View metadata, citation and similar papers at core.ac.uk

brought to you by CORE

provided by eScholarship@UMMS

University of Massachusetts Medical School

eScholarship@UMMS

Open Access Articles | Open Access Publications by UMMS Authors

2020-02-05

Benefits and harms of high-dose haemodiafiltration versus high-flux haemodialysis: the comparison of high-dose haemodiafiltration with high-flux haemodialysis (CONVINCE) trial protocol

Peter J. Blankestijn
University Medical Center Utrecht

Et al.

Let us know how access to this document benefits you.

Follow this and additional works at: https://escholarship.umassmed.edu/oapubs

Part of the Analytical, Diagnostic and Therapeutic Techniques and Equipment Commons, Female Urogenital Diseases and Pregnancy Complications Commons, Health Services Administration Commons, Health Services Research Commons, Male Urogenital Diseases Commons, and the Nephrology Commons

Repository Citation

Blankestijn PJ, Fischer KI, Barth C, Cromm K, Canaud B, Davenport A, Grobbee DE, Hegbrant J, Roes KC, Rose MS, Strippoli GF, Vernooij RW, Woodward M, de Wit GA, Bots ML. (2020). Benefits and harms of high-dose haemodiafiltration versus high-flux haemodialysis: the comparison of high-dose haemodiafiltration with high-flux haemodialysis (CONVINCE) trial protocol. Open Access Articles. https://doi.org/10.1136/bmjopen-2019-033228. Retrieved from https://escholarship.umassmed.edu/oapubs/4151

Creative Commons License

This work is licensed under a Creative Commons Attribution-Noncommercial 4.0 License

This material is brought to you by eScholarship@UMMS. It has been accepted for inclusion in Open Access Articles by an authorized administrator of eScholarship@UMMS. For more information, please contact Lisa.Palmer@umassmed.edu.

BMJ Open

Benefits and harms of high-dose haemodiafiltration versus high-flux haemodialysis: the comparison of high-dose haemodiafiltration with high-flux haemodialysis (CONVINCE) trial protocol

Peter J Blankestijn,[1] Kathrin I Fischer,[2] Claudia Barth,[3] Krister Cromm ,[4] Bernard Canaud,[4,5] Andrew Davenport,[6] Diederick E Grobbee,[7,8] Jörgen Hegbrant,[9] Kit C Roes,[7] Matthias Rose,[2,10] Giovanni FM Strippoli,[11,12] Robin WM Vernooij ,[1,7] Mark Woodward,[13,14,15] G Ardine de Wit,[7,16] Michiel L Bots[7]

To cite: Blankestijn PJ, Fischer KI, Barth C, *et al*. Benefits and harms of high-dose haemodiafiltration versus high-flux haemodialysis: the comparison of high-dose haemodiafiltration with high-flux haemodialysis (CONVINCE) trial protocol. *BMJ Open* 2020;**10**:e033228. doi:10.1136/bmjopen-2019-033228

► Prepublication history and additional material for this paper are available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2019-033228).

Received 26 July 2019
Revised 12 December 2019
Accepted 31 December 2019

Check for updates

© Author(s) (or their employer(s)) 2020. Re-use permitted under CC BY-NC. No commercial re-use. See rights and permissions. Published by BMJ.

For numbered affiliations see end of article.

Correspondence to
Dr Peter J Blankestijn;
P.J.Blankestijn@umcutrecht.nl

ABSTRACT

Introduction End-stage kidney disease (ESKD) is a major public health problem affecting more than 2 million people worldwide. It is one of the most severe chronic non-communicable diseases. Haemodialysis (HD) is the most common therapeutic option but is also associated with a risk of cardiovascular events, hospitalisation and suboptimal quality of life. Over the past decades, haemodiafiltration (HDF) has become available. Although high-dose HDF has shown some promising survival advantage compared to conventional HD, the evidence remains controversial. A Cochrane systematic review found, in low-quality trials, with various convective forms of dialysis, a reduction in cardiovascular, but not all-cause mortality and the effects on non-fatal cardiovascular events and hospitalisation were uncertain. In contrast, an individual patient data analysis suggested that high-dose HDF reduced both all-cause and cardiovascular mortality compared to HD. In view of these discrepant results, a definitive trial is required to determine whether high-dose HDF is preferable to high-flux HD. The comparison of high-dose HDF with high-flux HD (CONVINCE) study will assess the benefits and harms of high-dose HDF versus a conventional high-flux HD in adults with ESKD.

Methods and analysis This international, prospective, open label, randomised controlled trial aims to recruit 1800 ESKD adults treated with HD in nine European countries. Patients will be randomised 1:1 to high-dose HDF versus continuation of conventional high-flux HD. The primary outcome will be all-cause mortality at 3 years' follow-up. Secondary outcomes will include cause-specific mortality, cardiovascular events, all-cause and infection-related hospitalisations, patient-reported outcomes (eg, health-related quality of life) and cost-effectiveness.

Ethics and dissemination The CONVINCE study will address the question of benefits and harms of high-dose HDF compared to high-flux HD for kidney replacement therapy in patients with ESKD with a focus on survival, patient perspectives and cost-effectiveness.

Trial registration number Netherlands National Trial Register (NTR 7138).

Strengths and limitations of this study

- ► This is the largest randomised trial to assess the efficacy and safety of high-dose haemodiafiltration versus continuation of conventional high-flux haemodialysis in patients with end-stage kidney disease (ESKD).
- ► Information will be collected about patient-reported outcomes, particularly health-related quality of life.
- ► A cost-effectiveness analysis for the two treatment modalities will be performed.
- ► Information about co-medications, given that patients with ESKD have often comorbidities, will be collected during follow-up.

INTRODUCTION

End-stage kidney disease (ESKD) is a major public health problem, affecting more than 2 million people requiring kidney replacement therapy in 2015,[1] and the global prevalence of kidney replacement therapy is expected to double by the year 2025, reaching 4.9 million people.[2] ESKD is one of the most severe chronic non-communicable diseases worldwide associated with approximately 10%–20% mortality after 1 year.[3] The 5-year mortality rate is above that of some of the more common solid organ malignancies, including regional breast cancer, regional

BMJ Open: first published as 10.1136/bmjopen-2019-033228 on 5 February 2020. Downloaded from http://bmjopen.bmj.com/ on March 12, 2020 at Medical School Library University of Mass. Protected by copyright.

colon cancer and kidney cancer.[4 5] Kidney replacement therapy is generally required when residual kidney function falls below 10% of the normal value and therapeutic options include haemodialysis (HD), peritoneal dialysis and kidney transplantation. Regenerative medicine, to develop an implantable kidney, is still in the experimental phase and access to kidney transplantation varies between countries. Even in those countries with an active transplant programme, only around 20% of the dialysis population are listed for transplantation.[6] Worldwide, HD treatment is the standard of care for the vast majority of patients with ESKD.[1 7] However, the risk for fatal and non-fatal cardiovascular events, infections, hospitalisation and reduced quality of life is high among patients treated with HD.[7 8] Given the high prevalence and high mortality rates, improvements in the currently available standard HD care are needed.

High-flux HD is defined as HD using high-flux dialysis membranes and bicarbonate-based dialysate. Over the past decades, haemodiafiltration (HDF),[9] an alternative to standard HD, has become available. By adding convective clearance HDF removes middle and large uraemic compounds that accumulate due to kidney failure more effectively than standard high-flux HD. Greater convective exchange increases the clearance of uraemic toxins.[10] HDF might also improve survival by increasing the removal of middle-sized uraemic toxins, reducing oxidative stress[11 12] and improving intradialytic cardiovascular stability.[13] A recent individual patient-level data meta-analysis, including 2753 patients[14 15] has shown that, during a median follow-up of 2.5 years, compared to the standard HD, a high-dose HDF (convection volume >23 L/session) reduced the risk of all-cause mortality by approximately 22%, and of cardiovascular disease mortality by 31%,[14] the latter mostly due to reduction in coronary heart disease death.[16] However, a previous Cochrane systematic review reported that convective dialysis therapies appeared to reduce cardiovascular, but not all-cause, mortality and had uncertain effects on non-fatal cardiovascular events and hospitalisation compared to HD. The quality of evidence was considered low due to methodological limitations and poor reporting of the primary studies. In addition, the majority of trials were not specifically designed to assess the effects of various convection volumes. Thus, patients were not randomised to different targets of convective volumes and were not equally likely to achieve a specific convective volume (ie, healthier patients were more likely to achieve a higher convection volume).[15 17–19] Furthermore, there was remarkable heterogeneity in the dialysis interventions across studies, including differences in convective modalities ranging from haemofiltration, HDF with bagged solutions, and online HDF. When HDF was first introduced, small volume convective exchanges were performed with sterile bagged fluid replacement,[20] and it was only more recently, following technical advances in dialysis machines[21] and production of online ultra-pure dialysis water,[9] that higher volume convective exchanges were possible.[10] As such, depending on which studies were considered, published meta-analyses report either a beneficial effect for HDF or no benefit compared to conventional high-flux HD.[19 22 23]

We report on the design of the CONVINCE study, a randomised controlled trial that evaluates the benefits and harms of a high-dose HDF versus a conventional high-flux HD treatment in adults with ESKD.

Study objectives

Based on previous evidence, we hypothesise that high-dose HDF will significantly decrease mortality risk compared to conventional high-flux HD treatment in adults with ESKD. The objectives of our study are:

1. To evaluate the comparative efficacy of high-dose HDF and high-flux HD on all-cause and cause-specific death, fatal and non-fatal cardiovascular events, all-cause and cause-specific hospitalisations.
2. To evaluate the effect of high-dose HDF versus high-flux HD on patient-reported outcomes (PROs), particularly health-related quality of life.
3. To conduct a cost-effectiveness analysis for the two treatment modalities.

METHODS AND ANALYSIS

Study population

Eligible patients will be adults with ESKD treated with high-flux HD compliant with the inclusion and exclusion criteria outlined in table 1. Participants will be recruited in up to nine European countries. As of June 2019, we are active in France, Germany, Hungary, Poland, Portugal, Romania, Spain, The Netherlands and the United Kingdom. Around 70 sites will participate, including both academic and hospital based-dialysis centres, and private dialysis providers (Fresenius Medical Care, B. Braun Avitum and Diaverum).

Study design

The CONVINCE study is an international, prospective, randomised, controlled trial. Allocation to high-flux HD and high-dose HDF will be concealed by central randomisation, with a 1:1 ratio. A block randomisation scheme, stratified by centre, will be conducted.

Study intervention

The experimental intervention will be a high-dose HDF with online production of substitution fluid and ultrapure dialysis fluid. Substitution fluid should be infused in postdilution mode.[8] In case of different substitution modality (pre, mid or mixed dilution) a correction factor (2 to 1.5 times higher than in post dilution mode respectively) will be applied to match the performance as detailed in online supplementary appendix 1. High-dose HDF is defined as a convection volume of ≥23 L (range ±1 L). Previous studies have shown that it is also possible to achieve these convection volumes in older patients with comorbidities.[24 25] In cases where the target convection volume (≥23 L/ session; range ±1 L) is not

BMJ Open: first published as 10.1136/bmjopen-2019-033228 on 5 February 2020. Downloaded from http://bmjopen.bmj.com/ on March 12, 2020 at Medical School Library University of Mass. Protected by copyright.

Table 1 Inclusion and exclusion criteria for enrolment in CONVINCE

Inclusion criteria	A participant must meet ALL of the following criteria in order to participate: 1. Signed and dated written Informed Consent Form obtained from the participant or his/her guardian or in accordance with local regulations. 2. Aged ≥18 years. 3. Diagnosed with ESKD. 4. On HD treatment for ≥3 months. 5. Likely to achieve high-dose HDF (≥23 L, in postdilution mode), according to the protocol. 6. Willing to have a dialysis session with duration of ≥4 hours, three times a week. 7. Understands study procedures and is able to comply.
Exclusion criteria	A participant who meets any of the following criteria will be excluded from participation: 1. Severe participant non-compliance defined as severe non-adherence to the dialysis procedure and accompanying prescriptions, especially frequency and duration of dialysis treatment. 2. Life expectancy <3 months. 3. HDF treatment <90 days before screening. 4. Anticipated living donor kidney transplantation <6 months after screening. 5. Evidence of any other diseases or medical conditions that may interfere with the planned treatment, affect participant compliance or place the participant at high risk for treatment-related complications. 6. Participation in any other study will be discussed with and decided by the Executive Board. 7. Unavailable ≥3 months during the study conduct for study visits.

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

initially achieved, then steps should be undertaken in an effort to achieve the target convection volume which may require a stepwise adjustment of dialysis prescription to achieve this target over 2–3 weeks (online supplementary appendices 1-3 and table 2).[25 26] If the target convection volume still cannot be reached after these steps, then the highest volume possible should be used. Convection volume, and reasons why the target could not be reached, should be recorded into the electronic study case record form (eCRF). Centres are required to check dialysis water quality to ensure that all patients dialyse with ultra-pure water (online supplementary appendix 4).

The control group will receive high-flux HD using high-flux dialysis membranes and ultrapure bicarbonate-based dialysis fluid as standard of dialysis care.

Co-interventions

During follow-up, patients might receive (in a non-randomised fashion) additional co-interventions, including blood pressure modifying medication,

Table 2 Achieving convection volume ≥23 L/treatment session

	Processed BV (L)‡	FF 20	21	22	23	24	25	26	27	28	29	30	31*
Treatment time 3.5 hours													
Qb† 300 mL/min	63.0	12.6	13.2	13.9	14.5	15.1	15.8	16.4	17.0	17.6	18.3	18.9	19.5
Qb 350 mL/min	73.5	14.7	15.4	16.2	16.9	17.6	18.4	19.1	19.8	20.6	21.3	22.1	22.8
Qb 400 mL/min	84.0	16.8	17.6	18.5	19.3	20.2	21.0	21.8	22.7	23.5	24.4	25.2	26.0
Treatment time 4.0 hours													
Qb 300 mL/min	72.0	14.4	15.1	15.8	16.6	17.3	18.0	18.7	19.4	20.2	20.9	21.6	22.3
Qb 350 mL/min	84.0	16.8	17.6	18.5	19.3	20.2	21.0	21.8	22.7	23.5	24.4	25.2	26.0
Qb 400 mL/min	96.0	19.2	20.2	21.1	22.1	23.0	24.0	25.0	25.9	26.9	27.8	28.8	29.8
Treatment time .4.5 hours													
Qb 300 mL/min	81.0	16.2	17.0	17.8	18.6	19.4	20.3	21.1	21.9	22.7	23.5	24.3	25.1
Qb 350 mL/min	94.5	18.9	19.8	20.8	21.7	22.7	23.6	24.6	25.5	26.5	27.4	28.4	29.3
Qb 400 mL/min	108.0	21.6	22.7	23.8	24.8	25.9	27.0	28.1	29.2	30.2	31.2	32.4	33.5

This table shows the interaction between session treatment time, blood flow rate through the extra corporeal circuit and 'filtration fraction'. Convection volumes of ≥23 L/session are best achieved by a 4-hour session with a minimum blood flow of 350 mL/min. Convection volumes ≥23 L/treatment are marked in green.
Formula: Convection volumes in post-dilution HDF in relation to treatment time.
*Filtration fraction (as a percentage of blood flow: (convective flow rate / blood flow rate)×100).
†Effective blood flow rate (Qb).
‡ BV = blood volume
BV, blood value; FF, filtration fraction.

BMJ Open: first published as 10.1136/bmjopen-2019-033228 on 5 February 2020. Downloaded from http://bmjopen.bmj.com/ on March 12, 2020 at Medical School Library University of Mass. Protected by copyright.

medication used for managing co-morbid conditions and complications of chronic kidney disease, including diabetes, ischaemic heart disease and heart failure, as part of usual care. Additionally, erythropoiesis stimulating agents (ESAs), iron preparations, drugs for treatment of hyperkalaemia, phosphate binders, vitamin D and vitamin D analogues, parathyroid hormone (PTH) antagonists and extracorporeal anticoagulants might be applied, as these are considered part of routine clinical care.

Study procedures

Patient visits start at the time of randomisation, followed by monthly visits for the first 12 months and then 3 monthly from 12 months up to 36 months. After randomisation, patients will continue thrice weekly dialysis and have regular safety and dialysis efficacy assessments, as described in table 3. After initial study entry assessments, data will be collected and study specific activities will be performed every 3 months until the end of the study,

Table 3 Schedule of the activities in CONVINCE

Visit	Screening	Randomisation	V1	V2	V3	V4	V5	V6	Vn*	EOT
Month	−1–0 Days	Day 0	3 months	6 months	9 months	12 months	15 months	18 months	21 months	24–36 months
Visit window in days			±14 days	±14 days	±14 days	±14 days	±14 days	±14 days	±14 days	±14 days
Informed consent	X									
Inclusion and exclusion criteria†	X									
Demographics	X									
Medical history	X									
Randomisation		X†								
Vital signs and weight‡	X		X	X	X	X	X	X	X	X
Height	X									
Vascular access§	X		X	X	X	X	X	X	X	X
Laboratory¶	X			X		X		X		X
*Concomitant medication***	X		X	X	X	X	X	X	X	X
Patient Health Assessments††	X		X	X	X	X	X	X	X	X
Physical performance test	X									
EQ-5D-5L	X		X	X	X	X	X	X	X	X
Questionnaire about healthcare use, informal care and productivity	X		X	X	X	X	X	X	X	X
Dialysis specifics‡‡	X		X	X	X	X	X	X	X	X
Serious adverse events§§	X	X	X	X	X	X	X	X	X	X

Study procedures shown in italic are routine clinical practice procedures. Information from these procedures is expected to be available as part of routine clinical practice. If not routinely collected, it should be recorded in the electronic study case record form as non-available data.
*Participants are followed for at least 24 months. That means that for the first patient, the follow-up time will be the enrolment time up to the last patient in (12 months) plus the follow-up time of the last patient in (24 months). So there will be patients that have visits scheduled at 27 months, 30 months, 33 months and 36 months.
†Subjects randomised to high-dose HDF can continue the study after higher convection volume of ≥23 L in postdilution mode is reached. The reason for not reaching higher convection volume should be recorded.
‡Systolic and diastolic blood pressure and heart rate should be measured once before and after dialysis in a sitting position. The body weight before and after dialysis will be measured and reported.
§In case of vascular access (native fistula or graft) the results of vascular access flow assessment should be recorded at least twice a year (if available).
¶The following laboratory values will be recorded (incl. units) before dialysis (if available): haemoglobin, sodium, potassium, calcium, phosphate, creatinine, urea, magnesium, parathyroid hormone, C-reactive protein and residual renal function (urine sampling). After dialysis the following laboratory values will be recorded (incl. units): urea and creatinine. Single-pool Kt/V urea will be calculated and recorded together with the calculation method.
**The following concomitant medication, including dosage and frequency, will be recorded during screening: Antihypertensives: agents affecting the renin-angiotensin system, beta blockers; lipid modifying medication; medication used for diabetes; heparin; erythropoiesis stimulating agents; Iron preparations; drugs for treatment of hyperkalaemia; phosphate binders; vitamin D and vitamin D analogues; PTH antagonists. The following concomitant medication, including dosage and frequency, will be recorded during all study visits: Drugs for treatment of hyperkalaemia; phosphate binders; vitamin D and vitamin D analogues; PTH antagonists; erythropoiesis stimulating agents; medication used to treat SAEs.
††During the Screening visit the Patient Health Assessment Screening should be completed. During all other study visits the Patient Health Assessment quarterly. In between the study visits, during the first 12 months of study conduct the Patient Health Assessment Monthly should be completed every month. Questionnaires need to be completed within the first hour after the dialyses has started.
‡‡The following dialysis specifics will be recorded for all subjects: type of dialyser, delivered blood flow rate in the extracorporeal circuit, dialysis session time, anticoagulation, type vascular access, net ultrafiltration volume (=desired weight loss). Additional dialysis specifics will be recorded for subjects receiving high-dose HDF: achieved convection volume, substitution volume and number of treatment sessions not performed as HDF in the previous 3 months.
§§SAEs will be assessed from the signing of the Informed Consent Form until end of the study for the subject. If the subject drops out (eg, due to kidney transplantation) he/she will be followed for mortality and morbidity until the end of the study.
EOT, end of treatment; HDF, haemodiafiltration; PTH, parathyroid hormone; SAE, serious adverse event.

BMJ Open: first published as 10.1136/bmjopen-2019-033228 on 5 February 2020. Downloaded from http://bmjopen.bmj.com/ on March 12, 2020 at Medical School Library University of Mass. Protected by copyright.

apart from the Patient Health Assessment (PHA) questionnaire which is to be completed monthly for the first 12 months of the study.

Study measurements

After an initial screening visit to determine subject eligibility, suitable patients will be asked to take part in the study and provide written informed consent. Patients who fail to meet the study entry criteria will not be rescreened. Once entered into the study each participant recruited into the study will be given a unique study number. Data will be collected during routine clinical practice, including year of birth, gender, ethnicity, relevant medical history, lifestyle information (smoking, alcohol use, work status and use of informal care) concomitant medication and current medical conditions, including cause of ESKD and date of ESKD diagnosis. In keeping with routine clinical practice, pretreatment and post-treatment weight, along with systolic and diastolic blood pressure and heart rate, will be measured once before, and once after, the dialysis session in a sitting position during all visits. Height of the participant will be recorded at screening only. Vascular access flow assessments should be recorded at least twice a year.

During all follow-up visits, information will be collected on drugs for treatment of hyperkalaemia, phosphate binders, vitamin D and vitamin D analogues, PTH antagonists, ESAs and medication used to treat serious adverse events. During the screening visit, a physical performance test will be taken covering nine tasks to assess multiple domains of physical function, simulating activities of daily living. The physical performance test will be performed by dialysis centre staff or members of the research team.[27]

Laboratory measurements

During the study entry visit, at the 6, 12 and 18-month review visits, and end of the trial the following laboratory values will be recorded before dialysis: haemoglobin, sodium, potassium, calcium, phosphate, creatinine, urea, magnesium, PTH, C-reactive protein and residual renal function (urine sampling). Local laboratory procedures will be followed to perform these measurements. After dialysis, urea and creatinine will be recorded. Single-pool Kt/V urea will be calculated and recorded together with the calculation method. All assessments will be performed by a local laboratory and are part of standard assessments (ie, routine clinical practice) for dialysis participants. If centres do not routinely collect all of the data items, those items will then be recorded in the eCRF as not routinely collected.

Dialysis specific measurements

Information will be collected during screening, 6 monthly review visit, 12 monthly review visit, 18 monthly review visit and at the end of trial visit on type of dialyser, blood flow rate through the extracorporeal circuit, session time, anticoagulation (type and dosage), type of vascular access and net ultrafiltration volume (=sessional weight loss). For high-dose HDF patients, we will collect data on achieved convection volume, substitution volume and the number of treatment sessions not performed as high-dose HDF in the previous 3 months.

Study outcomes

The primary outcome will be all-cause mortality. Secondary outcomes will be cardiovascular events which comprise:

- Cause specific mortality (at least cardiovascular and non-cardiovascular death; others with high frequency may be added).
- Acute coronary syndrome.
- Myocardial infarction (STEMI/NSTEMI).
- Unstable angina pectoris.
- Congestive heart failure.
- Coronary artery bypass graft.
- Percutaneous transluminal coronary angioplasty and/or stenting.
- Transient ischaemic attack.
- Cerebral vascular accident.
- Therapeutic carotid procedure (endarterectomy and/or stenting).
- Vascular intervention of peripheral arterial ischaemia (revascularisation, percutaneous transluminal angioplasty and/or stenting using physician reporting based of standard consensus definitions)[28–32] (online supplementary appendix 5).
- Hospitalisation for infection related causes.[32]
- Any hospitalisation of more than 24 hours.

If a participant drops out (eg, due to kidney transplantation, switching to another dialysis modality or transferring out of the participating centre), effort will be made to collect information on his/her vital status until the end of the study follow-up.

Assessment of patient-reported outcomes

To determine whether high-dose HDF improves patients' self-reported outcomes (PROs), patients will be asked to complete the PHAs (box 1). These assessments were compiled following a construct-based approach. In due consideration of international initiatives, such as Standardised Outcomes in Nephrology (SONG)[33] and International Consortium for Health Outcomes Measurements (ICHOM),[34] and results of interviews with patients and healthcare professionals, we determined domains and symptoms most relevant to patients with ESKD. Based on these, validated questionnaires covering the respective health domains were compiled to the Patient Health Assessment sets. The PHA sets vary in coverage of included health domains. Whereas the baseline assessment is the most comprehensive, only a subset of domains are included in the monthly assessment (box 1).

Most health domains will be assessed by use of PROMIS measures[35] which are based on modern test theory methods. The PROMIS item banks allow to apply customised short forms as well as computer-adaptive tests, aiming

BMJ Open: first published as 10.1136/bmjopen-2019-033228 on 5 February 2020. Downloaded from http://bmjopen.bmj.com/ on March 12, 2020 at Medical School Library University of Mass. Protected by copyright.

Box 1 List of the patient reported outcomes (PROs questionnaires in CONVINCE)

Patient health assessments

The Patient Health Assessment Screening (PHA-Screening) is a comprehensive instrument to assess key sociodemographic information, study targeted information about the medical history, their treatment expectation and their perceived health status. This assessment will also include instruments to evaluate factors which may contribute to the outcome prediction model (ie, perceived stress, self-efficacy, social support). Instruments included in the initial assessment tools are:

- Sociodemographic variables & treatment information.
- PROMIS Fatigue 6-item customised short form.
- Time to recovery module.
- Modified Kidney Disease Quality of Life (KDQOL) symptom checklist.
- Health transition items (2 items of the SF-36).
- PROMIS Physical Function 4-item short form (part of the PROMIS Profile-29).
- PROMIS Cognitive Abilities 4-item customised short form.
- PROMIS Pain Interference 4-item short form (part of the PROMIS Profile-29).
- PROMIS Pain Intensity one item (part of the PROMIS Profile-29).
- PROMIS Anxiety 4-item short form (part of the PROMIS Profile-29).
- PROMIS Depression 4-item short form (part of the PROMIS Profile-29).
- PROMIS Ability to participate in social roles and activities 4-item short form (part of the PROMIS Profile-29).
- PROMIS Sleep disturbance 4-item short form (part of the PROMIS Profile-29).
- Perceived Stress Questionnaire 5-item short form.
- PROMIS Self-efficacy 4-item short form.
- MOS Social Support Scale 4-item short form.

The Patient Health Assessment Quarterly (PHA-Quarterly) is a comprehensive assessment of the participants health status, which includes the core instruments of the screening instruments:

- PROMIS Fatigue 6-item customised short form.
- Time to recovery module.
- modified KDQOL symptom checklist.
- 2 Health transition items (SF-36)–modified.
- PROMIS Physical Function 5-item short form (part of the PROMIS Profile-29).
- PROMIS Cognitive Abilities 4-item customised short form.
- PROMIS Pain Interference 4-item short form (part of the PROMIS Profile-29).
- PROMIS Pain Intensity 1-item (part of the PROMIS Profile-29).
- PROMIS Anxiety 4-item short form (part of the PROMIS Profile-29).
- PROMIS Depression 4-item short form (part of the PROMIS Profile-29).
- PROMIS Ability to participate in social roles and activities 4item short form (part of the PROMIS Profile-29).
- PROMIS Sleep disturbance 4-item short form (part of the PROMIS Profile-29).

The Patient Health Assessment Monthly (PHA-Monthly) will monitor the health status monthly with a parsimonious assessment of key health domains, including fatigue, physical function, depression, social participation and items asking about the recovery time. Instruments included for the monthly assessment are:

- Modified transition question (SF-36).
- PROMIS Physical Function 3-item short form (part of the PROMIS Profile-29).
- PROMIS Fatigue 3-item short form (part of the PROMIS Profile-29).

Continued

Box 1 Continued

- Two items time to recovery module.
- PROMIS Depression 3item short form (part of the PROMIS Profile-29).
- PROMIS Ability to participate in social roles and activities 3-item short form (part of the PROMIS Profile-29).

Based on the technical infrastructure and the availability of PROMIS item banks in participating countries (availability of translations) computer-adaptive tests (CATs) might replace the respective PROMIS short forms.

for higher measurement precision, while reducing respondent burden.

In addition, we will apply the SF-12 version 2[36] to assess overall health-related quality of life, and the PHQ-9[37] to assess depression.

The Patient Health Assessment sets will be applied at screening (PHA-Screening) and every 3 months (PHA-Quarterly). During the first 12 months, patients will complete a short assessment (PHA-Monthly) on a monthly base in between the scheduled visits.

Cost–utility analysis and budget-impact analysis

The economic evaluation will consist of a cost–utility analysis to express efficiency in terms of costs per Quality Adjusted Life Year (QALY). Incremental costs and effects of both treatments will be compared and Incremental Cost Utility Ratios will be estimated. The cost–utility analysis takes a societal perspective, implying that healthcare costs, patient and family costs and productivity costs are included. Healthcare use of patients in both groups will be monitored in the eCRF and via patient questionnaires. Patient and family costs, including informal care, and productivity losses are collected through patient questionnaires. These questionnaires consists of relevant parts of the institute of Medical Technology Assessment (iMTA) Productivity Cost Questionnaire (iPCQ), to capture productivity losses associated with ESKD or its treatment,[38] and the iMCQ, for healthcare use outside the hospital and for patient and family costs.[39] QALYs will be estimated by use of the EQ-5D-5L questionnaire.[40] The EQ-5D-5L is a questionnaires that covers five domains of quality of life (ie, mobility, selfcare, usual activities, pain/discomfort and anxiety/depression) each with five levels of functioning (no problems, some problems, moderate problems, severe problems, extreme problems). The EQ-5D-5L describes 3125 (5^5) unique health states, with associated values to be used for QALY calculations.[41] Based on trial data, probabilistic sensitivity analyses with 5000 bootstrap replications will be applied to estimate the Incremental Cost Effectiveness Ratio (ICER) and to plot cost-effectiveness planes and acceptability curves. In addition to the economic evaluation, budget impact analyses will be constructed for the different countries that participate in the trial, using country specific perspectives, depending on the health system of the country.

Monitoring data and safety

An independent Data and Safety Monitoring Board (DSMB), comprising two nephrologists and one

BMJ Open: first published as 10.1136/bmjopen-2019-033228 on 5 February 2020. Downloaded from http://bmjopen.bmj.com/ on March 12, 2020 at Medical School Library University of Mass. Protected by copyright.

biostatistician, has been established to monitor the progress of the study and ensure that the safety of participants enrolled in the study is not compromised. Details of the composition, meetings, roles, responsibilities and processes of the DSMB will be documented in the DSMB charter. The independent DSMB will review primary outcome and safety data at regular intervals. Reports and recommendations (continue, amend or stop the study, based on cumulative findings) will be reported to the Project Coordinator, who is responsible for informing the General Assembly (online supplementary appendix 6).

Sample size

The recent meta-analysis suggests a 2.5-year mortality rate of 40%[14] which is in line with multiple other sources, including the United States Renal Data System,[42] Dialysis Outcomes and Practice Patterns Study[43] and the aforementioned Cochrane systematic review.[19] We anticipate an expected risk reduction of 25%. The sample size calculation is driven by the assumed target HR, a two-sided type 1 error of 5% and specification of 90% power. This means that for a HR of 0.75, 515 events need to be observed. Given the above assumptions on the 2.5-year mortality rate, and an estimated average follow-up of approximately 2.5 years, an estimated number of participants of 900 (HR 0.75) per group will need to be recruited. Thus, the total sample size will be 1800 participants to be randomised. We intend to recruit 400 from academic and hospital based-dialysis centres and 1400 from private dialysis providers.

Data analysis

Before the anticipated end of the study a final statistical analysis plan will be drafted and agreed on by CONVINCE General Assembly. The primary analysis will be according to the principle of intention-to-treat using a Cox proportional Hazard regression model to estimate the HR for death from any cause adjusting for the major prognostic factors. Statistical analyses will be conducted that will account for postrandomisation events (such as treatment switches and kidney transplants) through causal models to arrive at adequate estimates of the difference between treatments. Finally, analyses, using interaction terms, to identify important subgroups of participants (particularly suited for high-dose HDF or the reverse) will be undertaken. Prespecified subgroup analyses by age (<50, 50–65, >65 years), sex, residual renal function (<200 mL/day, 200–1000 mL/day and >1000 mL/day), diabetes, cardiovascular disease,[26–30] a serum albumin ≤40 g/L, vascular access and dialysis vintage (<2 years, 2–5 years and >5 years) will be performed for exploratory purposes. Assumptions and fits of the statistical models will be evaluated using standard approaches.

The analyses of cause-specific deaths, total cardiovascular disease and hospitalisations will be as for the primary endpoint. PROs analyses will involve general linear models and generalised estimating equations of changes since baseline, after a transformation to approximate normality if required. This will be adjusted for the major prognostic factors, as for the primary endpoint, plus the baseline value of the index variable.

Interim analysis

Two formal interim analyses are planned using the Haybittle-Peto stopping criterion,[44 45] but subject to the opinion of the DSMB. This states that we should stop the trial at any interim analysis where the absolute value of the estimated treatment effect is bigger than three times its SE. Using this criterion, the final analysis can still be evaluated at the chosen level of significance (5% two-sided), without imposing any important degree of error.

Ethical considerations

The study will be conducted in full conformance with the principles of the 'Declaration of Helsinki' (64th World Medical Association (WMA) General Assembly, Fortaleza, Brazil, October 2013)[46] or with the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the participant. A written informed consent will be obtained in accordance with the Declaration of Helsinki, laws and regulations, the General Data Protection Regulation Data Protection Directive (Regulation 2016/679) and local regulations. The Investigator will prepare the informed consent form and provide the documents to the independent ethics committees for approval.

Patient or public involvement

Patients were not involved in the design and development of the protocol. We have informed key stakeholders, including international patient associations about our study prior to patient enrolment. The findings of our study will be discussed with patients, healthcare professionals, policymakers and the public during the course and at the end of our study.

ETHICS AND DISSEMINATION

On the basis of current evidence, the optimal HD modality for the management of patients with ESKD remains unclear. The CONVINCE study has been designed to determine the benefits and harms of high-dose HDF versus high-flux HD in people with ESKD. Patient perspectives along with a cost-effectiveness analysis will also be performed. The study has potential to deliver an answer on the vexing question as to which intervention gives the best patient relevant outcomes and is most cost-effective. We anticipate CONVINCE to be 'landmark' study, leading to an expected conclusive 'end of discussion' report.

CONVINCE website

https://www.ucl.ac.uk/convince-hemodiafiltration-dialysis-study/convince-study.

Author affiliations
[1]Department of Nephrology and Hypertension, University Medical Center Utrecht, Utrecht, The Netherlands
[2]Charité Universitätsmedizin Berlin, corporate member of Freie Universität Berlin, Humboldt-Universität zu Berlin, and Berlin Institute of Health, Center of Internal

BMJ Open: first published as 10.1136/bmjopen-2019-033228 on 5 February 2020. Downloaded from http://bmjopen.bmj.com/ on March 12, 2020 at Medical School Library University of Mass. Protected by copyright.

Medicine and Dermatology, Department of Psychosomatic Medicine, Berlin, Germany
[3]B. Braun Avitum AG, Medical Scientific Affairs, Melsungen, Germany
[4]Fresenius Medical Care Deutschland GmbH, Global Medical Office, Bad Homburg v.d.H, Germany
[5]Montpellier University, School of Medicine, Montpellier, France
[6]Department of Nephrology, University College of London, London, United Kingdom
[7]Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht University, Utrecht, The Netherlands
[8]Julius Clinical, Academic Clinical Research Organisation, Zeist, The Netherlands
[9]Department of Nephrology, Clinical Sciences, Lund University, Lund, Sweden
[10]Department of Quantitative Health Sciences, University of Massachusetts Medical School, Worcester, MA, USA
[11]Department of Emergency and Organ Transplantation, University of Bari Aldo Moro, Bari, Italy
[12]University of Sydney, School of Public Health, Sydney, New South Wales, Australia
[13]The George Institute for Global Health, University of Oxford, Oxford, United Kingdom
[14]The George Institute for Global Health, University of New South Wales, Sydney, New South Wales, Australia
[15]Department of Epidemiology, Johns Hopkins University, Baltimore, MD, USA
[16]Centre for Nutrition, Prevention and Health Services, National Institute of Public Health and the Environment, Bilthoven, The Netherlands

Contributors PJB and MB conceived the study. PJB, KIF, CB, KC, BC, AD, DEG, JH, KR, MR, GFMS, RWMV, MW, AAW and MLB contributed to protocol development. PJB and MB drafted the protocol. PJB, KIF, CB, KC, BC, AD, DEG, JH, KR, MR, GFMS, RWMV, MW, AAW and MLB contributed to refinement of the study protocol and approved the final manuscript.

Funding This investigator-initiated project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 754803. The governance is given in online supplementary appendix 6.

Competing interests None declared.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

Open access This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/.

ORCID iDs
Krister Cromm http://orcid.org/0000-0002-5324-0695
Robin WM Vernooij http://orcid.org/0000-0001-5734-4566

REFERENCES

1 National Kidney Foundation. Global facts: about kidney disease. Available: https://www.kidney.org/kidneydisease/global-facts-about-kidney-disease [Accessed 19 Feb 2019].
2 Fresenius Medical Care. Outlook. Available: https://www.freseniusmedicalcare.com/en/investors/at-a-glance/outlook/ [Accessed 19 Feb 2019].
3 Steenkamp R, Rao A, Fraser S. UK renal registry 18th annual report (December 2015) chapter 5: survival and causes of death in UK adult patients on renal replacement therapy in 2014: national and Centre-specific analyses. *Nephron* 2016;132(Suppl 1):111–44.
4 Nordio M, Limido A, Maggiore U, *et al*. Survival in patients treated by long-term dialysis compared with the general population. *Am J Kidney Dis* 2012;59:819–28.
5 Naylor KL, Kim SJ, McArthur E, *et al*. Mortality in incident maintenance dialysis patients versus incident solid organ cancer patients: a population-based cohort. *Am J Kidney Dis* 2019;73:765–76.
6 Kidney Care UK. Transplantation. Available: www.kidneycareuk.org/about-kidney-health/treatments/transplantation/ [Accessed 19 Feb 2019].
7 ERA-EDTA Registry. ERA-EDTA registry annual report 2013. Available: https://www.era-edta-reg.org/files/annualreports/pdf/AnnRep2013.pdf [Accessed 19 Feb 2019].
8 ERA-EDTA Registry. ERA-EDTA registry annual report 2014. Available: https://www.era-edta-reg.org/files/annualreports/pdf/AnnRep2014.pdf [Accessed 19 Feb 2019].
9 Tattersall JE, Ward RA, EUDIAL group. Online haemodiafiltration: definition, dose quantification and safety revisited. *Nephrol Dial Transplant* 2013;28:542–50.
10 Maduell F, Moreso F, Pons M, *et al*. High-efficiency postdilution online hemodiafiltration reduces all-cause mortality in hemodialysis patients. *J Am Soc Nephrol* 2013;24:487–97.
11 Massy ZA, Liabeuf S. From old uraemic toxins to new uraemic toxins: place of 'omics'. *Nephrol Dial Transplant* 2018;33:iii2–5.
12 Davenport A. Moving beyond small solute clearance: what evidence is there for more permeable dialyzers and haemodiafiltration? *Hemodial Int* 2018;22:S24–8.
13 Daugirdas JT. Lower cardiovascular mortality with high-volume hemodiafiltration: a cool effect? *Nephrol Dial Transplant* 2016;31:853–6.
14 Peters SAE, Bots ML, Canaud B, *et al*. Haemodiafiltration and mortality in end-stage kidney disease patients: a pooled individual participant data analysis from four randomized controlled trials. *Nephrol Dial Transplant* 2016;31:978–84.
15 Davenport A, Peters SAE, Bots ML, *et al*. Higher convection volume exchange with online hemodiafiltration is associated with survival advantage for dialysis patients: the effect of adjustment for body size. *Kidney Int* 2016;89:193–9.
16 Nubé MJ, Peters SAE, Blankestijn PJ, *et al*. Mortality reduction by post-dilution online-haemodiafiltration: a cause-specific analysis. *Nephrol Dial Transplant* 2017;32:548–55.
17 Davenport A. Dialysis and patient factors which determine convective volume exchange in patients treated by Postdilution online hemodiafiltration. *Artif Organs* 2016;40:1121–7.
18 Locatelli F, Karaboyas A, Pisoni RL, *et al*. Mortality risk in patients on hemodiafiltration versus hemodialysis: a 'real-world' comparison from the DOPPS. *Nephrol Dial Transplant* 2018;33:683–9.
19 Nistor I, Palmer SC, Craig JC, *et al*. Haemodiafiltration, haemofiltration and haemodialysis for end-stage kidney disease. *Cochrane Database Syst Rev* 2015:CD006258.
20 Locatelli F, Mastrangelo F, Redaelli B, *et al*. Effects of different membranes and dialysis technologies on patient treatment tolerance and nutritional parameters. The Italian cooperative dialysis Study Group. *Kidney Int* 1996;50:1293–302.
21 Davenport A. Role of dialysis technology in the removal of uremic toxins. *Hemodial Int* 2011;15(Suppl 1):S49–53.
22 Mostovaya IM, Blankestijn PJ, Bots ML, *et al*. Clinical evidence on hemodiafiltration: a systematic review and a meta-analysis. *Semin Dial* 2014;27:119–27.
23 Wang AY, Ninomiya T, Al-Kahwa A, *et al*. Effect of hemodiafiltration or hemofiltration compared with hemodialysis on mortality and cardiovascular disease in chronic kidney failure: a systematic review and meta-analysis of randomized trials. *Am J Kidney Dis* 2014;63:968–78.
24 Canaud B, Barbieri C, Marcelli D, *et al*. Optimal convection volume for improving patient outcomes in an international incident dialysis cohort treated with online hemodiafiltration. *Kidney Int* 2015;88:1108–16.
25 de Roij van Zuijdewijn CLM, Chapdelaine I, Nubé MJ, *et al*. Achieving high convection volumes in postdilution online hemodiafiltration: a prospective multicenter study. *Clin Kidney J* 2017;10:804–12.
26 Chapdelaine I, de Roij van Zuijdewijn CLM, Mostovaya IM, *et al*. Optimization of the convection volume in online post-dilution haemodiafiltration: practical and technical issues. *Clin Kidney J* 2015;8:191–8.
27 Reuben DB, Siu AL. An objective measure of physical function of elderly outpatients. The physical performance test. *J Am Geriatr Soc* 1990;38:1105–12.
28 Thygesen K, Alpert JS, Jaffe AS, *et al*. Fourth universal definition of myocardial infarction (2018). *Circulation* 2018;138:e618–51.
29 Metra M, Dinatolo E, Dasseni N, *et al*. The new heart failure association definition of advanced heart failure. *Card Fail Rev* 2019;5:5–8.
30 Cooper A, Calvert N, Skinner J, *et al*. *Chest pain of recent onset: assessment and diagnosis of recent onset chest pain or discomfort of suspected cardiac origin*. London: National Clinical Guideline Centre for Acute and Chronic Conditions, 2010. http://www.nice.org.uk/guidance/cg95/evidence/full-guideline-245282221
31 Mohr JP. History of transient ischemic attack definition. *Front Neurol Neurosci* 2014;33:1–10.
32 Powers WJ, Rabinstein AA, Ackerson T, *et al*. 2018 guidelines for the early management of patients with acute ischemic stroke: a guideline for healthcare professionals from the American heart Association/American stroke association. *Stroke* 2018;49:e46–110.

BMJ Open: first published as 10.1136/bmjopen-2019-033228 on 5 February 2020. Downloaded from http://bmjopen.bmj.com/ on March 12, 2020 at Medical School Library University of Mass. Protected by copyright.

33 The Song Initiative. *The song Handbook. Version 1.0*. Sydney, Australia, 2017.
34 International Consortium for health outcomes measurements. *Chronic kidney disease data collection reference guide*, 2017.
35 Cella D, Gershon R, Lai J-S, *et al*. The future of outcomes measurement: item banking, tailored short-forms, and computerized adaptive assessment. *Qual Life Res* 2007;16 (Suppl 1):133–41.
36 Ware JE, Kosinski M, Turner-Bowker DM, *et al*. *How to score version 2of the SF-12 health survey (with a supplement documenting version 1)*. Lincoln, RI: QualityMetric Incorporated, 2002.
37 Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. *J Gen Intern Med* 2001;16:606–13.
38 Bouwmans C, Krol M, Severens H, *et al*. The iMTA productivity cost questionnaire: a standardized instrument for measuring and valuing health-related productivity losses. *Value Health* 2015;18:753–8.
39 Bouwmans C, Hakkaart-van Roijen L, Koopmanschap M, *et al*. *Medical consumption questionnaire Handleiding*. Rotterdam: Institute for Medical Technology Assessment, 2013.
40 M Versteegh M, M Vermeulen K, M A A Evers S, *et al*. Dutch tariff for the five-level version of EQ-5D. *Value Health* 2016;19:343–52.
41 Herdman M, Gudex C, Lloyd A, *et al*. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). *Qual Life Res* 2011;20:1727–36.
42 United States renal data system. 2019 annual data report. Available: https://www.usrds.org/adr.aspx [Accessed 13 Nov 2018].
43 Dialysis outcomes and practice patterns study. Available: http://www.dopps.org/ [Accessed 13 Nov 2018].
44 Lai TL, Shih M-C, Zhu G. Modified Haybittle-Peto group sequential designs for testing superiority and non-inferiority hypotheses in clinical trials. *Stat Med* 2006;25:1149–67.
45 Haybittle JL. Repeated assessment of results in clinical trials of cancer treatment. *Br J Radiol* 1971;44:793–7.
46 World Medical Association. WMA Declaration of Helsinki – ethical principles for medical research involving human participants, 2013. Available: http://www.wma.net/en/30publications/10policies/b3/ [Accessed 19 Feb 2019].

BMJ Open: first published as 10.1136/bmjopen-2019-033228 on 5 February 2020. Downloaded from http://bmjopen.bmj.com/ on March 12, 2020 at Medical School Library University of Mass. Protected by copyright.