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Kidney End Points for Clinical Trials in Acute Kidney Injury

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Abstract

Acute kidney injury (AKI) is an increasingly common and feared complication in hospitalized patients. The selection of appropriate primary and secondary end points is critical to the design and eventual success of clinical trials aimed at preventing and treating AKI. In this article we provide an overview of AKI definitions and suggestions on the rational selection of end points for clinical trials in various settings, including prevention of contrast-induced AKI, prevention of cardiac surgery-associated AKI, treatment of established AKI, and treatment of dialysis-requiring AKI.

Keywords

Acute Kidney Injury (AKI); Acute Renal Failure (ARF); AKI definition; end point; outcome; clinical trial; biomarker; Randomized Controlled Trial; study design

End points are critical in the design, execution, and eventual success of clinical trials, both for early phases of drug development as well as eventual approval by regulatory agencies. In this article we provide a brief history of the evolution of acute kidney injury (AKI) definitions, and we discuss considerations for kidney end points for interventional studies using four commonly encountered clinical scenarios.

AKI Epidemiology

A common and often devastating disorder, AKI complicates the hospital course of many patients.¹ Epidemiologic studies have consistently found that even small increases in serum creatinine (SCr) among hospitalized patients are associated with worse outcomes,^{2, 3} while more severe AKI is associated with a markedly increased risk of death.^{2, 4} Patients who

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survive an episode of AKI have prolonged lengths of stay,⁵ and are at increased risk of rehospitalization,⁶ major adverse cardiac events,⁷ and chronic and end-stage kidney disease.⁸⁻¹¹ Thus, there is great interest in developing novel therapies to prevent and treat AKI. However, reaching a consensus on appropriate AKI definitions and kidney end points for clinical trials has proven challenging.

Markers Used in Renal and Nonrenal Acute Organ Failure

Definitions of AKI have consistently relied on acute changes in SCr and/or urine output. In **Table 1** we compare these “AKI” markers with markers used to define acute injury syndromes in non-renal organs. Several parallels can be drawn comparing definitions of renal versus non-renal organ injury. The P_aO_2/FiO_2 ratio (ratio of partial pressure arterial oxygen to fraction of inspired oxygen), used to define the acute respiratory distress syndrome, is a real-time physiologic marker, not unlike urine output. Similarly, the international normalized ratio (INR), used to define acute liver failure, is a blood test that reflects abnormal organ function, not unlike an elevated SCr. In contrast, neither the physical examination nor imaging studies, both of which are critical in diagnosing acute stroke, are currently used in official definitions of AKI, nor are they likely to be used to define AKI in the near future. Similarly, elevated direct injury markers (e.g., troponin), the cornerstone of the definition of acute myocardial infarction, have not been incorporated into current AKI definitions, although this is an area of active research. Indeed, many experts have argued that the lack of a reliable direct injury marker used to define AKI—in other words, a “renal troponin”—is largely responsible for the dearth of progress made in AKI research as compared to acute myocardial infarction.¹²

Novel AKI Biomarkers

A number of promising kidney injury biomarkers have been developed over the past decade, including urinary KIM-1 (kidney injury molecule 1), NGAL (neutrophil gelatinase-associated lipocalin), $[TIMP-2] \times [IGFBP7]$ (product of the urinary concentrations of tissue inhibitor of metalloproteinase 2 and insulin-like growth factor binding protein 7), and others. Some of these biomarkers may have the potential to identify kidney injury earlier than changes in SCr (see reviews^{13, 14}), and thus could be used to identify patients at risk of AKI. For the purpose of clinical trials, AKI biomarkers could be used as an enrichment strategy to maximize the AKI event rate and thereby facilitate clinical trial design (see reference 15 for an example of one such biomarker strategy that was only modestly successful). Biomarkers can also serve as surrogate end points in clinical trials. Although LDL cholesterol has been an acceptable surrogate end point for cardiovascular trials, the accumulated evidence base is massive, with tens of thousands of patients enrolled into randomized trials with LDL measurements. For the purpose of a phase 3 trial in AKI prevention or treatment, the evidence base for AKI biomarkers is still far too premature to consider their use as surrogate end points. Thus, despite an increasing body of literature that these novel biomarkers are important predictors of adverse clinical outcomes,¹⁶ they cannot be endorsed at this time as primary kidney end points for AKI trials, though their measurement as secondary end points or in early phase studies should continue and will undoubtedly add to our understanding of AKI pathophysiology.

Heterogeneity of AKI Definitions

A number of consensus definitions have been proposed by expert panels (e.g., RIFLE [risk, injury, failure, loss, end-stage renal disease]¹⁸, AKIN [AKI Network],¹⁹ and KDIGO [Kidney Disease: Improving Global Outcomes] criteria²⁰). Despite efforts at standardization, multiple AKI definitions continue to be used in clinical trials (**Table 2**). For example, contrast-induced AKI (CI-AKI) is often defined as an $\geq 25\%$ increase in SCr within 48 hours,²¹ but several other definitions have been used in the epidemiology literature and in clinical trials.²² Furthermore, while consensus definitions of AKI include both SCr and urine output-based criteria, most epidemiologic studies and AKI trials have focused exclusively on SCr, perhaps due to the difficulty of accurately recording hourly urine output, especially outside of the intensive care unit.

Selecting End Points for Clinical Trials in AKI

To frame the discussion, we start with a thought experiment: fast forwarding a decade or two into the future, what would success look like in the field of AKI interventional trials? In other words, what is it exactly that we hope to provide our patients in the future that we do not provide now in the area of AKI prevention or treatment? We envision the following concrete examples (summarized in **Table 3**), which we discuss in order to highlight the clinical assumptions and imperatives implicit in them:

Setting #1: A Drug That Prevents Small Increases in SCr Following Intravenous Contrast Administration

By 2016, at least 329 randomized controlled trials had been registered on ClinicalTrials.gov for prevention of CI-AKI. If we could eliminate CI-AKI as a disease entity altogether, what would that mean for our patients and for the public health? Undoubtedly it would be a relief to cardiologists, radiologists, nephrologists, and other health care providers. However, it would unlikely be a relief to the vast majority of patients with CI-AKI, since small increases in SCr do not generally affect how a patient feels or functions. Except in the case of CI-AKI which culminates in the need for RRT, or which precipitates volume overload due to kidney failure, patients are generally unaware of fleeting changes in SCr. So then why is it that CI-AKI continues to dominate the imagination and efforts of nephrologists and others who diagnose it, treat it (supportively), and design trials to prevent it? Most likely, it is because of the *downstream* consequences, not all of which have been demonstrated to be causally associated with CI-AKI.

First, if the association between mild AKI and future outcomes such as incident or progressive chronic kidney disease (CKD), which has been demonstrated in the epidemiology literature,²³ is truly causal, then perhaps preventing mild AKI will prevent such outcomes. This assumption has not been tested except in one case, in which prevention of AKI did not, in fact, presage an improvement in kidney function at 1 year.²⁴ The biological plausibility of preventing long-term kidney function decline by preventing a transient reduction in GFR is also not strong, in our opinion, particularly since CI-AKI may have a strong vasomotor component to it,²⁵ which is unlikely to lead to permanent parenchymal injury.

The second downstream consequence of a transient drop in GFR is related to healthcare providers' responses to that event: in the setting of even mild AKI, diuretics or angiotensin-converting-enzyme inhibitors may be held (perhaps inappropriately), duration of stay may be lengthened, and drug dosages may be incorrectly chosen. Each of these events could have significant clinical consequences. To the extent that preventing such a drop in GFR could prevent these events, a drug or intervention for CI-AKI could have real clinical value.

PRESERVE (Prevention of Serious Adverse Events following Angiography) is an ongoing randomized controlled trial that will be the largest AKI prevention study conducted to date.²⁶ The PRESERVE trial will enroll 8680 patients undergoing coronary or non-coronary angiography into an efficient 2×2 factorial design trial. The study will test the effects of IV isotonic sodium bicarbonate versus IV isotonic saline, and oral *N*-acetylcysteine versus oral placebo, on the prevention of a composite outcome of need for urgent RRT, 90-day increase in SCr of 1.5× the baseline level, or 90-day mortality. This composite end point has also been referred to as the “major adverse kidney events” outcome at 90 days, or MAKE90.²⁷ What can we learn from the design of this important study?

Composite end points—The advantages and disadvantages of using composite end points in clinical trials have been reviewed elsewhere in detail.²⁸ Composite end points are appealing because they increase event rates and thus statistical power. Additionally, composite end points have the potential to reduce bias due to competing risk (e.g., death is a competing risk for incident AKI, while RRT is a competing risk for doubling or tripling of SCr). However, composite end points may be misleading when they include outcomes that vary significantly in their clinical relevance and importance to patients, particularly since the least important outcomes typically contribute the greatest number of events and the greatest magnitude of treatment effect. In the Irbesartan Diabetic Nephropathy Trial,²⁹ for example, the benefit of irbesartan over amlodipine on the composite end point of doubling of SCr, ESRD, or death was driven entirely by doubling of SCr. Rates of death were, in fact, higher in the irbesartan group, though the difference was not statistically significant.

CKD as an end point in an AKI trial—Most clinical trials in AKI have not evaluated long term changes in kidney function, most likely due to logistical challenges. However, if the rationale for preventing AKI is to prevent long term kidney function decline, an assumption that has been shown in animals but remains controversial in humans,^{30, 31} then it seems quite reasonable to include CKD in a composite end point or as a pre-specified secondary end point. Of course, to the extent that prevention of AKI may result in decreased need for urgent RRT, decreased hospital length of stay, or even decreased rates of adverse drug events, all of which could be considered reasonable end points, evaluation of kidney function at 90-days may be superfluous and could conceivably even contribute to a null study. The imprecision and inaccuracy of estimating equations for eGFR using SCr—particularly if creatinine generation declines over time in patients recovering from AKI³²—may also frustrate attempts to reliably estimate change in kidney function.

Bottom line—Any large AKI prevention study looking at small increases in SCr should also include downstream events that are important to patients. These events could be captured by acute end points, such as hospital length of stay or need for urgent RRT.

Alternatively, these events could be captured by longer term end points such as kidney function at 90 days, though the limitations of GFR estimating equations need to be considered.

Setting #2: A Drug That Prevents AKI Following Cardiac Surgery

Cardiac surgery is an appealing setting in which to test novel interventions for AKI prevention. Similar to CI-AKI, the timing of injury in cardiac surgery-associated AKI can be anticipated, allowing for preventive therapies to be tested. However, consider an intervention that prevents a 0.3 mg/dl increase in SCr postoperatively. Would such an intervention have real importance to patients?

Strict versus liberal end points—In choosing ideal end points for AKI trials, there is an intrinsic “tug-of-war” between stricter end points (*e.g.* acute need for RRT), which have greater clinical relevance but lower event rates, versus more liberal end points (*e.g.* an increase in SCr 0.3 mg/dl), which have less clinical relevance but higher event rates (**Figure 1**). Clearly, the most appropriate end points will differ in smaller phase 1 and 2 studies versus larger phase 3 studies. More liberal end points are acceptable for smaller studies to establish proof-of-concept, whereas hard end points are more appropriate for larger studies, and would be needed to support new drug or device approval by regulatory agencies. In the case of CKD, detailed analyses have been conducted by the National Kidney Foundation and the US Food and Drug Administration to demonstrate the tradeoffs inherent in 30% versus 40% declines in GFR versus doubling in SCr as end points for clinical trials. Similar analyses for AKI end points would be informative to guide investigators in weighing the improvement in statistical power against the risk of erroneous conclusions that could result from using liberal end points.³³

Urgent RRT as an end point in cardiac surgery-associated AKI—Patients who require urgent RRT following cardiac surgery have in-hospital mortality rates that exceed 50%.² Thus, prevention of urgent RRT following cardiac surgery is an important goal, but event rates are low (~1%). Thus, focusing on high risk patients, a process known as enrichment, is critical to the success of such a study. Specifically, urgent RRT following cardiac surgery occurs almost exclusively in patients with CKD stages 4 and 5: in a *post hoc* analysis of a randomized controlled trial of 4465 adult patients who underwent cardiac surgery, we found that AKI requiring RRT occurred in 0 out of 2247 patients with a baseline eGFR>60 mL/min/1.73 m², 5 out of 1816 patients (0.3%) with CKD stage 3, 11 out of 300 patients (3.7%) with CKD stage 4, and 17 out of 102 patients (16.7%) with CKD stage 5.³⁴

Novel biomarkers as end points—Biomarkers of kidney injury that reflect response to tubular injury are appealing as early tests for AKI. As discussed above, it is currently unknown whether these biomarkers can reliably serve as surrogate end points for clinical trials. A number of criteria have been evaluated to assess the validity of surrogate biomarker end points, including the Prentice criteria.^{35, 36} One option for phase 2 studies that could be adapted from the heart failure literature³⁷ is the incorporation of surrogate end points into a “global rank” end point. Global rank end points allow dichotomous clinical events (*e.g.* death, RRT) and continuous variables (*e.g.* change in SCr, urine output, or novel injury

biomarkers) to be combined into a single comprehensive measure. Instead of examining a single end point, investigators rank trial participants on the basis of a number of end points, with assignment of different weight to different end points. For example, rank #1, in-hospital death; rank #2, RRT; rank #3, doubling of SCr; rank #4, oliguria or smaller changes in SCr; and rank #5, elevation in novel biomarkers. The groups are then compared on the basis of the sum of global rank scores.

Bottom line—It is appropriate for earlier phase studies to use more liberal end points, while larger studies should use hard end points such as doubling of SCr or urgent RRT. Furthermore, any AKI prevention trial evaluating urgent RRT following cardiac surgery as the primary end point would likely need to focus on an enriched cohort of patients with CKD stages 4 or 5 for feasibility. This approach could, however, lower the probability for success if diseased kidneys in advanced CKD are not as responsive to certain therapeutic interventions. Finally, incorporating later changes in kidney function through the use of composite outcomes such as MAKE90 could also be included in the design of prevention trials.

Setting #3: A Drug That Prevents AKI Progression in Patients With Established AKI Not Yet Receiving RRT

Most cases of severe AKI in hospitalized patients occur in those with multi-system organ failure, usually in the setting of septic shock or other critical illness such as severe trauma. In such conditions the timing of injury is often difficult to ascertain, and patients often arrive to the hospital or are transferred to the intensive care unit after AKI has already been established. Furthermore, the etiology of AKI in these cases is often multi-factorial, and the precise pathophysiological events are generally unknown: whether apoptosis, necrosis, mitochondrial dysfunction, inflammation, or vascular congestion and thrombosis are the most relevant target(s) is not well established, and is not answered by animal models currently in use.³⁸ How does one define appropriate kidney end points in patients with established AKI who are not yet receiving RRT?

New requirement for RRT is clearly an important end point. However, several caveats need to be considered. First, since requirement for RRT is highly subjective, standardized criteria for RRT initiation should be pre-specified, or, at the very least, providers making clinical decisions about RRT initiation should be fully blinded to treatment assignment. Second, RRT may be clinically indicated but not actually provided due to patient or healthcare proxy preference, vascular access issues, or other factors. Thus, prevention of “clinically indicated RRT” may be a more relevant end point than prevention of “RRT actually provided”. Third, since death is an important competing risk for RRT and acute mortality rates are exceedingly high in this patient population, we suggest that hospital mortality be included in a composite end point with RRT. One prominent example of this approach of combining acute mortality and need for RRT into a composite end point is the Anaritide in Acute Tubular Necrosis study, one of the largest randomized controlled trials ever conducted in AKI, in which the primary composite end point was dialysis-free survival at day 21.³⁹

An alternative end point to consider in this setting is kidney-failure-free days. The concept of organ-failure-free days is well known in the field of respiratory and critical care medicine, where “ventilator-free days” is an end point frequently used to assess duration of mechanical ventilation while adjusting for the competing risk of death. To calculate organ-failure-free days, the number of organ-failure days is subtracted from a fixed number of days (usually 28). Patients who die before day 28 are typically assigned a score of zero.⁴⁰ This concept has been adapted from ventilator-free days to include other organs, including the heart, liver, and kidneys. In the Rosuvastatin for Sepsis-Associated Acute Respiratory Distress Syndrome Trial, kidney-failure-free days was defined as the number of days (up to day 14) in which a patient had a SCr < 2.0 mg/dL.⁴¹ However, an important consideration for this type of end point is to consider the effect of RRT on SCr. In patients with AKI who are receiving RRT, extracorporeal clearance may lead to a reduction in SCr despite profound kidney failure, leading to misclassification as a kidney failure-free day.⁴² This type of misclassification can be avoided by including RRT in the definition of kidney failure.

Bottom line—In patients with established AKI who are not yet receiving RRT, a variety of kidney end points can be considered for interventional studies. Because of both its high clinical relevance as well as its potential to lead to outcome misclassification due to extracorporeal clearance of creatinine, RRT should be included in any such composite end point. Furthermore, hospital mortality should be included in any composite end point in this patient population since it represents an important competing risk.

Setting #4: A Drug or Device That Hastens Recovery in RRT-Dependent AKI

One of the most important patient-oriented outcomes in all of nephrology is recovery from RRT-dependence after AKI. Acute kidney injury requiring RRT is most common in patients with pre-existing CKD, and may also potentially predispose to advanced CKD and end stage kidney disease even after recovery. Despite the extraordinary costs, morbidity, and mortality associated with AKI requiring RRT, it is remarkable that very few trials have been performed in this extremely common clinical setting. In the few studies that have been performed in this patient population, the primary end point has typically been mortality rather than recovery from RRT. For example, in both the Acute Renal Failure Trial Network (ATN) Study⁴³ as well as the High-Dose Furosemide in Acute Renal Failure Study,⁴⁴ the primary outcome was survival, and RRT-dependence was evaluated as a secondary end point.

Bottom line—We suggest that interventional studies in patients with AKI requiring RRT evaluate both survival and RRT-dependence in a single composite end point. Such an end point could most easily be evaluated by assessing the number of RRT-free days, similar to kidney-failure-free days discussed in the previous section. Indeed, RRT-free days was a secondary end point in the ATN Study⁴³ and has also been used in other large clinical trials.⁴⁵

Conclusions

Even though AKI is one of the most feared complications of hospitalized patients and is the most common reason for inpatient nephrology consultation in most hospitals, no prevention or treatment strategy exists other than dialysis, avoidance of nephrotoxins, and maintenance of perfusion pressure. Thoughtful design of clinical trial end points is critical for translating advances in basic science and animal models into treatments that help our patients.

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Figure 1. Pros and cons of liberal versus strict AKI definitions and kidney end points
Abbreviations: RRT, renal replacement therapy; SCr, serum creatinine.

Table 1

Definitions of acute organ injury.

Organ System / Clinical Syndrome	Definition of Injury	Major Injury Marker	Type of Marker
Cardiovascular / Acute MI	Rise and/or fall of cardiac biomarker values with at least one value above the 99 th percentile upper reference limit and with at least one of the following: symptoms of ischemia, new significant ST-segment changes or new LBBB; development of pathological Q waves; imaging evidence of new loss of viable myocardium or new regional wall motion abnormality; intracoronary thrombus identified by angiography or autopsy ⁴⁶	Troponin	Direct Injury
Pulmonary / ARDS	Impairment of oxygenation ($P_aO_2 / FiO_2 \leq 300$) and all of the following: new or worsening respiratory symptoms during the past 7 days; bilateral opacities consistent with pulmonary edema on chest x-ray or computed tomography scan; respiratory failure must not be fully explained by cardiac failure or fluid overload ⁴⁷	P_aO_2 / FiO_2	Physiologic
CNS / Acute Stroke	Brain, spinal cord, or retinal cell death attributable to ischemia based on (i) pathological, imaging, or other objective evidence of focal ischemic injury in a defined vascular distribution, or (ii) clinical evidence of focal ischemic injury based on symptoms persisting ≥ 24 h or until death, and other etiologies excluded. ¹¹	Magnetic resonance imaging + Neurologic deficit	Imaging + Physical Exam
Hepatic / Acute Liver Failure	Rapid deterioration of liver function, resulting in coagulopathy (INR ≥ 1.5) and encephalopathy in a patient without preexisting liver disease ⁴⁸	INR + Encephalopathy	Functional + Physical Exam
Renal / AKI	An increase in Scr of ≥ 0.3 mg/dl within 48 hours or $\geq 50\%$ within 7 days, or the need for RRT, or urine output <0.5 ml/kg/h for ≥ 6 hours ²⁰	Urine output + Scr	Physiologic + Functional

Note: Conversion factor for Scr in mg/dL to (μ mol/L, $\times 88.4$).

Abbreviations: AKI, acute kidney injury; ARDS, acute respiratory distress syndrome; CNS, central nervous system; exam, examination; FiO_2 , fraction of inspired oxygen; INR, international normalized ratio; LBBB, left bundle branch block; MI, myocardial infarction; P_aO_2 , Partial pressure of arterial oxygen; RRT, renal replacement therapy; Scr, serum creatinine.

Table 2

Definitions of AKI and other kidney end points used in randomized controlled trials.

Classification	Definitions of AKI incidence and severity		Representative Trials
	Based on changes in Scr	Based on changes in Urine Output	
Consensus Criteria *			
RIFLE	Definition: Increase in Scr 1.5x or decrease in GFR 25% within 7 d Risk (R): Increase in Scr 1.5x or decrease in GFR 25% Injury (I): Increase in Scr 2x or decrease in GFR 50% Failure (F): Increase in Scr 3x or decrease in GFR 75%, or Scr>4 mg/dl with an acute increase >0.5 mg/dl	Definition: Urine output <0.5 ml/kg/h for 6 h Risk (R): output <0.5 ml/kg/h for 6 h Injury (I): output <0.5 ml/kg/h for 12 h Failure (F): output <0.3 ml/kg/h for 24 h or anuria for 12 h	Kaya <i>et al.</i> ⁴⁹
AKIN	Definition: Increase in Scr 0.3 mg/dl or 1.5x within <48h Stage 1: Increase in Scr 0.3 mg/dl or 1.5x Stage 2: Increase in Scr 2x Stage 3: Increase in Scr 3x, or Scr>4 mg/dl with an acute increase >0.5 mg/dl, or RRT	Definition: output <0.5 ml/kg/h for 6 h Stage 1: output <0.5 ml/kg/h for 6 h Stage 2: output <0.5 ml/kg/h for 12 h Stage 3: output <0.3 ml/kg/h for 24 h or anuria for 12 h	Zimmerman <i>et al.</i> ⁵⁰
KDIGO	Definition: Increase in Scr 0.3 mg/dl within 48 hours or 50% within 7 days Stage 1: Increase in Scr 0.3 mg/dl or 1.5x Stage 2: Increase in Scr 2x Stage 3: Increase in Scr 3x, or Scr >4 mg/dl, or RRT	Definition: output <0.5 ml/kg/h for 6 h Stage 1: output <0.5 ml/kg/h for 6 h Stage 2: output <0.5 ml/kg/h for 12 h Stage 3: output <0.3 ml/kg/h for 24 h or anuria for 12 h	Kowalczyk <i>et al.</i> ⁵¹
Other Criteria			
Contrast-induced AKI	Increase in Scr 0.5 mg/dl or 25% within 48 hours of receiving contrast		Er <i>et al.</i> ⁵²
Kidney-failure-free days to day 14	Kidney-failure day defined as Scr >2.0 mg/dl		Truwit <i>et al.</i> ⁵³
Other	Peak Scr > 2.0 mg/dl		Ali <i>et al.</i> ⁵⁴
Other	Time-averaged Scr increase from baseline to day 7		Endre <i>et al.</i> ¹⁵

Note: Conversion factor for Scr in mg/dL to $\mu\text{mol/L}$, $\times 88.4$.

Abbreviations: AKI, acute kidney injury; ; ESRD, end-stage renal disease; KDIGO, Kidney Disease: Improving Global Outcomes; RIFLE, risk, injury, failure, loss, and ESRD; RRT, renal replacement therapy; Scr, serum creatinine

^{*} RIFLE was adopted in 2004 by the Acute Dialysis Quality Initiative. AKIN was adopted in 2007 by the Acute Kidney Injury Network. KDIGO was adopted in 2012 by the KDIGO AKI Work Group

Table 3

Considerations for end points in AKI clinical trials.

Clinical Scenario	Suitable End Points	Unsuitable End Points	Comments
<u>AKI Prevention</u>			
Settings 1 & 2: Prevention of contrast-induced and cardiac surgery-associated AKI	<u>Phase I/II:</u> Time-averaged Scr; Urinary injury biomarkers; KDIGO-AKI <u>Phase III:</u> Severe AKI *; RRT/Death; MAKE90	<u>Phase I/II:</u> MAKE90 <u>Phase III:</u> Time-averaged Scr; Urinary injury biomarkers; KDIGO-AKI	Continuous end points such as Scr or urinary injury markers are reasonable for use in early stage clinical trials, as they provide increased statistical power compared to dichotomous end points, but cannot be endorsed for phase III studies. Conversely, phase I/II studies are underpowered for end points such as MAKE90. Composite end points increase statistical power and may reduce bias caused by competing risks (e.g., death), but may be misleading when they include outcomes that vary significantly in clinical relevance.
<u>AKI Treatment</u>			
Setting 3: Treatment of AKI not requiring RRT	<u>Phase I/II:</u> Time-averaged Scr; Progression of AKI stage; Kidney-failure-free days <u>Phase III:</u> RRT/Death; 90-d kidney function/death	<u>Phase I/II/III:</u> Any end point that fails to take into account the effect of RRT on Scr	Kidney-failure-free days incorporates mortality to avoid misclassifying early deaths as non-events while maintaining the end point as a continuous variable. For definitions of kidney-failure-free days based on changes in Scr (e.g., every day in the hospital with an Scr > 1.5× baseline might be considered a kidney-failure day), the effect of extracorporeal clearance of Scr in patients requiring RRT must be taken into account to avoid misclassification. Death is an important competing risk for RRT, especially in setting 4 where acute mortality rates are very high. Thus, death should be included in a composite end point with RRT-dependence.
Setting 4: Treatment of AKI requiring RRT	<u>Phase I/II:</u> RRT-free days <u>Phase III:</u> RRT-free days; RRT/death at 90 d	<u>Phase I/II/III:</u> Any end point that fails to take into account death as a competing risk	

Abbreviations and definitions: AKI, acute kidney injury; KDIGO, Kidney Disease: Improving Global Outcomes; MAKE90, major adverse kidney events at 90 d, which includes urgent RRT, 90-d increase in Scr 1.5× baseline, and 90-d mortality; RRT, renal replacement therapy; Scr, serum creatinine.

* Severe AKI is often defined as doubling of Scr and/or RRT, corresponding to stages 2 and 3 of the KDIGO-AKI criteria