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Pragmatic Platform Trials to improve the outcome of patients with acute kidney injury

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Abstract

Purpose of review—There is an important need for improved diagnostic strategies and treatment among patients with acute kidney injury (AKI). Classical randomized clinical trials (RCTs) have generated relevant results in AKI but are associated with shortcomings, such as high costs, and sometimes lack generalizability.

In this minireview, we discuss the value and limit of pragmatic trials and platform trials for AKI research.

Recent findings—The implementation of pragmatic and platform trials in critical care settings has generated relevant clinical evidence impacting clinical practice. Pragmatic and platform designs have recently been applied to patients at risk of AKI and represent a crucial opportunity to advance our understanding of optimized treatment and strategies in patients at risk of AKI or presenting with AKI. Trials embedded in electronic health records (EHRs) can facilitate patient enrollment and data collection. Platform trials have allowed for a more efficient study design. Although both pragmatic and platform trials have several advantages, they also come with the challenges and shortcomings discussed in this review.

Summary

Pragmatic and platform trials can provide clinical answers in “real-life” settings, facilitate a significant sample size enrollment at a limited cost, and provide results that can have faster implementation in clinical practice.

Conflicts of interest

There are no conflicts of interest.

Keywords

pragmatic trials; platform trials; clinical trial design; master protocol; acute kidney injury

Introduction

Despite the high number of patients suffering from acute kidney injury (AKI) each year and the large evidence of an association with the risk of chronic kidney disease and cardiovascular morbidity and mortality, treatments and strategies for preventing or treating AKI remain extremely limited and mostly nonsupported by strong evidence [1]. One of the reasons is the burden and cost of investing in interventions and strategies. Planning, designing, and running a classic randomized clinical trial takes years, is very costly, and carries significant shortcomings, often including the lack of generalizability of the results. Their goal is indeed to test an intervention's efficacy in a specific population and setting [1,2]. There has been a recent growing interest in developing more efficient trials to provide more rapid answers to research questions, at most often lower cost (e.g., increase trial efficiency). The community effort during the COVID-19 pandemic has highlighted the value of pragmatic trials in addressing important questions in a short period, dramatically impacting clinical care and patient outcomes. In addition, in combination with a pragmatic design, the use of platform trials allows the testing of several interventions and improves efficiency in clinical research, decreasing the time and cost to complete trials. In this short review, we will address the advantages and limitations of pragmatic and platform trials and discuss how they could impact the clinical care of patients at risk of AKI or presenting with AKI [3*,4*, 5*,6,7].

Challenges of clinical trials in AKI

Traditional explanatory clinical trials are designed to determine the effect of an intervention under ideal conditions ("efficacy") but can be poorly suited to evaluate daily interventions in AKI patients who would require a very large sample size to identify small but still clinically relevant effects (and would therefore be extremely costly and long to complete). In this line, many clinical trials never achieve the planned sample size and are terminated early due to a lack of recruitment [8–10]. Furthermore, restrictive inclusion and exclusion criteria in explanatory trials narrow the patient population and may result in missed opportunities to test the intervention in a broader population in which the intervention may be applied in clinical practice. Difficulties in securing funding and recruiting patients also limit the number of interventions that could be tested with traditional RCTs. Studies investigating the prevention of contrast-associated (CI) AKI are an example of these limitations [8]. While the PRESERVE trial was stopped early because of futility, other trials, such as the AMACING trial, presented inconclusive results due to significant underenrollment [9,10]. The PROMISS trial and the PRATO-ACS trial had reduced statistical power in some key subgroups [11,12]. The PROMISS trial included patients with a baseline serum creatinine (SCr) >1.1 mg/dL, and only 5.2% of patients had a clearance of creatinine (ClCr) < 30 ml/min (which may represent the population at higher risk). Although the results were positive in favoring statin use to prevent CI-AKI in patients with normal or mildly impaired

renal function, they were considered to be underpowered for patients with severely impaired renal function at baseline (ClCr < 30 ml/min) [11]. The PRATO-ACS trial showed an overall protective effect of statins in preventing CI-AKI (95% CI: 0.22 to 0.72; p= 0.003), even though the small sample size also limited the statistical power in patients with ClCr < 30 ml/min (3% of enrolled patients) or a high CI-AKI risk score (24% of enrolled patients) [12]. Pragmatic trials may at least partially overcome some of the limitations of traditional trials, especially facilitating patient enrollment, permitting patient stratification, and generating powerful results rather than indeterminate findings.

Pragmatic trials

Pragmatic trials attempt to evaluate how a studied intervention would perform when introduced into clinical practice (“effectiveness”) to produce results that are representative and generalizable [13*,14]. In addition to increasing the generalizability of clinical trials, these pragmatic design features can dramatically increase trial efficiency, allowing the enrollment of sufficiently large sample sizes to detect small but still clinically meaningful effect sizes and permit rapid dissemination of trial results to the community. Attractive examples of pragmatic trial design elements include limited exclusion criteria, absence of placebo, no blinding of the intervention, and collection of a limited amount of data [15]. The necessary elements of the positive aspects of pragmatic trials are to enroll representative populations, deliver the intervention as usual care would be conducted, and enroll sufficient patients to show differences in outcomes. Pragmatic trials can assess not only drugs but also processes of care with broader implementation into practice. Historically, concerns have been raised that pragmatic trials with broadening eligibility will result in clinical research predestined to fail by enrolling a highly heterogeneous population with highly variable responses to treatments and interventions. However, designing a pragmatic trial does not exclude focusing on a specific population or conditions (e.g., AKI associated with distributive shock or sepsis) and enrolling a sufficiently large sample size allow a better understanding of clinical response to interventions in subgroups (heterogeneity in treatment effect). Of note, a continuum exists between pragmatic and explanatory controlled trials, and trials may have a mix of pragmatic and explanatory design elements. Successful examples of pragmatic trials in AKI include SMART and PLUS trials [16*,17]. SMART was a pragmatic, unblinded, cluster-randomized, multiple crossover trial designed to evaluate the effect of balanced crystalloids vs. saline for intravenous fluid administration among critically ill patients admitted to intensive care units (ICUs). This study enrolled over 15,000 patients [3*,16*]. A lower incidence of major adverse kidney events at 30 days (MAKE30) was observed in the group receiving balanced crystalloids versus saline. The subgroup analysis of patients with sepsis diagnosis revealed mortality of 25,2% in the balanced crystalloid group vs. 29,4% in the saline group (adjusted odds ratio were 0,80; 95% CI, 0.67 to 0.97; p=0.02)[16*]. The PLUS study was a double-blinded, parallel-group, randomized, controlled trial designed to test the effect of fluid resuscitation and therapy using balanced multielectrolyte solution (BMS) or saline on 90-day mortality. The enrollment number in the PLUS trial was impacted by the pandemic, resulting in less than one-third of the sample size of the SMART trial (approximately 5,000 patients), even though it could achieve 90% power to detect an absolute difference of 3.8% point in 90-day all-cause mortality from

an estimated baseline mortality of 23% [17]. The PLUS study did not show a difference in mortality between the groups or even in subsequent subgroup analysis. Both trials present similar pragmatic elements: large sample size; research conducted in routine care where the treating clinicians decided the amount and rate of fluid administration (based on personal evaluation and clinical practice); and limited data collection through an EHR. The SMART trial also included a preprogrammed randomization. The randomization was programmed to monthly assign either balanced crystalloids or saline to each ICU to facilitate the research (the solution assignment followed a plan according to each ICU and month of the year) and involved the use of an electronic order-entry system and advisor to inform and guide providers to assign the randomized crystalloid, facilitating patient enrollment. By aligning pragmatic elements, the PLUS trial incorporated characteristics of classical RCTs, such as blinding the type of solution used to the patients, the patient's legally authorized representatives, the researchers, and the treating clinicians. Both studies demonstrated the possibility of conducting a pragmatic study including a heterogeneous population of critically ill patients and generating significant findings [18].

Platform trials

What is a platform trial?

The core of platform design remains on the adaptiveness of a unique research plan capable of englobing multiple interventional groups while focusing on studying a chosen disease or condition [19**,20**]. It works as if multiple trials using a shared main research plan, screening process, study governance, and outcomes were started concomitantly and/or subsequently.

Platform trials, in general, facilitate research processes but can eventually result in a more complex design. Although some research components (such as planning for scheduled visits, clinical examination components, measurement procedures, and outcome definitions) are shared, it is possible to add specificities to each intervention [19**,20**].

Pairing control and intervention groups is a cyclic event in platform trials, determined by trial results. The process of terminating or promoting an arm intervention is driven by decision rules. The decision rules are a relevant component of platform trial design and must be planned to minimize the risk of bias [19**]. These decision rules need testing throughout simulations during the planning phase and are determined before starting patient enrollment. A specific intervention appendix can be included to adjust the protocol to a specific intervention, but the main instructions are predetermined in the master protocol. The platform trials included periodic evaluations of the interventional group's results during the research process. These re-evaluations generate enough data that can be instantaneously released and implemented in clinical practice when access and dissemination of results are effective and have widespread reach [19**, 20**,21,22].

Changes in protocol and control group can also happen during new randomization momentums as this design allows adaptiveness during the process based on results and lessons learned while the trial is running [23**]. This implies constant data analysis [3*,5*,19**, 20**,21]. If an intervention is proven to be beneficial, it can be considered

as the new standard of care for subsequent groups. The possibility of promptly implementing a standard of care based on “real-life” results could change how we understand AKI subphenotypes and treatment responses [24,25]. Platform trial data analysis mostly uses Bayesian statistical methods. The Bayesian method uses the probability of data and probabilities of hypothesis. This approach can limit the sample size and/or increase statistical power [26].

An overview of the main characteristics and limitations of Platform trials compared to Classic RCTs is presented in Figure 1.

Successful examples of platform trials

Before COVID-19, platform trials were mostly applied to oncologic treatment investigations [22]. The COVID-19 pandemic increased the visibility and usage of platform trials among critically ill patients. The RECOVERY, I-SPY COVID, and REMAP-CAP trials demonstrated the feasibility of platform trial design in acute care settings [4**,5**,6,7]. The RECOVERY trial’s success is attributed to the high rate of patient recruitment, allowing a very large sample size and multiple treatment arms [27*]. I-SPY COVID is a project derived from I-SPY 2, an oncologic platform trial protocol with a particular model. I-SPY COVID could expand the initial model and connections, establishing relevant cooperation among researchers, statisticians, patient advocates, regulatory agencies, and companies to enable an adaptive Bayesian trial design within the complexities of a platform trial [5*,21]. The REMA-CAP trial - launched before COVID-19 - identifies potential patients for recruitment based on clinical records and uses electronic predetermination sets to facilitate monitoring and data collection and EHR to streamline trial procedures and data storage [6].

These trials answered relevant questions in acute illness due to COVID-19 infection using different formats. RECOVERY and REMA-CAP evaluated repurposed therapies previously tested in other settings (e.g., aspirin, steroids, hydroxychloroquine, interleukin 6 inhibitors). REMA-CAP also included an interventional analysis of protocolized mechanical ventilation strategies. On the other hand, the I-SPY trial focused on newly developed therapies.

Challenges with Platform trials

Platform trials require quality assurance in the research process. This includes having a solid plan for sample size calculation and adjustments, sufficient funding to complete the research, data collection management, and monitoring analysis strategies.

Sample Size—The sample size in platform trials is defined by singular aspects of the trial design. A shared control group favors an overall reduction in sample size and recruitment time. The shared control group and respective interventional groups assigned to the same period of investigation will, in the end, share the same time of randomization in the process. Nevertheless, as platform trials are submitted mainly to a Bayesian statistical method, it is necessary to have a sufficient number of patient enrollments for each interventional arm to produce data with significant results [22,26]. Platform trials are expected to undergo modification in the initial sample size calculation and funding plan over time. The adaptiveness of platform trials includes the possible adjustments in the sample size

according to partial trial results. The partial results can promote reallocation of efforts in a determined treatment arm and exclusion of arms with negative results. This strategy can lead to early stop enrollment in treatments with no beneficial findings and increase the enrollment to arms with more chances to deliver a significant result. A modification in sample size between the arms is expected and should therefore be anticipated and discussed with the researcher's sponsors and other stakeholders [19**].

Funding sources and budget allocation—The funding institutions in a platform trial can be from the public sector, private sector, or a collaboration of both. Independent of the funding agencies supporting a platform trial, the specificities within such trials require the sponsor's participation in the entire process of the project construction, from the initial planning to every stage of monitoring and data release. Platform trials are research designed to last years, and estimating costs can be difficult. Funding agencies supporting such projects are scarce. Investigators should guarantee sufficient information for the sponsors to understand the specificity of the trial design and the financial support requirements for the entire project. The sponsor's perceptions, beliefs, and expectations need to be discussed, emphasizing the possibility of multiple modifications in the costs, timeline, and data analysis over time [20**,21]. Brown et al. discussed the adaptations in budget decisions necessary for a ten-year platform trial, the FOCUS4 trial [23**]. The authors emphasize the complexity of data analysis of platform trials and the importance of allocating enough resources to data managers, database programmers, and statisticians, for example. As budget adjustments may be needed, these expected adaptations should be addressed from the planning phase. Allocating funds over time and adapting the budget extension can occur during a platform trial and should result from a responsible decision involving all the stakeholders included in the research.

As part of responsible resource allocation, choosing ideal research sites for the trial is key. It is preferable to have a few research sites with a crescent enrollment number rather than multiple sites enrolling a few patients. Each research site will demand training and periodic retraining, consuming time and resources. The researchers must be able to sustain working with multiple site PIs, knowing that the complexity of a platform trial can generate more specific demands for an extended period. The PIs' enthusiasm in recruiting patients should also be addressed regularly. Increasing the number of sites will increase the workload of the researchers and can impact the research development [23**].

Data collection and changes in practice over time—Data collection determination is part of the platform trial planning phase. Defining the variables of research interest will shape the database components shared by the control and interventional groups. It is relevant to recognize the variability of data generated from multiple interventional arms initiated at different periods of the research project to the data generated by arms initiated simultaneously. This variability occurs due to possible modifications of the initial control group as a consequence of partial data analysis or changes in practice over time. The data collected before a change in practice will impact the control group and may lead to bias and imbalance between groups when those changes are not recognized [20**].

Data monitoring—Monitoring a platform trial requires the comprehension and ability to analyze the trial performance of each interventional arm, evaluate the research safety, and provide partial results. Data monitoring needs to be more dynamic than traditional RCTs and can include multiple arms analysis at the same time frame to allow prompt adaptiveness to the trial. This task can be conducted by a monitoring committee. This committee can include the data and safety monitoring board and the committee for statistical analysis [21]. Establishing an efficient monitoring committee is essential. This committee should participate in the early phases of the research to define the rules that will guide the platform trial (e.g., definitions for when to stop an interventional arm), recognizing what results should be released to the investigators over time and those that should not be shared as partial results. A responsible decision in partial data release should result in avoiding the bias that could affect subsequent data analysis and/or the decision on allocation of the next group.

The success of platform trial design relies on extensive planning and addressing noteworthy aspects for the stakeholders involved in the research process, and this is probably the major challenge when implementing research following this specific design. Despite the difficulties that investigators and other stakeholders of this process may need to overcome, there are recent research studies involving critically ill patients that have succeeded when allaying pragmatic and platform design components. These successful platform trials in critical care studies can guide the specific construction of research in AKI, reducing underenrollment and making possible subgroup analysis and consistent results.

Pragmatic Platform trial in AKI: a framework proposal

We see significant value and opportunity for a pragmatic trial in patients with AKI. While the opportunity for investigating new drugs is thus far limited, repurposing drugs (e.g., anti-inflammatory drugs) and investigating their impact on recovery or incidence of AKI in critically ill patients certainly hold promise. Alternatively, investigating already existing treatment (i.e., fluids, vasopressors, diuretics, strategies of renal replacement therapy, etc.) in a phase 4 pragmatic platform trial would provide evidence on the best strategies to improve outcomes among critically ill patients with AKI.

EHR should ideally be used to streamline this process and help the intensivist recognize when the patient can be a candidate for randomization. Establishing the known contributing factors of AKI in the ICU setting as a filter to include patients would increase vigilance and potentially increase recruitment. For example, we could establish the clinical criteria that could lead to AKI potential candidates (e.g., septic patients on vasopressors) to initiate the search for patients who could be included in the trial. The main data collection should include information routinely collected in the ICU, such as kidney function, urine output, use of nephrotoxic medications, vasopressor doses, and fluid balance information. The main outcomes should follow simple definitions, such as kidney dysfunction markers, progression to hemodialysis, MAKE30, and patient-centered outcomes, such as renal recovery, mortality, or hospital-free days (Figure 2).

Conclusion

Platform trials can allow a continuum evaluation of new therapies and strategies that may impact patient outcomes, therefore increasing efficiency and shortening the time to deliver results. Platform trial design implementation offers a unique opportunity to rapidly advance our understanding of the best preventive and therapeutic strategies among patients at risk of AKI or suffering from AKI and ultimately improve patient outcomes.

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Key points

- Pragmatic trials permit intervention data collection in a “real world” scenario
- Both pragmatic and platform trials require exhaustive protocol planning
- The inclusion of the different stakeholders in the process improves the design and implementation of the research.
- Platform trials in AKI may improve patient enrollment and generate rapidly generalizable results.

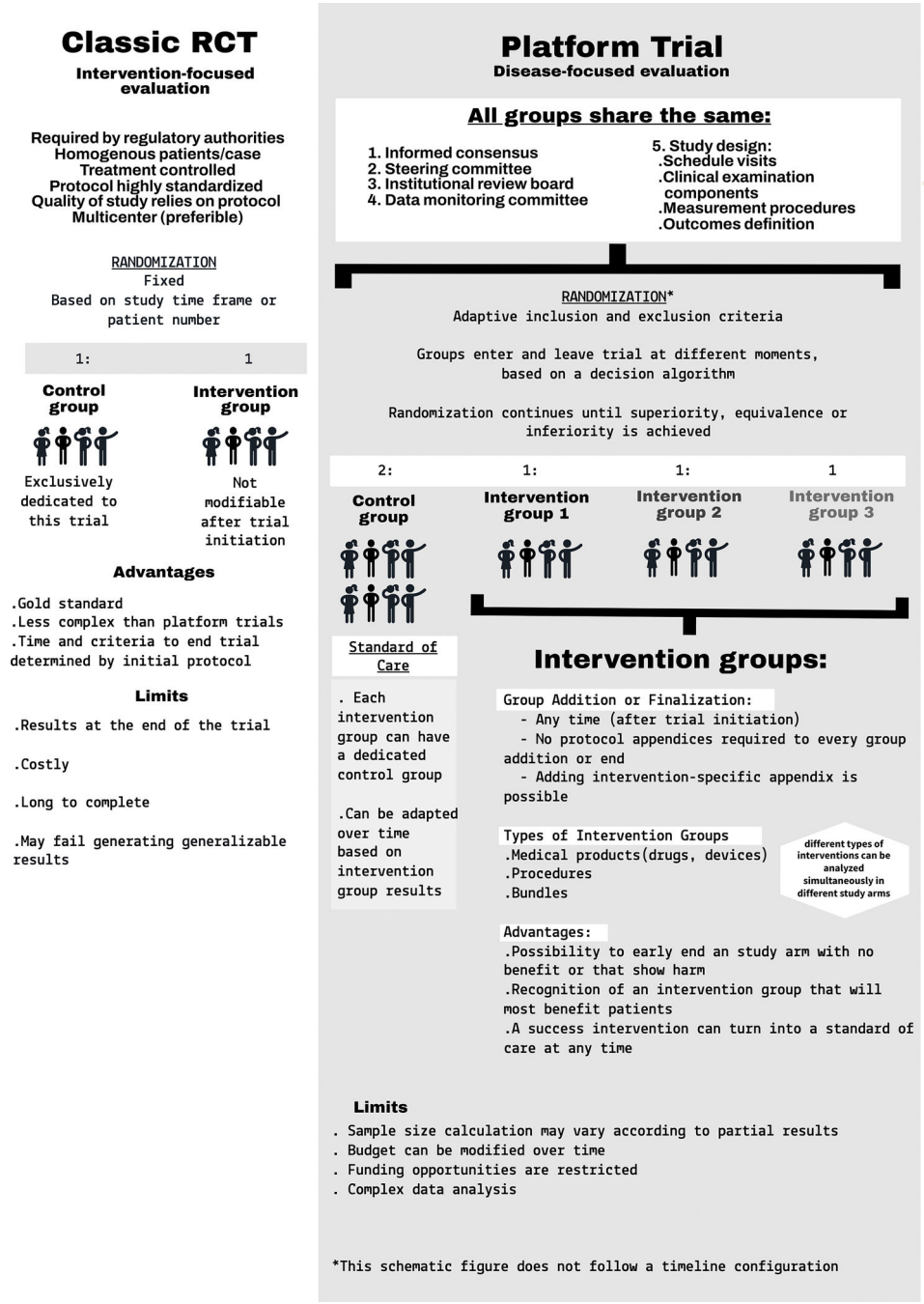
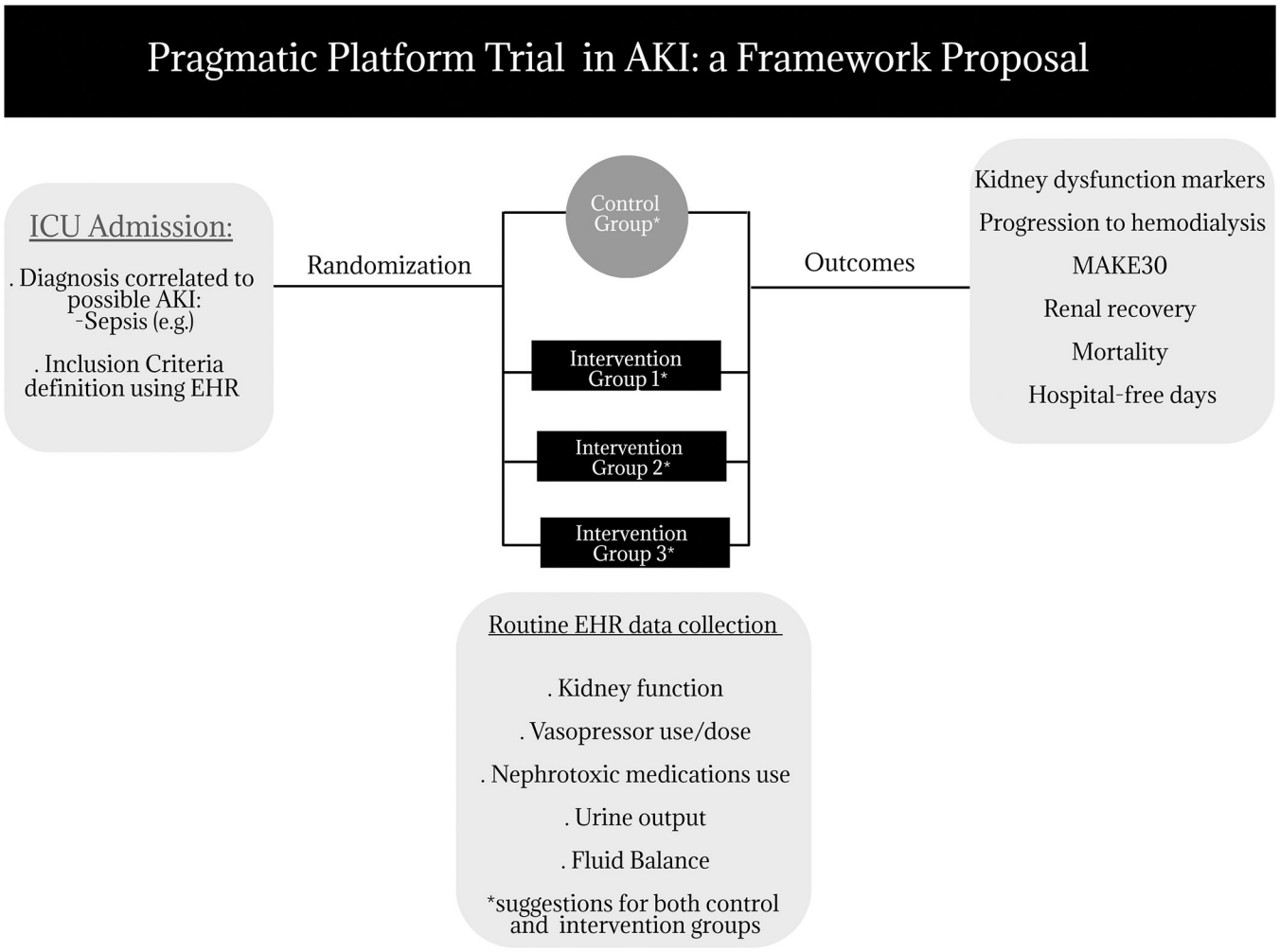


Figure 1.
Platform trial and classic RCTs' main characteristics and limitations



AKI: Acute Kidney Injury; EHR: Electronic Health Records; ICU: Intensive Care Unit; MAKE30: Major adverse kidney events by 30 days.

Figure 2.
Pragmatic Platform Trial: a framework proposal