Trends in Adaptive Design Methods in Dialysis Clinical Trials: A Systematic Review

Conor Judge, Robert Murphy, Catriona Reddin, Sarah Cormican, Andrew Smyth, Martin O’Halloran, and Martin J. O’Donnell

Rationale & Objective: Adaptive design methods are intended to improve the efficiency of clinical trials and are relevant to evaluating interventions in dialysis populations. We sought to determine the use of adaptive designs in dialysis clinical trials and quantify trends in their use over time.

Study Design: We completed a novel full-text systematic review that used a machine learning classifier (RobotSearch) for filtering randomized controlled trials and adhered to the Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) guidelines.

Setting & Study Populations: We searched MEDLINE (PubMed) and ClinicalTrials.gov using sensitive dialysis search terms.

Selection Criteria for Studies: We included all randomized clinical trials with patients receiving dialysis or clinical trials with dialysis as a primary or secondary outcome. There was no restriction of disease type or intervention type.

Data Extraction & Analytical Approach: We performed a detailed data extraction of trial characteristics and completed a narrative synthesis of the data.

Results: 57 studies, available as 68 articles and 7 ClinicalTrials.gov summaries, were included after full-text review (initial search, 209,033 PubMed abstracts and 6,002 ClinicalTrials.gov summaries). 31 studies were conducted in a dialysis population and 26 studies included dialysis as a primary or secondary outcome. Although the absolute number of adaptive design methods is increasing over time, the relative use of adaptive design methods in dialysis trials is decreasing over time (6.12% in 2009 to 0.43% in 2019, with a mean of 1.82%). Group sequential designs were the most common type of adaptive design method used. Adaptive design methods affected the conduct of 50.9% of trials, most commonly resulting in stopping early for futility (41.2%) and early stopping for safety (23.5%). Acute kidney injury was studied in 32 trials (56.1%), kidney failure requiring dialysis was studied in 24 trials (42.1%), and chronic kidney disease was studied in 1 trial (1.7%). 27 studies (47.4%) were supported by public funding. 44 studies (77.2%) did not report their adaptive design method in the title or abstract and would not be detected by a standard systematic review.

Limitations: We limited our search to 2 databases (PubMed and ClinicalTrials.gov) due to the scale of studies sourced (209,033 and 6,002 results, respectively).

Conclusions: Adaptive design methods are used in dialysis trials but there has been a decline in their relative use over time.

Randomized clinical trials (RCTs) are the gold standard for evaluating the efficacy, futility, or harm of new therapies. Compared with similar medical specialties, nephrology has traditionally had a low number of RCTs, particularly evident for patients with kidney failure requiring dialysis. The comparatively low number of trials is postulated to be due to difficult recruitment, previous history of underpowered trials, and lack of funding. Although the number of trials is increasing, nephrology continues to lag behind other specialties such as cardiology, hematology/oncology, and gastroenterology.

Adaptive clinical trials use interim data analyses to modify the trial design or duration in a predefined way without undermining the integrity or validity of the trial, thereby preserving the type 1 error (false-positive) rate. The most common type of adaptive design is the group sequential design, in which planned interim analyses permit stopping of trials for efficacy or futility. Other designs include sample size re-estimation, multistage trials, adaptive randomization, biomarker adaptive, and seamless phase 2/3 trials (Box 1).

Adaptive clinical trials appear particularly suitable for the evaluation of novel interventions in dialysis by reducing resource requirements, decreasing time to study completion, and increasing the likelihood of study success, that is, power to answer hypothesis. Previous trials in dialysis have overly relied on observational data to inform trial design, including assumptions of expected effect size and variance, rather than estimates from early-phase clinical trials. If incorrect, trials may be underpowered with an insufficient sample size to answer the underlying research question. Adaptive sample size re-estimation is a potential solution, as commonly used in cardiology trials, such as planned blinded sample size re-estimation, which identifies inaccurate assumptions, thereby triggering altered recruitment targets midtrial to ensure adequate power.

Adaptive design may also be relevant when evaluating more established interventions. For example, the Deutsche Diabetes Dialyse Studie (4D) reported that atorvastatin,
Adaptive designs make clinical trials more efficient and are one part of the solution for optimizing the design of clinical trials in dialysis. We performed a systematic review by searching 2 large databases for dialysis trials with adaptive designs and found 57 examples. They are used mostly in trials of acute kidney injury, affected (changed a trial) half the studies they were used in, and are usually not reported in titles or abstracts of articles. We also found that the relative use of adaptive designs in nephrology is decreasing over time. Greater knowledge of adaptive design examples in dialysis will further improve uptake in dialysis randomized clinical trials.

20 mg per day, did not reduce cardiovascular events in kidney failure requiring dialysis despite evidence of a 20% to 30% reduction in other populations.\(^{14}\) This trial included a single dose of statin; it is hypothesized that alternative or multiple doses may have been more beneficial in a dialysis population given the significantly altered pharmacokinetics and pharmacodynamics.\(^{11,15}\) An adaptive multiarm multistage trial design may be more appropriate with 1 interim analysis at the end of stage I to identify an optimum dose to take forward into stage II. For example, the Telmisartan and Insulin Resistance in HIV (TAILoR) trial used a multiarm multistage design with 1 interim analysis to identify the most appropriate dose among 3 telmisartan doses (20, 40, and 80 mg daily). All 3 doses were tested in stage I and telmisartan, 80 mg, was taken forward into stage II.\(^{16}\)

This systematic review aims to: (1) summarize the use of adaptive design methodology in RCTs in dialysis populations and populations at risk for requiring dialysis; (2) describe the characteristics of the trials that use adaptive designs, including dialysis modality, funding, and geographical location; (3) describe the characteristics of adaptive trial designs in dialysis trials; (4) estimate the percentage of adaptive clinical trials in dialysis among all dialysis RCT; and (5) outline temporal trends in all of the above.

**METHODS**

We performed a systematic review, reported according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines.\(^{17}\) The protocol was registered with PROSPERO (CRD42020163946) and published separately.\(^{18}\) There were no age or English language restrictions. After testing our predefined search strategy,\(^{18}\) we found a small number (\(n = 16\)) of dialysis RCTs that reported an adaptive design method. We discovered that the adaptive design methods are often not reported in the title and abstract of articles and would not be detected in a traditional systematic search. To overcome this, we developed a novel “full-text systematic review” protocol and to our knowledge, this is the first use of this methodology.

**Search Method for the Identification of Trials**

**Electronic Search: Dialysis Studies**

We performed an electronic search on MEDLINE (PubMed) and ClinicalTrials.gov from database inception until June 1, 2020. Zotero was used as our reference manager. The dialysis search terms were adapted from Beaubien-Souligny et al,\(^{17} \) 2019 (and included dialysis, peritoneal dialysis, hemodialysis, hemodiafiltration, hemodiafiltration, hemofiltration, haemofiltration, extracorporeal blood cleansing, haemodialysis, renal dialysis, renal replacement, end stage kidney, end stage renal, stage 5 kidney, and stage 5 renal (Table S1). The output was stored in the Research Information Systems file format for PubMed and XML files for ClinicalTrials.gov.
Machine Learning Classifier: RCTs
We used the high-sensitivity machine learning classifier (RobotSearch) to identify RCTs from the PubMed dialysis search output.\(^{15}\) RobotSearch is a machine learning classification algorithm combining an ensemble of support vector machines and convolutional neural networks with a reported area under the curve of 0.987 (95% CI, 0.984-0.989) for RCT classification. We adjusted the parameters of RobotSearch to perform a sensitive search to increase the proportion of RCTs that are correctly identified.\(^ {15}\) Studies classified as likely to be RCTs were sourced for the full-text systematic review.

Full-Text Systematic Review: Adaptive Design Methods
We used Recoll for Windows to perform a full-text systematic review on our dialysis randomized clinical trial search results from PubMed and ClinicalTrials.gov. Recoll is based on the Xapian search engine library and provides a powerful text extraction layer and a graphical interface. The adaptive design search terms were adapted from Bothwell et al.,\(^ {20}\) 2018, and included phase 2/3, treatment switching, biomarker adaptive, biomarker adaptive design, biomarker adjusted, adaptive hypothesis, adaptive dose finding, pick the winner, drop the loser, sample size re-estimation, re-estimations, adaptive randomization, group sequential, adaptive seamless, adaptive design, interim monitoring, Bayesian adaptive, flexible design, adaptive trial, play the winner, adaptive method, adaptive and dose adjusting, response adaptive, adaptive allocation, adaptive signature design, treatment adaptive, covariate adaptive, and sample size adjustment (Table S2).

Manual Full-Text Review
We then performed manual full-text review to confirm studies that were included in the final systematic review. This process is summarized in a PRISMA flowchart (Fig 1). Full-text review was performed by C.J., R.M., and C.R. Disagreements were resolved by consensus and when a resolution was not reached by discussion, a consensus was reached through a third reviewer (M.J.O.).

Inclusion/Exclusion Criteria for the Selection of Studies

Type of Study Design and Participants
RCTs of interventions in patients with kidney failure requiring dialysis and acute kidney injury (AKI) undergoing kidney replacement therapy including hemodialysis, peritoneal dialysis, hemodiafiltration, and hemofiltration. We did not limit our population to any specific disease. Additionally, we included studies that included dialysis as either a primary or secondary outcome.

Type of Intervention and Outcome
We did not place a restriction on the intervention type and included trials that studied medications during dialysis,
medical devices, dialysis parameters, and dialysis modality. Dialysis parameter is any specification of the dialysis treatment that can be changed at each session, for example, duration, ultrafiltration rate, and sodium profiling. We included all outcomes including surrogate markers, patient-centered outcomes, and hard clinical outcomes.

Selection and Analysis of Trials
C.J., R.M., and C.R. extracted the study characteristics independently and in parallel. Data collected included type of the adaptive design, stopping rule, impact of adaptive design (ie, stopping for futility or efficacy and sample size changes), trial population, intervention, dialysis modality, the country of the lead investigator, and the funder of the study (adapted from Hatfield et al, 2016; Table S3).

Assessment of the Quality of the Studies: Risk of Bias
We used the Cochrane Risk of Bias 2 Tool22 to assess methodological quality of eligible trials, including random sequence generation, allocation concealment, blinding of participants and health care personnel, blinded outcome assessment, completeness of outcome data, evidence of selective reporting, and other biases. Risk-of-bias assessments were performed independently by C.J., R.M., C.R., and S.C. and disagreements were resolved by consensus. If 1 or more domains was rated as high, the study was considered at high risk of bias. We summarized our findings in a risk-of-bias table using the revised Cochrane risk-of-bias tool for randomized trials23 (Table S4).

Data Synthesis
A descriptive synthesis of the data was performed. We reported overall outcomes and outcomes by: (1) frequency and type of adaptive design; (2) adaptive designs as a proportion of studies classified as dialysis RCTs by RobotSearch; (3) population, intervention, and outcome, including dialysis modality (hemodialysis, peritoneal dialysis, hemodiafiltration, and hemofiltration); (4) publication in high-impact journals; (5) geographic location and funding; (6) reporting of adaptive design methods in title and abstract; and (7) a risk-of-bias assessment.

RESULTS
The systematic search of articles on MEDLINE (PubMed) with dialysis keywords published before June 1, 2020, identified 209,033 results. A total of 5,452 articles were classified as probable RCTs by the machine learning classifier RobotSearch.15 Full-text articles were sourced (n = 5,022) and we performed a full-text systematic review using adaptive design keywords that identified 54 studies for full review and 9 studies were included. In total, 57 studies, available as 68 articles and 7 ClinicalTrials.gov summaries, were included in the final analysis. A total of 31 studies were conducted in dialysis populations and 26 studies included dialysis as a primary or secondary outcome.

Study Characteristics
Frequency and Type of Adaptive Design
Figure 2 reports the number of adaptive designs by year and alongside the proportion of all dialysis RCTs that used adaptive design methods. The absolute amount of dialysis trials using adaptive designs has increased each year but this has not matched the overall increase in dialysis trials and resulted in a relative decrease over time in the use of adaptive design methods in dialysis trials, ranging from 6.12% in 2009 to 0.43% in 2019, with a mean of 1.82%. A 1-way analysis of variance was conducted to determine whether the proportion of adaptive trials was different by year. Adaptive trials proportion was statistically significantly different between years, F17 = 3.391; P < 0.001. Tukey post hoc analysis revealed statistically significant differences between 2009 and 2013 (−5.96 [95% CI, −10.73 to −1.19]; P = 0.002); 2019 (−5.7 [95% CI, −10.36 to −1.04]; P = 0.003); 2018 (−5.62 [95% CI, −10.29 to −0.96]; P = 0.003), 2015 (−5.33 [95% CI, −10.21 to −0.45]; P = 0.02); 2020 (−5.07 [95% CI, −9.81 to −0.34]; P = 0.021); and between 2014 and 2019 (−3.67 [95% CI, −6.69 to −0.65]; P = 0.003) and 2018 (−3.6 [95% CI, −6.62 to −0.58]; P = 0.004).

Group sequential designs were the most common type of adaptive design method used; 35 (61.4%) trials (22 [71%] in dialysis populations and 13 [50%] in dialysis outcome trials; Table 124-65). The O’Brien-Fleming stopping boundary was the most common stopping rule, used in 9 trials (25.7%), followed by Lan DeMets, used in 8 trials (22.9%). A total of 29 trials (50.9%) were affected by the use of group sequential adaptive design, including 7 trials (41.2%) that stopped early for futility, 3 trials (17.6%) that stopped early for efficacy, and 4 trials (23.5%) that stopped early for safety.

Sample-size re-estimation was the second most common type of adaptive design, used in 14 trials (24.6%); 8 (25.8%) in dialysis populations and 6 (23.1%) in dialysis outcome trials (Table 266-82). Eight trials (57.1%) were affected by the use of sample-size re-estimation adaptive design including 6 trials (75%) that increased sample size.

Phase 2/3 seamless design was the third most common type of adaptive design; 5 trials (8.8%); 1 (3.23%) in dialysis populations and 4 (15.4%) in dialysis outcome trials (Table 383-89). Adaptive dose-escalation, Bayesian adaptive design, and interim analysis were used in 1 trial each.
Population, Intervention, and Outcome Studied
AKI was studied in 32 trials (56.1%), kidney failure requiring dialysis was studied in 24 trials (42.1%), and chronic kidney disease (CKD) was studied in 1 trial (1.75%). Figure 3 reports the number of each population under study per year and shows a larger increase in adaptive design methods in AKI populations compared with kidney failure requiring dialysis populations. Medications were the most common intervention type, evaluated in 35 trials (61.4%), followed by dialysis modality in 7 trials (12.3%) and dialysis parameter in 4 trials (7%). Hemodialysis was the most common dialysis modality studied in 32 trials (56.1%), followed by hemodialysis and hemodiafiltration in 8 trials (14%); hemodialysis, hemodiafiltration, and hemofiltration in 7 trials (12.3%); and peritoneal dialysis in 4 trials (7%). Hard clinical outcomes were selected in 34 trials (59.6%), followed by surrogate outcomes in 20 trials (35.1%) and mixed in 3 trials (5.3%). The outcome measure was continuous in 15 trials (26.3%) and dichotomous in 42 trials (73.7%). Phase 3 studies were the most common study phase, studied in 41 trials (71.9%; Tables 1-3).

Publication in High-Impact Journals
A total of 32 studies (56.1%) were published in a high-impact journal (impact factor > 9). Fourteen studies (24.6%) were published in the New England Journal of Medicine, 6 studies (10.5%) were published in the Journal of the American Medical Association, 4 studies (7%) were published in Trials, and 2 studies (3.5%) were published in the Journal of the American Society of Nephrology.

Geographic Location and Funding
The most common country of the lead author was the United States in 24 studies (42.1%), followed by Germany in 7 studies (12.3%), France in 4 studies (7%), the Netherlands in 4 studies (7%), Australia in 3 studies (5.3%), and the United Kingdom in 3 studies (6%; Tables 1-3). Forty-nine studies (86%) were multicenter trials. Twenty-seven studies (47.4%) were supported by public funding, 21 studies (36.8%) were supported by private funding, 7 studies (12.3%) were supported by both public and private funding, and 2 studies (3.5%) did not report the source of funding.

Reporting of Adaptive Design Method in Title and Abstract
A total of 44 studies (77.2%) did not report their adaptive design method in the title or abstract and would not be detected by a standard systematic review search.

Risk of Bias
Risk of bias was assessed for 40 trials (protocols and clinicaltrials.gov were excluded; Fig S1; Table S4). Overall risk of bias was deemed to be “low” in 17 trials (42.5%), “some concerns” in 13 trials (32.5%), and “high risk” in 10 trials (25%). The randomization process led to some concerns for 10 studies (25%). Deviations from intended interventions led to some concerns for 4 studies (10%) and high risk for 6 studies (15%). Missing outcome data were deemed to be some concerns for 2 studies (5%) trials and high risk of bias for 2 studies (5%). Measurement of

Figure 2. Adaptive design in dialysis randomized clinical trials by year. Abbreviation: GSD, group sequential design.
| Study                        | Stopping Rule          | Impact of Adaptive Design | Population                                                                 | Intervention                                                                 | Primary Outcome | Nature of Primary Outcome | Dialysis Modality | Sample Size of Study | Country          | Funder Type | Funder                  | Study Phase |
|------------------------------|------------------------|---------------------------|-----------------------------------------------------------------------------|--------------------------------------------------------------------------------|-----------------|---------------------------|------------------|-----------------------|------------------|-------------|-------------------------|-------------|
| AKI                          | Acker et al.24 (2000)  | Pocock                    | Significant difference in mortality observed at first analysis; trial       | Thyroxine                                                                     | Medication      | Percentage requiring      | HD/HF            | 59                    | US               | NR          | NR                      | Phase 3     |
| ATN25,96 (2008)              | Haybittle-Peto rule    | 2 interim analyses        | Critically ill patients with AKI and failure of at least 1                  | Intensive or less intensive KRT                                               | Dialysis        | parameter                | HD/HF            | 1,124                 | US               | Public      | Cooperative studies program | Phase 3     |
| Ejaz et al.26 (2009)         | Z boundary             | Study stopped after      | Critically ill patients with high-risk cardiac surgery                      | Nesiritide                                                                    | Medication      | Dialysis and/or all-cause mortality within 21 d | HD/HF            | 94                    | US               | Private     | Siscon Inc               | Phase 3     |
| IVOIRE27 (2013)              | NR                     | 2 interim analyses        | Critically ill patients with septic shock and AKI                        | HVHF                                                                           | Dialysis        | modality                 | HF/HF            | 140                   | France           | Public      | French Health Ministry    | Phase 3     |
| FENO HSR28 (2014)            | Rebouissin et al       | Stopped due to futility   | Critically ill cardiac surgery patients with AKI                          | Fenoldopam                                                                    | Medication      | Rate of KRT               | Any KRT           | 667                   | Italy            | Public      | Italian Ministry of Health | Phase 3     |
| FBI29 (2014)                 | Fleming-Harrington (O  | Trial not complete        | Critically ill patients with AKI receiving CKRT                           | Enoxaparin                                                                    | Medication      | Occurrence of venous thromboembolism           | HD/HF/HF         | 266                   | Denmark          | Public      | Danish society of anesthesiology; intensive medicines research initiative | Phase 3     |
| HEROICS30 (2015)             | Triangular test (Whitehead 1978) | At sequential interim analysis 3 trial was stopped for futility | Patients with severe shock requiring high-dose catecholamines 3-24 h post-cardiac surgery | Early HVHF                                                                    | Dialysis        | modality 30-d mortality   | HF/HDF            | 224                   | France           | Public and private | French Ministry of Health; Hospal-Gambro | Phase 3     |
| AKIK31,32 (2016)             | O Brien-Fleming boundary | 2 interim analyses        | Patients with severe AKI requiring mechanical ventilation, catecholamine infusion, or both | Early or delayed strategy of KRT                                            | Dialysis        | parameter Overall survival at d 60          | HD               | 620                   | France           | Public      | French Ministry of Health | Phase 3     |
| ELAIN Trial33,34 (2018)      | O Brien-Fleming boundary | 1 interim analysis        | Critically ill patients with AKI and plasma NGAL level > 150 ng/mL       | Early or delayed initiation of KRT                                           | Dialysis        | parameter Mortality at 90 d            | HD/HF            | 231                   | Germany          | Private     | Else-Kroner Fresenius Stiftung    | Phase 3     |
| LEVO-CTS35,36 (2017)         | O Brien-Fleming boundary | NR                        | Patients with EF < 35% undergoing cardiac surgery with cardiopulmonary bypass | IV levosimendan                                                              | Medication      | Composite of 30-d mortality, KRT, perioperative MI, or mechanical cardiac assist device through d 5 | HD/HF            | 882                   | US               | Private     | Tenax Therapeutics     | Phase 3     |
| CULPRIT-SHOCK37,38 (2018)    | O Brien-Fleming boundary | NR                        | Patients with cardiogenic shock complicating acute MI                     | Culprit lesion only, primary coronary intervention                           | Treatment        | strategy 30-d mortality or AKI requiring KRT | HD/HF            | 706                   | Germany          | Public      | EU; German Heart Research Foundation; German Cardiac Society | Phase 3     |

(Continued)
### Table 1 (Cont’d). Group Sequential Trials in Dialysis Randomized Clinical Trials

| Study | Stopping Rule | Impact of Adaptive Design | Population | Intervention | Primary Outcome | Nature of Primary Outcome | Dialysis Modality | Sample Size of Study | Country | Funder Type | Funder | Study Phase |
|-------|---------------|---------------------------|------------|--------------|----------------|--------------------------|------------------|----------------------|---------|-------------|--------|--------------|
| PRESERVE [30] (2018) | O’Brien-Fleming boundary | Sponsor stopped trial after prespecified interim analysis due to absence of between-group difference | Patients at high risk for kidney complications scheduled for angiography | 1.26% sodium bicarbonate or IV 0.9% sodium chloride and 5 d of oral acetylcysteine or oral placebo | Medication | Composite of death, need for dialysis, or persistent increase of at least 50% from baseline in Scr at 90 d | HD | 5,177 | US | Public | NIDDK; NIH; Boehringer Ingelheim | Phase 3 |
| VIOLET [30] (2018) | Lan DeMets | Study stopped for futility after interim analysis 1 | Acute respiratory distress syndrome, vitamin D deficiency, and critical illness | Vitamin D₃ | Medication | 90-d all-cause mortality | HD | 1,358 | US | Public | NHLBI | Phase 3 |
| Schanz et al [40] (2019) | Jennison and Turnbull | Study stopped prematurely after interim analysis due to futility | Patients at high risk for AKI | Screened with urinary [TIMP-2] [IGFBP7] | Other | Incidence of moderate to severe AKI within the first d after admission | HD | 100 | Germany | Public | Robert-Bosch-Foundation | Phase 3 |
| HYVITS (NCT03380507) (2019) | O’Brien-Fleming boundary | Trial not complete | Septic shock and critical illness | Hydrocortisone, vitamin C, and thiamine | Medication | Hospital mortality at 60 d | HD | 212 | Qatar | Industry | Hamad Medical Corp | Phase 2/3 |
| RICH [41,42] (2020) | O’Brien-Fleming boundary | Stopped early for efficacy | Critically ill patients with AKI | Regional citrate anticoagulation compared with systemic heparin anticoagulation | Dialysis parameter | Filter life span and 90-d mortality | HDF | 596 | Germany | Public | German Research Foundation | Phase 3 |
| REMOVE (NCT03266302) (2020) | Pocock | Trial not complete | Infective endocarditis | Hemoadsorber for removal of cytokines | Medical device | Change in mean total SOFA score | HD | 288 | Germany | Public and private | German Federal Ministry of Education and Research; CytoSorbents Europe GmbH | Phase 2 |
| ACTION II [43] (1999) | Lan-DeMets | Trial stopped at interim analysis 3 due to concerns about safety | HD patients with clinical evidence of congestive heart failure or ischemic heart disease | Epoetin and target hematocrit | Medication | Time to death or first nonfatal MI | HD | 1,233 | US | Private | Amgen | Phase 3 |
| Chapman et al [44] (2007) | Constrained stopping boundaries | 2 interim analyses, trial continued | Liver resection, spine, peripheral arterial bypass, and dialysis access surgery | Recombinant human thrombin (rhThrombin) | Medication | Time to hemostasis | HD | 76 | US | Private | ZymoGenetics, Inc | Phase 3 |
| DAC [45] (2008) | Lan DeMets | Enrollment stopped after 877 patients randomized based on stopping rule for intervention efficacy | Participants with ESKD undergoing new fistula creation | Clopidogrel | Medication | Fistula thrombosis | HD | 877 | US | Public | NIDDK; NIH | Phase 3 |
| DAC [46] (2009) | Lan DeMets | 5 planned interim analyses performed before final analysis; no change to trial | Participants with placement of a new arteriovenous graft dipyridamole plus aspirin | Medication | Loss of primary unassisted patency | HD | 649 | US | Public and private | NIDDK; NIH; Boehringer Ingelheim | Phase 3 |

*Kidney Failure Requiring Dialysis*

- **Besarab et al [47] (1998)**: Trial stopped at interim analysis 3 due to concerns about safety
  - HD patients with clinical evidence of congestive heart failure or ischemic heart disease
  - Epoetin and target hematocrit
  - Medication
  - Time to death or first nonfatal MI
  - HD: 1,233
  - US: Private
  - Amgen
  - Phase: 3

- **ACTION II [43] (1999)**: Terminated enrollment due to unfavorable perceived risk-benefit ratio
  - T2DM patients with kidney disease
  - Aminoguanidine
  - Medication
  - Doubling of Scr concentration
  - HD: 900
  - US: NR
  - NR
  - Phase: 3

- **Chapman et al [44] (2007)**: Constrained stopping boundaries
  - 2 interim analyses, trial continued
  - Liver resection, spine, peripheral arterial bypass, and dialysis access surgery
  - Recombinant human thrombin (rhThrombin)
  - Medication
  - Time to hemostasis
  - HD: 76
  - US: Private
  - ZymoGenetics, Inc
  - Phase: 3

- **DAC [45] (2008)**: Enrollment stopped after 877 patients randomized based on stopping rule for intervention efficacy
  - Participants with ESKD undergoing new fistula creation
  - Clopidogrel
  - Medication
  - Fistula thrombosis
  - HD: 877
  - US: Public
  - NIDDK; NIH
  - Phase: 3

- **DAC [46] (2009)**: 5 planned interim analyses performed before final analysis; no change to trial
  - Participants with placement of a new arteriovenous graft
  - Extended-release dipyridamole plus aspirin
  - Medication
  - Loss of primary unassisted patency
  - HD: 649
  - US: Public and private
  - NIDDK; NIH; Boehringer Ingelheim
  - Phase: 3
| Study | Stopping Rule | Impact of Adaptive Design | Population | Intervention | Primary Outcome | Nature of Primary Outcome | Dialysis Modality | Sample Size of Study | Country | Funder Type | Funder | Study Phase |
|-------|---------------|--------------------------|------------|--------------|----------------|--------------------------|-------------------|---------------------|---------|-------------|--------|-------------|
| AURORA48,49 (2009) | Event driven | Continuation of study was recommended by data and safety monitoring board | Maintenance HD patients | Rosuvastatin | Medication | Death from cardiovascular causes, nonfatal MI, or nonfatal stroke | HD | 2,776 | Sweden | Private | AstraZeneca | Phase 3 |
| ACCORD50 (2010) | Lan DeMets | Intensive therapy stopped before study end due to increased mortality | Volunteers with established T2DM, HbA1c ≥ 7.5%, and CVD or ≥2 CVD risk factors | Target HbA1c < 6.0% | Treatment target | Dialysis or kidney transplantation or Scr > 291.7 μL or retinal photocoagulation or vitrectomy | HD | 10,251 | US | Public | NHLBI | Phase 3 |
| OPPORTUNITY51,52 (2011) | Event-driven | Trial terminated early due to slow recruitment | Adult maintenance HD patients | Recombinant human growth hormone | Medication | Mortality | HD | 695 | US | Private | Novo Nordisk | Phase 3 |
| CONTRAST53,54 (2012) | Double triangular test (Whitehead 2007) | Board recommended to stop trial as enough evidence was provided for futility | Patients with ESKD | Online HDF | Dialysis modality | All-cause mortality | HD/ HDF | 714 | the Netherlands | Public and private | Dutch Kidney Foundation; Fresenius Medical Care; Gambro Lundia | Phase 3 |
| HONEYPOT55,56 (2014) | Haybittle-Peto rule | Stopping rule for efficacy not met and study was completed as per protocol | PD patients | Daily topical exil-site application of antibacterial honey | Medication | Time to first infection related to PD | PD | 371 | Australia | Public and private | Baxter Healthcare; Queensland Government; Comvita; Gambro | Phase 3 |
| HALT-PKD57 (2014) | Lan DeMets | Study extended due to lower-than-expected no. of end points | Patients with ADPKD | Lisinopril and telmisartan | Medication | Time to death, ESKD, or 50% reduction from baseline eGFR | HD | 486 | US | Public | NIDDK | Phase 3 |
| Knoll et al58,59 (2015) | O’Brien-Fleming boundary | Extended follow-up to 4 y to increase statistical power due to slower-than-expected recruitment | Kidney transplant patients with proteinuria and eGFR of 20-55 mL/min/1.73 m² | Ramipril | Medication | Doubling of Scr, ESKD, or death | HD | 528 | Canada | Public | Canadian Institutes of Health Research | Phase 3 |
| PAVE60 (2016) | Lan DeMets | Trial not complete | Patients with native arterovenous fistula | Paclitaxel-coated balloons | Medical device | Time to end of target lesion primary patency | HD | 211 | UK | Public | National Institute for Health Research EME programme | Phase 3 |
| OPN-305 (NCT01794663) (2016) | NR | Unknown | Kidney transplant recipients with delayed graft function | OPN-305 (tomilamib) | Medication | Measure of early graft function | HD | 252 | Ireland | Industry | Oposa Therapeutics Ltd | Phase 2 |
| FAVOURED61,62 (2017) | Haybittle-Peto rule | Early cessation of recruitment, only interim analysis 1 was performed | Participants with stage 4 or 5 CKD after arterovenous fistula creation | Fish oil supplementation | Medication | Fistula failure, a composite of fistula thrombosis and/or abandonment and/or cannulation failure, at 12 mo | HD | 567 | Australia | Public and private | National Health and Medical Research Council of Australia; Amgen Australia Pty Ltd; Mylan EDP | Phase 3 |
| CREDENCE63 (2019) | Alpha spending function | Prespecified efficacy criteria for early cessation were achieved so board recommended that trial be stopped | Patients with T2DM and albuminuric CKD | Canagliflozin | Medication | Composite of ESKD (dialysis, transplantation, sustained GFR < 15), doubling of Scr, or death from kidney or cardiovascular causes | HD | 4,401 | Australia | Private | Janssen Research and Development | Phase 3 |

(Continued)
outcome measures was deemed to be some concerns for 2 studies (5%) trials and high risk of bias for 1 study (2.5%). Selection of the reported result was deemed to be some concerns for 6 studies (15%) trials and high risk of bias for 1 study (2.5%).

DISCUSSION
In this systematic review, we report that adaptive design methods were used in 57 dialysis RCTs over a 20-year period. Although the absolute number has increased over time, the relative use of adaptive design methods in trials in dialysis populations and trials with dialysis as an end point has decreased.

First, we report that the relative proportion of adaptive design methods in dialysis trials has decreased over time. The absolute number of dialysis trials using adaptive designs has increased each year, but this has not matched the overall increase in dialysis trials and therefore resulted in a relative decrease. We were unable to compare this result with other specialties because recent systematic reviews have not reported the relative use of adaptive designs.21,90

Second, we report that group sequential designs are the most used type of adaptive design in dialysis trials. This is similar to previous systematic reviews in cardiology91 and oncology90 and in a review of registered clinical trials covering multiple specialties on clinicaltrials.gov.21

Third, we report that adaptive designs were more common in AKI (56.1% of trials) than kidney failure requiring dialysis (42.1% of trials). This may reflect increasing use of adaptive design methodology in critical care92 and sepsis-related trials,93 in which AKI is most common. There were very few trials of CKD with a dialysis outcome (2%) that used an adaptive design. Many reasons for the paucity of CKD trials have been previously suggested, including the use of treatments in CKD despite a lack of evidence, difficulty recruiting to CKD trials due to stringent eligibility criteria, and underpowered subgroup analysis.4,94 The infrequent use of adaptive designs in CKD trials may become a self-perpetuating barrier to using adaptive designs in future trials.21

Fourth, we report that adaptive design methods affected the conduct of the randomized trial in most studies (50.9%). For example, 17 (48.6%) trials were affected by the use of group sequential adaptive design, including 7 trials (41.2%) stopped early for futility, 3 trials (17.6%) stopped early for efficacy, and 4 trials (23.5%) stopped early for safety. This finding is similar to a systematic review of published and publicly available trials in which the most common reason for stopping group sequential trials was futility.26

Fifth, we found that the most common country of the lead author was the United States, 24 studies (42.1%), and the most common funding source was public, 27 studies (47.4%). This finding was different from a systematic review of published and publicly available trials in which 65% of trials reported industry funding.20

Funding for
## Table 2. Sample-Size Re-estimation in Dialysis Randomized Clinical Trials

| Study | Impact of Adaptive Design | Population | Intervention | Primary Outcome | Nature of Primary Outcome | Dialysis Modality | Sample Size | Country | Funder Type | Funder | Study Phase |
|-------|---------------------------|------------|--------------|-----------------|---------------------------|-------------------|-------------|---------|-------------|---------|-------------|
| AKI   |                           |            |              |                 |                           |                   |             |         |             |         |             |
| Hemodia66 (2006) | Sample size adjusted to include 180 patients per group | Critically ill patients with acute kidney failure as part of multiple-organ dysfunction syndrome | Intermittent HD vs CVHDF | 60-d survival | HD/HDF | 360 | France | Public | Societe de Reanimation de Langue Francaise | Phase 4 |
| Riley et al67 (2014) | Data from initial 10 randomized patients demonstrated >50% difference in urine output, revealing adequate power would be achieved with only 20 randomized patients | Infants < 90 d old with congenital heart disease who underwent bypass surgery and were postoperatively treated with CPD | Continue 24 h more CPD or discontinue CPD | Urine output (mL/kg per PD h) | Dialysis modality | 20 | US | Public | Baylor College of Medicine; Cincinnati Children - Hospital Medical Center | Phase 3 |
| SCD68 (2015) | Study terminated by sponsor at interim analysis because SCD treatment was often outside the recommended iCa range and therefore resulted in ineffective therapy | ICU patients with AKI | Selective cytokheretic device | 60-d mortality | HDF | 134 | US | Private | CytoPhex, Inc. | Phase 3 |
| TARTARE-2S69 (2016) | Trial not complete | Patients with septic shock | Targeted tissue perfusion vs macrocirculation-guided standard care | Alive at 30 d with normal arterial blood lactate and without inotropic or vasopressor agent | Dialysis strategy | 200 | Switzerland | Public | Signid Juselius Foundation; Instrumentarium Foundation; Helsinki University Hospital | Phase 3 |
| Kwiatkowski et al70 (2017) | NR | Infants after congenital heart surgery | PD | Dialysis modality | Negative fluid balance | PD | 73 | US | Public | American Heart Association Great Rivers Affiliate; internal funding from Cincinnati Children’s Hospital Medical Center | Phase 2 |
| ANDROMEDA-SHOCK71 (2018) | Trial not complete | Patients with septic shock | Peripheral perfusion-targeted resuscitation | Other | 28-d mortality | HD/HDF | 422 | Chile | Public | Departamento de Medicina Intensiva, Pontificia Universidad Catolica de Chile | Phase 3 |
| COACT72,73 (2019) | After interim analysis, data and safety monitoring committee advised that sample size not be increased | Post-cardiac arrest patients without signs of STEMI | Immediate coronary angiography and percutaneous coronary intervention | 90-d mortality | HD/HDF | 552 | the Netherlands | Public | Netherlands Heart Institute | Phase 3 |
| FRESH74 (2020) | Continue enrollment to increase sample size to maximum of 210 patients | Patients presenting to the ED with sepsis or septic shock and anticipated ICU admission | Dynamic assessment of fluid responsiveness (passive leg raise) | Difference in positive fluid balance at 72 h or ICU discharge | Dialysis strategy | 124 | US | Private | Cheetah Medical | Phase 3 |

(Continued)
Table 2 (Cont’d). Sample-Sized Re-estimation in Dialysis Randomized Clinical Trials

| Study | Impact of Adaptive Design | Population | Intervention | Primary Outcome | Nature of Primary Outcome | Dialysis Modality | Sample Size | Country | Funder Type | Funder | Study Phase |
|-------|---------------------------|------------|--------------|----------------|--------------------------|--------------------|--------------|---------|-------------|--------|-------------|
| PREDICT (2020) | Sample size amended from 220 to 238 for each group | Patients with CKD without diabetes | High and low hemoglobin groups (darbepoetin alfa) | Medication | Kidney composite end point (starting maintenance dialysis, kidney transplantation, eGFR < 6 mL/min/1.73 m², and 50% reduction in eGFR) | HD | 491 | Japan | Private | Kyowa Hakko Kirin; Otsuka; Dainippon Sumitomo; Mochida | Phase 3 |
| Kratochwill et al (2016) | Led to premature termination of patient recruitment | Stable PD outpatients | Alanyl-glutamine addition to glucose-based PD fluid | Medication | Heat-shock protein 72 expression | PD | 20 | Austria | Public | ZIT - Technology Agency of the City of Vienna; FFG - the Austrian Research Promotion Agency | Phase 2 |
| IDPN-Trial (2017) | Sample size was increased; primary outcome was significant | Maintenance HD patients with protein-energy wasting | IDPN | Medication | Prealbumin | HD | 107 | Germany | Private | Fresenius Kabi Germany GmbH | Phase 4 |
| CHART (2018) | Sample-size re-estimation not performed | Urologic patients undergoing elective cystectomy | Albumin 5% or balanced hydroxyethyl starch 6% | Medication | Ratio of serum cystatin C between last visit at d 90 and 1 preoperative visit 1 | HD | 100 | Germany | Private | CSL Behring GmbH | Phase 3 |
| KALM-1 (2019) | NR | HD patients with moderate to severe pruritus | Intravenous difelikefalin | Medication | 24-h Worst Itching Intensity Numerical Rating Scale | HD | 378 | US | Private | Cara Therapeutics | Phase 3 |
| Fujimoto et al (2020) | Sample size calculated by intermediate analysis of first 30 samples enrolled | Patients on maintenance HD 3×/wk | Lidocaine/prilocaine cream (EMLA) | Medication | Puncture pain relief, measured using a 100-mm visual analog scale | HD | 66 | Taiwan | Public | Grant-in-aid for Young Scientists from the Japan Society for the Promotion of Science | Phase 2 |

Abbreviations: AKI, acute kidney injury; CKD, chronic kidney disease; CPD, continuous peritoneal dialysis; CVHDF, continuous venovenous hemodiafiltration; ED, emergency department; eGFR, estimated glomerular filtration rate; HD, hemodialysis; HDF, hemodiafiltration; iCa, ionized calcium; ICU, intensive care unit; IDPN, intradialytic parenteral nutrition; NR, not reported; PD, peritoneal dialysis; SCD, selective cytophoretic device; STEMI, ST-elevation myocardial infarction.
| Study | Impact of Adaptive Design | Population | Intervention | Primary Outcome | Nature of Primary Outcome | Dialysis Modality | Sample Size | Country | Funder Type | Funder | Study Phase |
|-------|--------------------------|------------|--------------|-----------------|--------------------------|------------------|-------------|---------|-------------|---------|-------------|
| Phase 2a/2b Seamless Design | | | | | | | | | | | |
| STOP-AKI²⁸³¹⁸⁴ (2018) | Combined efficacy and dose-finding study | Critically ill patients with sepsis-associated AKI | Human recombinant alkaline phosphatase | Medication | Area under the time-corrected endogenous creatinine clearance curve from d 1-7 | HD | 301 | the Netherlands | Private | AM-Pharma | Phase 2a/2b |
| 2-Stage Seamless Adaptive Design | | | | | | | | | | | |
| Himmelfarb et al⁸⁵ (2018) | At end of each stage, data from patients are used to select the THR-184 dose arms for next stage | Patients at high risk for AKI after cardiac surgery | THR-184 | Medication | Proportion of patients who developed AKI | HD/ HDF/HF | 452 | US | Private | Thrasos Therapeutics, Inc | Phase 2 |
| Adaptive Phase 2b/3 | | | | | | | | | | | |
| SEPSIS-ACT³⁸ (2018) | Trial was stopped for futility at end of part 1 | Septic shock requiring >5 μg/min of norepinephrine |Selepressin | Medication | Vasopressor- and mechanical ventilator-free days (PVFDson) | HD | 868 | US | Industry | Ferring Pharmaceuticals | Phase 2/3 |
| Phase 2/3 Seamless Design | | | | | | | | | | | |
| COMBAT-SHINE²⁷ (2020) | Trial not complete | Patients with septic shock–induced endotheliopathy | Infusion of iloprost | Medication | Mean daily modified Sequential Organ Failure Assessment score | HD | 384 | Denmark | Public | Danish Independent Research Organisation | Phase 2 |
| Cohen et al (NCT04381052) (2020) | Trial not complete | Patients with life-threatening COVID-19 | Clazakizumab | Medication | Cumulative incidence of serious adverse events associated with clazakizumab or placebo | Any | 30 | US | Public and private | Columbia University; NYU Langone Health; CSL Behring | Phase 2 |
| Adaptive Dose-Escalation | | | | | | | | | | | |
| EMPIRIKAL³⁸ (2017) | Trial not complete | Patients after receiving deceased donor kidney transplants | Mirococept | Medication | Delayed graft function | HD/ HDF/HF | 560 | UK | Public | Medical Research Council | Phase 2 |
| Bayesian Adaptive Design | | | | | | | | | | | |
| ASTOUND (NCT02723591) (2019) | Trial shortened to 1 y due to a stopping rule | Kidney transplantation | Tacrolimus | Medication | Percentage of participants positive for de novo DSA or immune activation occurrence | HD | 599 | US | Industry | Astellas Pharma Inc | Phase 4 |

(Continued)
kidney research reached an all-time low in 2013 but this has recently changed in the United States with advocacy from scientific societies such as the American Society of Nephrology, whereby an executive order was signed in 2020 to reform the US end-stage kidney disease treatment industry. Adaptive designs are one part of the solution for optimizing the design of clinical trials in dialysis and nephrology and will benefit from the improvement in the funding landscape.

Our study has several limitations. First, we limited our search to 2 databases (PubMed and ClinicalTrials.gov) due to the scale of studies sourced (209,033 and 6,002 results). This was a deviation from our protocol but necessary to make this full-text review feasible. Second, we decided to include RCTs with dialysis outcomes in addition to patients currently receiving dialysis. This permitted a more comprehensive review of the full landscape of AKI, kidney failure requiring dialysis, and CKD trials, but was a deviation from our original protocol. Third, the denominator for calculating the proportion of adaptive designs in all dialysis RCTs will include some false positives, that is, either not RCTs or not dialysis. We modified the parameters of the machine learning classifier to perform a sensitive search to include as many true positives as possible. We expect this misclassification bias to be independent of time and bias every year equally and therefore not affect the trend. Fourth, publication bias, in which negative studies are not published, will bias out results toward the null, for example, our estimate of the impact of adaptive design (50.9%) would be higher if unpublished studies stopped for futility and not published were included.

In summary, we developed a novel full-text systematic review search strategy. Forty-four studies (77.2%) did not report their adaptive design method in the title or abstract and would not be detected by a standard systematic review methodology. This could introduce a reporting bias in which adaptive design methods are reported in the main article but not in the abstract. Our novel strategy combined classical systematic review, machine learning classifiers, and a novel full-text systematic review. This new method has broad applications in medical evidence synthesis and evidence synthesis in general.

Adaptive design methods improve the efficiency of RCTs in dialysis but their relative use in dialysis is decreasing over time. Greater knowledge of adaptive design examples in dialysis will further improve uptake in dialysis RCTs.
Table S2: Search strategy for Recoll (full-text search).
Table S3: Characteristics of the trials.
Table S4: Risk-of-bias assessment.

ARTICLE INFORMATION

Authors' Full Names and Academic Degrees: Conor Judge, MB, Robert Murphy, MB, Catriona Reddin, MB, Sarah Cormican, MB, Andrew Smyth, MB, PhD, Martin O'Halloran, PhD, and Martin J O'Donnell, MB, PhD.

Authors' Affiliations: HRB-Clinical Research Facility Galway (CJ, RM, CR, SC, AS, MJO) and Translational Medical Device Lab (CJ, MO), NUI Galway, Galway, Ireland; and Wellcome Trust-HRB, Irish Clinical Academic Training, Dublin, Ireland (CJ, CR, SC).

Address for Correspondence: Conor Judge, MB, HRB-Clinical Research Facility Galway, National University of Ireland Galway, Newcastle Road, Galway, Ireland H91YR71. Email: conorjudge@gmail.com

Authors' Contributions: Study design: CJ, RM, MJO; data acquisition: CJ, RM, CR, SC; statistical analysis: CJ; Project supervision: AS, MO, MJO; Each author contributed important intellectual content during manuscript drafting or revision and accepts accountability for the overall work by ensuring that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved.

Support: This work was performed within the Irish Clinical Academic Training Programme, supported by the Wellcome Trust and the Health Research Board (grant number 203930/B/16/Z), the Health Service Executive, National Doctors Training and Planning and the Health and Social Care, Research and Development Division, Northern Ireland. The funding source had no role in the study design, analysis, or writing of report.

Financial Disclosure: The authors declare that they have no relevant financial interests.

Peer Review: Received April 13, 2021, as a submission to the expedited consideration track with 2 external peer reviews. Direct editorial input from the Editor-in-Chief. Accepted in revised form July 11, 2021.

REFERENCES

1. Judge C, Murphy R, Reddin C, et al. Adaptive design methods in dialysis clinical trials – a systematic review. Posted January 26, 2021. medRxiv. 2021.01.22.21250343. https://doi.org/10.1101/2021.01.22.21250343
2. Bothwell LE, Greene JA, Podolsky SH, Jones DS. Assessing the gold standard — lessons from the history of RCTs. N Engl J Med. 2016;374(22):2175-2181.
3. Kovessy CP. Clinical trials in end-stage renal disease—priorities and challenges. Nephrol Dial Transplant. 2019;34(7):1084-1089.
4. Baigent C, Herrington WG, Coresh J, et al. Challenges in conducting clinical trials in nephrology: conclusions from a Kidney Disease—Improving Global Outcomes (KDIGO) Controversies Conference. Kidney Int. 2017;92(2):297-305.
5. Bryan L, Ibrahim T, Zent R, Fischer MJ. The kidney research predicament. J Am Soc Nephrol. 2014;25(5):898-903.
6. Chatzimanouil MKT, Wilkens L, Anders H-J. Quantity and reporting quality of kidney research. J Am Soc Nephrol. 2019;30(1):13-22.
7. Yaseen M, Hassan W, Awad R, et al. Impact of recent clinical trials on nephrology practice: are we in a stagnant era? Kidney Dis. 2019;5(2):69-80.
8. Chow S-C, Chang M, Pong A. Statistical consideration of adaptive methods in clinical development. J Biopharm Stat. 2005;15(4):575-591.
9. Pallmann P, Bedding AW, Choodari-Oskooei B, et al. Adaptive designs in clinical trials: why use them, and how to run and
report them. *BMC Med*. 2018;16(1). Accessed April 23, 2020. https://bmcmedicine.biomedcentral.com/articles/10.1186/s12916-018-1017-7

10. Adaptive Design Clinical Trials for Drugs and Biologics. U.S. Food and Drug Administration. 2019. Accessed November 18, 2019. http://www.fda.gov/regulatory-information/search-fda-guidance-documents/adaptive-design-clinical-trials-drugs-and-biologics

11. Novak JE, Inrig JK, Patel UD, Califf RM, Szcz ech LA. Negative trials in nephrology: what can we learn? *Kidney Int*. 2008;74(9):1121-1127.

12. Chaitman BR. Effects of ranolazine with atenolol, amlodipine, or diltiazem on exercise tolerance and angina frequency in patients with severe chronic angina a randomized controlled trial. *JAMA*. 2004;291(3):309-316.

13. Wanner C, Krane V, M€ arz W, et al. Atorvastatin in patients with type 2 diabetes mellitus undergoing hemodialysis. *N Engl J Med*. 2005;353(3):238-248.

14. Cheung BMY, Lauder IJ, Lau C-P, Kumana CR. Meta-analysis of large randomized controlled trials to evaluate the impact of statins on cardiovascular outcomes. *Br J Clin Pharmacol*. 2004;57(5):640-651.

15. Velenosi TJ, Urquhart BL. Pharmacokinetic considerations in chronic kidney disease and patients requiring dialysis. *Expert Opin Drug Metab Toxicol*. 2014;10(8):1131-1143.

16. Pushpakom S, Kolamunnage-Dona R, Taylor C, et al. TAiLoR (TelmisArtan and InsuLin Resistance in Human Immunodeficiency Virus [HIV]): an adaptive-design, dose-ranging phase iiib randomized trial of telmisartan for the reduction of insulin resistance in HIV-positive individuals on combination antiretroviral therapy. *Clin Infect Dis*. Accessed April 23, 2020. https://academic.oup.com/cid/advance-article/doi/10.1093/cid/ciz589/5527878

17. Moher D, Liberati A, Tetzlaff J, Altman DG; for the PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *BMJ*. 2009;339(1):b2535.

18. Judge C, Murphy RP, Cormican S, Smyth A, O’Halloran M. Adaptive design methods in dialysis clinical trials: a systematic review protocol. *BMJ Open*. 2020;10(8):e036755.

19. Beaubien-Souilgy W, Kontar L, Blum D, Bouchard J, Denault AY, Wald R. Meta-analysis of randomized controlled trials using tool-assisted target weight adjustments in chronic dialysis patients. *Kidney Int Rep*. 2019;4(10):1426-1434.

20. Bothwell LE, Avorn J, Khan NF, Kesselheim AS. Adaptive design clinical trials: a review of the literature and ClinicalTrials.gov. *BMJ Open*. 2018;8(2):e018320.

21. Hatfield I, Allison A, Flight L, Julious SA, Dimairo M. Adaptive designs undertook in clinical research: a review of the registered clinical trials. *Trials*. 2016. Accessed August 21, 2020. http://www.trialsjournal.com/content/17/1/1150

22. Sterne JA, Savovic J, Page MJ, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ*. 2019;366:doi: 10.1136/bmj.l4898

23. Higgins JPT, Altman DG, Gotzsche PC, et al. The Cochrane Collaboration’s tool for assessing risk of bias in randomised trials. *BMJ*. 2011;343(2):d5928.

24. Acker CG, Singh AR, Flick RP, Bernardini J, Greenberg A, Johnson JP. A trial of thyr oxine in acute renal failure. *Kidney Int*. 2000;57(1):293-298.

25. Sharma S, Kelly YP, Palevsky PM, Waikar SS. Intensity of renal replacement therapy and duration of mechanical ventilation. *Chest*. 2020;158(4):1473-1481.

26. Ejaz AA, Martin TD, Johnson RJ, et al. Prophylactic nesiritide does not prevent dialysis or all-cause mortality in patients undergoing high-risk cardiac surgery. *J Thorac Cardiovasc Surg*. 2009;138(4):959-964.

27. Joannes-Boyau O, Honor€ e PM, Perez P, et al. High-volume versus standard-volume haemofiltration for septic shock patients with acute kidney injury (IVOIRE study): a multicentre randomized controlled trial. *Intensive Care Med*. 2013;39(9):1535-1546.

28. Bove T, Zangrillo A, Guarracino F, et al. Effect of fenoldopam on use of renal replacement therapy among patients with acute kidney injury after cardiac surgery: a randomized clinical trial. *JAMA*. 2014;312(21):2244-2253.

29. Robinson S, Zuckn A, Larsen UL, Ekstr€ am C, Toft P. A feasible strategy for preventing blood clots in critically ill patients with acute kidney injury (FBI): study protocol for a randomized controlled trial. *Trials*. 2014;15(1). Accessed October 27, 2020. https://trialsjournal.biomedcentral.com/articles/10.1186/1745-6215-15-226

30. Combes A, Br€ echot N, Amour J, et al. Early high-volume haemofiltration versus standard care for post–cardiac surgery shock. the HEROICS Study. Am J Respir Crit Care Med. 2015;192(10):1179-1190.

31. Gaudry S, Hajage D, Schortgen F, et al. Initiation strategies for renal-replacement therapy in the intensive care unit. *N Engl J Med*. 2016;375(2):122-133.

32. Gaudry S, Hajage D, Schortgen F, et al. Comparison of two strategies for initiating renal replacement therapy in the intensive care unit: study protocol for a randomized controlled trial (AKIKI). *Trials*. 2015;16(1):170. https://doi.org/10.1186/s13063-015-0718-x.

33. Zarbock A, Kellum JA, Schmidt C, et al. Effect of early vs delayed initiation of renal replacement therapy on mortality in critically ill patients with acute kidney injury: the ELAIN randomized clinical trial. *JAMA*. 2016;315(20):2190-2199.

34. Zarbock A, Ger€ s J, Van Aken H, Boanta A, Kellum JA, Meersch M. Early versus late initiation of renal replacement therapy in critically ill patients with acute kidney injury (The ELAIN-Trial): study protocol for a randomized controlled trial. *Trials*. 2016;17(1). Accessed October 27, 2020. http://www.trialsjournal.com/content/17/1/1148

35. Mehta RH, Van Diepen S, Meza J, et al. Levosimendan in patients with left ventricular systolic dysfunction undergoing cardiac surgery on cardiopulmonary bypass: rationale and study design of the Levosimendan in Patients with Left Ventricular Systolic Dysfunction Undergoing Cardiac Surgery Requiring Cardiopulmonary Bypass (LEVO-CTS) trial. *Am Heart J*. 2016;182:62-71.

36. Thiele H, Akin I, Sandri M, et al. One-year outcomes after PCI in cardiogenic shock. *N Engl J Med*. 2018;379(18):1699-1710.

37. Thiele H, Desch S, Piek JJ, et al. Multivessel versus culprit lesion only percutaneous revascularization plus potential staged revascularization in patients with acute myocardial infarction complicated by cardiogenic shock: design and rationale of the CULPRIT-SHOCK trial. *Am Heart J*. 2016;172:160-169.

38. Weisbord SD, Gallagher M, Jneid H, et al. Outcomes after angiography with sodium bicarbonate and acetylcysteine. *N Engl J Med*. 2018;378(7):603-614.

39. The National Heart, Lung, and Blood Institute PETAL Clinical Trials Network. Early high-dose vitamin D₃ for critically ill, vitamin D–deficient patients. *N Engl J Med*. 2019;381(26):2529-2540.
40. Schanz M, Wasser C, Allgaeuer S, et al. Urinary [TIMP-2·
[49x290]$\text{FGFBP7}$]-guided randomized controlled intervention trial to
prevent acute kidney injury in the emergency department. 
_Nephrol Dial Transplant_. 2019;34(11):1902-1909.

41. Zarbock A, Küllmar M, Kindgen-Milles D, et al. Effect of regional citrate anticoagulation vs systemic heparin anticoagulation
during continuous kidney replacement therapy on dialysis filter life span and mortality among critically ill patients with acute kidney injury; a randomized clinical trial. _JAMA_. 2020;324(16):
1629-1639.

42. Meersch M, Küllmar M, Wempe C, et al. Regional citrate versus systemic heparin anticoagulation for continuous renal replace-
ment therapy in critically ill patients with acute kidney injury (RICH) trial: study protocol for a multicentre, randomised
controlled trial. _BMJ Open_. 2019;9(1):e024411.

43. Besarab A, Bolton WK, Browne JK, et al. The effects of normal
hemodialysis patients. _N Engl J Med_. 2012;367(6):493-501.

44. Chapman WC, Singla N, Genyk Y, et al. A phase 3, ran-
domized, double-blind comparative study of the efficacy and
safety of topical recombinant human thrombin and bovine
thrombin in surgical hemostasis. _J Am Coll Surg_. 2007;205(2):256-265.

45. Dember LM, Beck GJ, Allon M, et al. Effect of clopidogrel on
early failure of arteriovenous fistulae used for haemodialysis
patients undergoing haemodialysis. _N Engl J Med_. 2009;360(21):2191-2201.

46. Fellström BC, Jardine AG, Schmieder RE, et al. Rosuvastatin
and cardiovascular events in patients undergoing hemodialysis.
_N Engl J Med_. 2009;360(14):1395-1407.

47. Dixon BS, Beck GJ, Vazquez MA, et al. Effect of dipiridamole plus aspirin on hemodialysis graft patency. _N Engl J Med_.
2009;360(21):2191-2201.

48. Fellsström B, Holdaas H, Jardine AG, et al. Effect of rosuvastatin
on outcomes in chronic haemodialysis patients: baseline data from the AURORA Study. _Kidney Blood Press Res_.
2007;30(5):314-322.

49. Ismail-Beigi F, Allgaier S, et al. Outcomes of the randomised
controlled trial in chronic haemodialysis patients – the Dutch CONVective TRANsport Study (CONTRAST): rationale and design of a randomised controlled trial [ISRCTN3865125]. _Curr Control Trials Cardiovasc Med_. 2005;6(1). Accessed October 27, 2020. http://trialsjournal.biomedcentral.com/articles/10.1186/1468-6708-6-8

50. Johnson DW, Badve SV, Pascoe EM, et al. Antibacterial honey
for the prevention of peritoneal-dialysis-related infections (HONEYPOT): a randomised trial. _Lancet Infect Dis_.
2014;14(1):23-30.

51. Kopple JD, Cheung AK, Christiansen JS, et al. OPPORTUNITY:
a large-scale randomized clinical trial of growth hormone in
hemodialysis patients. _Nephrol Dial Transplant_. 2011;26(12):4095-4103.

52. Kopple JD, Cheung AK, Christiansen JS, et al. OPPORTUNITYTM: A randomized clinical trial of growth hormone on outcome in hemodialysis patients. _Clin J Am Soc Nephrol_. 2008;3(6):1741-1751.

53. Grootezan MPC, van den Dorpel MA, Bots ML, et al. Effect of
online hemodiafiltration on all-cause mortality and cardiovas-
cular outcomes. _J Am Soc Nephrol_. 2012;23(6):1087-1096.

54. The CONTRAST study group; Penne EL, Blankstijn PJ, Bots ML, et al. Effect of increased convective clearance by online
hemodiafiltration on all cause and cardiovascular mortality in
chronic hemodialysis patients – the Dutch CONVective TRANsport Study (CONTRAST): rationale and design of a randomised controlled trial [ISRCTN3865125]. _Curr Control Trials Cardiovasc Med_. 2005;6(1). Accessed October 27, 2020. http://trialsjournal.biomedcentral.com/articles/10.1186/1468-6708-6-8

55. Johnson DW, Badve SV, Pascoe EM, et al. Antibacterial honey
for the prevention of peritoneal-dialysis-related infections (HONEYPOT): a randomised trial. _Lancet Infect Dis_.
2014;14(1):23-30.

56. Pascoe EM, Lo S, Scaria A, et al. The Honeypot randomised
controlled trial statistical analysis plan. _Perit Dial Int_.
2013;33(4):426-435.

57. Torres VE, Abebe KZ, Chapman AB, et al. Angiotensin
blockade in late autosomal dominant polycystic kidney disease. _N Engl J Med_. 2014;371(24):2267-2276.

58. Knoll GA, Fergusson D, Chassé M, et al. Ramipril versus pla-
 placebo in kidney transplant patients with proteinuria: a multi-
centre, double-blind, randomised controlled trial. _Lancet Diabetes Endocrinol_. 2016;4(4):318-326.

59. Knoll GA, Cantarovich M, Cole E, et al. The Canadian ACE-
hinhibitor trial to improve renal outcomes and patient survival in kidney transplantation study design. _Nephrol Dial Transplant_.
2007;23(1):354-358.

60. Karunanithy N, Mesa IR, Dorling A, et al. Paclitaxel-coated
balloon fistuloplasty versus plain balloon fistuloplasty only
to preserve the patency of arteriovenous fistulae used for haemo-
dialysis (PAVE): study protocol for a randomised controlled trial. _Trials_. 2016;17(1). Accessed October 27, 2020. http://trialsjournal.biomedcentral.com/articles/10.1186/s13063-016-1372-7

61. Irish AB, Vecellii AK, Hawley CM, et al. Effect of fish oil supple-
mentation and aspirin use on arteriovenous fistula failure in
patients requiring hemodialysis: a randomized clinical trial. _JAMA Intern Med_. 2017;177(2):184-193.

62. Vecellii AK, Polkinghorne KR, Pascoe EM, et al. Fish oil and
aspirin effects on arteriovenous fistula function: Secondary outcomes of the randomised omega-3 fatty acids (Fish oils) and Aspirin in Vascular access OUtcomes in RENal Disease (FAVoured) trial._PLoS One_. 2019;14(3):e0213274.

63. Perkovic V, Jardine MJ, Neal B, et al. Canagliflozin and renal
outcomes in type 2 diabetes and nephropathy. _N Engl J Med_.
2019;380(24):2295-2306.

64. Wiviott SD, Raz I, Bonaca MP, et al. Dapagliflozin and cardio-
vascular outcomes in type 2 diabetes. _N Engl J Med_.
2019;380(4):347-357.

65. Blankstijn PJ, Fischer K, Barth C, et al. Benefits and harms of
high-dose haemodialfiltration versus high-flux haemodialysis: the comparison of high-dose haemodialfiltration with high-flux haemodialysis (CONVINCE) trial protocol._BMJ Open_.
2020;10(2):e033228.

66. Vinsonneau C, Camus C, Combes A, et al. Continuous veno-
ous haemodiafiltration versus intermittent haemodialysis for
acute renal failure in patients with multiple-organ dysfunction
syndrome: a multicentre randomised trial. _Lancet_.
2006;368(9533):379-385.

67. Riley AA, Jefferies JL, Nelson DP, et al. Peritoneal dialysis does not adversely affect kidney function recovery after congenital heart surgery. _Int J Artif Organs_. 2014;37(1):39-47.

68. Tumlin JA, Galphin CM, Tolwani AJ, et al. A multi-center, ran-
domized controlled study to assess the safety and efficacy of a selective cytopheretic device in patients with acute kidney injury. _PLoS One_. 2015;10(8):e031242.

69. Pettill T, Merz T, Wilman E, et al. Targeted tissue perfusion
versus macrocirculation-guided standard care in patients with
septic shock (TARTARE-2S): study protocol and statistical analysis plan for a randomized controlled trial. _Trials_ [Internet].
2016. Accessed October 27, 2020. http://trialsjournal.
biomedcentral.com/articles/10.1186/s13063-016-1515-x

70. Kwiatkowski DM, Goldstein SL, Cooper DS, Nelson DP,
Morales DLS, Krawczeski CD. Peritoneal dialysis vs furosemide

71. _Kidney Med_ Vol 3 | Iss 6 | November/December 2021

940
for prevention of fluid overload in infants after cardiac surgery: a randomized clinical trial. JAMA Pediatr. 2017;171(4):357-364.

71. The ANDROMEDA-SHOCK Study Investigators; Hernández G, Cavalcanti AB, Ospina-Tascón G, et al. Early goal-directed therapy using a physiological holistic view: the ANDROMEDA-SHOCK—a randomized controlled trial. Ann Intensive Care. 2018;8(1). Accessed October 27, 2020. https://annalsoffintensivecare.springeropen.com/articles/10.1186/s13631-018-0398-2

72. Lemkes JS, Janssens GN, van der Hoeven NW, et al. Coronary angiography after cardiac arrest without ST-segment elevation. N Engl J Med. 2019;380(15):1397-1407.

73. Lemkes JS, Janssens GN, Straaten HMO, et al. Coronary angiography after cardiac arrest: rationale and design of the COACT trial. Am Heart J. 2016;180:39-45.

74. Douglas IS, Alapat PM, Corl KA, et al. Fluid response evaluation in sepsis hypotension and shock. Chest. 2020;158(4):1431-1445.

75. Hayashi T, Maruyama S, Nangaku M, et al. Darbepoetin alfa in patients with advanced CKD without diabetes: randomized, controlled trial. Clin J Am Soc Nephrol. 2020;15(5):608-615.

76. Imai E, Maruyama S, Nangaku M, et al. Rationale and study design of a randomized controlled trial to assess the effects of maintaining hemoglobin levels using darbepoetin alfa on prevention of development of end-stage kidney disease in non-diabetic CKD patients (PREDICT Trial). Clin Exp Nephrol. 2016;20(1):71-76.

77. Kratochwill K, Boehm M, Herzog R, et al. Addition of alanyl-glutamine to dialysis fluid restores peritoneal cellular stress responses—a first-in-man trial. PLoS One. 2016;11(10):e0165045.

78. Marsen TA, Beer J, Mann H. Intradialytic parenteral nutrition in maintenance hemodialysis patients suffering from protein-energy wasting. Results of a multicenter, open, prospective, randomized trial. Clin Nutr. 2017;36(1):107-117.

79. Kammerer T, Brettner F, Hilferink S, et al. No differences in renal function between balanced 6% hydroxyethyl starch (130/0.4) and 5% albumin for volume replacement therapy in patients undergoing cystectomy. Anesthesiology. 2018;128(1):67-78.

80. Kammerer T, Klug F, Schwarz M, et al. Comparison of 6% hydroxyethyl starch and 5% albumin for volume replacement therapy in patients undergoing cystectomy (CHART): study protocol for a randomized controlled trial. Trials. 2015;16(1). Accessed October 27, 2020. http://trialsjournal.biomedcentral.com/articles/10.1186/s13063-015-0866-z

81. Fishbane S, Jamal A, Munera C, Wen W, Menzagli F. A phase 3 trial of difelikefalin in hemodialysis patients with pruritus. N Engl J Med. 2020;382(3):222-232.

82. Fujimoto K, Adachi H, Yamazaki K, et al. Comparison of the pain-reducing effects of EMLA cream and of lidocaine tape during arteriovenous fistula puncture in patients undergoing hemodialysis: a multi-center, open-label, randomized crossover trial. PLoS One. 2020;15(3):e0230372.

83. Pickkers P, Mehta RL, Murray PT, et al. Effect of human recombinant alkaline phosphatase on 7-day creatinine clearance in patients with sepsis-associated acute kidney injury: a randomized clinical trial. JAMA. 2018;320(19):1998-2009.

84. Peters E, Mehta RL, Murray PT, et al. Study protocol for a multicentre randomised controlled trial: Safety, Tolerability, efficacy and quality of life Of a human recombinant alkaline Phosphatase in patients with sepsis-associated Acute Kidney Injury (STOP-AKI). BMJ Open. 2016;6(9):e012371.

85. Himmelfarb J, Chertow GM, McCullough PA, et al. Perioperative THR-184 and AKI after cardiac surgery. J Am Soc Nephrol. 2018;29(2):670-679.

86. Laterre P-F, Berry SM, Blemings A, et al. Effect of selepressin vs placebo on ventilator- and vasopressor-free days in patients with septic shock: the SEPSIS-ACT randomized clinical trial. JAMA. 2019;322(15):1476-1485.

87. Bestle MH, Clausen NE, Søe-Jensen P, et al. Efficacy and safety of iloprost in patients with septic shock-induced endotheliopathy—protocol for the multicenter randomized, placebo-controlled, blinded, investigator-initiated trial. Acta Anaesthesiol Scand. 2020;64(5):705-711.

88. Kassimatis T, Qasem A, Douiri A, et al. A double-blind randomised controlled investigation into the efficacy of Mirococept (APT070) for preventing ischaemia reperfusion injury in the kidney allograft (EMPIRIKAL): study protocol for a randomised controlled trial. Trials. 2017;18(1). Accessed October 27, 2020. http://trialsjournal.biomedcentral.com/articles/10.1186/s13063-017-1972-x

89. Hosgood SA, Saeb-Parsy K, Wilson C, Callaghan C, Collett D, Nicholson ML. Protocol of a randomised controlled, open-label trial of ex vivo normothermic perfusion versus static cold storage in donation after circulatory death renal transplantation. BMJ Open. 2017;7(1):e012237.

90. Mistry P, Dunn JA, Marshall A. A literature review of applied adaptive design methodology within the field of oncology in randomised controlled trials and a proposed extension to the CONSORT guidelines. BMC Med Res Methodol. 2017;17(1):108.

91. Clayton JA, Arnegard ME. Taking cardiology clinical trials to the next level: a call to action. Clin Cardiol. 2018;41(2):179-184.

92. van Werkhoven CH, Harbarth S, Bonten MJM. Adaptive designs in clinical trials in critically ill patients: principles, advantages and pitfalls. Intensive Care Med. 2019;45(5):678-682.

93. Talisa VB, Yende S, Seymour CW, Angus DC. Arguing for adaptive clinical trials in sepsis. Front Immunol. Accessed January 14, 2021. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6031704/

94. Perkovic V, Craig JC, Chailimpamontree W, et al. Action plan for optimizing the design of clinical trials in chronic kidney disease. Kidney Int Suppl. 2017;7(2):138-144.

95. Zoccali C, Vanholder R, Wagner CA, et al. Funding kidney research as a public health priority: challenges and opportunities. Nephrol Dial Transplant. 2020. Accessed January 14, 2021. doi:10.1093/ndt/gfaa163

96. The VA/NIH Acute Renal Failure Trial Network. Intensity of renal support in critically ill patients with acute kidney injury. N Engl J Med. 2008;359(1):7-20.

97. Mehta RH, Leimberger JD, van Diepen S, et al. Levosimendan for prevention of fluid overload in infants after cardiac surgery. Kidney Int Suppl. 2017;7(2):138-144.