Range and Heterogeneity of Outcomes in Randomized Trials of Pediatric Chronic Kidney Disease

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Objective To determine the range and heterogeneity of outcomes reported in randomized controlled trials of interventions for children with chronic kidney disease (CKD).

Study design The Cochrane Kidney and Transplant Specialized Register was searched to March 2016. Randomized trials involving children across all stages of CKD were selected. All outcome domains and measurements were extracted from included trials. The frequency and characteristics of the outcome domains and measures were evaluated.

Results From 205 trials included, 6158 different measurements of 100 different outcome domains were reported, with a median of 22 domains per trial (IQR 13-41). Overall, 52 domains (52%) were surrogate, 38 (38%) were clinical, and 10 (10%) were patient-reported. The 5 most commonly reported domains were blood pressure (76 [37%] trials), relapse/remission (70 [34%]), kidney function (66 [32%]), infection (61 [30%]), and height/pubertal development (51 [25%]). Mortality (14%), cardiovascular disease (4%), and quality of life (1%) were reported infrequently. The 2 most frequently reported outcomes, blood pressure and relapse/remission, had 56 and 81 different outcome measures, respectively.

Conclusions The outcomes reported in clinical trials involving children with CKD are extremely heterogeneous and are most often surrogate outcomes, rather than clinical and patient-centered outcomes such as cardiovascular disease and quality of life. Efforts to ensure consistent reporting of outcomes that are important to patients and clinicians will improve the value of trials to guide clinical decision-making. In our study, non-English articles were excluded. *(J Pediatr 2017;186:110-7).*

Since the recognition of children as "therapeutic orphans" in the 1960s, there has been a wave of international efforts to improve trial-based evidence to support health interventions in children.[1-12] The past 2 decades has seen an increase in the number of trials conducted in children since the US and Europe revised legislation on labeling of medicines to mandate pediatric data.[3] Also, major pediatric trial networks have been established globally, including the US *Eunice Kennedy Shriver* National Institute of Child Health and Human Development Pediatric Trial Network and the Network of Pediatric Research at the European Medicines Agency, to improve infrastructure and capacity for pediatric trials.[13,14]

Despite this upsurge in pediatric clinical trials, the relevance and value of trials may be limited by problems in the prioritization, design, reporting, and dissemination of research, including outcomes measured and reported.[15-21] Trials are only as informative as their outcomes,[22] yet many report outcomes that may not be relevant directly to patients and clinicians and do not involve children and caregivers in the selection of outcomes.[23-25] Analyses of pediatric trials within specific health conditions have shown that the outcomes reported are extremely variable, including the definitions and measures used,[23-27] which limits comparability of the effectiveness of interventions across studies.[16] Initiatives to establish core outcomes,

BMI	Body mass index
CKD	Chronic kidney disease
QOL	Quality of life

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to be reported at a minimum in all trials with specific health condition, such as The Outcome Measures in Rheumatology (OMERACT), have demonstrated improvement in the relevance and reporting of outcomes in trials,[22,23,28-30] although core outcome sets generally are lacking in children.

Children with chronic kidney disease (CKD) have a mortality rate up to 30 times greater than the age-matched general population, and those who progress to end-stage kidney disease depend on dialysis or a kidney transplant for survival.[31,32] Although many trials have been conducted in children with CKD, the risk and prevalence of comorbid conditions, treatment complications, developmental problems, debilitating symptoms, such as fatigue, and impaired quality of life (QOL) remain high.[33-44] Improvements in healthcare and outcomes through research rely on the relevance and consistency of reported outcomes. Affected children depend on their caregivers and clinicians to provide long-term, complex, and highly technical treatments that have profound implications for their development and well-being. We aimed to describe the scope and consistency of outcome domains and measures in trials involving children with all stages of CKD, to inform strategies for establishing core outcomes that are important to children, families, and clinicians to be reported in trials, to inform clinical decision making, and ultimately to improve the outcomes for children with CKD.

Methods

We searched the Cochrane Kidney and Transplant Specialized Register for all randomized controlled trials involving children aged up to 21 years or younger (the upper age limit to define the pediatric population is up to 21 years in the US[45]) with any diagnosis of CKD and at treatment stage (CKD Stage 1-5 [not on renal replacement therapy], 5D [hemodialysis or peritoneal dialysis], and 5T [kidney transplant]) up to March 2016 (**Figure 1**; available at www.jpeds.com). We used search terms relating to children and pediatrics. Trials that included more than 50% of patients aged older than 21 years were excluded. Trials that included children with chronic conditions, but did not report data from the CKD population, were not eligible.

Data Extraction

We extracted the following characteristics from each trial: publication year, setting (participating countries), sample size, mean age of participants, study duration, intervention type, and all outcomes. We defined outcome measures as any measures reported separately for all trial arms. We extracted all specifications of the outcome measures, if reported, including the outcome domain (eg, blood pressure), specific measurement (eg, percentage of hypertensive patients), method of aggregation (eg, percentage change), specific metric (between commencement and end of the trial), and time point of measurement (defined as the time frame from trial commencement to when the outcome was measured).[46]

Statistical Analyses

We categorized all the outcome measures from all the included trials into outcome domains. The first author drafted the initial list of outcome domains. This was cross-checked by 4 reviewers and revised until consensus was achieved. The outcome measures were then grouped according to the final list of outcome domains, which was re-reviewed by the same 4 reviewers. All outcome domains were further categorized as surrogate (biochemical or physiological outcomes, ie, pathophysiological manifestations of health conditions, including such as blood pressure[47]), clinical (medical outcome of a condition or treatment), and patient-reported (outcomes reported on by patients and caregivers, typically related to how the patients function or feel in relation to a health condition or therapy), based on standard nomenclature.[48,49] Some outcome domains included measures that straddled several categories—surrogate, clinical, and patient-reported. Thus, classification of the domains was based on the largest proportion of outcome measures. The number of trials, and dialysis- and transplantation-specific trials that reported each outcome domain was calculated.

We conducted a detailed analysis of outcome measures of the 3 outcome domains in each category that were reported most frequently across trials, as well as the 3 pediatric-specific domains (height and pubertal development, weight/body mass index [BMI]/body composition, and school performance). The measurement, aggregation, metric, and timing as reported in the primary studies were analyzed. We retained the original term if studies did not further define or provide details on the outcome measure. Statistical analyses of frequency were conducted with R version *3.2.3* (R Foundation for Statistical Computing, Vienna, Austria; http://www.R-project.org/).

Results

Our search yielded 1266 trials, of which 205 included 2174 children with CKD (**Table I**). The trial characteristics are shown in **Table I**. Overall about one-half of trials involved children with CKD Stage 1 to 5 (123 [52.1%] trials), 32 [13.6%]) trials involved patients on hemodialysis, 40 [16.9%] involved peritoneal dialysis, and 41 (17.4%) involved kidney transplant recipients. The setting of the trials spanned 43 countries, including the US (51 [25%] trials), India (18 [9%]), Japan (15 [7%]), Germany (14 [7%]), and England (14 [7%]); 28 (13.7%) trials were multinational. The trials were published from 1970 to 2015. The median trial duration was 12 months (IQR 6-24 months), and the median sample size was 40 patients (IQR 22-76 patients), with only 6 (2.9%) larger than 200.

Across 205 trials, 6158 outcome measures were reported. The number of outcome measures per trial (including time points of measurement) ranged from 1 to 145, with a median of 22 per trial (IQR 13-41). The number of unique outcome measures per trial (excluding time points) ranged from 1 to 64, with a median of 15 (IQR 9-26). We excluded 382 outcome measures because they were not a direct health outcome measured in patients (eg, "mean cold ischemia time, and "medication dose/use/duration") or were specific to a single intervention within a trial (eg, "number of patients monitored and educated"). The remaining 5776 were classified into