

# **A META-ANALYSIS OF THE REPRESENTATIVENESS OF RANDOMIZED CONTROLLED TRIAL COHORTS IN END-STAGE KIDNEY DISEASE**

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*Key Points:*

*Question: How similar are dialysis-dependent patients recruited to large, multicentre randomized trials compared to the general dialysis-dependent population?*

*Findings: In this meta-analysis of 189 trials including 80,104 participants, trial participants were significantly younger, more likely to be male and less likely to have diabetes or diabetic nephropathy than patients in the US national registry. Moreover, their mortality rate was substantially lower than that of registry patients, both overall and when only studies recruiting participants from the US were considered.*

*Meaning: These findings imply that caution should be exercised when generalizing results from clinical trials to the broader dialysis-dependent patient population.*

*100/75-100 words*

*Tweet:*

*People in dialysis studies are younger and fitter than average dialysis patients. A reminder to consider more inclusive trials. @georgeinstitute*

## **Abstract**

### Importance

Systematic differences between patients included in randomized controlled trials (RCTs) and the general patient population may influence the generalizability of RCT findings. Comprehensive national registries of patients with end-stage kidney disease (ESKD) on dialysis provide a unique opportunity to compare trial and real-world patient cohorts.

### Objective

To determine if participants in large, multicentre dialysis trials were similar to the general dialysis population in terms of age, co-morbidities and mortality rate.

### Data Sources

Medline, PubMed and the Cochrane Central Register of Controlled Trials were systematically searched from 2007 to 2016. Data sources were published manuscripts, supplementary material and trial registration information. General dialysis population data was derived from US Renal Data System (USRDS).

### Study Selection

RCTs enrolling only participants on dialysis for ESKD; with  $\geq 100$  adult participants from  $\geq 2$  sites.

### Data Extraction and Synthesis

Abstract screening and data extraction were performed independently by two researchers. Data were pooled using a random-effects model.

### Main Outcome(s) and Measure(s)

The primary outcome was difference in mean age between the RCT and USRDS populations. Secondary outcomes included differences in mortality rate and co-morbidities.

### Results

We identified 189 RCTs, enrolling 80,104 participants. Compared to the 2011 USRDS population, RCT participants were younger (58.9 [95% confidence interval 58.3-59.5] vs 61.2 years;  $P < 0.001$ ), more

likely to be male (58.8% [57.5-60.0] vs 55.7%;  $P<0.001$ ) and to have coronary artery disease (26.7% [22.1-31.4] vs 17.7%;  $P<0.001$ ) and less likely to have diabetes (40.4% [36.9-43.8] vs 44.2%;  $P=0.035$ ) or heart failure (19.9 [15.6-24.3] vs 29.8;  $P<0.001$ ). The mortality rate during trial participation was less than half that of the USRDS population (8.92 [7.85-10.00] vs 18.59 per 100 patient-years;  $P<0.001$ ). The differences in age, mortality and coronary artery disease remained when studies recruiting only from the USA were considered. Diabetes was more common in RCT participants from the USA than in the registry population.

### Conclusions

Participants in large, multicentre dialysis RCTs are younger, have a different pattern of co-morbidities and a lower mortality rate than the general dialysis population. This finding has implications for the generalization of trial results to the broader patient population and for future trial design.

## Introduction

The single or pooled results of RCT are considered the highest level of evidence for treatment efficacy in modern medicine <sup>1</sup>. For the results of an RCT to be *generalizable* to a specific patient population, the study cohort and population of interest must be sufficiently similar in clinically relevant characteristics so that the intervention effect seen in the RCT can be reasonably expected to be replicated in the latter population. Such studies are crucial to the development of clinical practice guidelines and to informing health economic and health service provision decisions. However, studies in other specialties have found participants in RCTs are often not completely representative of the broader patient population in which the intervention is likely to be employed <sup>2-4</sup>. This has implications for clinicians and for health policy as intervention efficacy may be less than expected in some patient groups, such as older and frailer patients who tend to be underrepresented in clinical trials <sup>3,5</sup>.

Study generalizability may be more or less relevant depending on the study aims. Early phase and 'explanatory' studies may not prioritize generalizability as their aim is to provide proof of efficacy under ideal conditions. In contrast, generalizability is important for later phase and 'pragmatic' trials which aim to determine if an intervention is effective in the clinical practice. Such trials are typically larger, recruit from multiple sites and may have broader inclusion and exclusion criteria to increase the generalizability of the results.<sup>6</sup> Nephrology trials are reported as fewer in number, smaller and more likely to be Phase I or II compared to other disciplines in internal medicine <sup>7,8</sup> raising the possibility that nephrology RCTs may have limited generalizability. While RCT in kidney transplant recipients have been shown to enrol younger participants than the kidney transplant population of the USA (suggesting important limitations to generalizability) <sup>9</sup>, this question has not been addressed in the dialysis population.

We aimed to assess the generalizability of large, multicentre dialysis RCTs by comparing pre-specified measures of generalizability (age, comorbidities and mortality rate) between trial participants and patients in the largest dialysis registry, the United States Renal Data System (USRDS). We also aimed to determine if particular study factors (such as design, size and sponsorship type) were related to these measures of generalizability.

## Materials and Methods

We undertook a systematic search of Medline, PubMed and the Cochrane Central Register of Controlled Trials for randomized studies (including randomized cross-over trials and cluster randomized trials), published from 1 January 2007 to 31 December 2016, enrolling participants on maintenance dialysis for end-stage kidney disease (ESKD) at the time of randomisation. Both hemodialysis and peritoneal dialysis were included. Studies were included if they recruited participants from at least two sites (as defined by the study authors) and if at least 100 participants were randomized. Studies enrolling participants aged less than 18 years, with acute kidney injury, or with, or about to receive, a kidney transplant were excluded. No language restriction was used. The review protocol was registered (PROSPERO ID:CRD42018090862).

After removal of duplicates, titles and abstracts were screened for inclusion or exclusion by two of three lead researchers (BS, AH and KT) with discrepancies adjudicated by the third. Manuscripts were then reviewed independently by two of the three researchers. Inclusion and exclusion criteria were assessed and if included, the reviewer proceeded to data extraction. Supplementary online appendices, online trial registrations and accessory publications were also consulted if complete data was not present in the primary study manuscript. A single cohort of participants could be included only once; where multiple publications from the same cohort of participants were identified, the earliest publication with results was identified as the primary publication and was considered the primary source of information. Data discrepancies were resolved by discussion among the reviewers after data extraction was completed.

### *Data items*

Data were extracted on pre-defined study characteristics, participant characteristics and mortality. Study characteristics included trial registration number, type of study sponsor, country of sponsor, type of randomized study, type of intervention, primary endpoint(s), follow up time (planned and observed), included dialysis modalities, number of randomized participants and the number of recruiting sites and countries. Study sponsor information was obtained from trial registration information where available and, for commercial sponsors the country of origin was

determined by the location of the organisation's headquarters. Otherwise, if sponsorship was not stated, the allocation to commercial or non-commercial sponsor category was made based on the presence of a commercial entity in funding or acknowledgements statements. Baseline participant characteristics included age, gender, albumin, hemoglobin, dialysis modality, dialysis vintage, type of vascular access, erythropoietin stimulating agent use, cause of primary renal disease, proportion with co-morbid diabetes or cardiovascular disease. Mean and standard deviation were preferred to median and interquartile range (if both were presented). Mortality was recorded where available. Mortality rate (per 100 patient-years) was preferred. If reported per study arm, a weighted average was calculated. If no rate was reported, actuarial mortality rate was calculated from study duration and number of recorded deaths [see eMethods in the Supplement]. Studies which did not report on participant deaths were excluded from mortality analyses.

### *Comparison registry*

The 2011 cohort of the United States Renal Data System (USRDS) was chosen *a priori* as the reference registry because it is the largest single registry (with annual records for over 500,000 dialysis recipients), makes comprehensive data available online and represents the country likely to provide the largest share of study participants. The year 2011 was chosen for its position at the mid-point of the systematic review period. Information was sourced from data files provided with the 2013 and 2015 Annual Data Reports [available at <https://www.usrds.org/archive.aspx>] <sup>10-14</sup>.

### *Outcomes*

The primary outcome of this study was the age of RCT participants. Secondary outcomes included a variety of patient characteristics: sex, co-morbidities such as diabetes and cardiovascular disease, cause of renal disease, hemoglobin, albumin and type of vascular access; and study mortality. A number of outcomes and predictors were selected *a priori* for unadjusted and adjusted analyses to determine which study characteristics were associated with generalizability. Three participant characteristics – age, prevalence of diabetes and mortality rate – were selected as surrogate measures of generalizability in these adjusted analyses. Five study characteristics – sponsor type (commercial, non-commercial or unknown), type of study (parallel-group, cluster-

randomized or cross-over), number of participants, number of recruiting sites and year of publication – were selected as predictors of these generalizability outcomes.

### *Statistical Methods*

For each study, overall participant baseline characteristics were calculated by combining treatment allocation subgroup means or medians using weighting by subgroup size. Pooled standard deviations were calculated using the formula provided by Woodward <sup>15</sup>. The weighted mean standard deviation from all studies was used to impute the standard deviation for those studies which reported mean values without standard deviation. Age, albumin and hemoglobin were assumed to be normally distributed, permitting median values to be considered equivalent to means and the estimation of standard deviation from the interquartile ranges [see eMethods in the Supplement]<sup>16</sup>. Summary statistics were estimated by the random effects model of DerSimonian and Laird, applied to both continuous and categorical variables (those with more than two categories were analyzed as a series of dichotomous outcomes).

Primary and secondary outcomes were compared to the equivalent USRDS data by one sample Student's t-tests, where the USRDS value was considered the reference value and the test statistic was obtained from a random effects RCT meta-analysis. Categorical predictors were analyzed by one-way analysis of variance (ANOVA) and continuous variables by linear regression. Multivariable linear regression analysis was performed to determine the relationship between the five study characteristics and three primary generalizability outcomes. Where relevant, individual observations within statistical models were weighted by number of study participants. Statistical analysis was performed using Stata 15.0 (StataCorp, USA).

## **Results**

### *Study selection*

The database search on 6<sup>th</sup> January 2017 returned 5229 records. After removal of duplicates and screening of title and abstract, 545 full text articles were obtained. Of these, 356 were excluded leaving 189 studies, enrolling 80,104 participants, to be included in the analysis (Figure 1).



### *Study characteristics*

Studies were predominantly open-label (121/189, 64%), parallel group (171/189, 91%), surrogate primary outcome (128/189, 68%) and randomized participants receiving hemodialysis only (152/189, 80%) (Table 1). The most common class of intervention was dialysis practice change (41/189, 22%), encompassing a variety of interventions such as catheter locks, dressings, topical preparations and novel dialysis membranes. A minority of studies (35/189, 19%) employed an upper age exclusion criteria. Among these studies, the median upper age limit was 75 years (range 65-90).

Participants were recruited from 58 countries and 27% (50/189) of studies recruited from multiple countries. The USA was the most frequently represented country with 32% of studies including at least one site from the USA and 42% of all sites and 29% of study sponsors being located there (Table S2). Based on median values, the 'typical' study had 211 participants from 15 sites in a single country and a follow up time from randomisation to final data collection of 7 months. Seventy percent (133/189) reported their trial registration in the manuscript, 72% (96/133) of these were registered with ClinicalTrials.gov. Sponsorship could be determined in 95% (180/189) of trials, with 51% (96/189) being sponsored by a commercial entity.

### *Comparison of all participants with USRDS*

Compared to USRDS in 2011, study participants were significantly younger (58.9 [95%CI 58.3-59.5] vs 61.2 years;  $P<0.001$ ), more likely to be male and less likely to have diabetes, diabetes or hypertension as a cause of renal failure or to be dialysing with a catheter (Table 2). While they had a lower prevalence of heart failure, the prevalence of coronary artery disease, cerebrovascular disease and peripheral vascular disease was higher. Mean albumin levels were higher in study participants, although this was in comparison with incident dialysis patients in the USRDS (as prevalent patient albumin values are not reported). Mortality among study participants could be determined in 67% (126/187) of studies. In these studies, the mortality rate was less than half of that reported in the USRDS for 2011 (8.9 [95%CI 7.9-10.0] vs 18.6 per 100 patient-years in USRDS,  $P<0.001$ ).

### *Comparison of studies recruiting from the USA with USRDS*

The disparity in age between USRDS and the study population remained when considering only those 48 USA-predominant studies (ie. those with at least 50% of their sites in the USA) (58.3

[95%CI 57.5-59.0] vs 61.2 years;  $P<0.001$ ). In contrast to the overall RCT cohort, the prevalence of diabetes was higher than in the USRDS population (54.6 [95%CI 52.2-57.0] vs 44.2;  $P<0.001$ ) and mean hemoglobin was significantly higher than the USRDS prevalent hemodialysis population (112.6 [95%CI 110.4-114.8] vs 110.0;  $P=0.04$ ). The mortality rate remained significantly lower (10.3 [95%CI 10.2-10.4] vs 18.6 per 100 patient-years,  $P<0.001$ ).

When the analysis was further restricted to studies recruiting only from the USA (USA-only), the difference in age and mortality between trial participants and the 2011 USRDS population remained significant. This was despite a higher burden of co-morbid diabetes and coronary artery disease in the study population compared with the registry population (Table 2).

#### *Influence of study factors on participant age, co-morbid diabetes and mortality*

Participant age and prevalence of diabetes were significantly higher in cluster-randomized trials as compared to parallel group and cross-over studies, although mortality rates did not differ between these study types (Table 3). There were no differences in these participant characteristics between studies with commercial or non-commercial sponsors. Similarly, neither study size nor the number of recruiting sites were associated with participant age, proportion with diabetes or study mortality rate (data not shown). Between 2007 and 2016, the prevalence of diabetes in trial participants increased while the mortality rate decreased ( $P<0.001$  and  $P=0.001$ , respectively), with no significant change in average participant age ( $P=0.09$ )(see eFigure 1 in the Supplement). Adjusted analyses suggested that non-commercial studies and those published earlier were associated with a significantly higher mortality rate ( $P=0.04$  and  $P=0.003$ , respectively) (Table 4). No study characteristics were significantly associated with patient age or prevalence of diabetes.

## **Discussion**

These results show that participants in large, multicentre trials recruiting dialysis patients are younger and more likely to be male than the general dialysis population in the USA. Moreover, their pattern of co-morbidities differs; with a lower prevalence of diabetes, diabetic nephropathy and hypertensive nephropathy, but a higher prevalence of cardiovascular disease. The estimated mortality rates in trial participants were much lower than in the USRDS, suggesting that trial

participants are healthier on average than the general dialysis population. While some of the differences we observed between the RCT and registry cohorts were small in size, when considered collectively these differences may imply that the magnitude of treatment effects assumed from the evidence-base may not be realised when those interventions are applied to a more representative cohort of patients. This emphasises the importance of clinicians and policy makers carefully considering the generalizability of particular RCT results to their own distinct populations. It also supplies a clear rationale for increasing the effort to produce pragmatic randomized clinical trials. Such trials, for example the TASTE trial of thrombus aspiration after myocardial infarction <sup>17</sup> or the Initial Antidepressant Choice in Primary Care study <sup>18</sup>, are characterised by an effort to maximise generalizability by the minimisation of inclusion and exclusion criteria, the use where possible of routinely collected data and an emphasis on 'real-world' practice <sup>19</sup>.

Our results are in line with research in renal transplant recipients where a difference in age between registry and trial populations has been described <sup>9</sup>. Similar conclusions have also been drawn in other disciplines. For example, studies in cardiology, mental health and oncology have been found to recruit younger patients with fewer high-risk characteristics compared to real-world cohorts<sup>3,20</sup> and a meta-analysis of cardiology RCTs has found unselected registry patients to be twice as likely to die as those participating in a clinical trial <sup>21</sup>. Some difference in mortality between RCT cohorts and the general population receiving dialysis should be expected as many interventions in nephrology may not be relevant to patients with clearly limited life expectancy (eg. tight phosphate control, extended dialysis hours or intensive cardiovascular risk reduction). Despite this, the magnitude of the difference between RCT cohorts and the registry population in our study was large. Even when restricted to studies recruiting predominantly or only in the USA, who were much closer in terms of co-morbidity pattern to the USRDS population, the RCT mortality rate was still over 40% lower than the registry population. It is also notable that the observed mortality rate of 8.9 per 100 patient-years in RCT cohorts was also substantially lower than that reported for dialysis cohorts in Europe (19.2) <sup>22</sup> and Australia (13.3) <sup>23</sup>, although clearly higher than that reported in Japan (4.7) <sup>24</sup>. Reasons for the difference in mortality are likely to include study design (eg. inclusion and exclusion criteria, recruitment methods),<sup>3,25</sup> volunteer bias and differences between study and non-study sites.

Despite the difference in mortality, we found study cohorts in dialysis tended to have a higher burden of cardiovascular disease than the general dialysis population. While differences in comorbidity ascertainment between USRDS and clinical trials may contribute to this, it may also reflect the inclusion of RCT targeting cardiovascular disease in dialysis recipients (and so specifically recruiting participants at elevated cardiovascular risk). The coexistence of high-risk prognostic features with lower mortality, raises the possibility that, compared with non-participants, study participants have other positive prognostic characteristics (eg. a history of treatment compliance or stable, rather than recently active, cardiovascular disease) that were not measured in this analysis. Moreover, previous research has found study participants to differ from the general patient population in a range of socio-economic characteristics that have the potential to influence their underlying risk of adverse outcomes or response to therapy <sup>26</sup>.

Our analysis suggested that commercial sponsorship and more recent year of publication were independent predictors of lower mortality. This raises the possibility that commercially sponsored RCT are less generalizable, and indeed the potential for bias in commercially sponsored RCT in other fields is well described <sup>27</sup>. However, this hypothesis was not supported by our finding that sponsor type had no relationship to participant age or proportion with diabetes. It remains plausible that the association between sponsor type and mortality reflects other aspects of study design and target population that were not included in our model. The association with year of publication may reflect the similar small reduction in dialysis patient mortality seen in USRDS data over the period 2007-2015. It is not consistent with an improvement in RCT generalizability in the past decade, which would be expected to manifest as an increase in study mortality rates with time as the gap between trial and real-world populations narrowed. We also found that, at least in univariate analysis, cluster-randomized studies were more generalizable in terms of age and proportion with diabetic nephropathy, but not in terms of mortality rate. However, the hypothesis that cluster randomized trials were more generalizable was not supported in multivariable analysis.

This review also identifies areas for improvement in dialysis trial methodology. Almost 1 in 5 studies included an age-based exclusion criteria, some as low as 65 years. Avoiding unjustified age-based exclusion criteria represents a simple way to improve study generalizability. Approximately two-thirds of large trials were open label, and while many interventions in dialysis are difficult to

blind, a lack of double-blinding is associated with exaggeration of the intervention effect, particularly where the outcome is subjective <sup>28</sup>. There also is growing recognition of the importance of patient-centred outcomes – whether these are clinical events or patient-reported outcomes <sup>29</sup>. However, the primary outcome in two-thirds of included studies was a surrogate rather than an event of importance to the patient. This accords with an earlier survey of hemodialysis randomized trials (without a study size limitation) which found mortality, cardiovascular diseases, and quality of life to be reported in only 20%, 12%, and 9% of studies, respectively <sup>30</sup>. We also demonstrated a disproportionate number of male study participants in the RCT population. While this may reflect differences in the sex distribution of dialysis patients in countries outside of the USA <sup>31</sup>, it is an area that may warrant further research.

On the face of it, recruitment and follow up of patients with ESKD, who are perhaps uniquely dependent on a particular healthcare institution for their treatment and most of whom attend three times per week, should be straightforward. However, our results confirm the ongoing issues with small (median number of participants 211) and short-term (median follow up 7 months) trials in nephrology, particularly considering that this survey specified only those studies randomizing at least 100 participants. While, in part, this is likely to reflect institutional factors such as the commercial priorities of large dialysis providers and the relative shortage of research funding (both governmental and philanthropic) for nephrology <sup>32</sup>. It may also relate to more fundamental difficulties inherent in the specialty, for example, reluctance to engage patients in research who are already undertaking burdensome treatment and the long time to clinically meaningful outcomes. Fortunately, the nephrology community is engaging in innovative research methods that integrate trial conduct with registries and administrative data with the aim of reducing costs and the burden on participants while also improving the size and quality of RCTs <sup>33,34</sup>.

An important limitation of the present study is that the comparison was restricted to USRDS. The initial aim of comparing study participant characteristics to patients in multiple ESKD registries foundered owing to the limitations and wide variation in reported parameters across different registries. We suspect however that similar differences would be identified if our data were compared directly to European, Japanese or Canadian registries. For example, published data suggests that the mean age of dialysis patients is similar or higher to that in the USA <sup>35-37</sup>. In addition,

while the characteristics of study participants recruited from one global region may differ from those recruited elsewhere, evidence from such studies still informs the practice of clinicians and guideline authors internationally. Over one-quarter of RCTs in this analysis were international, with the median number of participating countries being 7.5. Moreover, meta-analysis frequently results in pooling of study population data from disparate regions. This provides a challenge for clinicians and policymakers who are required to make decisions based on available evidence. Our results need not discourage the use of evidence from a variety of sources, but do serve as a reminder of the caution that is required when generalizing evidence from any source to one's local population.

The primary limitation of our work was the lack of individual patient data. The heterogeneity in study reporting means that our analysis was limited to a few key population characteristics and co-morbidities. Even within these categories, we were reliant on reported aggregate data and could not independently verify their accuracy. There were also a substantial number of manuscripts where we were unable to determine if any participants died. We suspect that this lack of clarity reflects an assumption on the part of the authors that readers would assume a lack of deaths in cohorts of stable study participants. This leads us to believe that the true rate of within-study mortality may be lower than our analysis suggests. The limitations of study reporting also prevented us from exploring more nuanced indicators of participant health such as co-morbidity indices, functional metrics or measures of treatment adherence. Nor were we able to describe socioeconomic characteristics such as race, ethnicity, income or education. Important differences in these characteristics between participants and the general population have been reported in other disciplines <sup>38</sup>. The inclusion criteria for this review ( $\geq 100$  participants and  $\geq 2$  sites), while necessarily arbitrary, were designed to identify larger and later phase studies more likely to be considered generalizable and to inform clinical practice. The finding that increasing study size and site number was not associated with higher participant age, proportion of diabetes or mortality (our chosen surrogate measures of generalizability) supports our selection criteria in that higher values for inclusion would not have resulted in a more generalizable cohort. Finally, we did not make adjustment for multiple comparisons and so our conclusions beyond the primary outcome of age are necessarily tentative.

In conclusion, large, multicentre trials in dialysis enrol a younger participants with a different pattern of co-morbidities and substantially lower mortality than the general dialysis population. The

limitations of randomized evidence when applied to older or frailer populations should be recognized and efforts to broaden the generalizability of randomized trials are warranted.

### **Disclosures**

None

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**Table 1** Study characteristics [*N*=189]

Study characteristic	<i>n</i> (%)
Sponsor	
Commercial	96 (51)
Non-commercial	84 (44)
Unknown	9 (5)
Type of study	
Parallel group	171 (91)
Cluster	13 (7)
Cross-over	5 (3)
Multi-country	50 (27)
Number of countries in multi-country studies – median (IQR)	7.5 (3-11)
Intervention	
Dialysis practice change	41 (22)
Oral pharmaceutical	39 (21)
Phosphate binder	32 (17)
Erythropoietin Stimulating Agent	25 (13)
Injectable pharmaceutical	19 (10)
Other	15 (8)
Dietary	6 (3)
Fistula or graft related	5 (3)
Physical therapy	3 (2)
Increased hours/frequency of dialysis	2 (1)
Other surgical procedure or device	2 (1)
Type of primary outcome	
Surrogate	128 (68)
Clinical event <sup>1</sup>	48 (25)
Cardiovascular event(s)	12 (6)
Mortality	20 (11)
Complication of dialysis	23 (12)
Other	5 (3)
Patient reported	11 (6)
Other	2 (1)
Included modality	
Hemodialysis	152 (80)
Both hemodialysis and peritoneal dialysis	21 (11)
Peritoneal dialysis	16 (9)



Incident participants only	10 (5)
Primary outcome statistically significant <sup>2</sup>	137 (73)
Number of participants – median (IQR)	211 (146-339)
Number of sites – median (IQR)	15 (5-42)
Planned duration of follow up (months) – median (IQR)	7 (3-12)
Blinding	
Open-label	121 (64)
Double blind	61 (32)
Single blind	7 (4)
Upper age limit specified	35 (19)

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<sup>1</sup> Subcategories are overlapping owing to co-primary or composite endpoints

<sup>2</sup> Based on author-specified criteria for significance. Achievement of non-inferiority was considered significant where this was the stated primary outcome.

**Table 2** Study participant characteristics compared with USRDS

Variable	USR DS value	All RCT (mean, 95% CI)	N= 18 9	P- value	USA predominant RCT (mean, 95% CI)	N = 48	P- value	USA only RCT (mean, 95% CI)	N= 39	P- value
Age (years)	61.2	58.9 (58.3-59.5)	18 7	<0.00 1	58.3 (57.5-59.0)	48	<0.0 01	58.6 (57.8-59.5)	39	<0.00 1
Male (%)	55.7	58.8 (57.5-60.0)	18 6	<0.00 1	56.4 (54.4-58.4)	46	0.48	55.2 (52.9-57.4)	37	0.69
Co-morbid diabetes (%)	44.2	40.4 (36.9-43.8)	92	0.04	54.6 (52.2-57.0)	26	<0.0 01	55.7 (53.3-58.1)	22	<0.00 1
Primary Renal Disease (%)										
Diabetic nephropathy	44.2	27.4 (24.9-29.9)	89	<0.00 1	40.8 (38.1-43.5)	20	0.03	41.9 (38.6-45.3)	13	0.21
Hypertension/ Vascular	29.0	20.7 (18.3-23.0)	78	<0.00 1	32.8 (28.5-37.1)	20	0.10	31.6 (26.5-36.7)	13	0.33
Glomeruloneph ritis	9.5	25.5 (22.4-28.5)	84	<0.00 1	10.8 (8.4-13.2)	16	0.32	8.9 (6.4-11.5)	11	0.64
Cystic Kidney Disease	2.6	5.3 (4.6-6.1)	51	<0.00 1	3.2 (2.6-3.9)	10	0.09	2.8 (2.1-3.6)	6	0.59
Co-morbidities (%) (at start of RRT, all modalities, 2011-2013)										
Heart failure	29.8	19.9 (15.6-24.3)	33	<0.00 1	28.5 (23.2-33.8)	12	0.64	27.2 (22.0-32.5)	8	0.36
Coronary artery disease	17.7	26.7 (22.1-31.4)	36	<0.00 1	35.2 (30.2-40.2)	11	<0.0 01	34.6 (26.2-42.9)	8	0.005
Cerebrovascular disease	8.8	11.1 (9.6-12.5)	30	0.004	12.9 (9.3-16.5)	9	0.06	13.0 (7.5-18.5)	5	0.21
Peripheral vascular disease	12.0	15.2 (12.3-18.0)	26	0.04	15.4 (9.0-21.8)	9	0.33	15.0 (7.7-22.3)	6	0.46
Hemoglobin (g/ dL)										
Prevalent (HD)	11.0 0	11.01 (10.83-11.19 )	92	0.88	11.26 (11.04-11.48)	16	0.04	11.07 (10.74-11.4 0)	10	0.67
Prevalent (PD)	10.8 3			0.05			0.00 2			0.19

Albumin (g/dL)										
Incident (all modalities, 2011-2013)	3.20	3.78 (3.73-3.82)	79	<0.001	3.80 (3.72-3.88)	17	<0.001	3.77 (3.70-3.84)	13	<0.001
Vascular access (%)										
Catheter	21.2	12.9 (10.3-15.5)	22	<0.001	18.6 (12.0-25.2)	9	0.47	20.2 (11.0-29.5)	7	0.84
Mortality rate (per 100 patient years) (2011-2013)	18.6	8.9 (7.9-10.0)	12	<0.001	10.3 (7.4-13.2)	34	<0.001	10.6 (6.8-14.4)	26	<0.001

All USRDS values are for prevalent dialysis patients in 2011, unless otherwise specified.

**Table 3** Unadjusted analysis of participant age, prevalence of diabetes and mortality by sponsor and study type.  
Results from one-way ANOVA.

	Mean age (years, 95% CI)	P-value	Diabetes (% 95%CI)	P-value	Mortality rate (per 100 patient-years, 95% CI)	P-value
Sponsor		0.194		0.988		0.532
Commercial	59.3 (58.5-60.1)		44.9 (40.1-49.7)		8.7 (7.6-9.9)	
Non-commercial	60.1 (59.2-61.0)		45.0 (40.7-49.2)		9.5 (7.3-11.6)	
Study type						
Cluster-randomized	61.9 (60.7-63.0)	<0.001	56.6 (51.3-61.9)	<0.001	7.5 (2.9-12.0)	0.772
Parallel group	58.7 (58.1-59.4)		38.3 (35.2-41.4)		9.0 (7.9-10.1)	
Cross-over	59.1 (54.8-63.5)		20.2 (2.7-37.7)		6.4 (0.0-13.7)	

**Table 4** Adjusted analysis of age, prevalence of diabetes and mortality rate  
Results from weighted linear regression model.

	Age (Coeff, 95% CI)	P-value	Diabetes (Coeff, 95%CI)	P-value	Mortality rate (Coeff, 95% CI)	P-value
Sponsor (ref=Commercial)						
Non-commercial	0.91 (-0.69-2.51)	0.265	-0.020 (-0.093-0.053)	0.582	2.60 (0.09-5.10)	0.042

Study type (ref=Parallel group)						
Cluster-randomized	0.90 (-2.06-3.87)	0.548	0.059 (-0.054-0.173)	0.30 2	-0.31 (-5.98-5.36)	0.914
Cross-over	1.60 (-3.18-6.37)	0.510	-0.205 (-0.422-0.013)	0.06 5	-0.21 (-7.38-6.96)	0.956
Year of publication	0.04 (-0.21-0.29)	0.748	0.004 (-0.008, 0.017)	0.46 5	-0.59 (-0.97- -0.21)	0.003
Number of participants	0.0002 (-0.001-0.001)	0.751	$2 \times 10^{-5}$ ( $-2 \times 10^{-5}$ - $6 \times 10^5$ )	0.32 7	$9 \times 10^{-5}$ (-0.003-0.003)	0.956
Number of sites	0.002 (-0.015-0.019)	0.815	$-3 \times 10^{-4}$ ( $-9 \times 10^{-4}$ - $3 \times 10^4$ )	0.35 8	0.01 (-0.01-0.04)	0.356

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## Figure legends

**Figure 1** Study selection

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