**Pragmatic studies for acute kidney injury: consensus report of the Acute Disease Quality Initiative (ADQI) 19 Workgroup**

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**Abstract**

**PURPOSE**: Acute kidney injury (AKI) has become a major medical and financial burden in China along with the rest of the world. There have been considerable advances in the understanding of the epidemiology and pathogenesis of AKI. However, there is no consensus regarding the optimal care for patients. The Acute Disease Quality Initiative (ADQI) 19 meeting focused on identifying and designing relevant and achievable AKI-related studies in China.

**MATERIALS & METHODS**: The working group developed a list of preliminary questions and objectives and performed analysis of the existing literature. Relevant studies were identified through a literature search using the MEDLINE database and bibliographies of relevant research and review articles. We then used a two-step Delphi process to prioritize a research agenda and proposed specific study designs to address unmet needs.

**RESULTS**: Important gaps in existing knowledge were identified and pragmatic studies were proposed in three distinct areas: care bundles for AKI prevention, renal replacement therapy (RRT) for AKI, and fluid management. In addition, the use of biomarkers to guide clinical trials was discussed.

**CONCLUSIONS**: Consensus was reached on a research agenda for AKI with a specific focus on pragmatic trials in China.

**Key word:** acute kidney injury; sepsis; renal replacement therapy; resuscitation; pragmatic trials.

**Introduction**

Acute kidney injury (AKI) is a common problem in the intensive care unit (ICU), and is associated with increased mortality and high healthcare costs. However, information regarding the optimal care of patients with AKI is limited and there are numerous unanswered questions in the management of AKI during critical illness. Pragmatic trials with a focus on AKI could provide a path to better understanding of different aspects of AKI management. In particular, the questions of how to prevent AKI using care bundles, how to prescribe intravenous fluids in patients with or at risk for AKI, how to manage patients requiring renal replacement therapy (RRT) in the ICU and how to employ AKI biomarkers to improve outcomes in real world clinical settings could all be the subject of pragmatic trials. However, the best design for such studies requires detailed knowledge of existing practices to establish feasibility, equipoise, and sample-size. China, with its large population and rapidly increasing standard of medical care, is particularly burdened by the financial impact of AKI. Furthermore, with its large hospitals China is well-suited for pragmatic trials.

In a recent prospective, multicenter, cross-sectional survey of hospitalized adult patients in China, only 1-2% of hospitalized patients are diagnosed with AKI, corresponding to 1.4 to 2.9 million cases per annum [1]. Given that AKI are reported at nearly 10 times higher rates in many countries [2], China can expect to see it’s rates soar as recognition of AKI increases. In Chinese ICUs, rates of AKI have been reported to range from 32% to 51%, with an in-hospital mortality rate of up to 46% [3-5]—much more consistent with other countries [6]. Available evidence suggests that 20-25% of patients with AKI in ICUs in China are treated with RRT [3-5], almost exclusively with continuous modalities. As the prevalence and outcomes of AKI and RRT in Chinese ICUs appear comparable to those reported in North America and Europe, the results of pragmatic trials in China could be generalizable to other developed and developing countries.

In order to address the potential for the most feasible pragmatic trial design, we convened a two-day meeting (ADQI 19 consensus conference titled “Pragmatic Studies for AKI”) in Wuhan, China on April 3-4, 2017. In this report, we summarize the recommendations of the group and supporting evidence. We also discuss the gaps in our knowledge to identify future research directions.

**Methods**

The aims of 19th ADQI Consensus Conference were: *i.* to develop recommendations for the design and conduct of relevant and feasible studies in the field of critical care nephrology that could be carried out in China; and *ii.* to generate robust evidence informing management of AKI both in China and globally. The recommendations include the questions to be addressed in pragmatic trials and the suggested format of these trials. To achieve these goals the 19th ADQI Chairs empaneled a diverse group of 18 experts representing critical care and nephrology around the world including North America, Europe, Australia, and China.

Experts were divided into four groups, with each group composed of 4 or 5 individuals, to focus on four pre-determined topics: care bundles for AKI prevention, RRT for AKI complicating critical illness, fluid management before and after AKI, and biomarker-guided clinical trials. The aim was not to comprehensively document all potential research questions in these areas, but, as pragmatic research, to identify questions that would be both most informative to local clinical practice and most deliverable as studies conducted within the contemporary Chinese clinical environment. For the purposes of this exercise, we began with a broader scope of what could constitute a “pragmatic trial” including care bundles and biomarkers.

Group moderators (co-chairs) were responsible for guiding the discussion, as well as summarizing the results and producing the final document with summary recommendations for future practice and research. Each work group identified relevant literature by electronic searches. Studies identified for review were in the English language unless participants were able to provide a thorough translation. The group provided qualitative commentary when deemed necessary. Pragmatic trial designs were defined through a series of breakout sessions where individual workgroup members were required to identify key questions for each section and provide potentially suitable trial designs using the “PICO” (Population, Intervention, Control/Comparator, and Outcome) format.

Workgroup members were then asked to present their proposals to the entire group, revising each proposal as needed until a final version was agreed upon by all participants. All ADQI participants presented their proposed trial designs and, following each plenary session, the group revised the proposals as necessary to accommodate the consensus recommendations of all participants. Within this format the role of group four differed slightly, in that they focused on potential applications of AKI biomarkers across all the different study settings.

Statements were further refined until final versions were agreed upon. A writing committee assembled the individual reports from the workgroups into an overall summary document. The final paper including background, PICO statements and power calculations was sent to each participant for comment and revision.

**Results**

**Topic 1: Care bundles for AKI prevention**

The care of hospitalized patients with AKI has been shown to be very variable in routine clinical practice [7-12]. Systematic tools, including simple checklists, care bundles, and medical algorithms have been proposed and tested to improve the quality of care and patient outcomes. Although compliance with AKI bundles is generally low in routine clinical practice, when mandated or tested in clinical studies, utilization of these tools often leads to better outcomes as shown by studies in the UK and USA [13-19]. Whether they also have a role in the Chinese healthcare setting and whether there are any preferred options is not known.

Workgroup 1 was tasked to develop a clinical study that used a systematic tool to improve the management and outcome of patients with AKI or at risk for AKI. By consensus, they focused on oliguria, a frequent problem in hospitalized patients that is often not well-managed, especially in patients with AKI. The group proposed a 2-phase study whereby the first phase consists of a prospective observation period followed by a randomized controlled trial (RCT). The aim of the observation phase is to describe current management of oliguria in routine clinical practice and to identify the optimal systematic tool and its key components. The results will also inform the power calculation of a subsequent interventional study to be undertaken in the second phase. For this part, the group proposed an RCT whereby patients with oliguria are randomized to management as guided by a systematic tool versus standard clinical care. By consensus, the group opted for a checklist as the systematic tool of choice (**Figure 1**). To simplify the study and to improve feasibility, a cluster randomization process at hospital level rather than individual patient randomization was proposed (**Figure 2**). Time to first creatinine check after randomization was chosen as the primary outcome as it was considered to be a generic marker of the process of care. Potential secondary outcomes are severity of AKI within 72 hours of randomization, treatment with RRT and length of stay in the hospital.

Given the relative paucity of literature on the use of systemic tools in AKI, a power calculation was performed using reported data by Kolhe et al. [13]. Accordingly, a total sample size of 1300 patients per arm of the trial would be necessary, targeting a standard 2-tailed alpha error 0.05 and beta error of 0.20 (not encompassing more complex statistics required for the proposed clustered design). Quality measures to assure near complete compliance with the bundles can enhance the value of findings. Based on Kolhe et al. compliance with the AKI care bundle within 24 hours was only 2.2% and increased to 21.6% following implementation of interruptive alert [14].

**Topic 2: RRT for AKI**

Despite extensive research and numerous RCTs, modality and timing of initiation for RRT remain controversial [20-22]. Even dose of RRT has some variation, in part because fixed dosing strategies are out of step with modern provision of organ support. Moreover, within China, as in many other countries there is a perceived lack of standardization of acute RRT practice with significant variation between centers. Thus, the consensus was that the current primary research opportunity in China is to first document RRT delivery in Chinese ICUs and then investigate interventions to standardize and improve RRT delivery.

Workgroup 2 thus recommended first conducting a prospective observational study to describe the current practice and practice-variation in the delivery of acute RRT in Chinese ICUs. Data from such a study would serve as a benchmark for future studies of ICU-based RRT in mainland China and would provide essential data informing the design of interventional studies. In addition to documenting local practice, quality improvement tools could be tailored to meet locally relevant needs. Furthermore, the design of such a prospective observational study could utilize, as a template, studies examining the epidemiology of AKI in the ICU and the use of RRT in its treatment that have been undertaken elsewhere in the world [6]. This would allow swift adoption of a relevant data-collection protocol and would provide a ready international comparator for Chinese AKI epidemiology and clinical practice. It is essential that any study is comprehensive while avoiding onerous data collection. Potential primary data-points of interest for such a study are outlined in **Table 1**.

The suggested second stage of this project would then be to prospectively evaluate a quality improvement intervention to improve and standardize practice delivery of RRT across a cohort of Chinese ICUs. The proposed intervention would be to move all centers toward the practice patterns found to be associated with best outcomes in phase 1 (**Table 2**). It was agreed that to be feasible across diverse clinical settings the intervention would probably not be prescriptive in suggesting specific targets (beyond referring to existing international guidelines), but would merely mandate that explicit choices were made by treating clinicians for important treatment related variables including dose, fluid balance target, blood flow rate, modality, vascular access site, anticoagulation, monitoring. The intervention might also suggest an evaluation pathway to be used in response to premature filter loss. It was felt that a strategy of phased implementation of this intervention as a quality improvement process, would be acceptable to Chinese clinicians and patients enabling for a step-wedge cluster randomized trial design [23], evaluating stepwise adoption of the policy intervention in random sequence across ICUs throughout the time-course of the study. This design could potentially avoid the requirement for patient level consent (subject to local research ethics review and public consolation) as the ‘study’ would constitute implementation of a clinically-justifiable QI program, with collection of high-quality data to confirm the expected clinical effect. ICU level randomization was also regarded as an essential feature to minimize cross-contamination of practice between study arms.

The primary outcome of the proposed study would be to demonstrate an effect of the intervention on median filter lifespan during the first 72h of treatment. The group considered that this parameter represents a pragmatic and meaningful measure of well-delivered CRRT that would correlate with improved time on therapy, delivered-dose, as well as having important impact on cost of therapy, which might be particularly important in China where patients and their families are often required to contribute a proportion of the direct costs of care, including the filters. Based on this primary outcome it is anticipated that randomization of 10-15 ICUs would enable a clinically meaningful benefit to be detected, with a formal power calculation dependent on baseline data on intra- and inter-cluster variation in filter lifespan that would be gathered in the prior observational study. As an important secondary endpoint we would measure a more patient-centered clinical outcome - acute kidney disease status at hospital discharge (a composite of patient survival and renal recovery). Finally, an embedded process-evaluation would be an important component of this study to better understand the mechanism of the effect of the intervention on the study outcomes, whether positive or negative.

**Topic 3: Fluid resuscitation in the peri-acute kidney injury period**

Conceptually, resuscitation fluids can be administered either to prevent AKI or to promote recovery from AKI (**Figure 3**). However, it is unclear whether the use of resuscitation fluids are associated with lower risk or severity of AKI [24]. Furthermore, there is no framework for how fluid resuscitation trials should be designed for prevention or treatment of AKI. Group 3 was tasked to identify important knowledge gaps related to fluid use and design a pragmatic clinical trial of fluid resuscitation in the peri-AKI period for ICUs in China.

It was unclear to the group which fluid/fluid combination is more effective for correction of hypovolemia in high-risk patients [25-27]. Although the volume-sparing effect of colloids is considered an advantage, as it stays in the intravascular space for longer than crystalloids, no significant difference in 28-day mortality (the primary endpoint) was observed in a recent clinical trial comparing colloids to crystalloids (RR=0.96 [95% CI, 0.88 to 1.04]; P = 0.26)[28]. However, by 90 days, benefit was seen with colloids (RR=0.92 [95% CI, 0.86 to 0.99]; P = 0.03). A number of secondary endpoints were also met including days alive without mechanical ventilation; and alive without vasopressor therapy by 7 days and 28 days. Following a suggestion that albumin might be harmful, a large clinical trial of saline versus albumin in critically ill patients demonstrated no safety concerns for albumin apart from a subgroup with head injury [29]. Compared to crystalloids alone, the use of albumin has been associated with small but statistically significant increases in central venous pressure despite smaller fluid requirements and less positive fluid balances [29,30]. Thus, the choice between crystalloids and colloids for resuscitation should not be based on hemodynamic endpoints *per se*, but rather, should be based on other physiological outcomes. For instance, colloids could be used to limit fluid overload as fluid overload had been shown to be independently associated with mortality in observational studies [31,32]. There is also considerable evidence that hyperchloremia can alter renal function, perhaps worsening AKI, so that excessive use of saline solutions should be avoided [33-35]. In the presence of hyperchloremia or other forms of metabolic acidosis, balanced electrolyte solutions are preferred [36,37].

An important question that arises frequently in clinical practice is how much fluids should be given for treatment of hypovolemia in patients with oliguric AKI. Oliguria is the second most common reason for fluid administration after hypotension in critically ill patients [38]. However, treatment of oliguria with fluid administration can be associated with improved outcomes only when hypovolemia is present. Although no recommendations can be made on how much fluid should be administered, oliguria should serve as a biomarker for investigation for AKI including assessment of hemodynamics and renal hypoperfusion, nephrotoxin exposure, rather than default fluid administration.

Another common dilemma for clinicians is how treat a patients with oliguric AKI who continue to have hypovolemia/preload responsiveness and worsening/new tissue edema despite fluid administration. Oliguric patients are at a high risk for fluid overload, which is independently associated with poor outcomes [31]. In a recent point-prevalence study of fluid challenge in critically ill patients, no hemodynamic monitoring was used to guide fluid therapy in 43% of patients, and dynamic measures of preload responsiveness were used only in 22% of patients [38]. While judicious use of fluids may be warranted in hypovolemic patients who are pre-load responsive, fluid administration must be used with caution in patients who remain pre-load responsive and oliguric as fluid overload may worsen tissue edema impairing oxygenation and also impair repair recovery of renal function [39]. However, there are no well-designed clinical studies that address this critical clinical problem.

Another frequently asked question is what should be the outcome for fluid resuscitation trials in patients with established AKI. For trials designed to improve short-term recovery from early AKI, progression to KDIGO stage 2 or 3 or use of dialysis per se might be the best endpoint [40]. It is also important to note that when AKI is ascertained using serum creatinine, administration of large volumes of fluid may confound the ascertainment of AKI or its severity due to hemodilution [41]. It is also important that the timing of recovery is incorporated into the endpoint as delayed recovery or non-recovery might be influenced by several other interventions other than fluid administration and are also associated with different prognoses [42].

Long-term outcomes from AKI could be examined using “hard,” and “patient-centered” outcomes such as death, dialysis dependence or persistent renal dysfunction suggesting the onset of chronic kidney disease (CKD). The composite outcome of death, new dialysis, and worsened kidney function, defined as a 25% or 50% decline in eGFR, constitutes the major adverse kidney event (MAKE) outcome. MAKE30, 60, 90 are assessed after 30, 60, and 90 days, respectively [43]. MAKE90 is a frequent endpoint because this is typically the time point when CKD is diagnosed after AKI. Using a composite outcome increases the event rate and thus decreases the sample size requirement for conducting the studies. However, composite outcomes are problematic when individual components are affected differently by the intervention.

Based on the above questions, we proposed a pragmatic clinical trial focused on AKI recovery to be conducted in Chinese ICUs.Sepsis is the leading cause of AKI in critically ill patients worldwide with intra-abdominal sepsis being the most common in Chinese ICUs. Recent evidence from cohorts of patients with sepsis suggests that two-thirds of patients already have AKI at the time of presentation to the emergency room by serum creatinine [24,44]. Thus, a trial for prevention of AKI in patients with sepsis may not be feasible, but rather, interventions should focus on improving other patient-centered outcomes.

As the current standard of care with regards to fluid use in Chinese ICUs is highly variable and unclear, we proposed a two-step iterative process for designing a pragmatic clinical trial—STandardization of care for AKI Recovery (STAR) trial. First, it was recommended that a multi-center observational study be conducted to understand and identify current best practices of fluid use across Chinese ICUs in patients with intra-abdominal sepsis who undergo surgery and develop AKI. Second, we proposed to protocolize the best practices in Chinese ICUs with regards to fluid management, into an intervention. A pragmatic clinical trial should then be designed to compare the protocolized “best” practice care versus usual care in patients with intra-abdominal sepsis. Inclusion criteria should consist of patients with intra-abdominal sepsis who undergo exploratory laparotomy and develop AKI diagnosed either using the KDIGO definition or detected by a sensitive or predictive biomarker within 24 hours following surgery.

The primary outcome should be the proportion of patients alive and recovered from AKI within 7 days defined as return to < 150% of baseline serum creatinine without the need for renal replacement therapy. Secondary outcomes should include MAKE, either as the composite outcome of death, dialysis dependence or persistent renal dysfunction at hospital discharge at day 30 (MAKE30), or the individual components thereof. MAKE30 was proposed as an outcome since assessment of long-term outcomes might pose logistic issues related to patient follow-up post-discharge in China.

In a recently completed study of renal recovery in a large cohort of critically ill patients, nearly 64% of patients had early resolution of AKI within the first 7 days of hospitalization [42]. Of patients who recovered from early AKI, 27% of patients continued to recover in the second week, 22.5% of patients relapsed and then recovered subsequently, and 15% of patients had a relapse of AKI and never recovered. Of the 36.2% patients who did not recover early from AKI, 26.5% never ever recovered and 9.7% recovered late.

**Table 3** shows the hypothesized sample size calculation for absolute risk reductions (ARR) of 5% and 10% with protocolized care to enhance renal recovery. Using data from Kellum et al. [24], we varied the baseline renal recovery rate in the control arm between 50% and 70% for an ARR of 5% and 10%. We estimated that the sample size required per arm would vary between 2500 to 3120 patients for a 5% ARR and between 580 to 770 for a 10% ARR by the protocolized care.

**Topic 4: Biomarkers and the potential role in clinical trials of AKI**

Biomarkers may play a role throughout the patient encounter from risk stratification, to real time assessment of kidney function, and to the time AKI is established. Furthermore, molecular biomarkers have the ability to be used for monitoring the therapeutic intervention effects as well as recovery from renal injury or development of chronic kidney disease. The application of a particular biomarker within a clinical trial setting would reflect the characteristics of the biomarker tailored to the question being asked. Therefore, when biomarkers are integrated into the clinical trials, they can enrich for events or exclude patients who are too low risk or who already have AKI. In addition, biomarkers can even be used to help adjudicate endpoints [45]. This, in turn, may make the trials less costly and more feasible. This is best illustrated by considering an interventional trial in patients at high risk of AKI where an intervention is being put in place to either prevent progression of or enhance the chances of AKI recovery. **Figure 4** shows how employing biomarkers in different populations would impact the sample size needed. Within the PICO framework, biomarkers can address all four components.

*Patients*

A particularly promising area for the use of biomarkers in clinical trials is in patient selection. Trial enrichment through the application of biomarkers holds great promise not only in potentially differentiating causes of AKI, enabling the study of particular phenotypes but also by their impact on reducing necessary sample size. **Figure 5a** illustrates how biomarkers could be integrated into trial design. However, of potentially equal importance is the identification of patients who are biomarker positive but do not subsequently reach KDIGO criteria. Identifying patients with “subclinical” AKI is important, particularly in individuals with considerable renal reserve, as such patients are still at risk of long term sequelae following the insult.

*Intervention*

**Figure 5b** outlines biomarkers being integrated into an intervention arm of a trial. Following patient selection, patients may be randomized to an intervention or control arm involving a specific therapy. Examples of biomarker application to guide therapy include a biomarker-guided protocol for aggressive diuresis in patients with acute decompensated heart failure (markers of tubular injury may guide treatment), or when the nephrotoxicity of a new chemotherapeutic agent is being studied. In this design, biomarker-guided management would be compared with a control group who receives the same intervention without the guidance of biomarkers.

*Comparator*

This scheme is shown in **Figure 5c**. In this design, following an intervention, patients may be grouped according to the biomarker results. Under such conditions, the biomarker negative population may act as a control group.

*Outcome*

Clinical endpoints for studies in AKI have focused on changes in KDIGO classification or more clinically relevant endpoints such as MAKE. However, intervention studies using KDIGO are subject to shortcomings. For instance, if the outcome of interest includes stage 1 AKI (especially when AKI detected by urine output alone) due to its lack of specificity for worse long term outcomes, it may lead to findings of questionable clinical utility. Therefore, considering biomarkers for outcome adjudication, particularly in conjunction with currently defined outcomes based on serum creatinine and urine output, may allow more robust conclusions. Prognostic biomarkers, such as markers of fibrosis, may prove to be suitable for identifying trial endpoints if the intervention targets reductions in fibrosis and subsequent CKD progression after AKI. When biomarker negative patients are exposed to a high-risk procedure, becoming biomarker positive may be a clinically relevant endpoint (**Figure 5d)**.

**Conclusions**

The 19th International ADQI conference successfully reached consensus on a number of novel pragmatic trials to address gaps in knowledge for China and the world. The proposed trials were two-step designs. In the first step, prospective observational studies are conducted to better understand and document current practice. In some cases practice variation is embraced so as to find practices that are associated with best outcomes. In other cases, standardization is sought through checklists and related tools. In the second phase, prospective interventions (preferably randomized controlled studies) are proposed to evaluate the impact of each intervention in comparison with a control group.

We note that this is the first such attempt to establish consensus on a research roadmap for critical care nephrology in China. We hope that by explicitly defining a research agenda for pragmatic trials with detailed PICO-formatted design summaries we can enable future research in this important area of critical care.

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**Table 1.** Prospective observation study of RRT-practice data collection

|  |  |
| --- | --- |
| **Data** | **Description** |
| Overall occurrence of AKI | AKI rates as a denominator for RRT use |
| Clinical context | Describe population |
| Major prior comorbidities including CKD | Describe population |
| AKI stage at RRT commencement | Describe population |
| Primary indication for RRT | Describe RRT prescription |
| Duration of RRT treatment | Describe RRT practice |
| Initial modality, dose and anticoagulation | Describe RRT prescription |
| Vascular access site and type | Describe RRT practice |
| Time from decision to institution of RRT | RRT process outcomes |
| Solute, electrolyte acid base and fluid balance at 72h after initiating therapy | RRT process outcomes |
| For CRRT: |  |
| Filter lifespan in first 72h | RRT process outcomes |
| Time on therapy in first 72 h of  treatment | RRT process outcomes |
| Reason for filter loss | RRT process outcomes |
| Survival | Longer-term more patient-centered outcomes |
| Renal outcome (AKD status) at ICU and Hospital discharge | Longer-term more patient-centered outcomes |

**Table 2.** Prospective assessment of a QI intervention for prescription and delivery of CRRT

|  |  |
| --- | --- |
| **Aim of study** | To assess the impact of a QI intervention for prescription and delivery of CRRT in Chinese ICUs |
| **Design** | Step-wedge cluster-randomized controlled trial |
| **Population** | Adult patients undergoing CRRT for ‘conventional’ indications within participating ICUs |
| **Intervention** | CRRT quality checklist documenting Clinical and Technical aspects of prescription and delivery |
| **Comparator** | Patients treated in ICUs prior to implantation of checklist |
| **Outcomes** | Primary: Median filter lifespan in first 72h of CRRT    Secondary: Acute kidney disease status at hospital discharge    Process outcomes: Solute, electrolyte acid base and fluid balance at 72h  Health economics evaluation |

**Table 3.** Effect and Sample size Considerations for STAR trial

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | **Effect size** | **NNT** | **Control (%)** | **Intervention (%)** | **Sample size** |
| **Recovery** | 5% ARR | 20 | 50 | 55 | 3,120 |
| 5% ARR | 20 | 70 | 75 | 2,500 |
| 10% ARR | 10 | 50 | 60 | 770 |
| 10% ARR | 10 | 70 | 80 | 580 |
| **Mortality** | 2.2% ARR | 45 | 22.7 | 21.5 | 37,452 |

*STAR, STandardization of care for AKI Recovery;* *ARR, Absolute risk reduction; NNT, Number needed to treat*

**Figure Legends**

**Figure 1.** Potential elements of different systematic tools to improve management of oliguric AKI. Source: ADQI 19; [www.ADQI.org](http://www.ADQI.org), used with permission.



**Figure 2.** Proposal for clinical trial addressing aspects of AKI care. Source: ADQI 19; [www.ADQI.org](http://www.ADQI.org), used with permission.



**Figure 3.** Conceptual model for fluid resuscitation trial in the peri-AKI period.

A pragmatic fluid resuscitation trial can be designed for prevention of AKI in high-risk patients after exposure to risk factors in susceptible individuals. Such trial can also be designed to improve renal recovery after the development of AKI. Source: ADQI 19; [www.ADQI.org](http://www.ADQI.org), used with permission.



**Figure 4.** The effects of biomarker combination in different incident populations on potential sample size. Source: ADQI 19; [www.ADQI.org](http://www.ADQI.org), used with permission.



**Figure 5**. The roles of biomarkers in AKI trials within the PICO framework

(a):Patients; (b): Intervention; (c): Comparator; (d):Outcome. Source: ADQI 19; [www.ADQI.org](http://www.ADQI.org), used with permission.

