Instructions

Please read the instructions before continuing

- This document is a form. Specific areas within the document can be edited. These areas are known as form fields.
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- Although in some sections the space available appears limited, use as much space as you need. The section will expand to fit automatically up to the maximum character limit.
- When completed the document should be emailed to the Diabetes Australia Research Program research@diabetesaustralia.com.au
- Confirmation emails will be sent by return email.

Applications must reach the Diabetes Australia Research Program by midnight (Australian Capital Territory) Friday, 12 May 2023.

Grant Application 2024

GRANT TYPE

You are applying for (Choose **one only** of the following options)

- ☐ General Grant
- ☒ Millennium Award – Type 1 Diabetes
- ☐ Millennium Award – Type 2 Diabetes
- ☐ Charles Campbell Coghlan OAM Emerging Researcher Award

PROJECT INFORMATION

Project Title (250 character limit)

A randomised controlled trial of plasmalyte versus normal saline as resuscitation and maintenance fluid therapy for patients presenting with diabetic ketoacidosis (BEST-DKA)BalancEd fluids vs Saline Trial in Diabetic KetoAcidosis

Project Aim (Concisely describe the main aim of the project – 500 character limit)

Aim: To determine whether fluid therapy with Plasma-Lyte® 148 increases the number of hospital free days (HFD) up to day 28 compared to 0.9% sodium chloride in patients presenting to the Emergency Department) and deemed to require admission to a critical care area with moderate to severe diabetic ketoacidosis (DKA).

Hypothesis: That fluid therapy with Plasma-Lyte® 148, compared to 0.9% sodium chloride, for patients with moderate to severe DKA will result in superior clinical outcomes.

Expected Duration of the Project (Note: General Grants are for a maximum duration of 1 year. Millennium and Coghlan Awards are for a maximum duration of 2 years)

2 years

Main Focus (Choose **one only** of the following options)

- ☒ Type 1 diabetes
- ☐ Type 2 diabetes
- ☐ Diabetes in pregnancy (GDM or pre-existing)
- ☐ Pre diabetes

Type of Research (Choose **one only** of the following options)

- ☐ Basic science
- ☒ Clinical research
- ☐ Translational research

Population (Choose **one only** of the following options)

- ☐ Children
- ☐ Youth
- ☒ Adults
- ☐ Older people
- ☐ Indigenous
- ☐ Culturally and linguistically diverse

Classification (Choose **one only** of the following options)

- ☐ Self-management/education
- ☐ Psychological/behavioural research; and mental health and diabetes
- ☐ Glycaemic management - including use of technologies
- ☐ Complications - Vision/eye
- ☐ Complications - Kidney
- ☐ Islet biology
- ☐ Health care systems research
- ☐ Epidemiology
- ☐ Insulin resistance/obesity
- ☐ Exercise/nutrition

☐ Complications - Nerve
☐ Complications - Cardiovascular
☐ Complications - Foot problems and amputations
☒ Complications - Other

Does this project require ethics approval? (Note: successful applications requiring ethics approval will need to provide proof that approval has been granted before any funding will be provided)

☒ Yes ☐ No

OTHER GRANT OR FUNDING CURRENTLY HELD

Give details of grants or other support currently received by the Responsible Investigator and/or Participants from, or approved by, other bodies for this or related work. Indicate title, granting body, duration and amount of support for each year.

The study has received partial funding support from Baxter. Baxter has agreed to supply all study fluids including the blinding and masking of fluids and distribution to sites.
Bala Venkatesh has a Level 3 Investigator Grant from the NHMRC (GNT 2009203, 2022-2026) which will support the project manager, statistical support and database management at the George Institute.

PREVIOUS GRANTS FROM DIABETES AUSTRALIA RESEARCH

If the Responsible Investigator has received a previous grant from Diabetes Australia Research, please provide details of the outcomes (e.g. publications, other success in obtaining competitive funding) as well as the grant type and year of funding.

2015 Diabetes Australia Research Trust grant award. Xin Liu, Wendy Brown, Trisha O'Moore-Sullivan and Anthony Russell. A pilot study to assess the efficacy of Tai Chi in Type 1 diabetes. $60,000. This grant resulted in a publication: Xin Liu, Anthony Russell, Enamul Kabir, Wendy Brown. A Pilot Study to Assess the Effects of Tai Chi on Health Indicators in Type 1 Diabetes Patients. Health 2019 Vol.11 No.3, 341-350. DOI: 10.4236/health.2019.113030

RELATIONSHIP OF THE STUDY TO THE PROBLEMS OF HUMAN DIABETES

Describe in non-technical terms the significance of the study for human diabetes

Diabetic ketoacidosis (DKA) is a life-threatening complication of diabetes mellitus. Every year there are more than 7000 patients hospitalised in Australia with DKA. The incidence of Intensive Care Unit (ICU) admission of patients with severe DKA in Australia has increased 5-fold over the last decade with 2849 and 2862 admissions in 2019 and 2020, respectively.

Patients with DKA present with significantly elevated blood sugar levels, severe dehydration and a build up of acid levels in the blood termed acidosis. Because of the severity of dehydration, patients often require large volumes of fluids given through a drip.

While fluid resuscitation is a cornerstone of therapy, the choice of fluid that results in the best clinical outcome remains uncertain. Despite lack of evidence from randomised controlled trials (RCTs), 0.9% sodium chloride (saline) is recommended in clinical practice guidelines as the replacement fluid of choice for patients with DKA. Large volumes of saline, that is typically administered to acidotic patients with DKA, can prolong the duration of the acidosis. In other crititcally ill patients saline use has been associated with adverse outcomes such as infection, and kidney failure

"Balanced" salt solutions that contain lower chloride concentrations, are an alternative fluid option

The knowledge gap: Clinical studies have reported good blood sugar control and earlier resolution of metabolic acidosis with the balanced salt solution Plasma-Lyte-148® (Plasma-Lyte), compared to saline in patients with DKA. Our pilot RCT comparing Plasma-Lyte with saline demonstrated earlier resolution of acidosis by 24 hours in the Plasma-Lyte group: and a trend towards a shortened length of ICU and hospital stay.

There has been no systematic evaluation of any potential adverse effects of saline in the setting of DKA. There is no RCT with sufficient statistical power to assess the comparative efficacy and safety of Plasma-Lyte in patients with DKA. There is therefore a scientific, clinical and health economic imperative to conduct a high-fidelity study to provide definitive evidence to inform clinicians. The study we propose will address this critical knowledge gap.

DETAILS OF THE PROPOSED PROJECT

Details of the proposed project will need to be provided as a separate Portable Document Format (PDF) file. Please note that the maximum page length for details of the proposed project is four pages (excluding references) for the General Grants and nine pages (excluding references) for the Millennium and Coghlan Awards. In addition, the following requirements should be met:

- Font: Times New Roman at least 12pt
- Line spacing: at least Single
- Margins: at least 2 cm; and
- Any graphs, tables or pictures should be clear and legible.

Include:

i) An introductory summary of your previous work, and of the relevant work of others, which leads to the proposed project
ii) Detail the specific aims and potential significance of the project (you may need to use several paragraphs for this section). If hypotheses are to be tested, they should be clearly stated
iii) A research plan, giving details of experimental design and methods to be used
iv) Up to 12 references for General Grants and up to 20 references for Millennium and Coghlan Awards

PROPOSED BUDGET REQUESTED ($)		
i)	**Personnel** (indicate base salary and additional leave loading, payroll and other costs as required by employing body)	$ 144000
ii)	**Equipment** (Note: applications that include equipment costing over $5,000 will be ineligible)	$
iii)	**Travel** (field expenses etc. Note: applications that include conference travel will be ineligible)	$
iv)	**Consumables and Other Expenses** (itemise these expenses in the Budget Justification section below e.g. animals, printing and stationery, computing, radiochemical, etc.)	$
	Total Requested	$ 144000

BUDGET JUSTIFICATION

Please explain all proposed expenditure. If salaries are sought for specific known personnel, include details of qualifications and experience. Insufficient justification and details will disadvantage the assessment of this application.

The study has received partial funding support from Baxter. Baxter has agreed to supply all study fluids including the blinding and masking of fluids and distribution to sites. Bala Venkatesh has an Investigator Grant from the NHMRC (Improving outcomes in patients with sepsis through precision medicine. $1,870,806) which will support the project manager, statistical support and database management at the George Institute.

The funding that is being requested here is towards the cost of research coordinator support for patient enrolment and data collection. It is being costed at 300 AUD per patient and the total cost for 480 patients would be AUD 144,000. The research coordinator fees is to cover the cost of screening, randomisation, data collection, data entry, consent for D-28 follow up, D-28 quality of life questionnaire and providing documents to ethics committees as appropriate. This fee is paid to the particpating site to cover the cost of research coordinator time, estimated at 6 hours per patient.

NOTE: The Diabetes Australia Research Program does not fund any administrative or indirect charges by institutions.

CONTACT FOR ADMINISTRATION OF GRANT

Title	First Name	Surname
Dr	David	Robson
Mailing Address Monash University, Office of the Deputy Vice Chancellor (Research) and Senior Vice President 24 and 26 Sports Walk, Wellington Road		
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Country Australia		
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RESPONSIBLE INVESTIGATOR		
Title Prof	First Name Anthony	Surname Russell
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Country Australia		
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Email Address anthony.russell@alfred.org.au		
Academic and Professional Qualifications MBBS, PhD, FRACP		
Date of Attainment of PhD or equivalent (if applicable) PhD, Universtiy of Queensland, 2004		
Career Disruption (Please include the details of any career disruption that you wish to be taken into consideration. This is especially important when applying for a Coghlan Award). Nil		
Current Appointment Held Director Endocrinology and Diabetes, the Alfred and Professor, School Public and Preventive Health, Monash University		
Administering Institution (Name of institution that will administer the grant/award) School of Public and Preventive Health, Monash University		
Actual Institution if applicable (If the proposed research will not be undertaken at the above Administering Institution, then please provide the name of the Centre/Institution where the research will actually be conducted) The George Institute		
Average days per month devoted to this project 2	Average days per month devoted to all other projects 2	

PUBLICATIONS

Responsible Investigator

Provide a numbered list of articles published in books and refereed journals over the past five years. Indicate with an asterisk (*) the five most relevant articles to the proposed project.

I have 41 publications since 2018. Most related to health services researh - models of care for management of diabetes, pathways to assess fatty liver disease and novel markers of peripheral neuropathy. No specific papers related to ketoacidosis. Paper 11 - systematic review on digital interventions for inpatient management of diabetes.

1) Lu ZQ,… Russell A, Mugwagwa AN. Secular trends in the utility of SGLT-2 inhibitors in heart failure patients with type2 diabetes mellitus across Metro South Health hospitals in South-East Queensland. Int Med J. 11 Dec 2022

2) Ferrari-Cestari M, … Russell A, …Irvine KM. Serum CCL2 is associated with visceral adiposity but not fibrosis in patients with Non-alcoholic Fatty Liver Disease (NAFLD). Digestive Diseases 2022

3) Gracen L, … Russell A,…Powell EE, Valery PC. An exploration of barriers and facilitators to implementing a nonalcoholic fatty liver disease pathway for people with type 2 diabetes in primary care. Diabetic Medicine. 2022 Jun; 39(6).
4) Luisa H. Colorado, … Anthony Russell,… Katie Edward. Corneal dendritic cell dynamics are associate with clinical factors in Type 1 diabetes. JCM 2022; 11 (9); 2611
5) Silva C, …Russell A. A qualitative analysis of the needs and wishes of people with type 2 diabetes and healthcare professionals for optimal diabetes care. Diabetic Medicine. 2022; 39: e14886
6) Gracen, Lucy,… Russell, Anthony,…Powell, Elizabeth E. Implementing the right care in the right place at the right time for non-alcoholic fatty liver disease (NAFLD-RRR study): a study protocol for a community care pathway for people with type 2 diabetes. BMC Health Services Research. 2022; 22 (1): 1-11
7) Mayr H, …Russell A, Hickman I. Clinician perspectives of barriers and enablers to implementing the Mediterranean dietary pattern in routine care for coronary heart disease and type 2 diabetes: A qualitative interview study. Journal of the Academy of Nutrition and Dietetics. Accepted for publication Feb 2022.
8) Siskind D,…Russell A, … Motamarri B. Outcomes of A Co-Located Approach for Metabolic Health Care for People with Schizophrenia. Australas Psychiatry. 2022;in press
9) Radford-Smith D, …Russell A, Siskind D, Powell E, Probert F. Depressive symptoms in non-alcoholic fatty liver disease are identified by perturbed lipid and lipoprotein metabolism. PLOS One. 2022; e0261555
10) Amy L. Johnson,…Anthony W. Russell, Katherine A. Stuart, Sue Williams, Gunter Hartel, Patricia C. Valery, Elizabeth E. Powell. Predicting liver-related outcomes in people with non-alcoholic fatty liver disease: the prognostic value of non-invasive fibrosis tests. Hepatology Communications. Nov 15, 2021.
*11) Sly B, Russell A, Sullivan C. Digital interventions to improve safety and quality of inpatient diabetes management: a systematic review. International Journal of Medical Informatics. 2022 Jan.
12) Siskind D, Russell A, …, Baker A. CoMET: A Randomised Controlled Trial of Co-commencement of METformin versus placebo as an adjunctive treatment to attenuate weight gain in patients with schizophrenia newly commenced on clozapine. Therapeutic Advances in Psychopharmacology. 2021
13) Russell A, et al. eConsults: A proof of concept trial in Australia. Internal Medicine Journal 2021.
14) Engstrom T,… Russell AW,…Pole J.D. Toilet paper, minced meat and diabetes medicines: Australian panic buying induced by COVID-19. International Journal of environmental and Public Health. 2021; 18: 6954
15) De Camargo Catapan S, … Russell A. Same goals, different challenges: a systematic review of perspectives of people with diabetes and healthcare professionals on type 2 diabetes care. Diabetic Medicine. 2021 Jun 21: e14625
16) Perkins BA,…Russell A…, Malik RA. Corneal Confocal Microscopy Predicts the Development of Diabetic Neuropathy: A Longitudinal Diagnostic Multinational Consortium Study. Diabetes Care. 2021 Jul 1
17) Forbes, Josephine; …Russell, Anthony;…; O'Moore-Sullivan, Trisha. T cell expression and release of kidney injury molecule-1 in response to glucose variations initiates kidney injury in early diabetes. Diabetes. 2021; 70 (8): 1754-1766
18) Gong E, Baptista S, Russell A et al. My Diabetes Coach, a mobile application-based interactive conversational agent to support type 2 diabetes self-management: A randomized effectiveness-implementation trial. Journal of Medical Internet Research. 2020; 22 (11):e20322
19) Babptisa S and the My Diabetes Coach Research Group (Russell A et al). User experiences with a type 2 diabetes coaching app: a qualitative study. JMIR Diabetes. 2020 Jul 17;5(3):e16692

20) Donald M, …Russell A, Hollingsworth S. Community-based integrated care versus hospital outpatient care for managing patients with complex type 2 diabetes: a costing analysis. Australian Health Review. 2020; 45(1): 42-50
21) Babptisa S… and My Diabetes Coach Research Group (Russell A et al.). Acceptability of an embodied conversational agent for type 2 diabetes self-management education and support via a smartphone app: a mixed-methods study. JMIR mHealth and uHealth. 2020 Vol 8, e17038
22) Nam MCY,…Russell AW, Greaves K. An Experimental Series Investigating the Effects of Hyperinsulinemic Euglycemia on Myocardial Blood Flow Reserve in Healthy Individuals and on Myocardial Perfusion Defect Size following ST-Segment Elevation Myocardial Infarction. J Am Soc Echocardiogr. 2020 Jul;33(7):868-877
23) Ahn, Sang Bong, …Russell, Anthony et al. Type 2 Diabetes: A Risk Factor for Hospital Readmissions and Mortality in Australian Patients With Cirrhosis. Hepatology Communications 2020 hep4.1536
24) Siskind D, Russell A, et al. Metabolic Measures 12 months after a Randomised Controlled Trial of Treatment of Clozapine Associated Obesity and Diabetes with Exenatide (CODEX). J Psychiatr Res. 2020 May;124:9-12
25) Menon A,… Russell A. Outcomes of a Feasibility Trial using an Innovative Mobile Health Program to Assist in Insulin Dose Adjustment. BMJ Health and Care Informatics. 2019 Oct26 (1):e100068
26) Janubhai Patel,… Russell, Anthony Williaam…Elizabeth Ellen. Clinically Significant Fibrosis Is Associated With Longitudinal Increases in Fibrosis-4 and Nonalcoholic Fatty Liver Disease Fibrosis Scores. Clin Gastroenterol Hepatol. 2020 Mar;18(3):710-718
27) Xin L, Russell A, Kabir E, Brown A. A Pilot Study to Assess the Effects of Tai Chi on Health Indicators in Type 1 Diabetes Patients. Health 2019; 11: 341-350.
28) Menon A,…Russell A, Gray L. Rethinking model of outpatient specialist care in type 2 diabetes using eHealth: study protocol for a pilot randomised controlled trial. International Journal of Environmental Research and Public Health. 2019; 16(6):959
29) Villalba C… Russell A,…Hayman N. A mixed-methods retrospective study: 10 years of diabetic retinopathy screening in urban Aboriginal and Torres Strait Islander primary care. Australian Journal of Primary Health.
30) Lockett J,… Russell AW, Inder WJ. Urea treatment in fluid restriction-refractory hyponatraemia. Clin Endocrinol (Oxf). 2019; 90(4):630-636
31) Siskind, D… A.W.Russell,… BH Ebdrup. "Glucagon-Like Peptide-1 Receptor-Agonists for Antipsychotic- Associated Cardio-Metabolic Risk Factors: A Systematic Review and Individual Participant Data Meta-Analysis." Diabetes Obes Metab. 2019 Feb;21(2):293-302
32) Russell AW et al. Clinical outcomes of an integrated primary-secondary model of care for patients with complex type 2 diabetes: a non-inferiority randomized controlled trial. Diabetologia 2019 Jan;62(1):41-52

Other

Independent of the above, provide details of 3 articles published in books and/or peer reviewed journals by other authors over the past five years with significant relevance to this project. Please do not provide abstracts, work in preparation or copies of publications.

1) Ramanan M, ,,,Peake S,… Venkatesh B. Sodium chloride or Plasmalyte 148 evaluation in severe DKA (SCOPE DKA): a cluster, crossover, RCT. Intensive Care Med 2021 ;47:1248-1257

2) Tran TTT, … Ekinci EII. Review of Evidence for Adult Diabetic Ketoacidosis Management Protocols Front Endocrinol (Lausanne). 2017;8:106. doi: 10.3389/fendo.2017.00106

3) Alghamdi NA, … Ramanan M, Rochwerg B. Saline Compared to Balanced Crystalloid in Patients With DKA: A Meta-Analysis of RCT. Crit Care Explor.2022 6;4(1):e0613.

TRACK RECORD STATEMENT (COGHLAN AWARD ONLY)

Only applicants applying for a Coghlan Award are required to demonstrate past achievements as well as their potential to become an emerging leader in diabetes through a track record statement.

This statement should be no more than 2 pages and include information not listed elsewhere in the application.

For guidance on what to consider in preparing this statement, please refer to the Program Guidelines, section "Charles Campbell Coghlan OAM Emerging Researcher Award: Review Process".

The track record statement will need to be provided as a separate Portable Document Format (PDF) file. The maximum page length is two pages and the following requirements should be met:

- Font: Times New Roman at least 12pt
- Line spacing: at least Single
- Margins: at least 2 cm; and
- Any graphs, tables or pictures should be clear and legible.

AREA OF EXPERTISE (RESPONSIBLE INVESTIGATOR)

To facilitate the allocation of applications for review please select one classification from the Type of Research section below and up to three from the Expertise Classification section below that best describes your expertise.

Type of Research (Choose **one only** of the following options)

- ☐ Basic science
- ☒ Clinical research
- ☐ Translational research

Expertise Classification (Choose **up to three** of the following options)

- ☐ Gestational diabetes
- ☐ Paediatric
- ☐ Self-management/education
- ☐ Psychological/behavioural research
- ☐ Glycaemic management
- ☐ Exercise/nutrition
- ☐ Vision/eye health
- ☐ Nerve health
- ☐ Foot disease and wound healing
- ☒ Type 1 diabetes
- ☐ Indigenous
- ☐ Islet biology
- ☐ Health care systems research
- ☐ Epidemiology
- ☐ Insulin resistance/obesity
- ☐ Kidney health
- ☐ Cardiovascular health

Other (if not listed)

OTHER PARTICIPANTS

Are there any other participants?
☒ Yes ☐ No (Skip this section)

Participant 1

Title	First Name	Surname
Prof	Elif	Ekinci

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Country
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Academic and Professional Qualifications
FRACP, PhD

Involvement in days per month
2

AREA OF EXPERTISE

To facilitate the allocation of applications for review please select one classification from the Type of Research section below and up to three from the Expertise Classification section below that best describes your expertise.

Type of Research (Choose **one only** of the following options)

☐ Basic science ☒ Clinical research ☐ Translational research

Expertise Classification (Choose **up to three** of the following options)

☐ Gestational diabetes
☐ Paediatric
☐ Self-management/education
☐ Psychological/behavioural research
☐ Glycaemic management
☐ Exercise/nutrition
☐ Vision/eye health
☐ Nerve health
☐ Foot disease and wound healing
☒ Type 1 diabetes
☒ Indigenous
☐ Islet biology
☐ Health care systems research
☐ Epidemiology
☐ Insulin resistance/obesity
☒ Kidney health
☐ Cardiovascular health

Other (if not listed)

Participant 2		
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Country Australia		
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Academic and Professional Qualifications MBBS, MD, FCICM		
Involvement in days per month 10		

AREA OF EXPERTISE

To facilitate the allocation of applications for review please select one classification from the Type of Research section below and up to three from the Expertise Classification section below that best describes your expertise.

Type of Research (Choose **one only** of the following options)

☐ Basic science ☒ Clinical research ☐ Translational research

Expertise Classification (Choose **up to three** of the following options)

☐ Gestational diabetes
☐ Paediatric
☐ Self-management/education
☐ Psychological/behavioural research
☒ Glycaemic management
☐ Exercise/nutrition
☐ Vision/eye health
☐ Nerve health
☐ Foot disease and wound healing
☐ Type 1 diabetes
☐ Indigenous
☐ Islet biology
☐ Health care systems research
☐ Epidemiology
☐ Insulin resistance/obesity
☐ Kidney health
☒ Cardiovascular health

Other (if not listed)
Critical illness, Diabetic ketoacidosis research

Participant 3		
Title A/Prof	First Name Naomi	Surname Hammond
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Suburb NewTown	State NSW	Postcode 2042
Country Australia		
Telephone No. (Work)	Mobile No. 0404457790	
Email Address Nhammond@georgeinstitute.org.au		
Academic and Professional Qualifications PhD		
Involvement in days per month 7		

AREA OF EXPERTISE

To facilitate the allocation of applications for review please select one classification from the Type of Research section below and up to three from the Expertise Classification section below that best describes your expertise.

Type of Research (Choose **one only** of the following options)

☐ Basic science ☐ Clinical research ☒ Translational research

Expertise Classification (Choose **up to three** of the following options)

☐ Gestational diabetes
☐ Paediatric
☐ Self-management/education
☐ Psychological/behavioural research
☐ Glycaemic management
☐ Exercise/nutrition
☐ Vision/eye health
☐ Nerve health
☐ Foot disease and wound healing
☐ Type 1 diabetes
☐ Indigenous
☐ Islet biology
☐ Health care systems research
☐ Epidemiology
☐ Insulin resistance/obesity
☐ Kidney health
☒ Cardiovascular health

Other (if not listed)
Fluids translational research

Participant 4		
Title Prof	First Name Gerben	Surname Keijzers
Mailing Address Department of Emergency Medicine, Gold Coast University Hospital, 1 Hospital Blvd		
Suburb Southport	State QLD	Postcode 4215
Country Australia		
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Email Address gerben.keijzers@health.qld.gov.au		
Academic and Professional Qualifications FACEM, PhD		
Involvement in days per month 7		

AREA OF EXPERTISE

To facilitate the allocation of applications for review please select one classification from the Type of Research section below and up to three from the Expertise Classification section below that best describes your expertise.

Type of Research (Choose **one only** of the following options)

☐ Basic science ☒ Clinical research ☐ Translational research

Expertise Classification (Choose **up to three** of the following options)

☐ Gestational diabetes
☐ Type 1 diabetes
☐ Paediatric
☐ Indigenous
☐ Self-management/education
☐ Islet biology
☐ Psychological/behavioural research
☐ Health care systems research
☐ Glycaemic management
☐ Epidemiology
☐ Exercise/nutrition
☐ Insulin resistance/obesity
☐ Vision/eye health
☐ Kidney health
☐ Nerve health
☐ Cardiovascular health
☐ Foot disease and wound healing

Other (if not listed)
Emergency medicine, fluid resuscitation

Participant 5		
Title Dr.	First Name Ben	Surname Moran
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Suburb Gosford	State NSW	Postcode 2251
Country Australia		
Telephone No. (Work) 02 43202092	Mobile No. 0414549905	
Email Address bmoran@georgeinstitute.org.au		
Academic and Professional Qualifications FANZCA, FCICM		
Involvement in days per months 3		

AREA OF EXPERTISE

To facilitate the allocation of applications for review please select one classification from the Type of Research section below and up to three from the Expertise Classification section below that best describes your expertise.

Type of Research (Choose **one only** of the following options)

☐ Basic science ☒ Clinical research ☐ Translational research

Expertise Classification (Choose **up to three** of the following options)

☐ Gestational diabetes
☐ Type 1 diabetes
☐ Paediatric
☐ Indigenous
☐ Self-management/education
☐ Islet biology
☐ Psychological/behavioural research
☐ Health care systems research
☐ Glycaemic management
☐ Epidemiology
☐ Exercise/nutrition
☐ Insulin resistance/obesity
☐ Vision/eye health
☐ Kidney health
☐ Nerve health
☐ Cardiovascular health
☐ Foot disease and wound healing

Other (if not listed)
Consumer health, dissemination of research, advocacy

NOTE: Diabetes Australia Research will require a certification form to be completed if successful.

Agreement

I,Anthony Russell, of (institution) Monash University agree to the terms and conditions as set out in the 2024 Diabetes Australia Research Program Guidelines. I understand that in submitting this application I acknowledge my obligation to participate in the Diabetes Australia Research Program peer review process and I have advised all named Participants of their obligation; specifically, as part of the peer review process, they may be required to review up to three other applications.

Please note agreement to the terms and conditions as set out in the Diabetes Australia Research Program Guidelines is a requirement for your application to be considered.

Save this document prior to emailing

Send via Email to research@diabetesaustralia.com.au

A. Research proposal *(maximum nine A4 pages)*

Balanced salt solution versus 0.9% sodium chloride as fluid therapy for patients presenting with severe diabetic ketoacidosis

OVERVIEW

The problem: Diabetic ketoacidosis (DKA) is a life-threatening complication of diabetes mellitus. Every year there are more than 7000 patients hospitalised in Australia with DKA (1). The incidence of Intensive Care Unit (ICU) admission of patients with severe DKA in Australia has increased 5-fold over the last decade (2) with 2849 and 2862 admissions in 2019 and 2020, respectively.

While fluid resuscitation using crystalloid solutions is a cornerstone of therapy, the choice of crystalloid fluid that results in the best clinical outcome remains uncertain. Despite lack of evidence from randomised controlled trials (RCTs), 0.9% sodium chloride (saline) is recommended in clinical practice guidelines as the replacement fluid of choice for patients with DKA (3,4,5). Large volumes of saline, that is typically administered to acidotic patients with DKA, often results in hyperchloraemic metabolic acidosis (6). Hyperchloraemia is associated with adverse outcomes such as infection, renal failure and increased mortality in critically ill (7,8). Consequently, "balanced" salt solutions that contain lower chloride concentrations, are increasingly being used in these patients.

The knowledge gap: Both prospective and retrospective studies have reported equivalent glucose control and earlier resolution of metabolic acidosis with the balanced salt solution Plasma-Lyte-148® (Plasma-Lyte), compared to saline in patients with DKA. (9,10) Our phase II RCT comparing Plasma-Lyte with saline demonstrated earlier resolution of acidosis by 24 hours in the Plasma-Lyte group: 69% vs. 36% (odds ratio [OR] 4.24, 95% CI 1·68 to 10·72, p=0·002). (11) Plasma-Lyte was also associated with shortened length of ICU and hospital stay. Despite the presence of acetate in Plasma-Lyte, its use was not associated with increased ketosis.

There has been no systematic evaluation of any potential adverse effects of saline in the setting of DKA. There is no RCT with sufficient statistical power to assess the comparative efficacy and safety of Plasma-Lyte in patients with DKA. There is therefore a scientific, clinical and health economic imperative to conduct a high-fidelity study to provide definitive evidence to inform clinicians. The study we propose will address this critical knowledge gap.

The intervention: We will conduct a Phase III multi-centre, blinded, cluster crossover RCT to determine whether fluid therapy with a buffered salt solution (Plasma-Lyte) increases the number days alive and out of hospital (hospital-free days) compared to 0.9% sodium chloride (saline) in critically ill patients admitted with DKA.

The team: This study was co-designed with a consumer representative, endorsed by the Australasian College of Emergency Medicine, Diabetes Australia and will be conducted by the George Institute for Global Health. The investigators on this application have a stellar track record in completing large scale clinical trials in intensive care and successful collaborations with emergency medicine investigators (PMID 15163774, 19318384, 2307512, 29347874, 25272316).

Significance: This innovative and unique trial will examine the safety and efficacy of the intervention on a clinically relevant endpoint, thereby generating new knowledge that will result in implementable findings for the benefit of human health.

Consumer statement (Participant Moran): "When you have DKA, all you can smell and taste is acetone. You can't catch your breath. The thirst you feel is unquenchable. You are physically and mentally exhausted because of how diabetes infiltrates every aspect of your life and that you have failed again. This failure is compounded as the noise and monitors of the ICU trigger flashbacks to your first DKA admission. You wish for a cure that will never come, to alleviate the pain of failure that persists until you are discharged home. Earlier discharge will minimise this burden, physically and psychosocially. This clinical trial offers hope that we may get home sooner, reducing suffering and improving our physical, mental and emotional recovery. We need this trial."

AIMS AND HYPOTHESES

Aim: To determine whether in critically ill patients presenting to the Emergency Department (ED) with DKA, fluid therapy with Plasma-Lyte compared to saline increases the number days alive and out of hospital (hospital-free days)

Hypotheses: In patients admitted to an ICU with DKA;

- Fluid therapy with Plasma-Lyte increases hospital-free days compared to saline,
- The increase in hospital-free days associated with the use of Plasma-Lyte will translate to overall cost savings.

BACKGROUND

The incidence of DKA is increasing in Australasian ICUs: DKA is a life- threatening complication of diabetes mellitus, described in patients with both type-1 diabetes, and type-2 diabetes. Data from the Australian Institute of Health and Welfare suggest that between 2009-10 to 2014-15, there has been a 21% increase in the hospitalisation amongst young people with DKA (1). The Australian and New Zealand Intensive Care Society (ANZICS) Centre for Outcomes Research (CORE) database revealed that the incidence of ICU admission of patients with DKA in Australia and New Zealand increased 5-fold between 2000 and 2013 (0.97/100000, 95%CI 0.84 to1.10) in 2000 to (5.3/100000, 95%CI 4.98 to 5.53, (P<0.0001) (2).

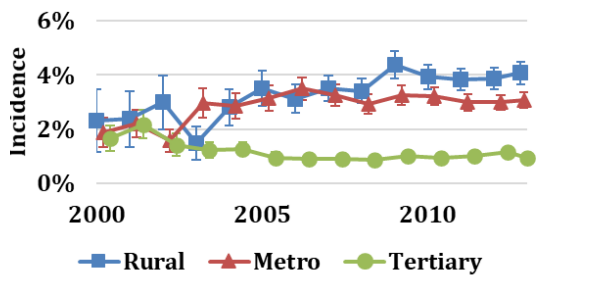


Figure 1: Annual trends in ICU admissions with DKA

Increasing incidences were observed predominantly in rural and metropolitan hospitals (**Figure 1**), About 88% of the admissions to the ICU were from the ED. The median (IQR) ICU and hospital length of stay were 1.8 (1-2.8) and 4 (2.6-7.4 days) respectively. Recent data from the ANZICS-CORE database confirmed the persistent high admission rate of severe DKA to Australian ICUs - 2849 and 2862 admissions in 2019 and 2020.

Current recommendations for fluid therapy in DKA: Patients with DKA present with hyperglycaemia, severe dehydration and a metabolic acidosis. Intravenous fluid replacement and insulin therapy remain cornerstones of therapy. The therapeutic goals of fluid management are directed at: a) Correcting dehydration and hypovolaemia over the first 24-48 hours (3,4,5) b) Reducing serum osmolality and plasma glucose concentrations towards normal levels c) Improving glomerular filtration rate to enhance ketone clearance d) Correcting electrolyte imbalances and e) Limiting the risk of complications such as cerebral oedema

Should saline be the fluid of choice in the treatment of DKA?: Current international guidelines recommend saline as the replacement fluid of choice, although no robust data from RCTs support these recommendations (3-5). The rationale for using saline is based on historical and anecdotal preferences, its efficacious restoration of the circulating volume and improvement of tissue perfusion. Despite these recommendations, the use of saline as the initial fluid therapy in DKA varies globally (UK 96%, USA 20-87% Denmark 97%) (PMID: 26286235, 23187990, 26582306, 17126447)

Within Australia, Queensland guidelines led by **RI-Russell** (12) recommend saline whilst NSW guidelines (13) advocate the use of Plasma-Lyte A study by **P-Venkatesh** evaluating the impact of rate of correction of hyperglycaemia in DKA also identified that 88% of ED physicians use normal saline and the median volume of fluid administered in the ED was 3L (range 2-4L) (PMID: 28866977). A survey (led by **P-Venkatesh**) of ICU physicians from Australian ICUs admitting >25 patients with DKA annually also demonstrated variation in practice: 79% of responding clinicians use saline, while 21% use either Plasma-Lyte or compound sodium lactate (Hartmann's solution).

The use of saline for fluid replacement causes hyperchloraemic acidosis: The non-physiologic

chloride concentration of saline as compared to plasma (154 vs 100 mmol/L) leads to hyperchloraemia and metabolic acidosis if saline is administered rapidly and in volumes greater than about 2L that are typically seen in DKA with increments in serum chloride from 99 +/- 0.6 mmol/L on admission to 110 +/- 1.1 mmol/L at 24 hrs (6).

Hyperchloraemia and acidosis increase morbidity: A high serum chloride concentration may have important adverse effects (7,8). A meta-analysis of high chloride vs low chloride fluid resuscitation in peri-operative and critical care patients reported that saline was associated with a higher risk of acute kidney injury (AKI), metabolic acidosis and increased duration of mechanical ventilation (7). In a large pragmatic RCT (n=13347) evaluating balanced salt solutions vs saline, the use of balanced solutions resulted in a lower incidence of major adverse kidney events than saline (4.7% vs. 5.6%; adjusted OR 0.82; 95%CI 0.70 to 0.95; P=0.01) (14).

There has been no systematic evaluation of any potential adverse effects of saline in the setting of DKA. The absence of robust evidence from RCTs supporting the recommended use of saline, the clear evidence of metabolic disturbances associated with the use of saline and the risk of adverse outcomes associated with the development of hyperchloraemia, mandate clinicians consider using balanced crystalloids to avoid the harmful effects of hyperchloraemia.

Plasma-Lyte is a promising alternative fluid replacement in DKA but there is insufficient evidence to guide practice (33):

Plasma-Lyte, is an isotonic intravenous crystalloid solution used in clinical practice to provide water, electrolytes and calories to patients. (15) The sodium and chloride composition of Plasma-Lyte more closely reflects that of human plasma compared with Saline and other buffered solutions (**Table 1**: Electrolyte compositions are in mmol/L). Plasma-Lyte is available in 1000 mL and 500 mL Viaflex® containers. The formulation is approved by the Australian Therapeutics Goods Administration.

Table 1: Electrolyte composition

	Plasma	Saline	Plasmalyte	Hartmann's
Na	143	154	140	129
K	4		5	5
Mg	2		3	
Ca	1			4
Cl	107	154	98	109
Acetate			27	
Gluconate			23	
Lactate				29
pH	7.4	4.0-7.0	6.5-8.0	5.0-7.0

Two specific properties of Plasma-Lyte make it suited for fluid therapy in DKA:

1) Plasma-Lyte is an alkalinising solution because of acetate and gluconate buffers, and it has lower chloride concentrations compared to saline minimising the risk of hyperchloraemic acidosis).

2) The metabolism of acetate and gluconate does not adversely affect plasma glucose, as opposed to Hartmann's solution which contains lactate, and its use may result in hyperglycaemia.

Studies of Plasma-Lyte in DKA: In a multi-centre retrospective analysis (P-Venkatesh) of adults admitted to the ICU for treatment of DKA, patients received almost exclusively either Plasma-Lyte (n=9) or saline (n=14) infusion up until 12 hours post-ICU admission (9). Serum bicarbonate elevation was higher in the Plasma-Lyte) group at 4 to 6 hours (8.4 vs. 1.7 mEq/L) and 6 to 12 hours (12.8 vs. 6.2 mEq/L) from baseline ($p<.05$). Cumulative fluid requirement was less in the Plasma-Lyte group (9).

In a subgroup analysis of patients with DKA (n=172) included in 2 cluster trials evaluating balanced crystalloids vs saline, the time to DKA resolution was shorter in the balanced crystalloids group

(median [IQR]: 13.0 hours; [9.5-18.8] than the saline group (median [IQR]: 16.9 hours; [11.9-34.5) (adjusted hazard ratio 1.68; 95% CI, 1.2 -2.4; P =0.004) (16).

Pilot Phase II study of Plasma-Lyte in DKA: P-Venkatesh supervised a Phase II cluster crossover study of Plasma-Lyte vs saline in patients with severe DKA to assess feasibility, compliance with fluid therapy, pilot data on efficacy and safety from 6 ICUs in regional Queensland over a 12-month

period (11). Out of 100 eligible patients, 90 were enrolled, (Plasma-Lyte n=48, Saline n=42). Compliance with allocated treatment was comparable between the two groups.
There was a faster resolution of metabolic acidosis in the Plasma-Lyte group. At 24 hours, DKA had resolved in 69% (Plasma-Lyte) and 36% (saline) of patients (OR 4.24, 95% CI 1·68 to 10·72, p=0·002). Despite an acetate concentration of 27 mmol/L in Plasma-Lyte, there was no increase in ketosis associated with its use. Median blood ketones at 48 hrs were 0·3 mmol/L (IQR 0·1-0·5) vs 0·3 (IQR 0·1-0·5) in the Plasma-Lyte and saline groups. The median ICU and hospital lengths of stay were 49 hours (IQR 23-72) vs 55 hours (IQR 41-80) and 81 hours (IQR 58-137) vs 98 hours (IQR 65-195) in the Plasma-Lyte (PL) and saline groups respectively. (11). (**Figures 2a and 2b**)

Figure 2a: KM curve- Time to ICU discharge

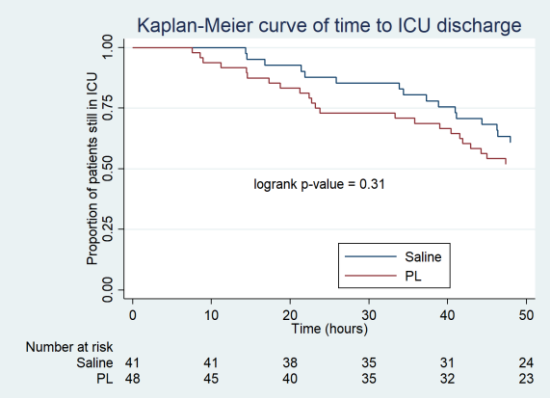
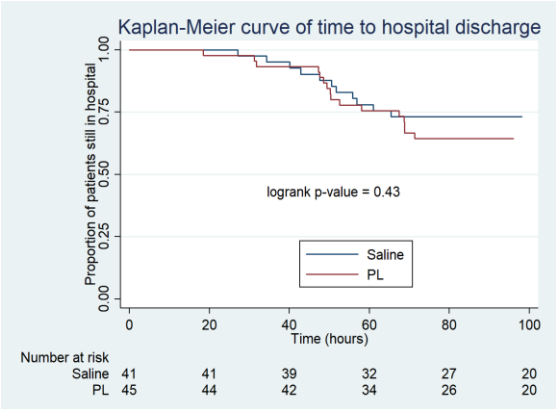


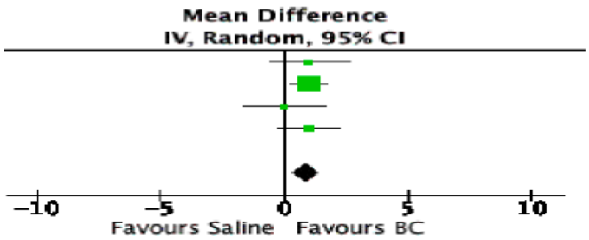
Figure 2b: KM curve- Time to hospital discharge



Adverse events were similar between groups, hypoglycemia 19% vs 26%, hypophosphatemia 69% vs 81%,, persistent ketosis 10% vs 12% and and severe hypokalaemia 10% vs 17% in the Plasma-Lyte and saline groups respectively.

Results of Meta-analyses

Figure 3: Meta-analyses Results



A recent meta-analysis comparing saline and balanced crystalloid in hospitalised patients (ICU and non-ICU) with DKA concluded that the use of saline was associated with longer time to DKA resolution, lower post-resuscitation serum bicarbonate levels, and longer hospital stay compared with balanced crystalloids (17).

The safety and efficacy of Plasma-Lyte 148 in DKA has to be confirmed in a large trial: In a recent RCTs of 11052 patients comparing Plasma-Lyte vs. saline in critically ill patients, there were no significant differences between the two groups with respect to 90-day mortality or adverse outcomes (18). DKA as a subgroup was not specifically reported in the trial.

There have been reports of cerebral oedema in DKA, particularly in children when hypotonic fluids have been used (19). To date, there are no published reports of any association between Plasma-Lyte and cerebral oedema in patients with DKA.

It is possible that the more rapid resolution of ketoacidosis with Plasma-Lyte may be countered by undesirable adverse effects on patient's neurological status. These effects are difficult for treating clinicians to detect in routine practice and may only be quantified in a high-quality, randomised controlled clinical trial in these patients and a clinically compelling reason to conduct this trial.

Variability in practice of fluid therapy in DKA: A major review of DKA management protocols in 2017 led by P-Ekinci concluded that there are major deficiencies in evidence for optimal management of DKA (20). Current practice is guided by weak evidence and consensus opinion.

Studies comparing Plasma-Lyte vs. saline in DKA demonstrate a trend towards a more rapid resolution of acidosis, equivalent glucose control and stable ketones with Plasma-Lyte. In addition,

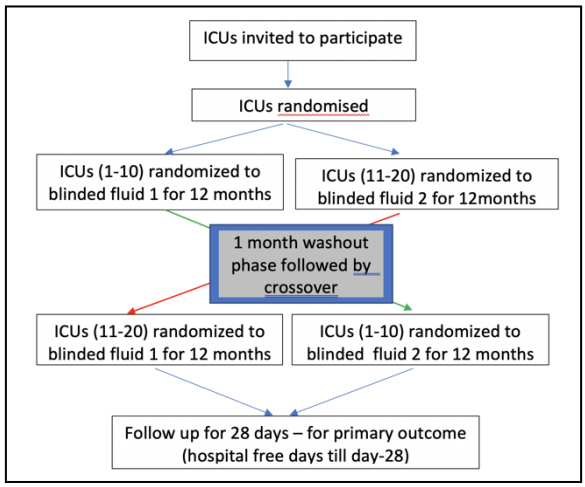
there are trends towards reduced length of ICU and hospital stay with the use of Plasma-Lyte.

Given the clinical uncertainty and substantial variability in practice, there is a scientific, clinical and health economic imperative to conduct a high-fidelity study to provide definitive evidence to inform clinicians' choice of resuscitation fluids for patients with DKA. The study we propose will address this critical knowledge gap.

Study design:

The proposed study is a multi-centre, blinded, cluster crossover trial conducted in 20 Australian ICUs, consisting of two 12-month intervention periods with a one-month inter- period gap in between.

Figure 4: Study Methodology



Each ICU is a single cluster, with all patients admitted with DKA to that ICU during the intervention periods potentially eligible for inclusion in the trial. After the first 12-month intervention period during which recruited patients will receive either Plasma-Lyte or Saline, there will be a one-month interperiod gap during which patients will not be recruited into the trial. Following this each ICU will change to using the fluid to which they were not assigned for the first period (Figure 4). All included patients will receive blinded fluids (Plasma-Lyte or Saline) as part of their DKA therapy depending on the fluid assigned to the site for the relevant intervention period.

Study population: The inclusion-exclusion criteria are summarised below.

Inclusion criteria:	***Exclusion criteria***
Patients ≥ 18 years of age, admitted via the ED with a diagnosis of moderate to severe DKA with all of the following criteria: (adapted from the American Diabetes Association diagnostic criteria) (3) • Blood glucose level > 14mmol/L • pH < 7.25 • serum bicarbonate <15 mmol/L • elevated anion gap > 12mmol/L • Ketones positive on urine dipstick measurements and • in the judgement of the treating clinician ICU admission is required	• age < 18 • Patients with hyperosmotic hyperglycemic non-ketotic syndrome

All patients 18 years of age and over who present to the ED or ICU at a participating site during either intervention period with severe DKA will be eligible for recruitment. Moderate to severe DKA was defined as arterial pH≤7·25 (or serum bicarbonate ≤15 mmol/L) and blood glucose ≥14·0 mmol/L and requirement for ICU admission in the judgement of the treating clinician.

Randomisation: Participating sites will be allocated using randomly generated computer tables in a 1:1 ratio to Plasma-Lyte or saline for the first intervention period. All sites will cross over to the alternate allocation for the second intervention period.

Participant recruitment: We estimate that between 400-480 patients will be recruited from 20 hospitals throughout Australia. Potential participants will be identified by ED or ICU clinicians.

Study treatment and blinding: Following randomisation, study participants will receive either Plasma-Lyte or saline. Study treatments will be supplied in identical 1000 mL bags with standardised fluid administration sets without revealing the fluid type. Both fluids are colourless, clear solutions and macroscopically indistinguishable. Both participants and study investigators will be blinded to study treatment allocation. The feasibility of blinding (**Figure 5**) of Plasma-Lyte and Saline has already been established with the PLUS study (**P-Hammond**.PMID: 35041780)

Study fluid regimen: The volume and rate of blinded study fluid administered will be guided by the standard clinical endpoints determined by the treating clinician. Study treatments will continue until discharge from ICU or for a maximum of 48 hrs, whichever is earlier. Glucose containing solutions can be added in as required for blood glucose or ketosis management. The use of bicarbonate therapy and the need for potassium, phosphate and magnesium supplementation will be at the discretion of the treating clinician and data on its use will be collected.

Figure 5: Blinded study fluid example

Follow-up schedule and data collection: Whilst in the ICU and hospital, study participants will have relevant study data extracted from their medical record to confirm study eligibility, assess baseline balance, demographics, admission diagnosis, and clinical information to derive standard measures of illness severity such as ICU severity of illness scores. Additionally, we will collect and report to the Data Safety and Monitoring Board (DSMB) serious adverse events and adverse events attributable to study treatments that are not already collected as study outcomes.

Primary outcome: Hospital-free days up to 28 days after randomisation has been chosen as the primary outcome as this is the most relevant patient-centred outcome in this cohort of patients and endorsed by the ANZICS Clinical Trials Group (PMID 22963216). In DKA, the primary determinants of clinical recovery from illness are the resolution of acidosis and correction of dehydration. In discussion with our consumer representative, a shorter length of hospital stay is an important patient-centred outcome, as this would not only reflect improving physical health but also have positive psychosocial impact.

Other outcomes: Secondary and tertiary outcomes and process measures are in **Table 2** below:

Table 2	
Secondary outcomes	• ICU free days upto 28 days after randomisation • ICU and hospital readmissions upto 28 days after randomisation • Acute kidney injury assessed by comparing serum creatinine • Episodes of post-randomisation decrease in GCS<9 in the first 24 hours • Time to resolution of ketosis • Cumulative insulin dosage in the first 48 hours
Tertiary outcomes	• Cost-effectiveness analysis
Process measures	• Serum acetoacetate and β-hydroxybutyrate at 12, 24 and 48 hours • Serum base excess at 6, 12 and 24 hrs • Serum Na /K and Cl concentration at 24 hours

Sample size: The primary outcome is hospital-free days (HFD) up to Day 28, which accounts for the competing risk of death by allocating zero hospital free days to any patient who dies before day 28 even if death occurs after hospital discharge. Since post-discharge mortality is very low in patients with DKA, hospital length of stay is the predominant determinant of hospital-free days and was used to inform power calculations.

There are 20 clusters in each interventional period. Based on our phase II data, the average enrolment per cluster is expected to be 10-12 patients per period. Over the 2 periods, 20-24 patients per cluster are expected to be enrolled, generating an anticipated sample size ranging between 400-480 patients.

Based on HFD assuming no hospital readmissions from our Phase-II study (mean HFD=21.4, SD 6.46 in saline group and mean HFD=23.3 SD 3.86 in Plasmalyte group), we have 91.4% power to identify a difference of 1.9 HFD between arms with a sample size of 400 and 94% power if we enrol 480 patients. A 1–2-day difference in HFD is consistent with effect size reported in a recent SRMA and is still important to both patients and healthcare resource utilization as these patients often require admission to high-dependency units for IV insulin and frequent blood testing.

These calculations are based on a level of alpha = 0.05, and intra-cluster coefficient of 0.01. This study size allows for a potential withdrawal and loss to follow-up rate of 1% (based on the recently

completed large-scale ICU trials) with negligible effect on study power.

Statistical analysis: All analyses will be conducted on an intention to treat basis using standard statistical methods for continuous and categorical data. The primary outcome will be analysed using a mixed model considering the cluster-effect and sequence allocation. Time to hospital discharge will be analysed using a survival analysis with death as a competing risk (and robust standard errors at cluster level). Pre-defined subgroups will include Type I vs Type II diabetes, patients on SGLT2 inhibitors, and severity of acidosis defined by admission pH of 7.00-7.25 or pH <7.0. Analyses will be based on complete-case sets but a multiple imputation approach to deal with missing data will be considered according to the magnitude and patterns of missing data. A statistical analysis plan will be finalised and published before data-lock as we have done with our previous trials.

Cost-effectiveness analysis: The primary cost-effectiveness analysis, led by a health economist from the George institute (TGI), will be conducted from the Australian healthcare payer's perspective using a within-trial analytical time horizon of 28 days. We will calculate incremental cost-effectiveness ratios, including the cost per hospital bed day saved and the cost per ICU bed day saved for Plasma-Lyte compared to saline. Assessment of resource use will be restricted to the index hospital admission. We will calculate the cost of hospital admissions using data on ICU and hospital length of stay using published Australian data. To increase the robustness of the sampling distribution, we will use non-parametric bootstrapping with unrestricted random sampling to produce cost and effectiveness replications, and confidence intervals for the cost-effectiveness ratios. The team from TGI have successfully completed studies of costs and cost-effectiveness analysis of fluid resuscitation therapies. (PMID: 32828672)

DSMB and Interim analyses: One interim analysis will be conducted by the DSMB, when 200 patients have been enrolled and followed until hospital discharge with additional analyses and safety reviews performed at the discretion of the DSMB. Specific stopping rules will be developed in consultation with the DSMB pertaining to serious adverse events and futility measures and included in the charter

Feasibility of an Australia-New Zealand trial of fluids in DKA: This study will be conducted by the George Institute for Global Health and has been endorsed by the Australasian College of Emergency Medicine. TGI has an unrivalled track record in conducting and completing large scale clinical trials in intensive care. SAFE (n= 6997), NICE-SUGAR (n=6,104), CHEST (n=7000) ADRENAL trials (n=3800)(PMID 15163774, 19318384, 2307512, 29347874),. There is a strong track record collaborative ICU-ED trials demonstrated by the ARISE study (P-Keijzer). The incidence of ICU admissions with DKA in ANZ is well known, allowing for robust sample size estimations. In our Phase II study, the 6 participating units enrolled 90% of the eligible patients. Through the ANZICS database, we have identified 20 units which admit > 25 patients with DKA per year. Even recruitment of 80% of the eligible cohort will allow the enrolment of 480 patients within the 2-year time frame. There is strong commitment and equipoise amongst clinicians in these units to take part in this unique study. We have demonstrated the feasibility of use of Plasma-Lyte. Study fluids will be manufactured and supplied with masking by Baxter Health Care, Sydney, Australia (Letter available with research office).

Team Quality and Capability

We are a strong, diverse research team of Diabetes, Intensive Care, and Emergency Medicine, with substantive expertise in diabetes, ketoacidosis, acid-base balance, and fluid therapy. The team, comprising of 2 female and 4 male Investigators, includes experienced (40%), early /mid-career researchers (60%). with exceptional track records in conducting large-scale randomised controlled trials collectively publishing > 200 papers in these key areas.

RI-Russell is an endocrinologist, President of the Australian Diabetes Society who led the development of guidelines for DKA in Queensland and will play a major role in study conduct, engagement of endocrinologists and guideline update following study completion.

P-Venkatesh led the NHMRC funded world's largest study of septic shock (ADRENAL), published in the New England journal of Medicine (PMID 29347874). He led the largest epidemiological

study of DKA in Australia and supervised the novel Phase II study of a buffered salt solution (Plasma-Lyte vs sodium chloride in DKA (SCOPE-DKA) that informed the design of this study.

P-Ekinci is a nationally recognised academic endocrinologist who has published widely in diabetes and DKA and sits on numerous national scientific, clinical and educational committees. Her systematic review of the literature on the evidence for the treatment of DKA identified fluid therapy as a key target area.

P-Keijzer is an academic Emergency Medicine physician who has been involved in several RCTs of interventions in patients presenting to Emergency Departments that have resulted in practice-changing publications. He will coordinate the nationwide ED participation in the study.

P-Hammond is the Critical Care Program Lead at the George Institute and NHMRC Emerging Leader nurse researcher with an exceptional track record relative to opportunity. She has developed the translational fluid resuscitation program providing evidence of increased use of balanced salt solutions nationally and internationally. (PMID: 28498856)

P-Moran is a consumer advocate who has suffered from DKA, provided lived experience and feedback on protocol development and relevant patient outcomes. He will contribute to all aspects of the study design, operations and play a major role in the dissemination of results.

Timelines: The study is projected to last 3 years (**Table 3**).

Table 3: Timeline

Jan -June 2024	**Jun 2024-Dec 2026**	**Jan 2027-Mar 2027**	**Apr-June 2026**
Staff recruitment, study set up, ethics approvals, staff education, data base set up, start of patient enrolment	Completion of data collection	Database lock, data analysis, initial results.	Presentation and first publication

Ethical Considerations: The study will comply with all aspects of the National Statement and jurisdictional legal requirements. The study has been approved by the Metro North Queensland ethics committee. Both fluids, Plasma-Lyte and saline are routinely used in the management of DKA. Involvement in this research carries no additional risk to the baseline risk that is applicable to all patients presenting with DKA. The potential benefits from the research are faster resolution of acidosis, and shorter ICU and hospital lengths of stay All study data will be stored securely in encrypted spreadsheets on password-protected servers.

Community engagement and Translation of Results: We will publish the results of this work in high impact medical journals and ensure presentation at major scientific meetings. The investigators are leaders of their respective intensive care, emergency medicine and diabetes societies and will be involved in guideline development. We will undertake translational studies led by P-Hammond to evaluate clinician uptake of the results of our work as we have done with our previous trials (PMID 28498856). All components of the research program including protocol development, choice of primary outcome involved end-user representatives through **P-Moran** who will also play a role in dissemination of results.

Justification of our study design: While designing our trial, we considered the relative merits and disadvantages of several designs, including individual patient randomization. We chose a cluster cross over design to study the effects of interventions in a real-world, clinical environment. As clinical practice guidelines emphasize prompt initiation of fluid resuscitation for many illnesses in the ED including DKA, resuscitation fluids are often administered within minutes of a patient reaching the ED making it impractical for investigators to assign 0.9% saline versus Plasma-Lyte after patient arrival in the ED and before initiation of fluid administration.

Treatment allocation on an individual patient basis, as with an individual RCT, would likely lead to frequent crossover in the type of fluids received by individual patients initiated by clinicians immediately after ED arrival and the fluid type assigned by the study at a later time. This would bias results toward the null. Moreover, this trial will be conducted predominantly in rural and regional centres, where the research capacity is more suited to cluster trials as demonstrated by our Phase II

study. The trial design accords with other cluster crossover fluid trials in the ICU. (PMID 26444692).

As this is a pragmatic trial testing one intervention within an overall treatment strategy for DKA, we also elected not to prescribe a protocol for fluids and insulin therapy, as there is an expectation that standard treatment guidelines for DKA will be followed. Evidence that clinicians follow standard guidelines is shown in the sensitivity analysis (Table 4) from our large epidemiological study demonstrating similar key outcomes across the 4 categories of ICUs in Australia (2).

Table 4: **Sensitivity analysis of guideline adherence**

Category of ICU	Mean ICU LOS (days)	Highest plasma HCO3 mmol/L in the 1st 24 hrs in ICU (marker of fluid therapy and reversal of ketosis)	Hospital mortality
Tertiary	2.2±1.9	20.3±5.8	1.3%
Metro	2.3±2.1	19.9±5.6	1.3%
Rural	2.4±2.6	19±5.8	1.7%
Private	2.3±2.4	20.8±5.2	1.9%

Strengths of our study: Our pragmatic effectiveness trial is designed with statistical power to detect a clinically plausible effect on a clinically important, patient-centred outcome. The statistical analysis will be adjusted for clustering, temporal correlations, and period effects. To mitigate the risk of bias, we will use a central randomization process, allocation concealment blinding of the intervention and include a pre-specified statistical analysis plan that will include a hierarchical logistic regression model to adjust for cluster size and a robust assessment of intervention adherence.

Risks and Mitigation Strategies: We will adhere to the organisational risk policies in managing risks with significant implications for the Health Service or patient safety as outlined below:

***Failure to recruit at the expected level*:** The number of DKA admissions to Australian ICUs is known. At the ANZICS Clinical Trials Group meeting in 2021, a poll of clinicians indicated that 100% of responding clinicians were prepared to take part in a clinical trial of Plasma-Lyte vs. saline in patients with DKA. Site educational initiatives will be maintained to ensure target recruitment.

Difficulties in obtaining interventions: The two interventions being evaluated are manufactured in Australia by Baxter and they have agreed to supply the study fluids with masking.

Impact of Covid: Covid-19 risk minimisation strategies will be utilised, including flexible consent models, remote monitoring, and source data verification.

OUTCOMES AND SIGNIFICANCE

Knowledge gain: The optimal fluid therapy in DKA has long been debated and remains unclear. Our unique Phase III study will be conducted in a homogeneous patient population and will provide clinically meaningful data to address an important question.

Clinical significance: Every year there are more than 7000 patients in Australia diagnosed with DKA, of whom a third require admission to an ICU. If Plasma-Lyte is demonstrated to increase hospital free days, (HFD) it could be used widely across the hospitals which would reduce hospitalisation by 1-2 days for more than 7000 patients. There may also be reductions in ICU length of stay which will have implications for the availability of ICU beds and triage.

Economic significance: A 1 day increase in HFD (which translates to a 1-day reduction in hospital length of stay (each hospital day is about 2223AUD) would translate to savings of 15.6 million dollars per year for 7000 patients. (Data from independent hospital pricing authority)

Research capacity building: As this study will be recruiting patients predominantly from rural and regional hospitals, they will have now become involved in a large randomised, controlled trial, allowing them to acquire the necessary research infrastructure and skills for future investigations and to make clinical research an integrated component of patient care.

Global relevance: Our 400-participant trial will inform policy and practice not only in in Australia but also around the world. Plasma-Lyte is inexpensive and, if shown to be beneficial, there should be no barrier to rapid implementation into routine clinical practice, including outside the ICU, in developing as well as developed countries.

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