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Clinical trials and research priorities in dialysis Patients: Time for a new approach?

Historically, the number of RCTs performed in the ESRD population has been very low compared to other medical subspecialties. Furthermore, several of the few large RCTs conducted in patients with ESRD have yielded inconclusive or negative results, dampening enthusiasm for future investment in similar trials. It is therefore important for the Nephrology community to examine its research priorities and to adopt novel approaches to scientific inquiry. More patient participation in determining research priorities and the prioritization of patient-centered outcomes could result in improved recruitment and retention in clinical trials of ESRD patients, and the implementation of novel design strategies could potentially lead to more affordable RCTs with improved internal and external validity.

Patients with end-stage renal disease (ESRD) experience extremely high morbidity and mortality, and there are virtually no therapeutic interventions besides dialysis treatment which are proven, in properly designed randomized controlled trials (RCTs), to improve outcomes. A recent systematic review of hemodialysis RCTs found that, among 10,713 outcome measures, the most common were surrogates such as phosphate, dialysis adequacy, anemia, inflammatory markers, and calcium. Patient-centered outcomes such as mortality, cardiovascular disease, and quality of life were reported very infrequently.

Recent initiatives promoting a focus on patient-centered outcomes and more active patient and caregiver involvement in the planning and conduct of clinical trials may result in more clinically relevant RCTs and broader participation from patients representing the diversity of the ESRD population. For example, the "Standardized Outcomes in Nephrology" (SONG) initiative established fatigue, cardiovascular disease, vascular access and mortality as the core outcomes that are critically important to all stakeholders. Other initiatives by national organizations in the US, Canada and Australia have also emphasized the importance of patient-centered outcomes such as enhanced quality of life.

"The ESRD population is diverse and complex, making it difficult to test interventions within the framework of a traditional RCT design that has resulted in unexpectedly low

event rates and high drop-out and cross-over rates, rendering results internally invalid and yielding inconclusive results”, explains Professor Csaba P. Kovesdy, author of a review entitled *Clinical trials in end-stage renal disease—priorities and challenges* that was published today in NDT. “The recent emergence of various RCT designs could aid in making ESRD clinical trials more successful.”

Pragmatic clinical trials (PCTs) have been introduced as a means of enhancing the external validity of clinical trials, by implementing broad enrolment criteria, clinically relevant comparators, evaluation of interventions within clinical practice, and the testing of practical, meaningful outcomes. The broad utilization of electronic health records (EHRs), the standardized application of multiple medical and technical interventions within the framework of routine clinical practice, and the clustering of patients within dialysis units using uniform clinical practices make PCTs particularly feasible in the hemodialysis population. In addition to PCTs, there are other emerging RCT designs that could result in more successful testing of interventions in ESRD, such as adaptive platform designs.

“The application of such novel RCT designs could result in benefits including reduced trial cost, the examination of a broader, more representative population, and the testing of a higher number and more clinically relevant interventions, which is really needed”, concludes Professor Kovesdy.

[1] Csaba P. Kovesdy^{1,2}Clinical trials in end-stage renal disease—priorities and challenges. NDT 2019. June 13 [epub]

About ERA-EDTA

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