HEALTH ECONOMIC ANALYSIS PLAN FOR A RANDOMISED CONTROLLED TRIAL COMPARING BALANCED MULTI-ELECTROLYTE SOLUTION WITH 0.9% SODIUM CHLORIDE AS FLUID THERAPY FOR DIABETIC KETOACIDOSIS

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Investigators and personnel

Name	Role in Study	Email	Organisation
Dr Alisa Higgins	Principal Investigator	lisa.higgins@monash.edu	Australian and New Zealand Intensive Care Research Centre (ANZIC-RC), School of Public Health and Preventive Medicine, Monash University. Level 3, 553 St Kilda Road, Melbourne, VIC, 3004, Australia.
Dr Zhomart Orman	Co-investigator	zhomart.orman1@monash.edu	
Mr Mahesh Ramanan	Co-investigator	Mahesh.Ramanan@health.qld.gov.au	Intensive Care Unit, Caboolture Hospital, QLD
Prof Bala Venkatesh	Co-investigator	bvenkatesh@georgeinstitute.org.au	The George Institute for Global Health

Abbreviations

AN-SNAP	Australian National Subacute and Non-Acute Patient Classification
ANZIC-RC	Australian and New Zealand Intensive Care Research Centre
ANZICS	Australian and New Zealand Intensive Care Society
AUC	Area under the curve
AUD	Australian dollars
BEST-DKA	Balanced Multi-Electrolyte Solution versus Saline Trial for Diabetic Ketoacidosis
$DAOH_{28}$	Days alive out of hospital at home at 28 days
HHS	Hyperosmolar hyperglycaemic non-ketotic syndrome
HRQoL	Health-related quality of life
ICER	Incremental cost-effectiveness ratio
ICU	Intensive care unit
IHACPA	Independent Health and Aged Care Pricing Authority
NHCDC	National Hospital Cost Data Collection
NMB	Net monetary benefit
PPP	Purchasing power parity
QALY	Quality-adjusted life year
RCT	Randomised controlled trial

Table of Contents

1. Administrative information

This Health Economics Analysis Plan outlines the planned analysis of economic data for a multi-centre, blinded, cluster-crossover randomised controlled trial comparing Plasma-Lyte® 148 with 0.9% sodium chloride as a fluid therapy for diabetic ketoacidosis. It should be read in conjunction with the published trial protocol, which provides detailed information on the objective, design, outcomes, data management, and statistical considerations.[1]

2. Background

Diabetic ketoacidosis (DKA) is an acute, life-threatening emergency that most commonly affects people with type I diabetes mellitus, though it can occur in all patients with diabetes mellitus. It arises from absolute or relative insulin deficiency, which forces the body to metabolise fat for energy, causing hyperglycaemia (blood glucose ≥200 mg/dL/11.1 mmol/L), ketosis (β-hydroxybutyrate ≥3.0 mmol/L), and metabolic acidosis (pH <7.3 and/or bicarbonate <18 mmol/L).[2] The resulting hyperglycaemia causes osmotic diuresis, leading to excessive loss of water and electrolytes (polyuria), followed by dehydration and excessive thirst (polydipsia). As dehydration progresses, patients may experience weight loss, reduced urine output, and altered consciousness, and can deteriorate rapidly without prompt hospital treatment.

Patients experiencing DKA use substantially more healthcare resources than those without DKA.[3] Among individuals with type I diabetes, those with DKA are hospitalised 2.5 times more often, have nearly twice as many ED visits (1.9 vs. 0.9), spend three times longer in hospital for any cause (8.7 vs. 2.7 days), and require almost twice as many outpatient visits (9.1 vs. 5.1). Over the past decade, healthcare utilisation among this population has increased by at least 20% annually.[4] Moreover, DKA accounts for approximately 60% of the total direct medical costs for patients with type I diabetes.[3] Given this substantial burden, identifying cost-effective treatments for DKA is essential to reduce its economic burden.

The cornerstone of DKA management is fluid replacement, insulin therapy, and electrolyte (especially potassium) correction, supported by close monitoring and treatment of the underlying precipitating cause (e.g., infection, missed insulin, or new-onset diabetes).[2] Fluid replacement can be achieved using either isotonic saline (0.9% sodium chloride) or balanced electrolyte solutions (BES), such as Plasma-Lyte® 148 (PL), which more closely approximate normal plasma composition. Compared with human plasma, isotonic saline has a lower pH, higher osmolarity, and elevated sodium and chloride concentrations, while lacking calcium, potassium, and magnesium. In contrast, PL more closely resemble physiological electrolyte and pH levels.[5,6]

Despite these differences, some clinical guidelines continue to recommend isotonic saline as the initial resuscitation fluid because of its wide availability, low cost, and proven effectiveness in restoring intravascular volume.[7-9] Survey data suggest that approximately one third of intensive care unit (ICU) clinicians use isotonic saline exclusively, one third use BES only, and the remaining third use both.[10] When administered in large volumes, isotonic saline can lead to hyperchloremic metabolic acidosis and may be associated with longer ICU and hospital stays.[11] Emerging evidence shows that, compared with isotonic saline, BES are associated with faster DKA resolution.[12-14] Nonetheless, these findings are based on relatively small studies (≤172 participants) and require confirmation in larger, adequately powered trials.

Only two small trials have directly compared PL with isotonic saline in adults with DKA.[15,16] Mahler et al. randomised 22 patients to PL and 23 to isotonic saline , reporting that PL resulted in lower serum chloride and higher bicarbonate levels, reducing the risk of hyperchloremic metabolic acidosis.[15] Ramanan et al. randomised 48 patients to PL and 42 to isotonic saline, finding that PL led to faster resolution of metabolic acidosis without differences in ICU admission rates.[16] However, evidence regarding mortality, morbidity, patient-reported outcomes, and cost-effectiveness associated with PL remains limited. To address this knowledge gap, a large cluster-randomised trial is currently underway comparing PL with isotonic saline for the management of DKA, incorporating an economic evaluation of the two fluids.[1]

3. Trial design

The *Balanced Multi-Electrolyte Solution versus Saline Trial for Diabetic Ketoacidosis* (BEST-DKA) is a multi-centre, blinded, cluster-randomised, and cross-over trial comparing PL with isotonic saline for the management of DKA.[1] The trial will enrol critically ill adults presenting to the ED with moderate to severe DKA who are deemed eligible for ICU admission across 20-23 Australian hospitals. Participating hospitals will be randomised prior to trial commencement to administer either PL or isotonic saline during the first 12-month intervention period, followed by a 1-month washout period, after which they will cross over to the alternate fluid for the second 12-month intervention period. No patient recruitment will occur during a one-month washout phase. Hospitals are eligible if they have an ED and have historically treated at least 20 patients with DKA requiring ICU admission per year, as recorded in the Australian and New Zealand Intensive Care Society (ANZICS) Core Database.[17] Sites will be excluded if they are unable or unwilling to adhere to trial protocols or cannot collect the minimum dataset required for the study.

Participants must meet all of the following criteria:

- Aged ≥ 18 years

- Presenting to the ED with a primary diagnosis of moderate to severe DKA for which both PL and isotonic saline are considered appropriate
- Blood glucose level > 14mmol/L
- Arterial or venous pH < 7.25
- Serum bicarbonate < 15 mmol/L
- Elevated anion gap > 12mmol/L
- Positive ketones on finger-prick measurement
- In the judgement of the treating clinician, admission to an ICU is required

Patients will be excluded from if any of the following criteria apply:

- Receipt of > 2000 ml of non-study fluid prior to enrolment
- Serum sodium (Na) > 155 mmol/L or < 120 mmol/L
- Known contraindication to either study fluid (e.g., prior allergic reaction to PL)
- Hyperosmolar hyperglycaemic non-ketotic syndrome (HHS)
- Clinical conditions that preclude administration of large-volume fluid resuscitation
- Previous enrolment in the BEST-DKA trial within the preceding 28 days

Study treatments will be started following study enrolment and continue until discharge from a critical care area or for a maximum of 72 hrs, whichever is earlier. If patients are re-admitted to the critical care area within 72 hours with a relapse of ketoacidosis, the clinician may use open label fluids for the managements of ketoacidosis.[1]

Primary outcome of the trial is the number of days alive out of hospital and at home at 28 days after enrolment ($DAOH_{28}$). Secondary outcomes that are relevant to this economic analysis include all-cause mortality and health-related quality of life (HRQoL) at Day 28 post-enrolment.[1] ClinicalTrials.gov: NCT05752279.

4. Objective

The objective of this study is to assess the cost-effectiveness of PL compared with isotonic saline for the management of DKA in adults in Australia.

5. Economic evaluation

An economic evaluation will be conducted alongside the BEST-DKA trial, comparing PL with isotonic saline for the management of DKA, adhering to intention-to-treat principles and adopting a healthcare system perspective, specifically that of the government funder. Cost-effectiveness results will include the cost per $DAOH_{28}$ gained and the cost per quality-adjusted life year gained at 28 days (QALY), acknowledging the short follow-up period. Additionally, the cost per hospital bed-day saved and cost per ICU bed-day saved mentioned in the published study protocol will be explored. Findings will be reported in accordance with the 2022 Consolidated Health Economic Evaluation Reporting Standards.[18] As the follow-up period does not exceed 12 months, discounting of costs and benefits will not be applied.[1]

5.1 Data variables

Data collected during the trial via case report forms and used for this economic evaluation will include:

1. Socio-demographic characteristics: age; sex; and ethnicity.
2. Baseline clinical characteristics: body mass index (BMI); type and duration of diabetes; history of previous DKA; trigger of the current DKA; systolic blood pressure; pulse;

APACHE II score within the first 24 hours in ICU; and Glasgow Coma Scale (GCS) score.

3. Baseline (pre-enrolment) blood characteristics: blood glucose and HbA1c levels; pH; pCO_2; pO_2; HCO_3; base excess; ketone levels; serum beta-hydroxybutyrate; potassium; sodium; chloride; creatinine; anion gap; and urine output.
4. DKA treatment details during the index hospitalisation (doses and volumes): PL; isotonic saline, Hartmann's solution; 4% dextrose + 0.18% sodium chloride; 5% dextrose; 8.4% sodium bicarbonate; 4% albumin; 20% albumin, and other administered fluids; potassium replacement; and insulin.
5. Healthcare services post-enrolment up to Day 28: date and time of index ED, hospital, and ICU admission and discharge; organ support including mechanical ventilation (MV), vasoactive infusions, and renal replacement therapy (RRT); dates of admission and length of stay (in days) for any subsequent ED, hospital, and ICU readmissions up to Day 28; and number of primary care visits.
6. Clinical outcomes: date of death (if applicable); and HRQoL assessed at Day 28 post-enrolment.

5.2 Health outcomes

The health outcomes will include $DAOH_{28}$, derived from survival and hospital stay data, and QALYs, estimated from survival and HRQoL data both collected at Day 28 post-enrolment. HRQoL will be assessed using the EQ-5D-5L instrument.[19] EQ-5D-5L responses will be converted into utility scores using the Australian national value set, where 0 represents death and 1 represents full health.[20] QALYs will be calculated using the area under the curve (AUC) method, assuming a linear change in utility between baseline (enrolment) and Day 28.[21] In particular, mean QALYs will be calculated by multiplying the mean utility value by 28 and dividing by 365, with a utility score of zero assigned at enrolment to reflect the acute DKA episode at presentation. Patients who die prior to day 28 will be assigned 0 QALYs. Differences in $DAOH_{28}$ and QALYs between the PL and isotonic saline groups will be reported as measures of incremental effectiveness.

5.3 Health resource use and costs

Healthcare resource use from enrolment to Day 28 will be quantified for each study group using patient-level data collected through CRFs. This will include the index hospitalisation, subsequent hospitalisations, and primary care visits. Resource use during the index hospitalisation will encompass the ED presentation, DKA treatment (intravenous fluids including PL, isotonic saline, and Hartmann's solution) administered within ≤72 hours post-enrolment, and ICU and ward stays, including details on organ support (MV, vasoactive infusions, and RRT). Subsequent hospitalisations between the index discharge and Day 28 post-enrolment will include ED visits, ICU and ward stays, and details of organ support, but will exclude DKA treatment details. ED and primary care visits will be captured as counts only, without further detail.

Costs will be estimated by assigning unit costs to the corresponding quantities of healthcare resource use (Table 1). As hospitalisation represents the largest component of the total medical costs[3] and the most recent available unit cost data are from 2024, all costs will be reported in 2024 Australian dollars ($). Where necessary, costs will be adjusted for inflation using health price indices published by the Australian Institute of Health and Welfare.[22] In particular, a unit cost of $1,872 per ED visit will be applied for ED presentations. This estimate is based on the average of the Australian Refined Diagnosis Related Groups (AR-DRG) codes E1010A and

E1010B (Diabetes, Complexity levels A and B) from the 2022–23 National Hospital Cost Data Collection Public Sector (NHCDC) published by the Independent Health and Aged Care Pricing Authority (IHACPA).[23]

Consistent with the 2024-25 National Pricing Model by the IHACPA, a unit cost of $6,000 per ICU bed-day will be applied for ICU stay, derived by multiplying the national ICU rate of $250 per hour by 24 hours.[24] Where relevant, ICU stay will be further categorised by the number of organ support using cost weights from the National Cost Collection reported by the National Health Service in England.[25] Applying the English cost weights to the Australian daily costs results in daily costs from $5,220 per bed-day for ICU care without organ support to $8,929 per bed-day for care requiring three types of organ support as shown in Table 1.

For medical ward stays during the index hospitalisation and any subsequent hospitalisations, a unit cost of $2,673 per bed-day will be applied. This estimate is derived by dividing the 2023-24 national average hospitalisation cost (AUD $6,415) by the average length of stay (2.4 days), based on data from the NHCDC.[23] Primary care visits will be costed using a unit cost of $99 per visit, assuming longer consultation for post-ICU patients. This unit cost represents the average of two Medicare Benefits Schedule item numbers: 36 (≥20 min consultation, $80.1) and 44 (≥40 min consultation, $118).[26]

Table 1. Unit costs for healthcare resource use

Cost item	Unit cost (AUD)	Description and source
Emergency Department presentation	1,872 per visit	Based on AR-DRG codes E1010A-E1010B (Diabetes, Complexity levels A and B). Source: Independent Health and Aged Care Pricing Authority. National Hospital Cost Data Collection (NHCDC) Public Sector 2023–24 https://www.ihacpa.gov.au/resources/national-hospital-cost-data-collection-nhcdc-public-sector-2023-24
Intensive care unit admission	$6,000 per bed-day, or by the number of organ support: 0 – $5,220 per bed-day 1 – $5,947 per bed-day 2 – $7,969 per bed-day 3 - $8,929 per bed-day	Estimated using the national ICU cost rate of AUD $250 per hour, multiplied by 24 hours. Source: Independent Health and Aged Care Pricing Authority. National Pricing Model 2023–24 https://www.ihacpa.gov.au/resources/national-pricing-model-technical-specifications-2023-24 Organ support categories derived from the National Cost Collection 2022-23 reported by the National Health Service in England. https://www.england.nhs.uk/costing-in-the-nhs/national-cost-collection
Hospital admission (medical ward)	$2,673 per bed-day	Estimated by dividing the national average hospitalisation cost (AUD $6,415) by the average length of stay (2.4 days). Source: Independent Health and Aged Care Pricing Authority. National Hospital Cost Data Collection (NHCDC) Public Sector 2023–24 https://www.ihacpa.gov.au/resources/national-hospital-cost-data-collection-nhcdc-public-sector-2023-24
Primary care visit	$99 per visit	Calculated as the average of two Medicare Benefits Schedule item numbers: 36 (≥20 min consultation, AUD $80.1) and 44 (≥40 min consultation, AUD $118). Source: Australian Government Department of Health and Aged Care (2023). Medicare Benefits Schedule Book Operating from 1 March 2024 https://www.mbsonline.gov.au/
Plasma-Lyte 148 intravenous solution	$2.52 per litre	Prices reported from Queensland Health
Isotonic saline (sodium chloride 0.9%) intravenous infusion	$1.45 per litre	

Sodium lactate Hartmann’s solution for injection	$1.45 per litre	

5.4 Cost-effectiveness analyses

This trial-based economic evaluation will include a cost-effectiveness analysis (CEA) estimating the cost per $DOAH_{28}$ gained, cost per QALY gained, cost per hospital bed-day saved and cost per ICU bed-day saved. The cost per outcome will be expressed as the incremental cost-effectiveness ratio (ICER), calculated by dividing the incremental cost by the incremental effect. Incremental costs will be estimated as the difference in mean total per-patient costs between the PL and isotonic saline groups, while incremental effectiveness will be estimated as the difference in mean effectiveness measures (e.g., $DAOH_{28,}$ QALY). Additionally, net monetary benefit (NMB) will also be calculated by valuing QALY gains at an assumed willingness-to-pay (WTP) threshold of $50,000 per QALY and subtracting incremental costs. A positive NMB will indicate that PL is cost-effective at this threshold, whereas a negative NMB will suggest it is not.[21]

Additionally, between-group differences in mean total per-patient costs and mean total per-patient outcomes ($DAOH_{28}$, QALYs, hospital and ICU bed-days) will be analysed using a mixed effects generalised linear model. This approach appropriately accounts for clustering and period effects, modelling treatment group (PL vs isotonic saline) and period (1 vs 2) as fixed effects, and hospital as a random effect. Baseline covariate adjustment will include age, diabetes type, anion gap, and ED pH, consistent with the study protocol.[1] To address potential small-sample bias, the Kenward–Roger degrees-of-freedom correction will be applied.

All analyses will be conducted using Stata Statistical Software (StataCorp, 2023: Release 18. College Station, TX). Missing data will be addressed in accordance with established methodological guidance.[27] The process will begin with a descriptive analysis to assess the extent and distribution of missing data by trial group, identify potential patterns of missingness, and examine associations with baseline characteristics and observed outcomes. These analyses will inform assumptions about the underlying missing data mechanism. Multiple imputation by chained equations and likelihood-based models will be applied, and their results compared to identify the most suitable approach.

5.5 Sensitivity and scenario analyses

Several sensitivity analyses will be performed to assess the robustness of the cost-effectiveness findings. In particular, probabilistic sensitivity analyses using non-parametric bootstrapping with 1,000 replications will be conducted to quantify confidence intervals around NMB and uncertainty around incremental costs and effects arising from sampling variation in the trial data. The bootstrapped ICERs will be plotted on cost-effectiveness planes and a cost-effectiveness acceptability curve (CEAC) will be generated to show the probability that the PL is cost-effective at different willingness-to-pay (WTP) thresholds. The probability of PL being cost-effective compared to isotonic saline will be presented across a range of WTP thresholds (e.g., from $10,000 to $200,000 per QALY gained).

Additionally, deterministic sensitivity analyses will be undertaken to test the robustness of base-case results to changes in key assumptions. In particular, one-way (varying one parameter at a time over plausible bounds) and/or multi-way (changing two or more key drivers together) sensitivity analyses will include unit costs (±20%), adjustments of base cost to 2025 values through inflation, and baseline utility assumption 0 vs. 0.3. Scenario analyses will further explore time window: index admission only vs. index + readmissions to Day 28. Results will be presented as tornado diagrams and ICER ranges.

5.6 Subgroup analyses

Consistent with the BEST-DKA trial, pre-specified subgroup analyses for this trial-based economic evaluation will include comparisons by:

- Type of diabetes: type I vs. type II
- Severity of acidosis: based on the first pH result in ED and the last value prior to enrolment, defined as pH of 7.00-7.25 or pH < 7.0
- Type of pre-enrolment fluid: isotonic saline vs. BES
- Volume of open label pre-enrolment fluids: above vs. below the median volume
- Sex: male vs. female
- Use of SGLT-2 inhibitors: patients on SGLT-2 inhibitors vs. those not on SGLT-2 inhibitors

Subgroup effects will be assessed via interaction terms (treatment × subgroup) in cost and outcomes. Where appropriate, ICERs and NMB will be presented by subgroups, with cost-effectiveness planes used to illustrate uncertainty.

6. Presentation of results (dummy tables and figures)

The following tables and figures will be presented to summarise the findings from the cost-effectiveness analysis.

Table 1. Baseline characteristics of study participants by treatment groups

Table 2. Resource utilisation and costs by treatment groups

Table 3. Summary of cost-effectiveness results

Figure 1. Cost-effectiveness planes

Figure 2. Cost effectiveness acceptability curves

Supplementary Table 1. Unit costs

Supplementary Table 2. Comparison of baseline characteristics between study participants with and without missing data

Supplementary Table 3. Subgroup analyses

7. Ethics approval

Ethics approval was granted by the Metro North Human Research Ethics Committee ‘A’ (HREC/2022/MNHA/91605) with a waiver of consent under Section 2.3.10 of the National Statement on Ethical Conduct in Human Research,[28] as patients with moderate to severe DKA are often unable to consent due to the urgency of treatment. Written informed consent for data use and Day 28 follow-up will be obtained from the patient or their surrogate decision-maker before hospital discharge, with the option to withdraw at any time.

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