Appendix

This appendix was part of the submitted manuscript and has been peer reviewed. It is posted as supplied by the authors.

Supplemental material

Baseline Data

Baseline data

- Patient demographics
- ICU admission diagnosis (as collected for ANZICS APD)
- Admission category (elective/emergency | surgical/medical)
- APACHE II/III score (as collected for ANZICS APD)
- SOFA score (closest prior to randomisation)
- Mechanical ventilation (within 1 hour prior to randomisation)
- Renal replacement (within 1 hour prior to randomisation)
- HbA1c (at admission or on recruitment)
- Blood lactate (Level closest but prior to randomisation)
- Serum creatinine (Level closest but prior to randomisation)
- Corticosteroids (Y/N and equivalent dose of hydrocortisone)
- Catecholamines (Y/N and equivalent µg/min of noradrenaline)
  *only if the participant is receiving noradrenaline, adrenaline, vasopressin or terlipressin.
- Duration of diabetes
- Treatment of diabetes (oral metformin, oral other, s/c insulin once or twice a day and units/24 h, s/c insulin > 2 times a day and units/24 h, and s/c other)
  *if receiving multiple treatments, hierarchy will be S/C over oral).
- How was the diagnosis of T2DM determined? (patient notes, direct questioning of patient, direct questioning of substitute decision maker or other)
- Presence or absence of known cardiovascular disease (Y/N/Unknown)
- Presence or absence of known retinopathy (Y/N/Unknown)
- Presence or absence of known nephropathy (Y/N/Unknown)
- Estimated body mass index

Infective complications reported

All positive blood cultures after randomisation with an organism not recorded prior to randomisation, except for ‘frequent contaminant’ organisms.

Designated ‘frequent contaminant’ organisms:

- Coagulase-negative staphylococci
- Corynebacterium
- Bacillus
- Propionibacterium

However, if the latter organisms (of the same sub-type or with an identical anti-biogram) are reported in more than one bottle in a 24 hour period it will be recorded as a blood stream infection.

Management Committee

Authors

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Supplemental material 4

Proposed tables and Figures

Proposed tables and figures for the manuscript	
Table 1:	Baseline patient characteristics by treatment group
Table 2:	Primary and secondary outcomes by treatment group
Figure 1:	Flow of participants through the trial (see Figure 1)
Figure 2:	Population-averaged mean blood glucose (by treatment)
Proposed tables and figures for the supplementary appendix	
Table S1:	Description of consent process
Table S2:	Process of care measured in ICU
Table S3:	Subgroup analysis (primary and secondary outcomes for HbA1c ≥ 7.0%)
Table S4:	Summary of protocol deviations/adverse events
Figure S1:	Insulin administration vs. time (Units per day)
Figure S2:	Population-averaged mean blood glucose (by treatment) for subgroup HbA1c ≥ 7.0%

Table 1. Baseline patient characteristics.

Characteristic	**Liberal**	**Standard**
Number (%)		
Age (years), median [IQR]		
Sex (male), no. (%)		
Weight (kg), median [IQR]		
Body-mass index (kg/m^2), median [IQR]		
Admission category, no. (%) Medical / Surgical Elective / Emergency		
ICU admission source, no. (%) Emergency department Ward Other hospital Other ICU Operating or recovery room		
APACHE II Score, median [IQR]		
APACHE III Score, median [IQR]		

Organ failure or dysfunction, No. (%)		
Respiratory Dysfunction (SOFA score 1,2) Failure (SOFA score 3,4)		
Coagulation Dysfunction (SOFA score 1,2) Failure (SOFA score 3,4)		
Liver Dysfunction (SOFA score 1,2) Failure (SOFA score 3,4)		
Cardiovascular Dysfunction (SOFA score 1,2) Failure (SOFA score 3,4)		
Central Nervous System Dysfunction (SOFA score 1,2) Failure (SOFA score 3,4)		
Renal Dysfunction (SOFA score 1,2) Failure (SOFA score 3,4)		
Estimated duration of type II diabetes, no. (%) <1 year 1-5 years 6-19 years ≥20 years Unknown		
Treatment of diabetes, no. (%) Diet Oral metformin Oral other S/C Insulin		
Relevant past medical history, no. (%) Chronic cardiovascular Retinopathy Nephropathy		
Glycated haemoglobin (%), median [IQR]		
Glucose (mmol/L), median [IQR]		
Creatinine (µmol/L), median [IQR]		
Lactate (mmol/L), median [IQR]		
Invasive Ventilation, no. (%)		
Renal replacement therapy, no. (%)		
Systemic Corticosteroids Number (%) Equivalent hydrocortisone dose (mg/day)		
Catecholamines, no. (%) None Low ≤ 5 mcg/min Medium 6-30 mcg/min		

High > 30 mcg/min		
Nil		
Nutrition – no. /total no. (%) Fasted Oral diet Enteral nutrition Parental nutrition Combination		

Table 2. Outcomes (modified intention to treat).

Outcome	**Liberal**	**Standard**
Primary		
Incident hypoglycaemia (BGL < 4.0mmol/L) Total events, no. (%) Proportion of patients (≥1 event), n (%) Incident rate per study period exposure		
Secondary		
Blood glucose (mmol/L) Patient minimum, median [IQR] Patient maximum, median [IQR] Population averaged mean (sd)		
Glycaemic control episodes, n. (%) Relative hypoglycaemia (1 or more episodes) Glucose > goal limit (14 or 10 mmol/L)		
Clinical outcomes		
Mortality (90-days), no. (%)		
Length of Stay (days), med [IQR] Intensive care unit Hospital		
Patients with blood stream infection no. (%)		
Cardio-thoracic surgical patients with sternal wound infection no. (%)		
White blood cell count ($x10^9$/L), median [IQR])		
C-Reactive protein (mg/L), median [IQR])		
Hospital discharge destination, no. (%) Home Rehabilitation Other acute ICU Other acute hospital Long term care Other		

Table S1. Description of consent process

Initial Consent Type	
Prior participant consent - n. (%)	
Prior medical treatment decision maker - n. (%)	
Delayed participant consent - n. (%)	
Delayed medical treatment decision maker - n. (%)	

Table S2. Process of care measured in ICU

End Point	**Liberal**	**Standard**
Blood glucose measurement technique, no. (%) Local laboratory Blood gas analyser Point of care glucometer Unknown		
Nutrition, days of, no. (%) Enteral Nutrition Parenteral nutrition Fasted Oral nutrition Combination of nutrition		

Table S3. Primary and secondary outcomes for subgroup analysis (HbA1c > 7.0%)

Outcome	**Liberal**	**Standard**
Primary		
Incident hypoglycaemia (BGL < 4.0mmol/L) Total events, no. (%) Proportion of patients (≥1 event), n (%) Incident rate per study period exposure		
Secondary		
Blood glucose (mmol/L) Patient minimum, median [IQR] Patient maximum, median [IQR] Population averaged mean (sd)		
Glycaemic control episodes, n. (%) Relative hypoglycaemia (1 or more episodes) blood glucose ≥ goal limit (14 or 10 mmol/L)		
Clinical outcomes		
Mortality (90-days), no. (%)		

Length of Stay (days), med [IQR] Intensive care unit Hospital		
Patients with blood stream infection no. (%)		
Cardio-thoracic surgical patients with sternal wound infection no. (%)		
White blood cell count ($x10^9$/L), median [IQR])		
C-Reactive protein (mg/L), median [IQR])		
Hospital discharge destination, no. (%) Home Rehabilitation Other acute ICU Other acute hospital Long term care Other		

Table S4. Summary of protocol deviations/adverse events

Protocol Deviations	**Liberal** (N=x)	**Standard** (N=y)
Patient randomised and not eligible, no. (%)		
Adult patient aged < 18 years		
Patient did not have either an arterial or central line in situ		
Patient does not have type 2 diabetes		
At time of enrolment death during ICU admission is deemed to be inevitable, not committed to full active treatment		
Admitted to the ICU for treatment of diabetic ketoacidosis or hyperosmolar state		
Patient has juvenile type 1 diabetes		
Requirement for specific blood glucose target as determined by the treating doctor		
Patient has previously suffered hypoglycemia without documented full neurological recovery		
At time of enrolment patient had been in the study ICU or another ICU for ≥ 24 h during the index admission		
Patient has previously been enrolled in LUCID		
Females who are pregnant or suspected to be pregnant determined by a positive serum or urine human chorionic gonadotropin (hCG) test		
Insulin administered outside of protocol parameters		

Insulin administration outside of protocol parameters, no. (%) Administration error Patient safety Wrong insulin protocol used Other		
Adverse event / Serious adverse event, no. (%) Adverse event Serious adverse event		
Suspected relationship of AE to therapy, no. (%) Not related Unlikely Possibly Probably Definitely		
Action taken on insulin protocol, no. (%) None Temporarily held Permanently discontinued		
Outcome of Event, no. (%) Resolved Resolved with sequelae		
Serious Adverse Event (SAE) type, no. (%) Death Prolonged hospitalisation/readmission Life threatening Permanent disability Congenital anomaly Medically important		

Data Safety Monitoring Committee (DSMB) Charter

This Charter is based on the recommendations of the DAMOCLES Study Group (1).

Members

Prof Bala Venkatesh (Chair)	Senior Clinician	University of Queensland
Prof Michael Bailey	Senior Statistician	Monash University

Introduction

The DSMB will meet via telephone once after 200 patients have been enrolled. The LUCID Project Manager (Mr Alex Poole) will provide support in setting up this teleconference but will not attend the teleconference. All DSMB members must be on the teleconference for a decision to be made. The LUCID biostatistician (Dr Mark Finnis) will provide access to trial data to the DSMB biostatistician (Prof Michael Bailey) so that the interim analysis can be completed. Access to these data will be provided two weeks prior to the DSMB meeting. Prior to, or following their meeting, the DSMB may request any additional trial data from the LUCID Management Committee.

DSMB Objectives

To safeguard the interests of trial participants, assess the safety and efficacy of the interventions during the trial, and monitor the overall conduct of the clinical trial.

DSMB Terms of Reference

The DSMB should receive and review the progress and conduct an interim analysis based on data as specified in the statistical analysis plan (below), and then provide advice on the conduct of the trial to the LUCID Management Committee.

1. The DSMB should not advise the LUCID Management Committee to cease the trial based on either futility or that the intervention appears superior to standard care.

2. The DSMB should advise the LUCID Management Committee to cease the trial if the intervention appears to be causing harm. Determination of trial stopping rules remains the prerogative of the DSMB.

3. The DSMB should assess mean (SD) glucose in the standard group and report to the LUCID Management Committee whether patients in this group are achieving mean blood glucose concentrations within the standard range.

4. The DSMB should report the number of patients in the standard group who have received insulin in the first 48 hours and report to the LUCID Management Committee whether the eligibility criteria are satisfactory to identify a group that will receive insulin during the study period.

5. The DSMB should assess mean (SD) and daily peak glucose in the intervention group and report to the LUCID Management Committee whether patients in this group are at risk from blood glucose concentrations in excess of the range targeted.

6. The DSMB should comment to LUCID Management Committee the feasibility of the trial based on current recruitment per site per month

7. The DSMB should report on the safety of the trial based on the number of protocol deviations and serious adverse events.

Trial synopsis

LUCID is a 450 patient, multicentre, parallel group, single blinded, RCT to compare the outcomes of targeting 'liberal' blood glucose concentrations (10-14 mmol/L) to 'standard care' glucose control (6-10 mmol/L) in critically ill patients with T2DM.

450 critically ill adults (≥18 years of age) with known T2DM and arterial or central venous access who are expected to remain in the ICU for >48 hours will be eligible to be enrolled. Study participants will receive the intervention whilst in ICU or until 28 days from randomisation. Blood glucose will be measured every 1-4 hours according to each local ICU existing protocol.

The trial will compare two thresholds to start insulin and target blood glucose concentrations:

1. In the 'liberal' group, insulin (actapid) will be commenced when blood glucose >14.0 mmol/L and blood glucose targeted to 10-14 mmo/l.

2. 'Standard' care will be commencement of insulin (actapid) when blood glucose is > 10.0 mmo/l to target blood concentrations at 6-10 mmol/L.

The primary outcome is incident hypoglycaemia, defined as blood glucose < 4.0 mmol/L.

Secondary physiological outcomes include: the severity of hypoglycaemia (nadir), frequency of hypoglycaemia, relative hypoglycaemia, glycaemic variability, population-averaged mean glucose and peak blood glucose.

Secondary feasibility outcomes include: the consent rate is ≥75% of substitute decision makers approached to consent, chose to participate in the study, in the standard care group insulin administration is required in ≥ 70% of study participants, recruitment rate ≥ 1.8 patients per site per month, protocol adherence ≥ 80% of time spent enrolled and in ICU.

Tertiary outcomes include all-cause mortality and infections.

The trial is registered (ANZCTR number 12616001135404).

Statistical analysis plan for an interim analysis

Patient population eligible to the interim analysis

Inclusion criteria: The first 200 patients enrolled in the study censored 7 days after the 200th patient is enrolled.

Exclusion criteria: Patients who withdrew the consent of participation to the study.

Data used in the interim analysis

Baseline data: (age, gender and HbA1c).

Primary outcome data: Number of hypoglycaemic events.

Secondary outcome data: Nadir of hypoglycaemic events.

Secondary outcome data: ICU daily data on blood glucose concentrations (mean ±SD) for all time-points censored at day 7.

Secondary outcome data: ICU daily data on blood glucose concentrations maximum and minimum censored at day 7.

Feasibility data: Number of patients in standard care arm who have received any insulin during this first 48 hours.

Feasibility data: Recruitment per site per month.

Feasibility data: Consent data (number prior consent, consent to continue, consent not obtained).

Tertiary outcome data: ICU daily data on number of blood cultures positive censored at day 14.

Tertiary outcome data: Day 28 assessment (alive, dead or lost to follow up).

Safety data: All protocol deviations including number of patients randomised and not eligible and number of patients consent to continue was withdrawn.

Safety data: All reported serious adverse event.

Timing

The interim analysis will be conducted when all the data for the analysis of the first 200 patients are entered for the 28 day outcome assessment.

DSMB report

If the DSMB is concerned that study participants are being harmed by the intervention or the conduct of the trial, the DSMB Chair will contact the LUCID Management Committee Chair as soon as possible (within 72 hours) to recommend cessation of recruitment. This advice will be followed-up with a written report and recommendations that will be emailed to the LUCID Management Committee Chair (carbon copy to the project manager and biostatistician) within 28 days of this advice.

If the DSMB recommends continuation of the trial with modifications to the protocol these should be compiled into a written report and emailed to the LUCID Management Committee Chair (carbon copy to the project manager and biostatistician) within 28 days of the meeting.

If the DSMB recommends continuation of the trial without modification to the protocol, this advice should be emailed to the LUCID Management Committee Chair (carbon copy to the project manager and biostatistician) within 28 days of the meeting.

References

1. Damocles Study Group NHSHTAP. A proposed charter for clinical trial data monitoring committees: helping them to do their job well. Lancet 2005;365(9460):711-722.

Human Research Ethics Committee Approvals

Central Adelaide Local Health Network – Human Research Ethics Committee

HREC Reference: HREC/16/RAH/316

Initial approval: 23rd September 2016

Central Australian Human Research Ethics Committee

HREC Reference: HREC-16-446

Initial approval: 7th March 2017

Northern A Health and Disability Ethics Committee

HREC Reference: 18/NTA/144

Initial approval: 9th November 2018

Government of South Australia
SA Health

Central Adelaide Local Health Network
Royal Adelaide Hospital Human Research Ethics Committee
Level 4, Women's Health Centre
Royal Adelaide Hospital
North Terrace
Adelaide, South Australia, 5000
Telephone: +61 8 8222 4139
Email: Health.CALHNResearchEthics@sa.gov.au

Approval Date: 23 September 2016

A/Prof Adam Deane
Intensive Care Unit
ROYAL ADELAIDE HOSPITAL

Dear A/Prof Deane,

Project Title: "Liberal glUcose Control in critically Ill patient with pre-existing type 2 Diabetes (LUCID): A phase II multicentre randomised controlled trial."

HREC reference number: HREC/16/RAH/316

CALHN Reference number: R20160810

Thank you for submitting the above project for ethical and scientific review. This project was first considered by the Royal Adelaide Hospital Human Research Ethics Committee at its meeting held on 25 August 2016.
I am pleased to advise that your protocol has been granted full ethics approval and meets the requirements of the *National Statement on Ethical Conduct in Human Research, incorporating all updates*.
The documents reviewed and approved include:

- NEAF Application: AU/1/E6E7211. Sites covered by this approval:
  - Royal Adelaide Hospital, SA : CPI – A/Prof Adam Deane
  - Royal Melbourne Hospital, VIC : PI – Dr James Anstey
  - The Austin Hospital, VIC : PI – Prof Rinaldo Bellomo
  - The Lyell McEwin Hospital, SA : PI – Dr Vishwanath Biradar
  - Western Hospital, VIC : PI – A/Prof Craig French
  - Princess Alexandra Hospital, QLD : PI – A/Prof Peter Kruger
  - Geelong Hospital, VIC : PI – Dr Matthew Maiden
  - St Vincent's Hospital Melbourne, VIC : PI – A/Prof Antony Tobin
  - The Alfred Hospital, VIC : PI – A/Prof Andrew Udy
  - Royal North Shore Hospital, NSW : PI – Professor Simon Finfer
- Cover letter , dated 3 August 2016
- Protocol: LUCID, Version 2, dated 22 September 2016
- Master NOK and Patient Information Sheets and Consent Forms, Version 2, dated 13 September 2016
- RAH NOK and Patient Information Sheets and Consent Forms, Version 1, dated 21 July 2016
- Letter addressing NHMRC National Statement, dated 8 August 2016
- NOK Letter patient deceased pre consent, dated 23 September 2016
- NOK Notification to participant
- Product Information, Actrapid Insulin, rev date 01 November 2012
- Victorian-Specific Module, A/Prof Adam Deane, Royal Adelaide Hospital, SA.
  - *Note that Section 3 involves information about 'Collection of information' in relation to Victorian Privacy Laws, and should be reviewed through the Governance Processes at Victorian sites.*

HREC approval is valid for **5 years** from **23 September 2016 to 23 September 2021.**

Please quote the **HREC Reference number, HREC/16/RAH/316** and the **CALHN Reference number, R20160810** allocated to your study on all future correspondence.

GENERAL TERMS AND CONDITIONS OF ETHICAL APPROVAL:

- For all clinical trials, the study must be registered in a publicly accessible trials registry prior to enrolment of the first participant.
- This HREC is certified with the NHMRC for National Mutual Acceptance of Single Ethical and Scientific Review of Multi-centre Clinical Trials. This HREC will act as a 'lead HREC' for the purpose of this ethics approval. Any study sites that are not listed on this letter are not covered by this ethics approval. Any study-sites that wish to be added must contact the CPI, who must write formally to this HREC requesting the additional study site.

- Adequate record-keeping is important. If the project involves signed consent, you should retain the completed consent forms which relate to this project and a list of all those participating in the project, to enable contact with them in the future if necessary. The duration of record retention for all clinical research data is 15 years.
- Researchers must notify the Research Ethics Committee of any events which might warrant review of the approval or which warrant new information being presented to research participants, including:
  (a) serious or unexpected adverse events which warrant protocol change or notification to research participants,
  (b) changes to the protocol,
  (c) premature termination of the study
- The Committee must be notified within 72 hours of any serious adverse event occurring at each approved site.
- Confidentiality of the research participants shall be maintained at all times as required by law.
- Approval is valid for 5 years from the date of this letter, after which an extension must be applied for.
- Annual review reports must be submitted to the HREC, every 12 months on the anniversary of the above approval date. Each site covered by this HREC must submit a report, and it is the responsibility of the Coordinating Principal Investigator to ensure this is provided to the RAH HREC Executive Officer, within 10 working days on each anniversary of the approval date, using the Annual Review Form available at: https://www.rahresearchfund.com.au/rah-research-institute/for-researchers/human-research-ethics/
- The REC must be advised with a final report or in writing, and a copy of any published material, within 30 days of completion.

You are reminded that this letter constitutes ethical approval only. You must not commence this research project at any site until separate authorisation from the Chief Executive or delegate of that site has been obtained. For any queries, please contact the CALHN Governance Office: *Health.CALHNResearchGovernanceIP&Contracts@sa.gov.au*

This Committee is constituted in accordance with the NHMRC's *National Statement on the Ethical Conduct of Human Research (2007)* incorporating all updates.

Should you have any queries about the HREC's consideration of your project, please contact Mrs Heather O'Dea, Executive Officer on 08 8222 4139, or Health.CALHNResearchEthics@sa.gov.au.

The HREC wishes you every success in your research.

Yours sincerely,

Executive Officer
for

A/Prof A Thornton
CHAIRMAN
RAH HUMAN RESEARCH ETHICS COMMITTEE

cc: Site Research Governance Officer

Consent process

If the substitute decision maker remains in the hospital and the investigator at that site considers it appropriate, the substitute decision maker will be approached prior to leaving the hospital. It is anticipated that this would happen infrequently.

- If the substitute decision maker has left hospital or the investigator at that site considers it inappropriate to immediately approach them, between 7 and 14 days after death the research coordinator from each site will call the listed substitute decision maker to arrange a meeting with the investigator from that site.

- If the substitute decision maker declines to attend the research coordinator will provide information via phone and if the substitute decision maker agrees a follow up information sheet will be sent.

- If the research coordinator is unable to speak with the substitute decision maker after making three attempts, they will send an information sheet to the substitute decision maker.

At some institutions delayed consent is not permitted due to legal and local governance requirements, in these locations prior next of kin consent or prior participant consent will only be used.

List of mutually agreed co-enrolment studies

PLUS	A multi-centre, blinded, randomised, controlled trial 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 with the same treatment using 0.9% sodium chloride (saline).
SPICE III	A prospective multicentre randomised controlled trial of early goal directed sedation compared with standard care in mechanically ventilated patients in intensive care
ICU-ROX	A phase 2b, multicentre, randomised, single blinded clinical trial parallel groups comparing liberal versus conservative oxygen therapy in mechanically ventilated adults in the ICU
VITAMINS	A pilot, multi-centre, randomised, open-label controlled, feasibility study to compare the administration of vitamin C, thiamine and hydrocortisone vs hydrocortisone alone in critically ill patients with septic shock
STARRT-AKI	Standard versus accelerated initiation of renal replacement therapy in acute kidney injury
SOFter	Skeletal Outcomes Following Intensive Care: Effect of denosumab on bone turnover markers in critically ill women - A safety and feasibility, randomised, placebo controlled trial
INTENT	Intensive nutrition therapy compared to usual care in critically ill adults randomised controlled trial
TAME	Targeted therapeutic mild hypercapnia after resuscitated cardiac arrest: A phase III multi-centre randomised controlled trial
TTM2	Targeted hypothermia versus targeted normothermia after out-of-hospital cardiac arrest 2, a randomised clinical trial
Neb-Hep	A multi-centre, randomised, double blind, placebo controlled trial of nebulised heparin for lung injury
SuDDICU	A cluster RCT of the clinical effectiveness and cost-effectiveness with a contemporaneous study of the ecological impact of selective decontamination of the digestive tract in critically ill patients treated in ICUs