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Prognostic Enrichment Design in Clinical Trials for Autosomal Dominant Polycystic Kidney Disease

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Clinical trials on autosomal dominant polycystic kidney disease (ADPKD) prove to be a challenging endeavor because of recruitment issues, the need for a large sample size to evaluate efficacy, and the long duration of study to prove safety, efficacy, and cost.[1] Adaptive trial design has been proposed as a means to increase the efficiency of randomized clinical trials.[2] Inclusion criteria for entry into a study seems easy to handle for established investigators until one encounters the many patients who prove to be ineligible because they are "just below the margins" of potential inclusion. Every study seems to be hampered by study sites that overestimate their pool of potential study subjects. Then there is a scramble to recruit the last cohort of patients to meet enrollment goals, even though there can be a question of stretching inclusion criteria.

Industry-sponsored studies are appropriately concerned about cost overruns, occurring often by screening patients who prove to be ineligible for the proposed study. Expanded eligibility criteria may achieve the desired number of recruitment subjects, but the power of the study suffers by enrolling patients who may not benefit from the proposed intervention.

Irazabal and colleagues report, in this issue,[3] the impact on the number of recruitment subjects needed and the cost savings if prognostic enrichment strategies were used for the Tolvaptan TEMPO 3:4 study. Their retrospective analysis of entry criteria for this study led to the conclusion that "a specific image classification should be used in randomized clinical trials to increase power and reduce costs." Their approach is recommended for clinical trials in ADPKD, because results can be achieved by selecting a group of patients with larger height-adjusted total kidney volumes (TKVs) who have exhibited some early progression of their disease state. In a shorter period of time, these patients would be expected to demonstrate adverse consequences of their PKD. Therefore, this cohort would more likely benefit from an intervention that proves to be successful, as illustrated by the statistically significant positive impact of the V2 receptor antagonist on TKV, estimated glomerular filtration rate, and pain (when analyzing data via the enhancement approach).

Pragmatism in clinical trials arose from concerns that many trials do not adequately inform practice because they are optimized to demonstrate efficacy.[4] However, a critique of "prognostic enhancement" design is raised if the sample size of highly selected participants is reduced, as proposed in the above classification schemata, the potential benefit could be overestimated, and harm underestimated. The goal of any medication study is to determine the greatest benefit /enhanced effectiveness relative to risk.

The population studied in the randomized Tolvaptan Tempo 3:4 study were relevant for the intervention. Analysis of the selected PKD study cohort showed characteristics associated with a more rapid rate of disease progression: largest height-adjusted total kidney volume (htTKV); greater TKV slope (percentage per year); hypertension requiring treatment; male sex; and increased estimated glomerular filtration rate slope of decline. The treatment effect was most noted in the group with the highest risk stratification. Investigation of the enriched cohort is the essence of a pragmatic trial—to inform a clinical or policy decision by providing evidence for adopting the intervention. The study participants must be similar to patients who would receive the intervention if it were to become usual care. Therefore, if the drug is approved by the Food and Drug Administration, the medication labeling needs to indicate restricted use to patients who most closely match the study cohort.

Refined genotype–phenotype correlation, coupled with targeted next-generation sequencing of PKD1 and PKD2, may provide

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useful clinical prognostication for ADPKD.[5] The future of medication trials may well be satisfied by the "clinical trials in a dish" concept. With increasing use of genome sequencing as an integral aspect of disease evaluation and potential treatment, disease models can be created via use of stem cell technology, as has been accomplished in PKD.[6] Divided cell cultures will allow treated and control lines that are perfectly matched. The medication being studied can be added to the cultured cells at different doses. Proof of principle, or lack thereof, can be detected in a relatively short period of time. Patient trials, if justified, can then proceed in a more focused approach. Hence, pragmatic trial principles will allow for shorter-length studies in a well-defined population. Reduced costs of trials will encourage more of them. With the recent direct isolation and characterization of human nephron progenitors, this *in vitro* system facilitates studies of human renal development and can be a novel future tool for bioengineering purposes.[7] Until this approach comes to fruition, the prognostic enhancement study design will be a positive step forward.

DISCLOSURE

The author declared no competing interests.

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