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ARISE FLUIDS comment on the CLOVERS trial

Early Restrictive or Liberal Fluid Management for Sepsis-induced Hypotension. NHLBI PETAL Network. N Engl J Med 2023, Jan 21.

The ARISE FLUIDS management committee congratulate the CLOVERS team on the publication of their trial.

CLOVERS randomised 1554 patients presenting to the ED with suspected sepsis and hypotension to either a liberal or restricted IV fluid resuscitation strategy. Participants in the restricted group received significantly less fluid over 24 h (-2134 ml, 95% CI -2318 to -1949 ml) and had earlier commencement of vasopressors (-1.4 h, 95% CI -2.0 to 0.8 h). There was no difference in the primary outcome of in-hospital mortality at 90 days and no difference in any of the secondary outcomes, including safety events.

CLOVERS provides important evidence to inform management of patients meeting the trial's inclusion criteria. There are however some important differences between CLOVERS and the ARISE FLUIDS trial.

Trial differences include:

	ARISE FLUIDS	CLOVERS
Inclusion criteria	SBP < 90 mm Hg and Lactate > 2.0 mmol/L	SBP < 100 mm Hg
Pre-randomisation fluid	Up to 2 L	Up to 3 L
Time to enrolment	Within 6 h of presentation	Within 24 h of presentation
Interventions	Fluids or vasopressors according to study protocol guided by *usual bedside clinician assessment*	Fluids or vasopressors according to study protocol guided by *study-specific, pre-specified haemodynamic parameters*
Target MAP	Determined by clinician	≥ 65 mm Hg
Primary outcome	Days alive out of hospital at 90 days	Hospital mortality within 90 days

In summary, ARISE FLUIDS aims to recruit patients with septic shock compared to the broader population with sepsis and hypotension in CLOVERS. Additionally, it is important to note that the CLOVERS trial was stopped early with recruitment of approximately 2/3rds of planned sample size.

ARISE FLUIDS uses a composite outcome measure of days alive out of hospital in part because the anticipated mortality rate, based on our observational data, is such that it would be unfeasible to undertake a trial of sufficient size to have power to detect differences in this as a primary outcome measure. We note that in CLOVERS the pre-specified secondary outcome of days alive out of hospital at day 28 there was a difference of 0.8 days (95% CI -0.3 to 1.9 days) in favour of the restricted fluid regimen, although as the CLOVERS trial stopped early it is underpowered.

A planned individual patient data meta-analysis of ARISE FLUIDS, CLOVERS, CLASSIC and the UK-based EVIS trials aims to address important remaining questions regarding the initial haemodynamic management of patients with septic shock including important subgroups.

Due to the differing patient populations, early compared to later recruitment, protocolisation of the intervention in CLOVERS and other differences listed above, the generalisability of the CLOVERS results to the Australian and New Zealand population is limited. It remains important that we continue to recruit patients into ARISE -FLUIDS to address this important question for our patients.

We thank all our site staff who have shown their dedication to ARISE FLUIDS and through their efforts will make this trial a success.

Chief Investigators Professor Sandra Peake and Clinical Associate Professor Stephen Macdonald