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**RE: Recent publication of AKIKI (NEJM) and ELAIN (JAMA) trials focused on timing of initiation of renal replacement therapy in critically ill patients with acute kidney injury**

Dear STARRT-AKI Investigators and Coordinators:

As you may be aware, two high profile randomized trials both focused on timing strategies for initiation of renal replacement therapy (RRT) in critically ill patients with acute kidney injury (AKI) have recently been reported.

The **Artificial Kidney Initiation in Kidney Injury (AKIKI)** trial was published on May 15<sup>th</sup>, 2016 in the *New England Journal of Medicine* (<https://www.ncbi.nlm.nih.gov/pubmed/27181456>). This was a French multicentre (31 sites) randomized trial of 620 critically ill adults allocated to two strategies of initiation of RRT: i) **EARLY** – defined by initiation of RRT within 6 hours of fulfillment of KDIGO stage 3 AKI or ii) **DELAYED** – defined by initiation of RRT following development of a complication related to AKI (e.g., hyperkalemia; metabolic acidosis; pulmonary edema; uremia; and oliguria >72 hours). Other eligibility criteria included AKI consistent with acute tubular necrosis and the receipt of mechanical ventilation and/or vasoactive support.

The main finding in AKIKI was that the allocated RRT strategy did not show a difference in the primary endpoint of 60-day mortality (48.5% in EARLY vs. 49.7% in DELAYED,  $p=0.79$ ); however, among those allocated to the DELAYED strategy, 49% did not receive RRT.

The **Early Versus Late Initiation of Renal Replacement Therapy In Critically Ill Patients With Acute Kidney Injury (ELAIN)** trial was published on May 22, 2016 in *JAMA* (<https://www.ncbi.nlm.nih.gov/pubmed/27209269>). This was a single-centre randomized trial of 231 critically ill adults who were allocated to two strategies of RRT initiation, with stratification by SOFA score and the presence of oliguria: i) **EARLY**– defined by starting RRT within 8 hours of diagnosis of KDIGO stage 2 AKI or ii) **DELAYED**– defined as starting RRT within 12 hours of diagnosis of KDIGO stage 3 AKI or development of an absolute indication for RRT (e.g., uremia, hyperkalemia, hypermagnesemia, oligo-anuria or organ edema resistant to diuretics). To be eligible, participants had to have KDIGO stage 2 AKI, a plasma NGAL > 150 ng/mL, and one of: sepsis, vasoactive support, refractory fluid overload, or worsened SOFA score.

The main finding in ELAIN was that allocation to the EARLY RRT strategy resulted in a 15.4% absolute decrease in the primary endpoint of 90-day mortality (39.3% vs. 53.6%; HR 0.66, 95% CI, 0.45-0.97). In total, 90.7% of those allocated to the DELAYED strategy received RRT. The EARLY strategy was also shown to improve kidney recovery by day 90 (53.6% vs. 38.7%), reduce duration of RRT (by ~ 18 days), and reduce duration of hospitalization (by ~ 37 days).

We salute the AKIKI and ELAIN investigators for successfully completing their respective trials. These two studies represent important contributions to the field of critical care nephrology by addressing a fundamental area of uncertainty in clinical practice. Moreover, we are grateful that these trials, and their publication in high-profile journals, have stimulated robust discussions on the issue of optimal timing of RRT initiation in AKI.

However, there are some important considerations we believe should be emphasized when interpreting these two conflicting trials:

- In both AKIKI and ELAIN, the criteria for trial eligibility were largely based on achieving different thresholds for increases in serum creatinine and/or degrees of oliguria, consistent with the KDIGO staging classification for AKI. Moreover, in the DELAYED arm of ELAIN, achieving KDIGO Stage 3 AKI was the primary trigger for RRT initiation in 85% of instances. While increases in the serum creatinine concentration and/or the extent of oliguria are widely used by clinicians to ascertain the severity of AKI and contribute to the decision-making around initiation of RRT, clinicians always integrate their perception of the larger clinical picture when considering the initiation of RRT. We have thus opted to take a slightly different approach in STARRT-AKI. Specifically, attending clinician(s) is/are given the option to “veto” a patient’s entry into the trial, temporarily or definitively, if he/she does not believe that equipoise exists regarding the timing of RRT initiation for that patient at that time. Our intent is that the design of STARRT-AKI has fostered a situation where recruited patients constitute a population for whom the decision to start RRT or not is an actual clinical dilemma. This is meant to ensure that each STARRT-AKI participant is a patient for whom RRT is *likely* to be needed but the timing of such initiation is unclear. The effectiveness of this strategy is supported by our pilot data.
- Both AKIKI and ELAIN were likely under-powered for the detection of realistic survival differences that might be conferred by optimizing the timing of RRT initiation. The sample size in AKIKI was based on the hypothesis that the DELAYED strategy would confer a 15% *reduction* in mortality as compared to EARLY RRT. Though it is plausible that DELAYED RRT might be safer, a 15% survival benefit of any RRT strategy is not conceivable. ELAIN studied only 231 patients in a single ICU (~80% surgical; ~50% cardiac surgical) and demonstrated a much larger treatment effect (absolute difference in mortality 15.4% favoring an EARLY strategy) than what many clinicians might consider plausible for the experimental intervention. Importantly, ELAIN has a very low Fragility Index of 3, whereby adding 3 more deaths to the EARLY group or 3 fewer deaths to the DELAYED group would render the trial null [by Fishers Exact]. (See: <https://www.ncbi.nlm.nih.gov/pubmed/26963326>).
- In ELAIN, a kidney damage biomarker was used to exclude “low-risk” patients. A plasma NGAL > 150 ng/mL was selected based on extrapolation of existing operative characteristics in the literature. Of note, this threshold only resulted in the exclusion of 3 of 604 patients screened. In our STARRT-AKI pilot trial, we utilized plasma NGAL as a discriminator of risk and a marker of severe AKI but selected a threshold of >400 ng/mL. The participants we enrolled had a median plasma NGAL above the upper limit of the assay threshold (>1300 ng/mL). We omitted the inclusion of an NGAL threshold from the principal trial because we found that it had limited value.

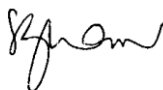
While we believe that AKIKI and ELAIN were well conceived and rigorously conducted, release of their findings may have generated greater controversy as a result of the trials' dichotomous findings and inherent limitations. As pointed out by Drs. Chertow and Winkelmayr in the concluding statement of their editorial on the ELAIN trial: *"In view of the provocative findings...it is the responsibility of the nephrology and critical care communities to confirm or refute these findings across multiple sites in a much larger, diverse population."*

STARRT-AKI is poised to provide the definitive evidence to inform this issue. Rather than making STARRT-AKI redundant, as some might suggest, the reporting of the AKIKI and ELAIN trials have highlighted the urgent need to complete STARRT-AKI.

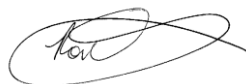
The AKIKI and ELAIN trials have now been carefully reviewed by our DSMB, chaired by Professor Kathy Rowan (ICNARC). We are pleased that the Board has unanimously and unequivocally supported our position on the need for continuation of the STARRT-AKI trial.

If you have further comments or queries, please contact us at your convenience. We thank you again for your continued support of the STARRT-AKI program.

Sincerely,



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**Table:** Summary of RCT design differences between ELAIN, AKIKI and STARRT-AKI.

Feature	ELAIN	AKIKI	STARRT-AKI
<b>Country</b>	<b>Germany</b>	<b>France</b>	<b>Multiple</b>
<b>No. of Sites</b>	1	31	>60
<b>Participants</b>	231	620	2,866*
<b>Sample size calculation (ARR)</b>	18%	15%	6%
<b>Clinical Equipoise Confirmed</b>	No	No	Yes
<b>Intervention Strategies:</b>			
<b>EARLY</b>	KDIGO stage 2	KDIGO stage 3	KDIGO stage 2
<b>DELAYED (Conservative)</b>	KDIGO stage 3	Specific criteria	Specific criteria
<b>Primary Endpoint</b>	90-day mortality	60-day mortality	90-day mortality

Abbreviations: ARR = absolute risk reduction (in primary endpoint)

\*target enrollment