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November 5, 2018

RE: Recent publication of French multi-center IDEAL-ICU trial (NEJM) focused on timing of initiation of renal replacement therapy in critically ill patients with sepsis and acute kidney injury.

Dear STARRT-AKI Investigators and Coordinators:

As you may be aware, the **Initiation of Dialysis Early versus Delayed in the Intensive Care Unit (IDEAL-ICU)** trial was published on October 10, 2018 in the *New England Journal of Medicine* (https://www.nejm.org/doi/full/10.1056/NEJMoa1803213). This was a French multi-center (29 sites) randomized controlled trial of 488 critically ill adults with sepsis and AKI allocated to two strategies of RRT initiation: i) EARLY – defined by initiation of RRT within 12 hours of fulfillment of the RIFLE AKI category of FAILURE or ii) DELAYED – defined by initiation of RRT triggered by clinical urgency or after a 48 hour protocolized period of observation in the absence of renal recovery.

The main finding in IDEAL-ICU was that the allocated RRT strategy did not show a difference in the primary endpoint of 90-day mortality (58% in EARLY vs. 54% in DELAYED, p=0.38). In the DELAYED strategy group, 38% did not receive renal replacement while 17% fulfilled "emergent" indications for RRT initiation. The IDEAL-ICU was terminated prematurely for futility after achieving approximately 56% of targeted enrollment.

We have extended our congratulations to the IDEAL-ICU investigative team, some of whom have also participated in STARRT-AKI, for completing and publishing their trial. IDEAL-ICU is an important contribution by improving our understanding of this issue and will no doubt stimulate discussion. However, we would like to provide context and emphasize why the STARRT-AKI trial should continue as planned to completion:

- STARRT-AKI will be the only international trial to address the issue of timing of RRT initiation among critically ill patients with AKI. As such, it will have greater generalizability than trials that have been completed to date, including single-country AKIKI (France) and ELAIN (Germany) trials that were published in 2016. We appreciate the support of the IDEAL-AKI, AKIKI and ELAIN

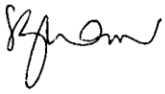
investigators, many of whom have participated or are presently participating in the STARRT-AKI trial.

- STARRT-AKI will be the largest trial to date - larger than all preceding trials combined - on the topic of RRT initiation in AKI. The sample size estimation for STARRT-AKI assumed a control group event rate for 90-day mortality of 40% with power to detect a 6% absolute reduction in the accelerated arm. We believe this is a clinically meaningful and realistic reduction in mortality and as such, will provide greater confidence in effect estimates than prior trials.
- STARRT-AKI is the only trial to integrate clinician judgement (i.e., mandating that treating intensive care and nephrology clinician's declare equipoise) prior to confirming full eligibility for the trial. In contrast to prior trials, we believe this pragmatic design will ensure that only patients for whom the clinical dilemma of "if to start and when to start" will be enrolled. As such, STARRT-AKI aims to enroll patients with a high likelihood of receiving RRT while excluding patients in whom early kidney recovery appears imminent.
- STARRT-AKI does not mandate patients allocated to the standard (i.e., delayed) strategy be started on RRT under any circumstance, even when confronted with "persistent AKI". Again, we believe this pragmatic approach aligns with the bedside dilemma confronted by clinicians.

The IDEAL-ICU trial has now been carefully reviewed by Steering Committee and our Data Safety Monitoring Board, chaired by Professor Kathy Rowan (ICNARC). We are pleased that the Steering Committee and Board have unanimously and unequivocally supported our position on the need to finish the STARRT-AKI trial as planned.

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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