in dialysis numbers, proportion of patients with concurrent diabetes and waiting time for kidney transplantation. FINESSE trial will provide a new perspective on uraemic neuropathy in the modern era and add substantially to current understanding of the benefits of HDF.

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Contributors BS contributed to the analysis and interpretation, and drafted the manuscript. MG, CH, AVK, MK and VP are Trial Steering Committee members, contributed to the study design, and oversaw the conduct of the study. MF and PS are Trial Steering Committee members, and oversaw the conduct of the study. SH, KG, JB, AH and AK contributed to the acquisition of data. MJJ, Chair of the Trial Steering Committee, is primarily responsible for the conception and design of the study and oversees the conduct of the study.

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Competing interests MJ serves on an advisory board for Baxter Healthcare.

Patient consent for publication Not required.

Ethics approval Ethics Review Committee (Royal Prince Alfred Hospital (RPAH) Zone) of the Sydney South West Area Health Service (HREC/09/RPAH/268)

Provenance and peer review Not commissioned; externally peer reviewed.

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