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REstrictive versus StandarD FlUid Management in Mechanically Ventilated ChildrEn Admitted to PICU: study protocol for a pilot randomised controlled trial (REDUCE-1)

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ABSTRACT

Introduction Intravenous fluid therapy is the most common intervention in critically ill children. There is an increasing body of evidence questioning the safety of high-volume intravenous fluid administration in these patients. To date, the optimal fluid management strategy remains unclear. We aimed to test the feasibility of a pragmatic randomised controlled trial comparing a restrictive with a standard (liberal) fluid management strategy in critically ill children.

Methods and analysis Multicentre, binational pilot, randomised, controlled, open-label, pragmatic trial. Patients <18 years admitted to paediatric intensive care unit and mechanically ventilated at the time of screening are eligible. Patients with tumour lysis syndrome, diabetic ketoacidosis or postorgan transplant are excluded. Interventions: 1:1 random assignment of 154 individual patients into two groups—restrictive versus standard, liberal, fluid strategy—stratified by primary diagnosis (cardiac/non-cardiac). The intervention consists of a restrictive fluid bundle, including lower maintenance fluid allowance, limiting fluid boluses, reducing volumes of drug delivery and initiating diuretics or peritoneal dialysis earlier. The intervention is applied for 48 hours postrandomisation or until discharge (whichever is earlier). Endpoints: The number of patients recruited per month and proportion of recruited to eligible patients are feasibility endpoints. New-onset acute kidney injury and the incidence of clinically relevant central venous thrombosis are safety endpoints. Fluid balance at 48 hours after randomisation is the efficacy endpoint. Survival free of paediatric intensive care censored at 28 days is the clinical endpoint.

Ethics and dissemination Ethics approval was gained from the Children's Health Queensland Human Research Ethics Committee (HREC/21/QCHQ/77514, date: 1 September 2021), and University of Zurich (2021-02447, date: 17 March 2023). The trial is registered with the Australia New Zealand Clinical Trials Registry (ACTRN12621001311842). Open-access publication in high impact peer-reviewed journals will be sought. Modern information dissemination strategies will also be used including social media to disseminate the outcomes of the study.

Trial registration number ACTRN12621001311842.

Protocol version/date V5/23 May 2023.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This is a multicentre, open-label, pragmatic, pilot randomised controlled trial that compares restrictive fluid strategy to standard care in patients <18 years admitted to paediatric intensive care unit and mechanically ventilated at the time of screening.
⇒ Enrolled patients receive either a restrictive fluid strategy that incoporates maintenance intravenous fluid therapy, fluid boluses, drug dilutions and fluid removal strategies or standard care.
⇒ The duration of intervention is for 48 hours postrandomisation or until discharge (whichever is earlier).
⇒ Fluid balance at 48 hours after randomisation is the efficacy endpoint, while new-onset acute kidney injury and the incidence of clinically relevant central venous thrombosis are safety endpoints.

INTRODUCTION

Over 100 000 patients are admitted to paediatric intensive care units (PICUs) across the USA every year, and similar admission rates per population have been reported in other continents.[1 2] Intravenous fluid therapy (IVFT) remains the most common intervention in critically ill patients and includes both fluid boluses and maintenance fluids.[3] Maintenance intravenous fluid regimens, dating back to observational landmark studies in the 1950s,[4] have led to a clinical practice that favours wide use of fluid therapy. While a number of studies indicate worse outcomes

with fluid resuscitation and liberal IVFT, it is unclear what would constitute 'appropriate IVFT'.[5–9]

Fluid overload may impair oxygen delivery to tissues and lead to end-organ dysfunction.[10] Several retrospective studies, across different patient cohorts, have reported an association between fluid overload, and fewer ventilator-free days, prolonged PICU length of stay[8 9 11–15] and mortality.[16–21] A recent systematic review reported a 6% increase in the odds of mortality for every 1% increase in fluid overload in critically ill children.[22] A Cochrane review of liberal versus restrictive fluid therapy in children with sepsis or septic shock observed an increased risk of in-hospital death by 38% with liberal fluid therapy. However, of the three paediatric randomised controlled trials included, only one study investigated restrictive maintenance fluid regimen. The number of patients recruited to each of the interventions arms was not reported, making inclusion of these results in the meta-analysis impossible.[23] The latest paediatric surviving sepsis campaign guidelines recommend limiting fluid boluses in settings where intensive care is not available primarily based on one trial.[6 24] Interestingly, a small prospective observational study in critically ill children found that nearly 50% of IVFT administered was potentially modifiable.[25] Furthermore, another study observed higher in-hospital mortality in patients who received maintenance fluids more than daily hydration requirements.[26]

Despite mounting observational data suggesting the potential for harm associated with fluid overload in critically ill children, there is lack of evidence that define the optimal fluid management to avoid fluid overload.[27 28] International consensus clinical practice guidelines suggest restriction of total intravenous maintenance fluid (as traditionally calculated) based on low-quality evidence.[29] There is, thus, an urgent need for interventional trials testing fluid management regimens designed to reduce fluid overload. To date, there have only been a few small pilot trials that investigated this topic.[30–32] We hypothesised that restrictive fluid management could be achieved by lesser maintenance fluid allowance, strategies to limit fluid boluses and drug dilutions, as well as early removal of excess fluid. Accordingly, we designed the REstrictive versus StandarD FlUid Management in Mechanically Ventilated ChildrEn Admitted to PICU pilot study protocol with the following objectives:

1. To investigate if it is possible to recruit critically ill children into a trial investigating restrictive fluid strategy versus standard care.
2. To investigate if it is safe to restrict intravenous fluid administration in critically ill children.
3. To establish if a negative to neutral fluid balance can be achieved within 48 hours of randomisation in a restrictive fluid management protocol.
4. To explore if there are any effects of a restrictive fluid strategy on patient-centred outcomes compared with standard (liberal) management.

METHODS: PARTICIPANTS, INTERVENTIONS AND OUTCOMES

Trial design

Multicentre, binational pilot, randomised, controlled, open-label, pragmatic trial.

Study setting

Patients from the three participating tertiary PICUs (Queensland Children's Hospital (QCH), Brisbane, Australia; Sydney Children's Hospital, Randwick, New South Wales, Australia and University Children's Hospital Zurich, Zurich, Switzerland) are being enrolled. The study started recruitment on 24 November 2021 with intended completion date of 31 December 2023.

Eligibility

Children aged under 18 years and admitted to PICU with mechanical ventilation are eligible. Detailed inclusion and exclusion criteria are provided in table 1.

Interventions

Individual children will be randomised into two groups—restrictive versus standard (liberal) fluid strategy. Each strategy is composed of a bundle of care specific to maintenance fluids, drug dilutions, nutrition and bolus fluid therapies. The restrictive bundle of care is described in table 2. The description of standard care in table 2 is a summary of current reported clinical practice across the

Table 1 Eligibility criteria

Inclusion	Exclusion
► Admitted to PICU. ► Age >0 days to <18 years. ► Mechanically ventilated at the time of randomisation. ► If randomised at admission, the patient is expected to be ventilated for ≥6 hours. ► If randomised on day 1 or 2—already ventilated for ≥6 hours from admission to time of randomisation.	► Admitted to PICU for ≥48 hours. ► Children readmitted to PICU≤6 months of randomisation to REDUCE-1. ► Children needing hyperhydration to prevent or treat tumour lysis syndrome. ► Children with diabetic ketoacidosis. ► Children postorgan transplant. ► Children in whom end-of-life care or palliative care has been instituted.

PICU, paediatric intensive care unit; REDUCE, REstrictive versus StandarD FlUid Management in Mechanically Ventilated ChildrEn Admitted to PICU.

Table 2 Interventions as per protocol

Intervention	Restrictive fluid strategy	Standard (liberal) fluid strategy
Intravenous fluid therapy		
Maintenance	Reduce maintenance to 50% for all patients	75% maintenance for non-cardiac bypass patients. 50% maintenance for those who undergo cardiopulmonary bypass surgery.
Bolus volumes	Give smaller fluid boluses—5 mL/kg	5–20 mL/kg
Restrict further fluid boluses	Limit further fluid bolus(es) if no or minimal derangement of perfusion markers (lactate <3 mmol/L, urine output ≥0.5 mL/kg/hour)	Not usual practice
Drug dilutions, 'To keep vein open' infusions, Post medication flushes	Assess on daily rounds options to reduce fluid administration: use maximal permissible concentration for drug infusions. Limit 'to keep vein open' infusions to a maximum of 12 mL/24 hours. Consider locking the lumen with haprin (10 units/mL) if central line/percutaneously inserted central venous catheter is not in use. Limit drug flushes to 3 mL.	Standard drug concentration 'to keep vein open' infusions—1 mL/hour Drug flushes up to 10 mL
Earlier use/of inotropes/vasopressors		
Initiation	Consider starting inotropes and/or vasoconstrictors when the child has received 20 mL/kg fluid bolus in the first 24 hours from randomisation. Initiation and escalation will be guided by the clinician.	Start after fluid bolus resuscitation of 40–60 mL/kg in sepsis; variable in other disease states
Total parenteral nutrition		
Use	Assess on daily ward rounds options to reduce fluid administration. Consider use of a higher concentration to limit volume where central venous access available. Concentrated neonatal or paediatric parenteral nutrition solution Concentration of total parenteral nutrition will depend on availability at each site.	Administer if unable to start enteral feeds for a prolonged period. Clinician decision on when to start. Standard strength neonatal or paediatric parenteral nutrition solution. For the cardiac patients, standard care does include high concentration total parenteral nutrition.
Fluid removal		
Diuretics	Start within 24 hours of randomisation if clinically indicated and appropriate	Clinician decision to start when patient assessed to be fluid overloaded.
Peritoneal dialysis (where available)	Start within 24 hours of randomisation if clinically indicated and appropriate.	Clinician can choose to start peritoneal dialysis when they perceive a clinical need.

three study sites. Modifications are allowed to accommodate unit-specific variations. The interventions will continue for 48 hours from randomisation or until discharge (whichever is earlier). There is no restrictions to enteral feeds volume within study in either of the arms. There is no preference within the protocol between the use of peritoneal dialysis (where available) and diuretics.

Rules to accommodate for clinician variability

The clinicians will direct the intravenous fluid type, the choice of inotropes/vasopressors and the choice of enteral and/or parenteral nutrition. Clinicians can choose to initiate peritoneal dialysis or renal replacement therapy in the context of metabolic derangement and start inotropes for cardiac dysfunction. Where the child does not have a central venous line, clinicians can choose to give fluid bolus instead of starting an inotrope and administer a fluid bolus when there is a clinical suspicion of intravascular hypovalaemia. These instances will not comprise protocol deviations.

Protocol deviations

Deviation in prescribed fluid management in patients (as per table 2) will not be considered protocol deviations and will instead be captured using the adherence assessments.

Endpoints

The endpoints were chosen to assess feasibility, safety and efficacy. Clinical endpoints will be used for sample size calculations for a potential future larger trial that has a patient centred primary outcome (table 3).

Definitions

New-onset acute kidney injury (AKI)—If patient develops AKI within the first 7 days following randomisation,

Table 3 Description of feasibility, safety and efficacy endpoints

Endpoints	
Feasibility	► No of patients recruited per month ► Proportion of recruited to eligible patients ► No of patients randomised at admission, on day 1 and day 2 ► Adherence to each of the bundle elements in patients randomised to restrictive arm
Safety	► Negative fluid balance >10% body weight in 24 hours in the first 48 hours after randomisation ► New-onset acute kidney injury defined as per Kidney Disease Improving Global Outcome (KDIGO) criteria[33] in the first 7 days after randomisation ► Incidence of clinically relevant central venous thrombosis in the first 7 days after randomisation ► Incidence of secondary lactate rise ≥3 mmol/L from baseline value at randomisation in the 48 hours after randomisation ► Incidence of urine output <0.5 mL/kg/h for four consecutive hours in the 48 hours after randomisation
Efficacy	► Fluid balance at 48 hours after randomisation
Clinical, observational and balancing measures	► Survival free of paediatric intensive care censored at 28 days ► Ventilator free days censored at 28 days ► Length of stay in PICU ► Length of stay in hospital ► Mortality censored at 28 days ► Duration of inotropic support (in hours) censored at 7 days or discharge from PICU ► Proportion of patient with a Vasoactive Inotrope Score ≥20 in the 48 hours after randomisation

PICU, paediatric intensive care unit.

defined as an increase in serum creatinine by >26.5 µmol/L within 48 hours from randomisation or to 1.5 times baseline or more within last 7 days as per the Kidney Disease Improving Global Outcomes (KDIGO) criteria.[33] Baseline creatinine will be defined with the following priority: up to 24 hours before PICU admission, −12 to +2 hours around PICU admission or −12 to +2 hours around randomisation.[34] If there was no baseline creatinine measurement, a predicted normal baseline creatinine will be calculated from reported equations.[35 36] New-onset AKI will be reported as a grouped outcome (no AKI vs those patients who developed AKI irrespective of the stage). Those who already had AKI on admission will not be included in this analysis.

Survival free of paediatric intensive care will be censored at 28 days from randomisation. Patients who die within 28 days after randomisation will be allocated zero PICU-free days. Patients will exit study on PICU discharge and will not be eligible for rerandomisation if readmitted within 6 months of the index admission. Other definitions are detailed in online supplemental file 1.

Adherence assessment

Adherence will be defined as receiving the assigned study fluid strategy which will be assessed by reviewing the clinical information system for documentation of the prescribed and administered fluid strategy. Data will be collected through review of the medical record, and where feasible, will be supplemented with automated extraction. Data will be reviewed for all participants irrespective of assigned fluid strategy to assess adherence.

Adherence metrics that will be collected for all recruited patients (both arms) are listed below:

- Was ≤50% maintenance fluid used—Y/N.
- If fluid bolus(es) administered, was it as 5 mL/kg—Y/N.
- If fluid bolus(es) administered, was it given when there was no derangement in perfusion markers (considered to be normally perfused when lactate <3 mmol/L or urine output ≥0.5 mL/kg/hour)—Y/N.
- If patient received >20 mL/kg of fluid boluses in a 24 hour period, was an inotrope started—Y/N.
- Was drug dilution reduction considered in the ward round and documented—Y/N/unknown.
- Was total parenteral nutrition volume reduction considered in the ward round and documented—Y/N/unknown.
- Was diuretic started in the first 24 hours as evidenced by ward round or medical progress note documentation or prescription—Y/N.
- Was PD started in the first 24 hours as evidenced by ward round or medical progress note documentation or prescription—Y/N.

Schedule of evaluations

Table 4 details the evaluations for the study.

Sample size

Enrolment of 154 of 204 eligible patients will yield a recruitment rate of 75% with a one-sided lower 95% CI limit of 70%, which aligns with our expectations for our recruitment rate feasibility outcome. Additionally, assuming an extra small effect size for the continuous clinical outcome used in a main trial, this pilot meets the recommendations for pilot trial sample size to minimise the sample size required for the main trial.[37]

Table 4 Evaluations

Assessment	Screening: on admission to PICU, day 1 and day 2	Baseline: on admission to PICU	PICU stay
Demographics	X		
Blood biochemistry	X	At admission or at randomisation	Everyday while the patient is in PICU or until 7 days whichever is earlier
Vital signs—organ dysfunction/ support	X	X	Everyday while the patient is in PICU or until 7 days whichever is earlier
Inclusion/exclusion criteria	X		
Review of adherence to bundle elements			Assessed for 48 hours from randomisation
Adverse events			Assessed for the duration of PICU stay

PICU, paediatric intensive care unit.

Recruitment

On weekdays, the research nurse will screen all patients admitted to the PICU each morning. During on-call hours and weekends, clinical staff will screen for eligibility.

Assignment of interventions

Allocation

Electronic variable block randomisation schedule with block sizes of 4 and 6 and 1:1 allocation into restrictive-fluid and standard (more liberal) care arms will be generated and imported into the study REDCap database by the data manager. Patients will be stratified by primary diagnosis (cardiac/non-cardiac) at time of randomisation. Allocation will be concealed until randomisation is undertaken by the enrolling clinician or research nurse.

Blinding

As a pragmatic trial, we have chosen a non-blinded study design. It is not possible to blind the clinician as the elements of the management bundle are multiple interventions.

Data collection, management and analysis

Data collection methods and management

A purpose built study database will be constructed in REDCap, hosted by The University of Queensland.[38 39] Daily blood sampling is recommended as part of the data collection. Multiple data sources will be used such as the PICU clinical information system (MetaVision, iMDsoft, Wakefield, USA), integrated Electronic Medical Record (iEMR, Cerner, Missouri, USA), Australia New Zealand Paediatric Intensive Care Registry,[40] Healthtrack (dedicated cardiology clinical information system, Australia) or paper documentation where a clinical information system is not available. When available, data will be extracted directly from the clinical systems by the data manager and imported into REDCap, otherwise, data will be manually collected on e-case report forms within REDCap by the clinical research nurse at each site. Screening data will be collected every day of the week, while clinical and biochemical variables of randomised patients will be collected for every day of PICU stay (until discharge or 28 days, whichever occurs first). All data will be recorded in the REDCap trial database. Sources of data and further methods are detailed in online supplemental file 2. A risk assessment was undertaken to guide the development of the data monitoring plan. Data monitoring activities implemented for the study include the following:

1. Onsite and/or virtual monitoring to conduct source data verification of all data items relating to screening eligibility, consent, randomisation, efficacy, clinical and safety endpoints for every enrolled patient.
2. An audit of the MetaVision data extract for a random sample of 5% of enrolled patients to verify accuracy and completeness.
3. Centralised monitoring to evaluate rates of recruitment and withdrawals across study sites and a review of discrepancies generated by data quality rules in the REDCap study database.

Statistical analysis plan

Descriptive statistics will be used to report on the baseline characteristics of the total study cohort, each intervention group and the predefined subgroups. All endpoints will be presented using the appropriate descriptive statistics. The estimate of the effect size (along with the 95% CI) will be calculated and presented; no p values will be reported as the study is not powered for efficacy endpoints. Participants will be evaluated in the groups to which they were randomised, regardless of treatment received (ie, an intention-to-treat analysis, including participants who were randomised and consented, and consent was not withdrawn). Additionally, we will perform two modified per-protocol analyses. First, we will include only those participants where (1) in the standard (liberal) care arm, no components of the bundle align with the corresponding restrictive fluid bundle component and (2) in the restrictive fluid bundle arm, all components of the bundle were adhered to. Second, we will limit examination of the bundle components to the objective measures relating to maintenance fluid, fluid bolus, initiation of

inotropes and fluid removal (diuretics and/or peritoneal dialysis), and as such include only those participants where (1) in the standard care arm, no components of the bundle align with these corresponding restrictive fluid bundle components and (2) in the restrictive fluid bundle arm, all of these four components of the bundle were adhered to.

A priori subgroup analyses, for metrics known at randomisation, will be for primary admission diagnosis (cardiac/non-cardiac; stratification variable), age (neonates, >1 month to <1 year and ≥1 year), admission type (elective/non-elective), and high and low patient acuity stratified according to admission Paediatric Index of Mortality 3 (PIM3) scores. High acuity will be defined as PIM3≥0.05 and low acuity<0.05. To explore the effect of enteral feeding on fluid balance, we will perform a subgroup analysis of patients who received >65% of their goal nutrition as enteral feeds at 48 hours from randomisation.[41]

Trial oversight

The trial will be overseen by a trial steering committee (TSC), the membership of which includes: the PI, and at least two other investigators. The role of the TSC will be to monitor and supervise progress of the trial and review at regular intervals relevant information from other sources.

The trial will also be monitored by a data and safety monitoring board (DSMB), comprising an intensivist, a clinician researcher from an unrelated field and a statistician. The remit of the DSMB is to review accruing recruitment and safety data; there is no remit to assess efficacy endpoints.

There are no defined preset stopping rules. Three interim analyses are planned: (1) after recruitment of 20 cardiac patients to assess safety and protocol adherence, (2) after recruitment of 50 patients to assess safety and protocol adherence (including a subgroup analysis for cardiac patients) and (3) at 100 patients to assess adherence metrics.

Adverse events and serious adverse events

An adverse event (AE) is defined as any unfavourable and unintended diagnosis, symptom, sign (including an abnormal laboratory finding), syndrome or disease which either occurs during the study, having been absent at baseline, or if present at baseline, appears to worsen. Adverse events (AEs) are recorded regardless of their relationship to the study intervention.

A serious AE is defined as any untoward medical occurrence that results in death, prolongs PICU admission (>28 days), or results in persistent or significant disability/incapacity.

Commonly expected complications related to the underlying disease will not be reported as an AE. This may be organ dysfunction, need for inotropic support or death. Renal dysfunction will be noted separately, as this is a predefined safety endpoints. Potential intervention specific AEs might be new-onset AKI and clinically relevant central venous thromboses.

Laboratory biochemistry values will be reviewed every day by the attending clinician and where concerns of an AE exist, this will be discussed with the PI and documented by the clinical research nurse. As these events may be due to underlying disease, the attending clinician will be requested to state if in their personal opinion, the event potentially could be related to the intervention.

AEs will be reported to the PI as soon as possible. The PI will review all AEs and determine relatedness and severity. Complications and side effects will be reported using the existing hospital internal reporting structures. The PI will then report back to the patients where appropriate and the Children's Health Queensland Human Research Ethics Committee.

ETHICS AND DISSEMINATION

Formal ethics approval was gained from the Children's Health Queensland Human Research Ethics Committee (HREC/21/QCHQ/77514, Date: 1 September 2021), and University of Zurich (2021-02447, 17 March 2023). All protocol amendments are detailed in online supplemental file 3.

Consent

Written informed consent will be sought from parents/carers. Consent will be sought by a senior doctor or the clinical research nurse prospectively or as consent-to-continue within 24 hours after randomisation. Consent-to-continue will be limited to scenarios where prospective consent was not possible due to unavailability of parents/carers. In rare circumstances, where parents are not available on the unit, consent will be sought using phone contact and will be followed up with written consent. The master consent form is included as online supplemental file 4.

Confidentiality

Participant data will be held in trust by the investigators and the sponsoring institution. The study protocol, data and all other information generated will be held in confidence. All electronic records will be stored in the study REDCap database. No information concerning the study, or the data will be released to any unauthorised third party, without prior written approval of the sponsoring institution. Clinical information will not be released without written permission of the participant, except as necessary for monitoring by HREC or regulatory agencies.

Patient and public involvement

While parent/carer involvement was not sought in study design, we plan to seek input from them at the results dissemination phase of the study.

Dissemination policy

Open-access publication in high impact peer-reviewed journals will be sought. Modern information

dissemination strategies will also be used including social media to disseminate the outcomes of the study. Parents will also be able to access results through these media posts.

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Contributors SRaman is responsible for the conceptualisation, sourcing funding, project administration, writing up results and reporting adverse events. KSG advised on conceptualisation and trial conduct. KSG will perform the statistical analysis. MK is responsible for coordination, screening, consenting, data collection, monitoring and adverse event reporting. SRahiman, AM, PV, CM, QT, JW, FZ and EK advised on trial design and review manuscripts. PS, FZ, EK and LJS advised on trial design, facilitate recruitment and will review manuscripts. LJS also advised on trial methodology. Trial steering committee is formed by SRaman, KG and LJS. Queensland Children's Hospital is the lead site. SRaman and MK are responsible for HREC approvals and AE reporting. MK facilitates data monitoring. All authors will need to adhere to authorship guidelines to be listed as an author in any publication that stems of this work.

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Competing interests None declared.

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