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CONFERENCE REPORTS AND EXPERT PANEL

Recommendations for clinical trial design in acute kidney injury from the 31st acute disease quality initiative consensus conference. A consensus statement

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Abstract

Purpose: Novel interventions for the prevention or treatment of acute kidney injury (AKI) are currently lacking. To facilitate the evaluation and adoption of new treatments, the use of the most appropriate design and endpoints for clinical trials in AKI is critical and yet there is little consensus regarding these issues. We aimed to develop recommendations on endpoints and trial design for studies of AKI prevention and treatment interventions based on existing data and expert consensus.

Methods: At the 31st Acute Disease Quality Initiative (ADQI) meeting, international experts in critical care, nephrology, involving adults and pediatrics, biostatistics and people with lived experience (PWLE) were assembled. We focused on four main areas: (1) patient enrichment strategies, (2) prevention and attenuation studies, (3) treatment studies, and (4) innovative trial designs of studies other than traditional (parallel arm or cluster) randomized controlled trials. Using a modified Delphi process, recommendations and consensus statements were developed based on existing data, with > 90% agreement among panel members required for final adoption.

Results: The panel developed 12 consensus statements for clinical trial endpoints, application of enrichment strategies where appropriate, and inclusion of PWLE to inform trial designs. Innovative trial designs were also considered.

Conclusion: The current lack of specific therapy for prevention or treatment of AKI demands refinement of future clinical trial design. Here we report the consensus findings of the 31st ADQI group meeting which has attempted to address these issues including the use of predictive and prognostic enrichment strategies to enable appropriate patient selection.

Keywords: Clinical trials, Endpoints, AKI, Prevention, Treatment, Enrichment

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Introduction

Increased morbidity, mortality, and health care utilization are common among patients with acute kidney injury (AKI) [1, 2]. Defined by changes in serum creatinine and urine output, the term "AKI" describes a variety of pathophysiologic processes and as such, no single intervention to prevent, mitigate, or treat AKI has yet been reported. Despite encouraging preclinical results, trials investigating new therapies to treat AKI have failed to demonstrate efficacy [3]. Such failures likely reflect not only the heterogeneous nature of the syndrome and the complexity of the underlying pathophysiology, but potentially also a lack of appropriate endpoints or adequate and timely identification of patients likely to develop AKI, and /or benefit from the intervention in question. To address these problems, the 31st Acute Disease Quality Initiative (ADQI) was convened to develop a common framework for further research. The group focused on four main areas: (1) patient enrichment strategies, (2) prevention and attenuation studies, (3) treatment studies, and (4) innovative trial designs of studies other than traditional (parallel arm or cluster) randomized controlled trials (RCTs).

Methods

The conference chairs (AZ, LGF, and JAK) were appointed by the ADQI executive committee once a topic was decided upon. The faculties were chosen primarily from experts identified by citations on AKI as compiled by expertscape.com. We were limited in the number of experts who could be invited for logistical reasons and we acknowledge that not all experts in AKI trials were invited or available. This list was further refined and developed to include relevant expertise outside of AKI especially on statistics, hierarchical composites, adaptive trial design, and persons with lived experience. Finally, the conference chairs extended invitations to achieve diversity for sex, career stage, specialty including adult and pediatrics, and country of practice.

The Conference Chairs of the 31st ADQI consensus committee convened a diverse panel of adult and pediatric clinicians, researchers, statisticians, and clinical trialists representing relevant disciplines—critical care medicine, anesthesiology, nephrology, and clinical pharmacology—from Europe, North and South America, Asia, and Australia, to discuss endpoints in clinical trials in AKI. Furthermore, a person with lived experience (PWLE) with severe AKI was included in the faculty (DD). The conference was held over 2.5 days in Stresa, Italy, on October 25–28, 2023. This consensus meeting followed the established ADQI process and used a modified Delphi method to achieve consensus, as previously described (additional information in the electronic supplementary material, ESM) [4, 5]. Each ADQI conference is divided into three phases: pre-conference, conference, and post-conference. In the pre-conference phase, the groups that are assigned to specific topics identify a list of key questions, conduct a literature search, and generate a bibliography of key studies. The conference itself is divided into breakout sessions, where workgroups address the issues in their assigned topic area and plenary sessions, where their findings are presented to the entire faculty, debated, and refined. This approach has led to important practice guidelines with wide acceptance and adoption into clinical practice [6]. Given the nature of the topic, consensus statements were not graded by evidence but instead a vote and approval of the consensus recommendations were undertaken. The Delphi process was continued virtually and by email after the conference, until > 90% consensus was achieved. Changes to the statements made after the conference and during manuscript preparation were not substantive. These were subsequently reviewed and approved by all authors.

Take-home message

Well designed clinical trials have to be designed and implemented to investigate the efficacy of new interventions. Predictive and prognostic enrichment strategies as well as the selection of primary and secondary endpoints are important components of designing such trials.

General statements for AKI trials

Consensus statement 1

We **recommend** that researchers, trialists, funding agencies, industry, and regulatory authorities acknowledge the fundamental importance of the perspectives of PWLE in the design and selection of endpoints in clinical trials evaluating AKI, and that PWLE are involved in the clinical trial process, including data analysis, interpretation, and dissemination (supplementary Table 1).

Clinical trials in AKI aim to improve the care and outcomes that are experienced by, and matter to, patients [7]. PWLE, defined as persons regarded as experts by first-hand experience with a diagnosis or health condition, have seldom been involved in the design of clinical AKI trials. However, there is a strong rationale to include PWLE as partners to inform health research to realize improved outcomes, particularly those that are viewed by PWLE as important [7–9]. (supplementary Fig. 1) PWLE can give experienced examples of what they went physically, emotionally, mentally and spiritually. Quality of care is the physicians' first priority but quality of life is the patient's priority. In contrast to critically ill patients without an AKI, patients with a severe AKI often receive treatment with renal replacement therapy, have

an increased risk to develop chronic kidney disease, and have a longer length of stay in the intensive care unit and hospital.

There is a "call to action" and established principles on how PWLE can engage in research [7, 9–12]. Evidence has shown that building meaningful partnerships with PWLE can translate into improved quality and relevance of research [8, 13]. However, to realize the value of PWLE partners, we suggest to fully integrate them into all aspects of the research process [14].

Patient enrichment strategies

Consensus statement 2

We **recommend** that investigators consider enriching patient selection for enrollment in AKI clinical trials given the heterogeneous nature of AKI syndromes.

AKI is complex and multifactorial, with multiple conditions presenting with clinically indistinguishable features [15, 16]. The heterogeneous nature of AKI syndromes refers to the different exposures that may all lead to acute decreases in glomerular filtration rate (GFR), but the underlying mechanisms are quite different (cyclosporin-induced AKI vs septic AKI vs cardiorenal AKI). However, a kidney damage without a loss of function is also associated with worse outcome. Heterogeneity in AKI development and clinical course stems from numerous factors including susceptibility, underlying comorbidities, severity of acute illness, presence of extra-renal organ failures, and the type and severity of the insult leading to AKI. Patient baseline variability, including known and unknown differences in chronic and acute characteristics, can drive differential responses to different interventions and will contribute to the heterogeneity of treatment effects observed in clinical trials.

Several approaches can be considered to minimize baseline variability in clinical trials. These include stratified randomization to balance key known or clinically apparent baseline characteristics (e.g., chronic kidney disease [CKD]), use of standardized protocols to minimize process of care variability, selection of a particular clinical setting to focus on a homogenous type of insult (e.g., post-cardiopulmonary bypass), or use of improved diagnostics (e.g., biomarkers) to better identify patient subtypes. Application of prognostic and predictive enrichment strategies (supplementary Table 2) would be expected to identify patients most likely to develop an outcome of interest and respond to an intervention. Precise differential diagnosis may contribute to trial efficiency by selecting patients with traits more likely to favorably respond to candidate therapies. Implementation of enrichment strategies in AKI could enable identification of the right patients for discrete prevention, treatment, and kidney rehabilitation interventions.

Consensus statement 3

We **recommend** that prognostic enrichment be considered to identify patients who have a greater likelihood of meeting a defined primary endpoint and/or outcome while minimizing the competing risks of undesired endpoints/outcomes.

Prognostic enrichment using various tools can provide an estimate for the risk of an endpoint and help ensure enrollment of ideal patients [17–19] (supplementary Fig. 2). This reduces inclusion of high-risk patients destined to meet a given endpoint regardless of the intervention being tested and conversely prevents enrolling low risk patients who are unlikely to meet the endpoint [18, 20, 21]. Not all risks are modifiable and no risk score/biomarkers are perfect, so caution should be taken to ensure that the correct tools for prognostic enrichment are employed. While older AKI risk scores were static, measuring time-fixed AKI susceptibility, increasingly, new risk scores are dynamic and may employ real-time data allowing for changes in AKI susceptibility and accounting for multiple exposures with the aim of improving risk stratification [22–25]. Urine and serum biomarkers have been used for prognostic enrichment, pairing biomarkers of tubular damage and/or stress with clinical care bundles to improve patient outcomes [18, 26–28]. While prognostic enrichment seeks to increase the probability of a given endpoint/outcome in a trial, it does limit the generalizability of trial findings to only those meeting the enrichment criteria. In the future, prognostic enrichment may combine biochemical biomarkers with real-time risk scores to optimize clinical trial enrollment, outcomes, and costs.

Consensus statement 4

We **recommend** consideration of predictive enrichment and diagnostic precision strategies to identify patients with shared underlying pathobiology.

Predictive enrichment seeks to increase trial efficiency and reduce sample size by optimizing enrollment of patients who will favorably respond to the candidate intervention. Such an approach can avoid exposure/potential toxicity of patients who are unlikely to benefit from an intervention. Various methods to identify patients who are more likely to respond to a specific intervention exist, including biomarkers or clinical features that identify a specific endotype targeted by the intervention. For example, in catecholamine-resistant vasodilatory shock, measuring renin may help to identify

patients for whom treatment with angiotensin II has a beneficial effect on clinical outcomes [29]. Urine tumor necrosis factor-α and interleukin-9 levels have recently been explored to discriminate acute interstitial nephritis from acute tubular necrosis [30, 31]. Such a strategy could lead to specific interventions including immunosuppressive agents.

Consensus statement 5

Enrichment may not be appropriate for all AKI clinical trials.

Enrichment strategies may not be applicable to all trial designs. Generalizability and trial implementation feasibility are two issues that need to be harmonized. Increasing enrichment by restricting enrollment to unique pathobiology will limit the external validity of the intervention and might require more studies with accompanying increased costs to be performed in different populations. Pragmatic trials that are embedded into clinical settings with minimal exclusion criteria are unlikely to be able to accommodate enrichment strategies that may increase implementation complexity and, therefore, decrease enrollment. However, enrollment of a population in a clinical trial that are unlikely to benefit from an intervention is unlikely to be worthwhile.

Prevention and attenuation studies

Consensus statement 6

We **recommend** that when selecting endpoints for AKI prevention studies, investigators consider trial design and endpoint characteristics including: i) biological plausibility; ii) validity in the target population; iii) practicality; and iv) patient centeredness.

We recommend that when selecting endpoints for AKI prevention studies, investigators consider trial design and endpoint characteristics including: i) biological plausibility; ii) validity in the target population; iii) practicality; and iv) patient centeredness.

Numerous factors should be considered when selecting appropriate endpoints for trials examining prevention or attenuation (interventions after exposure but before clinical manifestation) of AKI with some measure of acute injury, damage, stress, or dysfunction as the primary endpoint (Fig. 1, supplementary Tables 3, 4, and 5) [32, 33]. Moreover, endpoint selection should be appropriate for the trial phase [34]. Surrogate endpoints of kidney injury (e.g., functional, damage or stress biomarkers) may be appropriate for phase 2 trials where they capture the effect of the intervention and allow inference of likely clinical outcomes. However, for phase 3 trials, an internationally accepted consensus definition of AKI (currently based on the Kidney Disease: Improving Global Outcomes (KDIGO) 2012 criteria) may be preferable [35]. It makes intuitive sense to measure the occurrence of AKI if the goal of an intervention is to prevent it. The severity of AKI chosen as the primary endpoint in phase 3 trials requires consideration regarding tradeoff between statistical power (as gained by including all stages of AKI) and identification of definitive renal injury (as is more likely when only severe AKI is studied). Major adverse kidney events (MAKE) [36, 37] is usually not an appropriate endpoint for prevention trials, because the rate of events is too low, and it may be affected by several factors apart from the AKI event. Safety, cost-effectiveness, patient-centered outcome measures, and resource utilization may also be important outcomes for secondary endpoints in phase 2–3 or as primary endpoints for phase 4 studies [38].

Characteristics of appropriate trial endpoints include biological plausibility, validity, practicality, and patient centeredness. A biologically plausible relationship between AKI and an endpoint is highly desirable, particularly when selecting surrogate outcomes (such as biomarkers) in phase 2 trials. Endpoints must have been validated in the target population, especially when studying unique cohorts including pediatrics, pregnant women, and patients with low muscle mass. The practicality of measuring an endpoint has significant implications for trial conduct and future translation into clinical practice, so consideration should be given to ease measurement and general availability. Endpoints must be linked to patient-centered outcomes, especially in phase 3 trials, to ensure that findings align with, and are clinically meaningful, to either patients or caregivers [39, 40]. Finally, confounding and competing events must also be accounted for when interpreting endpoints. Death, intensive care unit (ICU)/hospital discharge, and continuous renal replacement therapy (CRRT) initiation for non-AKI indications are common competing events in AKI prevention studies that must be considered. Management of such events can be handled in the endpoint selection (e.g., through a composite outcome) or in the analysis phase (e.g., through a competing risk analysis). Hierarchical approaches (e.g. win ratio [41]) may also be suitable for analysis of composite endpoints. This technique has been employed successfully for over a decade in the cardiovascular literature and is gaining acceptance in the kidney disease community as well.

AKI is a significant health concern across the entire pediatric age spectrum, with the potential to impact life-course outcomes, highlighting a great need for early prevention and treatment strategies in children [42, 43]. Given the unique challenges with pediatric trials, including competition for funding with adult studies

Prevention Trials[#]		Treatment Trials	
Endpoints	Clinical Trial Phase	Endpoints	Clinical Trial Phase
• Molecular biomarkers of kidney injury	1 or 2	• Rate of change in GFR	2
• Physiological biomarkers such as urinary oxygen tension	1 or 2	• Sustained change in GFR	2
• Molecular biomarkers of kidney injury or kidney function	2	• Change in biomarker values specific for kidney damage	2
• Renal functional reserve (physiological biomarker)	2	• Change in genomic or metabolomic variables	2
		• Change in levels of inflammatory mediators	2
		• Presence or progression of protenuria	2
• Stage of AKI	3	• Major Adverse Kidney Events	3 or 4
• AKI duration	3	• Days free of organ support therapies: -Renal replacement therapy free days -Invasive mechanical ventilation free days -Intensive care/hospital fre and alive days	3 or 4
• Transition from AKI to acute kidney disease	3		
• Development or worsening of chronic kidney disease based on molecular biomarkers such as albuminuria	4	• Death	3 or 4
		• AKI trajectories	3 or 4
• Development or worsening of chronic kidney disease based on clinical endpoints such as eGFR (or eGFR slope) or reduction of eGFR by 50%	4	• Dialysis	3 or 4
		• Hospital readmission	3 or 4
• Development or worsening of chronic kidney disease based on clinical endpoints such as need for diasysis or kidney death	4	• eGFR reduction or CKD progression	3 or 4

Fig. 1 Different endpoints should be used in AKI trials on the bases of the type of intervention (prevention or treatment study) and the clinical trial phase (phase 1, 2, 3, or 4). [#] Endpoints that are used for phase 3 trials may also be used as endpoint in phase 4 trials

and, in many cases, classification as an orphan disease due to relatively lower population numbers, the application of prognostic and predictive enrichment strategies is particularly pertinent in pediatric trials. Innovative trial designs and the continued growth of collaborative multi-national groups are critical to addressing these pediatric study challenges. Importantly, children are a heterogeneous group, ranging from preterm neonates to post-pubertal adolescents [44]. Physiological and developmental characteristics differ significantly from adults, vary from newborns to adolescents and young adults, and are dynamic across longitudinal studies [45]. As children progress through various developmental stages, the same outcome measures may not be appropriate when comparing children of different ages. Notably, evaluating baseline kidney health in pediatric studies presents challenges as these measures change from birth to adulthood. Endpoints such as neurodevelopmental outcomes and growth are germane and should be considered in phase 3 and 4 pediatric trials. In addition, it is important for researchers to recognize the importance of qualitative outcome measures relevant to the child and caregivers, including the impact of AKI and treatment on quality of life [46].

Consensus statement 7

We **recommend** that when selecting endpoints for AKI prevention studies, investigators consider trial design and endpoint characteristics including: i) biological plausibility; ii) validity in the target population; iii) practicality; and iv) patient centeredness.

Baseline kidney health may be assessed in a variety of ways ranging from clinical history to detailed evaluation of numerous measures of kidney functional capacity and cellular/tissue pathology (Fig. 2) [47]. These methods vary in availability, cost, practicality, and accuracy, representing distinct aspects of kidney health (function vs. extent of underlying renal parenchymal disease) [48]. A basic assumption in AKI studies is that individuals recruited for trials have quantified, stable kidney health before the insult occurred even though measures of premorbid kidney function may be unavailable. In these cases, it may be reasonable to impute baseline kidney function based

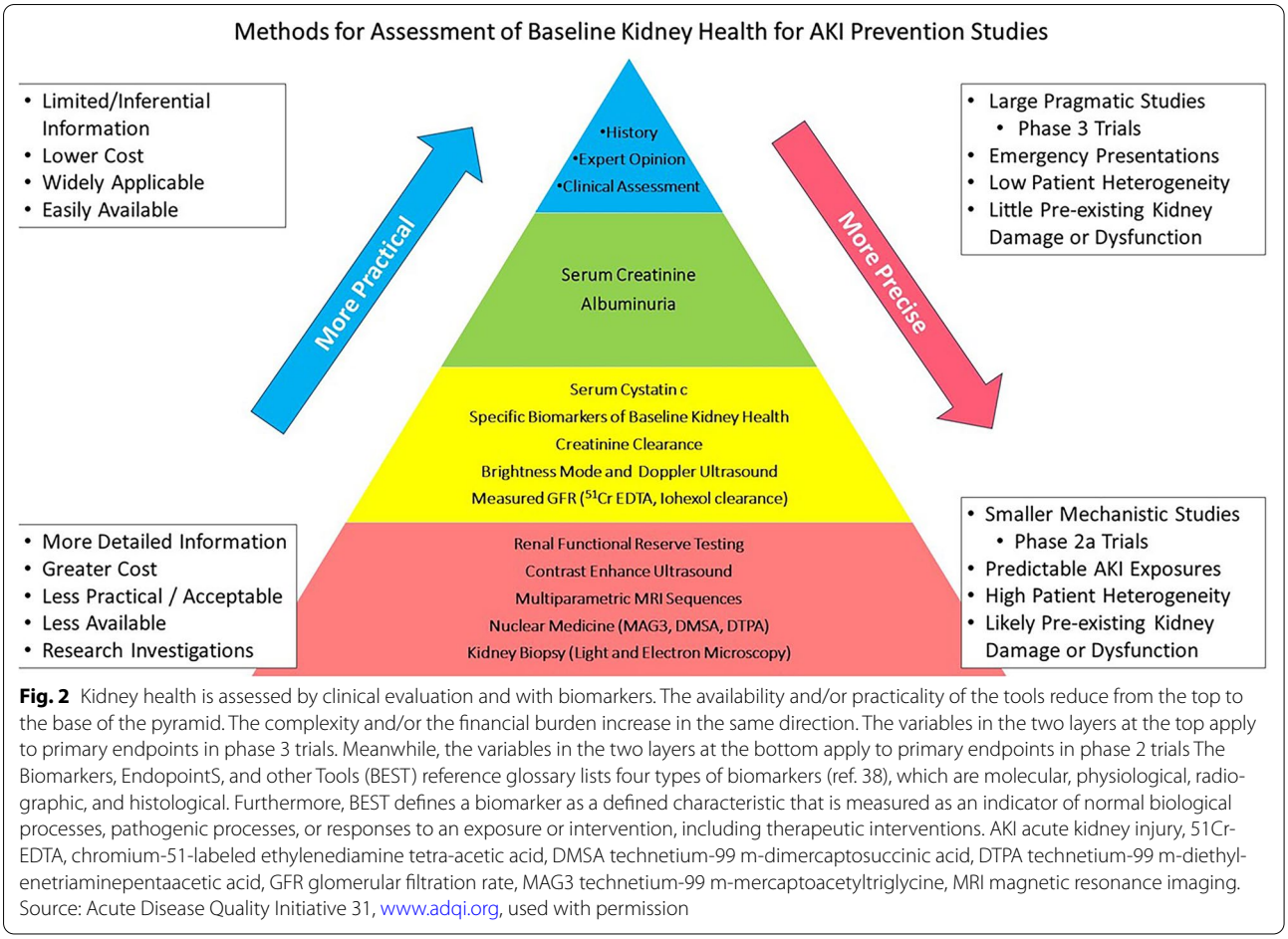

Fig. 2 Kidney health is assessed by clinical evaluation and with biomarkers. The availability and/or practicality of the tools reduce from the top to the base of the pyramid. The complexity and/or the financial burden increase in the same direction. The variables in the two layers at the top apply to primary endpoints in phase 3 trials. Meanwhile, the variables in the two layers at the bottom apply to primary endpoints in phase 2 trials The Biomarkers, EndopointS, and other Tools (BEST) reference glossary lists four types of biomarkers (ref. 38), which are molecular, physiological, radiographic, and histological. Furthermore, BEST defines a biomarker as a defined characteristic that is measured as an indicator of normal biological processes, pathogenic processes, or responses to an exposure or intervention, including therapeutic interventions. AKI acute kidney injury, 51Cr-EDTA, chromium-51-labeled ethylenediamine tetra-acetic acid, DMSA technetium-99 m-dimercaptosuccinic acid, DTPA technetium-99 m-diethylenetriaminepentaacetic acid, GFR glomerular filtration rate, MAG3 technetium-99 m-mercaptoacetyltriglycine, MRI magnetic resonance imaging. Source: Acute Disease Quality Initiative 31, www.adqi.org, used with permission

on clinical background as recommended in the KDIGO guideline [35].

Consensus statement 8

For phase 2 prevention trials, we **recommend** that measures of kidney function or damage in the acute phase are used as primary endpoints for AKI prevention studies. For phase 3 trials, we recommend use of AKI (stage) as the primary endpoint.

Phase 2 trials evaluate the efficacy of drugs or devices, in preventing the occurrence of new kidney damage or injury and to determine mechanistic pathways and establish biological plausibility for the interventions. These trials are usually smaller than phase 3 trials. Markers of kidney function may be more sensitive than clinical AKI at indicating whether an intervention affects kidney function. Similarly, measuring kidney damage markers, such as urine sediment, proteinuria, or biomarkers, may allow evaluation whether the intervention mitigates new, or different types of damage in the kidneys [49]. In phase 3 trials, the efficacy and safety of interventions are evaluated in larger patient cohorts. As the goal of these interventions is to prevent AKI, we recommend a primary endpoint of KDIGO-defined AKI.

Treatment studies

Consensus statement 9

We **recommend** that endpoints for phase 2 trials in AKI be selected to directly inform on efficacy, dose–response, biologic response to the treatment, and safety and ideally, correlate with patient-centered outcomes.

Phase 2 trials serve a key fundamental purpose in the development of treatments for AKI, encompassing evidence of efficacy and dose–response, safety, and feasibility (Fig. 1). The endpoints selected to evaluate efficacy must provide a reliable measure of response to the treatment [50, 51]. This can be qualified as categorical (i.e., no response; favorable response; adverse response) or as continuous (i.e., changes in measures of kidney function, damage or other biological variables). Evidence-informed thresholds for endpoints are necessary to describe but are currently largely uncertain. Ideally, these endpoints

are highly correlated, and even causally correlated, with validated patient-centered endpoints. There is recognition that the trial design may guide the selection of context-specific endpoints for phase 2 trials [23, 52–54]. For example, a phase 2 trial evaluating a novel drug or biologic agent to modify kidney injury in patients with persistent AKI may have endpoints that differ from a phase 2 trial evaluating the implementation of a care process bundle in clusters of patients with persistent AKI.

Consensus statement 10

We **recommend** that feasibility measures be explicitly defined for phase 2 trials and encompass measures of success across domains of recruitment, randomization, protocol fidelity, and endpoint measurement.

A key objective of phase 2 trials is an evaluation of whether the trial is feasible to successfully perform and complete given that phase 2 trials have a fundamental role in the rationale and justification for progression to a phase 3 trial [55]. The pursuit of phase 3 trials based on non-feasible phase 2 trials may ultimately compromise the rigorous evaluation of promising treatments for AKI. This may result from premature termination, loss of internal validity due to protocol violations (e.g., treatment crossover), and information bias due to missed or incomplete endpoint assessment. There are abundant measures of feasibility that phase 2 trials must consider: randomization features [56–58], enrollment measures, protocol fidelity (e.g., treatment delivery), and endpoint measures (e.g., biologic sampling; ascertainment).

These feasibility measures may be independent of the expected biologic action (or clinical action) of the treatment being evaluated.

Consensus statement 11

We **recommend**, when selecting a composite endpoint including hierarchal composite endpoints (HCE), component selection be context-specific when necessary, evidence-informed, and guided by PWLE.

The main objective for a phase 3 trial of treatment for AKI is to establish the effectiveness of the treatment to modify outcomes that are important to patients or society. Regulatory bodies have accepted the MAKE endpoint as indicative of an intervention that meets the "feels, functions or survives" concept of an effective

Table 1 Definitions for phase 2 trial endpoints

Category	Definition	Examples
Efficacy	The ability of a treatment to produce the intended outcome under controlled conditions	Biomarker signatures AKI trajectory Persistent AKI eGFR (delta) Renal functional reserve
Feasibility	The practicality and potential for successful implementation of a treatment	Patient recruitment Patient and clinician Engagement Protocol compliance Data collection/management
Safety	The potential adverse effects or risks associated with a treatment	Adverse events Adverse drug reactions Risk–benefit assessment

AKI acute kidney injury, *eGFR* estimated glomerular filtration rate

Table 2 A comparison of composite and hierarchical composite endpoints for AKI treatment trials

	Composite endpoint	Hierarchical composite endpoint
Recognition of clinical priorities	• Generally does not distinguish the relative clinical significance of each component	• Formulates the component endpoint into a hierarchy based on their relative importance
Familiarity	• Well known	• A newer statistical method
Statistical efficiency	• Reduced sample size requirement when compared to testing individual endpoints	• Reduced sample size requirement when compared to testing individual endpoints • Can be extended to account for recurrent events without statistical complexity • Requires the calculation of a win ratio which requires statistical software
Cost	• Reduced costs when compared to testing individual endpoints	• Reduced costs when compared to testing individual endpoints

treatment for AKI. However, achieving success with MAKE has proved difficult and this, in turn, has led to efforts to provide suitable alternatives. The selection of endpoints for phase 3 trials of treatments for AKI have often focused on conventional endpoints with clinical importance and composite endpoints [56, 59] (Table 1). These endpoints may align with the principles of patient-centeredness but have seldom been directly informed by PWLE. Composite endpoints have the recognized advantage of improving trial efficiency but they also have drawbacks (Table 2). Selected composite endpoints can have importance to both PWLE and potentially society as a whole. For example, "organ-support"-free days, ICU-free days or alive and out-of-hospital are composite endpoints that integrate both patient centeredness and resource utilization [60–62]. The increased use of hierarchical composite endpoints (HCE) (e.g., win ratio) represents an innovation that we suggest can be applied to treatment trials in AKI and also be leveraged to integrate outcomes perceived as important to PWLE [41, 63–65]. HCE select a range of endpoints ranked in order of importance (supplementary Fig. 3). Their advantages and disadvantages have been reviewed elsewhere [66]. One disadvantage of the win ratio is that this strategy does not allow for an accurate calculation of the number needed to harm or treat (magnitude of the overall effect). Another limitation is that, although hierarchically ordered, each component of the hierarchical endpoint is weighted the same when using the win ratio, so it could be driven by its least clinically meaningful component. Surrogate measures with correlation to clinically important outcomes can also be integrated into HCE. Innovation in selection of endpoints and in the analytic strategies utilized may further improve and simplify the interpretation of phase 3 trials for PWLE and knowledge users of health research, along with facilitation of clinical adoption [56, 63, 67].

Designs of studies other than traditional randomized clinical trials (RCT)

Consensus statement 12

We **recommend** the use of an innovative clinical trial design when it addresses challenges of AKI that are relevant to the research question, or when it provides one or more advantages over traditional designs. Elements to be considered when designing innovative clinical trials include unit of randomization, design features, and analytic strategy.

For decades, the gold standard for experimental design was the two-arm, parallel group RCT [56, 68]. This design is well suited when there are two alternative approaches to care, and the anticipated benefits are expected to accrue evenly to all recipients. There are, however, many clinical situations where there may be multiple approaches to care, and benefits may be heterogeneous. In such situations, researchers often reduce the complexity of the clinical problem to a testable question under this design, running the risk of oversimplification. Risks include failing to detect the benefit of a therapy that works differentially in different subsets of patients and failing to determine the optimal manner of delivering a therapy when there are more than two approaches. Given advances in statistical design and software, there are now several robust alternative study design choices that can be chosen to match the complexity of the clinical problem. Adopting this rubric of selecting a trial design that is fit for purpose may well be advantageous in the study of therapies for AKI, especially in late phase and post-approval settings.

The nature of AKI itself poses several challenges for standard 2 arm RCTs of an intervention at a single point in time (supplementary Fig. 3) [69, 70]. Specifically, the timing of disease presentation is heterogeneous as the timing between AKI onset and clinical presentation is often difficult to ascertain. Furthermore, there is no current method to distinguish the course of AKI at the time of initial presentation. Given the window to intervene on AKI may be narrow, the time frame to more precisely define AKI or its characteristics is compressed when considering potential enrollment into trials. This is in contrast to oncology, for example, where it is possible to perform detailed molecular phenotyping over the course of several days to determine participant eligibility. Innovative clinical trial designs may overcome some of these challenges; for example, basket [71] or SMART clinical trials may allow for the testing of one intervention across the spectrum of AKI and acute kidney disease (AKD) (supplementary Table 5).

In addition to the potential benefit of innovative designs on some of the specific challenges faced in clinical trials for AKI, other benefits include increased efficiency, improved feasibility, expanded access/equity, and the ability to test the effect of one or more interventions across the continuum of a disease. For example, a platform design can allow for rapid and more cost-effective testing of an intervention [72]. If the standard of care for AKI changes over time, this can be incorporated into the platform trial (supplementary Table 5). Bayesian analysis, when prior probabilities can be estimated with some degree of confidence, can reduce sample size compared to frequentist analyses.

Innovative clinical trials may randomize patients at the individual or at the population level, e.g., clusters. Clusters can occur at many levels, including the hospital unit, hospital itself, or provider level. Within cluster

RCTs, crossover designs may lead to contamination of the intervention as the clusters cross over repeatedly; the stepped-wedge design avoids this issue yet allows for a cluster to serve as its own internal control. Cluster randomized trials use a pragmatic study design that is increasingly used to evaluate service delivery-type interventions. However, cluster trials with individual recruitment and without concealment of allocation (or blinding of the intervention) are at risk of selection biases. As described in supplementary Table 5, a number of different innovative clinical trial design features can be considered; each has pros and cons that need to be considered vis-à-vis the specific intervention to be tested. Pragmatism is a concept that refers to the utility of interventions in daily clinical practice and is typically applied in the context of process of care interventions or established therapeutics, rather than regulatory trials for novel therapeutics, devices, or diagnostics. The pragmatism of a trial can be evaluated using the PRECIS-2 tool [73]. In contrast to a frequentist framework, where analysis is based on the absolute probability of a result, Bayesian analytic frameworks use pretest probability to inform the likelihood of a result. With rigorously established priors, Bayesian analytic frameworks can reduce the sample size needed for a clinical trial.

Limitations

A limitation that affects all AKI trials is the definition of AKI, because it uses very non-specific markers (serum creatinine and urine output) to define a syndrome that encompasses a broad range of pathophysiological processes. Another limitation is that some of the statements are rather general, and could apply to other forms of critical illness or to good clinical trial design of any sort. In addition, the group mainly focused on processes rather than on goals.

Conclusion

There are many challenges to prevention and treatment trial design in AKI. However, we have highlighted approaches which, if adopted, may allow for use of clinically meaningful and patient-centered approaches which, in turn, will promote trials with a greater potential for finding therapies that prevent or treat AKI effectively.

Supplementary Information

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