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AJKD

Platform Clinical Trials Within Nephrology—Interpreting the Evidence

Sradha Kotwal, Vlado Perkovic, and Hiddo J.L. Heerspink

The prevalence of chronic kidney disease (CKD) continues to grow, with parallel rises in associated mortality. Despite the development of renin-angiotensin system blockers decades ago, new treatments to halt the progression and reduce the mortality due to CKD remain highly desired.[1,2] Fortunately, progress has been made in the form of sodium/glucose cotransporter 2 (SGLT2) inhibitors and mineralocorticoid receptor antagonists,[3,4] which have been shown to reduce the risk of kidney failure. Although these significant advances in the pharmacotherapies for CKD have improved the prognosis for such patients, not every patient will benefit from or tolerate these drugs and a substantial proportion remain at risk of progressive kidney function loss. Innovative approaches to prevent kidney damage, and to test new agents in a rapid and efficient manner, are needed. While there are many drugs in the pipeline targeting novel pathways of CKD progression, the challenge of assessing the efficacy and safety of these interventions in a timely fashion persists, since confirmatory phase 3 clinical trials in CKD are often large and lengthy.[2]

Novel Trial Designs

Novel trial designs using a master protocol can improve the current clinical trials framework in terms of time, complexity, and costs. Overall, novel trial designs focus on 1 disease rather than a specific intervention. Basket and umbrella trials—or more commonly, platform trials—are clinical trial design innovations that assess the effects of multiple interventions simultaneously using adaptive designs and Bayesian statistical comparisons.[5] Basket trials evaluate the same targeted therapy for multiple diseases, while umbrella trials test multiple targeted therapies for a single disease. A platform trial, on the other hand, often tests multiple interventions against a common control group and can run in perpetuity.[6] A common feature of a platform trial is a standard protocol that defines key clinical trial elements.[5] For each specific assessment conducted within a platform, minor adaptations to the master protocol can be made or an appendix added depending on the specific scientific question, therapeutic agent, or approach being tested, but the key trial infrastructure remains constant. Bayesian statistical comparisons use what is already known to generate probabilities of success or failure for a specific treatment and provide a formal method for making decisions about treatment efficacy at interim analyses during the conduct of the trial.[7] Platform trials using Bayesian statistics require extensive planning, statistical input, and modeling during the design phase.

Innovative trial design elements are now being incorporated in clinical trials, such as the recent basket trial assessing the efficacy and safety of the endothelin receptor antagonist atrasentan in patients with diabetic kidney disease, IgA nephropathy, focal segmental glomerulosclerosis, and Alport syndrome.[8] However, platform trial methodologies are not widely used in nephrology. One explanation may be a lack of a global cohort of trial-ready patients, which is key to the uptake of platform trials. The International Society of Nephrology has led an initiative to develop a collaborative partnership of global networks of trial-ready cohorts such as the Global Kidney Patient Trials Network and the Rare Diseases Registry in the United Kingdom, among others.[9] It is anticipated that more platform trials will be initiated in nephrology in the near future.[10,11] Understanding the concepts of platform trials and how to appraise them is therefore timely and relevant. Here we discuss platform trials in other therapeutic areas and summarize the key design elements necessary to assist clinicians in interpreting and applying the results of platform trials conducted in patients with CKD.

The STAMPEDE Trial as an Example of a Platform Trial

The STAMPEDE trial, which randomizes patients with high-risk localized, nodal, or metastatic prostate cancer or with aggressively relapsing disease after initial therapy for local disease, is one of the most successful platform trials.[12] This 6-arm, 5-stage, open-label, randomized trial with a single control arm has successfully recruited more than 10,000 participants. The trial's stages range from initial confirmation of safety to phase 3 survival end points. The STAMPEDE trial has characterized the efficacy and safety for various agents over the last decade in an efficient manner. The researchers planned for addition of arms as well as for inactive treatments to be dropped from further study at an early stage, ensuring that more patients received active and potentially beneficial treatments.

Advantages and Disadvantages of Platform Trials

The main advantage of platform trials is the ability to make earlier decisions about the success and failure of treatments, allowing multiple treatments to be tested in the same amount of time and leading to shorter, more efficient trials.[5,13] This was highlighted by the RECOVERY trial, which recruited patients hospitalized for COVID-19.[14] Eligible patients were randomly allocated between multiple treatment arms (dexamethasone,

tocilizumab, etc), each treatment to be given in addition to usual standard of care with a common placebo arm.[15-17] The primary outcomes were mortality, hospital discharge, and need for ventilation and kidney replacement therapy with 28 days' follow-up after randomization. The dexamethasone arm reported first (fewer than 100 days from the protocol's first being drafted), and subsequently the trial has reported on many therapies and continues to study other potential treatments.[15,17] According to the RECOVERY investigators and international experts, the key drivers of this trial's success have been the agility of being able to add and remove arms, and a common representative placebo arm, which are key features of platform trial design. The other potential advantages are reduced costs, thanks to earlier decisions and efficiencies, and better buy-in from stakeholders owing to the higher probability of receiving the active treatment.

The disadvantage of platform designs is the complex planning and design phase, with a higher statistical burden compared to conventional trials. The decision rules require several (sometimes hundreds of) simulations that must account for type 1 and type 2 errors. This complexity also lends itself to longer lead-in times, which can impact budget.

Key Features to Review for Critical Appraisal

Critical appraisal by clinicians reading platform clinical trials requires attention to specific design components, especially those that are different from conventional trials; we summarize these in a checklist in Table 1.[18,19]

Control Group

The constitution of the control group, as well as whether it is contemporaneous or historical, is an important study design element because standard of care can change over the course of the trial as new treatments become incorporated into clinical practice (eg, SGLT2 inhibitors in CKD management).[3] Conventional trials exclusively use contemporaneous control groups. The differences in allocation to control or active groups is another important element to appraise. Allocation of more patients to the control group may increase study power, while the use of response-adaptive randomization (allocating more patients to the superior treatment arm as the trial progresses and more data are collected) leads to randomization of more patients to the active arms, such as in the

Table 1. Checklist for Critical Appraisal of Platform Trials

Trial Feature	Question to ask
Design of control group	
Active or placebo control group	Did the control group receive any active treatment or only placebo (eg, standard of care)?
Contemporaneous or historical controls	Were the control group participants recruited at the same time (contemporaneous) as the study cohort or were they recruited earlier (historical)?
Allocation ratios of control to treatment arms (use of response adaptive randomization)	Were the participants allocated to the control and treatment arms in a 1:1 ratio or in a way that more patients were allocated to the active treatment arm (response-adaptive randomization)? Both might be appropriate.
Statistical components	
Multiple interventions and hypothesis are often tested and adjustments for multiple comparisons should be made	Check if 2 interventions are being compared to each other or to placebo; if the statistics account for the different interventions being tested at the same time; and if the analysis accounts for multiple intervention arms, as each additional arm may require additional follow-up time.
Power and sample size calculations	Which comparisons underlie the powering and sample size calculations—is it 1 intervention to another or 1 intervention to placebo? Also address whether this is consistent with the study design and analysis plan.
Interim analysis and appropriate adjustment of α	Check if the final analysis accounts for the interim analysis and adequately adjusts for α.
Subgroups	As for conventional trials, subgroups should be prespecified.
Clinical outcomes	
Surrogate outcomes (eg, albuminuria or eGFR slope) vs hard outcomes (eg, kidney failure or death)	Were hard or surrogate end points used? If surrogate outcomes were used, were they validated markers of hard end points (eg, albuminuria or eGFR slope is a validated surrogate end point for kidney failure)?
Outcomes used for primary and interim analyses	Were the same outcomes used for the primary as for the interim analysis?
Timing and frequency of interim analysis	Was the timing of the interim analysis appropriate (ie, long enough to see an impact from the treatment on the selected outcome)?

RECOVERY trial.[5] Both approaches may be appropriate, depending on the intervention and disease process being studied; for example, in the setting of a pandemic, randomizing more people to the treatment arm might be more ethical, while maximizing study power might be more valuable in other settings. In conventional trials, the allocation ratios do not change after trial commencement.

Statistical Considerations

Multiple interventions and hypotheses can be tested in a platform trial, and it is important to note which comparison the statistical power for the study is based on and whether adjustments for multiple comparisons are made.[5,20] The decision rules for interim analyses should be made and finalized before the interim analysis. The maximum number of active intervention arms to be included simultaneously should be listed, as every additional arm (may be added after study commencement) may require longer follow-up, if the same recruitment rate is maintained, or an increase in recruitment targets to maintain study power.[18] An understanding of whether the primary outcomes are the same as or different from those used in the interim analysis is vital—if there is not a strong association between the two, the trial could yield erroneous results. In conventional trials, once the trial has commenced, a substantial protocol amendment is required to make any changes to the powering, and cessation with commencement of a new trial is needed if new interventions are to be added or removed.

Clinical Outcomes

In non-kidney platform trials, progression-free survival is often used as a surrogate for survival, as in the STAMPEDE trial.[12] In kidney disease trials, progression to kidney failure can take decades, and as such, validated surrogates for progression such as slope of estimated glomerular filtration rate (eGFR) or albuminuria may be used for both primary and interim analyses.[21,22] eGFR slope and albuminuria are validated surrogate end points for kidney disease progression and the former is an accepted outcome by the US Food and Drug Administration in clinical trials testing investigational products in kidney disease. This is important because a key feature of platform trials is the ability to identify successful and futile treatments early, which requires study outcomes that occur over shorter periods of time. Conventional trials have used progression to kidney failure as trial outcomes for decades, but with the validation of eGFR slope and albuminuria, these outcomes are also being used in conventional trials. In addition, when multiple interventions are compared, statistical adjustments for multiple comparisons should be considered to exclude chance findings. The timing of the interim analyses also determines if enough time has been given to see an effect so that interventions are not falsely labeled as "ineffective" if adequate time was not provided for them to have an effect.

Other Aspects

Subgroup effects are important to understand the impact of the intervention on a heterogeneous patient population and should always be prespecified. Moreover, the processes, timings, and scientific merits of addition or removal of interventions should be predefined, and all trials should have a documented robust governance process.

Conclusions

New approaches to the conduct of clinical trials such as platform clinical trials are an important development. Incorporating novel statistical and methodological approaches, platform trials offer a range of opportunities to develop new therapeutic strategies in a timely and affordable fashion, and we expect that their uptake will increase in nephrology.

Article Information

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