PLUS Study Protocol Synopsis

Plasma-Lyte148® versUs Saline

Title	A multi-centre, blinded, randomised, controlled trial (RCT) to determine whether fluid resuscitation and therapy with a "balanced" crystalloid solution (Plasma-Lyte 148®) decreases 90-day mortality in critically ill patients requiring fluid resuscitation when compared to the same treatment with 0.9% sodium chloride (saline)
Short Title	**P**lasma-**L**yte 148® vers**U**s **S**aline **(PLUS)** Study
Design	Prospective, multi-centre, parallel group, concealed, blinded, randomised, controlled trial
Outcomes	Primary Death from all causes within 90 days after randomisation Secondary • Mean and peak serum creatinine concentration during the first seven days • Maximum post-randomisation increase in serum creatinine in ICU during the index hospital admission • Proportion of patients newly treated with renal replacement therapy up to 90 days after randomisation • Proportion of patients treated with and duration of treatment with vasoactive drugs • Duration of Mechanical Ventilation in ICU • Length of stay and all-cause mortality at ICU discharge • Length of stay and all-cause mortality at 28 days • Length of stay and all-cause mortality at hospital discharge • Quality of life assessed at six months after randomisation • Health services use during the six months after randomisation • Subgroup analyses: Outcomes will also be examined in four subgroups defined by the following baseline characteristics; patients with or without kidney injury (defined by threshold creatinine concentration), with or without sepsis (defined using 2016 SOFA-based criteria), admitted to the ICU directly after surgery or not, low versus high severity of illness (defined by APACHE II score <25 or ≥25)
Intervention	Plasma-Lyte 148® or 0.9% saline for all resuscitation episodes and compatible crystalloid therapy whilst in ICU, from the first episode of fluid resuscitation (randomisation) for up to 90 days
Sample Size	8,800 patients
Eligibility Criteria	Inclusion Criteria • The patient will receive fluid resuscitation defined as at least 500mls or at least 5ml/kg for patients weighing <100kg, administered over one hour or less to increase or maintain intravascular volume that is in addition to maintenance fluids, or specific fluids used to replace non-physiological fluid losses • The patient is expected to remain in the ICU beyond the calendar day following the day of enrolment • The patient is not expected to be well enough to be eating on the day following enrolment • An arterial or central venous catheter is in situ, or placement is imminent as part of routine management • Both Plasma-Lyte 148® and 0.9% saline are considered equally appropriate for the patient • The requirement for fluid resuscitation is supported by at least one of seven pre-specified clinical signs: heart rate > 90 beats per minute; systolic blood pressure < 100 mmHg or mean arterial pressure < 75 mmHg; central venous pressure < 10 mmHg; pulmonary artery wedge pressure < 12 mmHg; capillary refill time > 1 second; OR urine output < 0.5 ml/kg for at least one hour Exclusion criteria • Age less than 18 years • Patients who have previously received fluid resuscitation (as defined above) prescribed in the ICU during this current ICU admission • Patients transferred directly from another ICU who have received fluid resuscitation (as defined above) during that ICU admission • Contraindication to either study fluid e.g. previous allergic reaction to Plasma-Lyte 148® • Patients admitted to the ICU with specific fluid requirements: the treatment of burns; following liver transplantation surgery; for correction of specific electrolyte abnormalities • Patients with traumatic brain injury or those considered at risk of developing cerebral oedema • Patients in whom death is deemed imminent and inevitable • Patients with an underlying disease process with a life expectancy of <90 days • Patients in whom it is unlikely the primary outcome can be ascertained • Patients who have previously been enrolled in PLUS