APPENDIX 1

Specialist Treatment of Inpatients: Caring for Diabetes (STOIC-D)

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N/A

Statement of Compliance

This study will be conducted in compliance with all stipulation of this protocol, the conditions of the ethics committee approval, the NHMRC National Statement on ethical Conduct in Human Research (2007) and the Note for Guidance on Good Clinical Practice (CPMP/ICH-135/95).

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1. STUDY SYNOPSIS

Provide brief information

Title:	Specialist Treatment of Inpatients: Caring for Diabetes
Short Title:	STOIC-D
Design:	Prospective randomised controlled trial (RCT)
Study Centers:	Melbourne Health
Hospital:	The Royal Melbourne Hospital City Campus
Study Question:	Does proactive (early intervention) specialist care for hospital inpatients with diabetes or new hyperglycaemia improve glucometric and clinical outcomes?
Study Objectives:	Primary objectives To determine if proactive (early intervention) specialist care of hospital inpatients with diabetes or new hyperglycaemia results in improvements in: • Mean patient-day glucose Secondary objectives To determine if proactive specialist care of hospital inpatients with

	diabetes or new hyperglycaemia results in improvements in: • Healthcare-associated infection (HAI) incidence • Proportion of participants with mean glucose < 12.0 mmol/L • Mean patient-day weighted mean glucose • Length of stay in ICU

Inclusion Criteria:	• Admission to the Royal Melbourne Hospital City Campus during the study period
	• Either:
	  o a diagnosis of diabetes recorded in the clinical record at the time of hospital admission, or
	  o a random glucose result ≥ 11.1 mmol/L recorded during the admission
	• Age ≥ 18 years
	• Non-pregnant
	• Admission to a study ward as defined in the protocol
	• Admission under a study admitting unit as defined in the protocol

Number of Planned Subjects:	T1DM: 200-400. Medical: 1,376. Surgical: 1,376.
Investigational product:	N/A
Safety considerations:	N/A
Statistical Methods:	Primary analysis: intention-to-treat basis Sensitivity analysis: per-protocol basis Patient-day mean glucose: modelled using a GEE with an autoregressive correlation structure Infection rates: two-sided test for proportions with un-pooled variance
Subgroups:	Trial populations – Participants belonging to the following populations will be analysed separately as distinct trial populations: • Participants with a diagnosis of type 1 diabetes mellitus (T1DM) • Participants admitted under a medical admitting unit • Participants admitted under a surgical admitting unit

2. GLOSSARY OF ABBREVIATIONS & TERMS

Abbreviation	Description (using lay language)
ACEI	Angiotensin Converting Enzyme Inhibitor
ACS	Acute Coronary Syndrome
AIDS	Acquired Immunodeficiency Syndrome
AGD	Adverse Glycaemic Day
ARB	Angiotensin II Receptor Blocker
AUC	Area Under the Curve
BDR	Bedside Diabetes Review
BGL	Blood Glucose Level
CCI	Charlson Comorbidity Index
CGM	Continuous Glucose Monitoring
CHF	Chronic Heart Failure
CKD	Chronic Kidney Disease
COPD	Chronic Obstructive Pulmonary Disease
CSN	Contact Serial Number – A number assigned by the electronical medical record to each patient admission to hospital.
DKA	Diabetic Ketoacidosis
DPPIVI	Dipeptidyl Peptidase IV Inhibitor
EDR	Electronic Diabetes Review
eGFR	Estimated Glomerular Filtration Rate
EMR	Electronic Medical Record
GCP	Good Clinical Practice
GEE	Generalised Estimating Equation
GLP1RA	Glucagon-Like Peptide 1 Receptor Agonist
HAI	Healthcare-Associated Infection

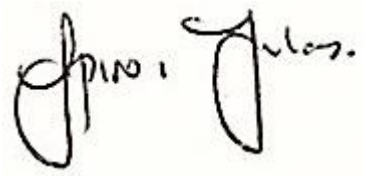
HHS	Hyperglycaemic Hyperosmolar State
HIV	Human Immunodeficiency Virus
ICU	Intensive Care Unit
IDS	Inpatient Diabetes Service
LADA	Latent Autoimmune Diabetes in Adults
NBGM	Networked Blood Glucose Monitoring
PVD	Peripheral Vascular Disease
RCT	Randomised Controlled Trial
REDCap	Research Electronic Data Capture – An electronic data storage system for research
RMH	Royal Melbourne Hospital
SGLT2I	Sodium-Glucose Transporter 2 Inhibitor
T1DM	Type 1 Diabetes Mellitus
T2DM	Type 2 Diabetes Mellitus
T3cDM	Type 3c (pancreatogenic) Diabetes Mellitus
TIA	Transient Ischaemic Attack

3. INVESTIGATOR AGREEMENT

By my signature, I confirm that I have read and understand this protocol, and agree to conduct this clinical study in accordance with the design and provisions of the protocol as documented herein. In particular, I/we have agreed to:

- Abide by all appropriate regulatory authorities' guidelines.
- Have a clear understanding of all aspects of the protocol.
- Maintain confidentiality and assure security of confidential documents such as the protocol, case report form, final study reports, manuscript drafts, unpublished data, correspondence, etc.
- Assure direct access by the Human Research and Ethics Committees and/or representatives of these organisations to original source documents.
- Obtain Human Research and Ethics Committee approval of the study, any amendments to the study and periodic re-approval as required.
- Keep the Human Research and Ethics Committee informed of adverse events and periodically report status of the study.
- Obtain written informed consent from each participant or their legal representative.
- Make prompt reports of serious adverse events to the Human Research and Ethics Committee and regulatory authorities and/or the representatives of these organisations.
- Cooperate fully with any study-related GCP audit.

- Abide by the established grant payment guidelines.
- Abide by manuscript preparation/authorship guidelines established at the outset of the study.



A/Prof Spiros Fourlanos 27/07/2020

Primary Investigator Signature | Primary Investigator Name | Date

4. STUDY SITES

4.1 STUDY LOCATION/S

Site	Address	Contact Person	Phone	Email
Royal Melbourne Hospital City Campus	300 Grattan Street, Parkville VIC 3050	Dr Rahul Barmanray	9342 7365	rahul.barmanray@mh.org.au

5. INTRODUCTION/BACKGROUND INFORMATION

5.1 LAY SUMMARY

Over a third of patients in hospital have diabetes at any one time. We know that managing the blood levels of glucose, a type of sugar, in people with diabetes who are in hospital is very important as glucose that is too high or low results in many problems including infections. At the Royal Melbourne Hospital there are two major changes underway that will improve our ability to monitor glucose levels in patients admitted to hospital. One is the institution of Networked Blood Glucose Monitoring, glucose testing devices that send glucose results immediately to the diabetes specialists. At present, the diabetes specialists must in most cases wait for other medical teams looking after patients with diabetes to refer to the specialists before becoming aware of them to be able to be involved in their care. The other major change is the institution of an Electronic Medical Record. At present, all doctors must retrieve and record information regarding any patient in the hospital via the paper record, kept at each patient's bedside while admitted to hospital. The electronic record will allow all doctors including the diabetes specialist team to review and record information about patients without having to physically go to the bedside, which will greatly improve efficiency.

On the basis of previous research done by our group, it is likely that a specialist diabetes team being able to be involved in the care of patients with diabetes earlier results in improved glucose levels for patients while in hospital, which in turn reduces the risk of infections acquired while in hospital. We plan to conduct a study where all patients with diabetes or high glucose levels at the time of admission to hospital are separated into two groups. One group will receive early and proactive diabetes specialist care while the other group will receive the same care they currently receive. Comparing outcomes between these two groups will

tell us whether, in which ways, and by how much early in-hospital specialist care of diabetes improves these outcomes.

5.2 INTRODUCTION

A consequence of the increasing prevalence of diabetes in Australia is up to 35% of hospital inpatients have diabetes(1). Hyperglycaemia and hypoglycaemia in this population increases rates of many adverse outcomes including Healthcare-Associated Infection (HAI)(2). Significant evidence links hyperglycaemia to altered immune function that predisposes to such HAIs. Recent evidence suggests adverse outcomes can be reduced through the implementation of a proactive diabetes management, with a particular improvement noted in nosocomial or HAI rates(3). This represents a significant cost saving to the health system.

Inpatient glycaemia is often suboptimal due to clinical inertia on the part of treating teams(4). The RAndomised clinical trial of a Proactive Inpatient Diabetes Service (RAPIDS) parallel cluster randomised controlled trial (RCT) conducted at the Royal Melbourne Hospital (RMH) investigated the impact of a proactive model of diabetes care which consisted of early intervention for people with diabetes(3). The intervention, adjusted for patient clinical features, resulted in 28% fewer adverse glycaemic days (any day where blood glucose (BG) >15 or <4 mmol/L) and a 62% significant decrease in HAI incidence pre- and post- intervention (6.4% vs. 2.4%, p=0.04) in the intervention but not the control wards (7.0% vs. 8.6%). RAPIDS was a proof-of-concept study that demonstrated the potential benefits of early intervention for people with diabetes admitted to hospital but this model of care has low feasibility given all patients in the RAPIDS intervention were seen at the bedside by a specialist diabetes team.

Following the findings of the RAPIDS trial, in 2019 the RMH established NBGM use across all inpatient wards of the hospital and became the first hospital in Australia to implement a full glucose measurement network for inpatient care. This new glucose meter electronic infrastructure alongside the introduction of an electronic medical record (EMR) system i.e. Epic® provided an unprecedented opportunity at RMH to assess the relationship between glycaemia and adverse events, in particular HAIs, across all diabetes inpatient groups.

This research project hypothesises that proactive (early intervention) specialist care for hospital inpatients with diabetes or new hyperglycaemia improves glucometric and clinical outcomes. Adults who are admitted to the RMH during the trial period with either a diagnosis of diabetes recorded in the clinical record at the time of hospital admission or a random glucose result ≥ 11.1 mmol/L recorded during the admission will be randomised to either the intervention or the control arm of trial. Participants randomised to the intervention will receive early proactive specialist management of their diabetes and/or glucose while those randomised to the control arm will receive the same standard and processes of care they currently receive in the pre-trial hospital environment.

This project combines technology (NBGM and the EMR) with early proactive specialist care of diabetes and glucose, which has never previously been performed. If it shows benefit it will stimulate a significant change in the standard model of inpatient diabetes care.

5.3 BACKGROUND INFORMATION

Glycaemia and adverse outcomes

A consequence of the increasing prevalence of diabetes in Australia is up to 35% of hospital inpatients have diabetes(1). When these patients experience hyperglycaemia or hypoglycaemia (adverse glycaemia or dysglycaemia) a large body of evidence suggests this is associated with increased rates of a range of adverse outcomes including Healthcare-Associated Infection (HAI)(2). There is strong mechanistic evidence for a deleterious effect of hyperglycaemia on immune function, in particular on innate immunity, which predisposes to HAI. Hyperglycaemia has been associated with reduced polymorphonuclear leukocyte

chemotaxis(5), reduced superoxide radical production(6), and reduced neutrophil degranulation(7), all of which leads to reduced microbial neutralisation and elimination. It has been shown that hyperglycaemia inhibits macrophage phagocytosis and interleukin-1 release(8). There is a further effect on adaptive immunity due to increased non-enzymatic glycosylation of immunoglobulin(9).

There is general international consensus that optimal glycaemia in the non-critical care hospitalised patient consists of maintaining the blood glucose (BG) in the range of 5.0 – 10.0 mmol/L(10-12). Both hyperglycaemia and hypoglycaemia in inpatients are associated with increased mortality and length of stay (LOS) compared to normoglycaemia(13, 14). The mechanisms for this are multiple and include increased rates of infection, cardiac arrhythmia, myocardial stress, acute kidney injury, and neurologic events(15-17).

Recent evidence suggests adverse outcomes can be reduced through the implementation of a proactive diabetes management, with a particular improvement noted in nosocomial or HAI rates(3). Clinical evidence for a reduction in HAI rates related to intensive glycaemic control in the non-critical care setting comes predominantly from a number of small uncontrolled studies, however, a meta-analysis of trials of intensive glycaemic control in this setting found a decreased risk (odds ratio 0.41) of infection(18). This represents a significant cost saving to the health system. For example, deep surgical site infections cost on average $13,187 (AUD) per patient in 2013(19). If the infection involves a surgical joint prosthesis, costs can extend to more than $70,000 (AUD) per case.

Proactive inpatient diabetes care

Inpatient glycaemia is often suboptimal due to clinical inertia on the part of treating teams(4). Recent evidence suggests the Melbourne Glucose alert pathway (GAP) can help guide health professionals to manage adverse glycaemia in hospital. GAP is a safe, acceptable, and effective intervention that improves clinician responsiveness(20). Use of GAP increased medical and nursing staff action by 40% and 70% respectively in response to adverse glycaemia(20).

Apart from better pathways for inpatient diabetes care, international consensus guidelines advocate for the implementation of a specialist multi-disciplinary inpatient diabetes team (IDT) by health services(12, 21). Whilst the majority of IDT studies have assessed reactive teams, there are 12 published studies of proactive IDTs. These latter trials have showed mean BG reduction of 1.0 – 2.0 mmol/L(22, 23), increased BG proportion within range(24), and a decrease in LOS(22, 25), with no specific assessments of HAI rates.

The RAndomised clinical trial of a Proactive Inpatient Diabetes Service (RAPIDS) parallel cluster randomised controlled trial (RCT) conducted at the Royal Melbourne Hospital (RMH) investigated the impact of a proactive model of diabetes care which consisted of early intervention for people with diabetes(3). A total of 1,002 non-critical care patients across 8 wards were cluster-randomised by ward to a proactive IDT intervention or usual care. The intervention consisted of proactive assessment by the IDT aiming to see patients with diabetes within 24 hours of admission, assisted by the novel Melbourne Glucose Alert Pathway (GAP). Diabetes and adverse glycaemia was identified by the use of networked blood glucose meters (NBGMs) on interventional and control wards, which allowed the real-time remote monitoring of glycaemia by the IDT. The trial recruited 1,002 patients, predominantly with type 2 diabetes, and including 19,062 BG tests over 5,447 patient-days. The intervention, adjusted for patient clinical features, resulted in 28% fewer adverse glycaemic days (any day where blood glucose (BG) >15 or <4 mmol/L) and a 62% significant decrease in HAI incidence pre- and post- intervention (6.4% vs. 2.4%, p=0.04) in the intervention but not the control wards (7.0% vs. 8.6%). RAPIDS was a proof-of-concept study that demonstrated the potential benefits of early intervention for people with diabetes admitted to hospital but this model of care has low feasibility given all patients in the RAPIDS intervention were seen at the bedside by a specialist diabetes team. The generalisability of the RAPIDS findings to other hospitals in Australia and internationally is yet to be established.

Following the findings of the RAPIDS trial, in 2019 the RMH established NBGM use across all inpatient wards of the hospital and became the first hospital in Australia to implement a full glucose measurement network for inpatient care. This new glucose meter electronic infrastructure alongside the introduction of an electronic medical record (EMR) system i.e. Epic® provided an unprecedented opportunity at RMH to assess the relationship between glycaemia and adverse events, in particular HAIs, across all diabetes inpatient groups. It will foster the development of interventions and further cluster-randomised trials to characterise the effects of maintaining normoglycaemia on reducing adverse diabetes events in diabetes patients generally and in specific diabetes sub-populations. Furthermore, the findings of the RAPIDS trial, suggesting a reduction in HAIs following proactive glycaemic intervention, need to be tested for reproducibility and further validation.

6. STUDY OBJECTIVES

6.1 HYPOTHESIS

Proactive (early intervention) specialist care for hospital inpatients with diabetes or new hyperglycaemia improves glucometric and clinical outcomes.

6.2 STUDY AIMS

- To determine if proactive specialist care of hospital inpatients with diabetes or new hyperglycaemia results in improvements in glucometric outcomes.
- To determine if proactive specialist care of hospital inpatients with diabetes or new hyperglycaemia results in improvements in clinical outcomes e.g. Healthcare-associated Infections (HAIs).
- To assess the feasibility and acceptability of a hospital-wide proactive specialist inpatient diabetes service.

6.3 OUTCOME MEASURES

Primary outcome

To determine if proactive specialist care of hospital inpatients with diabetes or new hyperglycaemia results in a reduction in **patient-day mean glucose**.

Patient-day mean glucose is calculated by grouping all glucose results by patient-day and returning a mean value for each patient-day of all hospital admissions that comprise the study population(26).

Secondary outcomes

Key secondary outcomes

To determine if proactive specialist care of hospital inpatients with diabetes or new hyperglycaemia results in improvements in:

- Healthcare-associated infection (HAI) incidence
    - Defined as a sterile-site positive culture or clinician action on a suspected infection (antibiotic prescription) where both the positive culture was taken and the antibiotic prescription commenced at least 48 hours following admission.
- Proportion of participants with patient-day-weighted mean glucose < 12.0 mmol/L
- Mean participant patient-day-weighted mean glucose
    - Defined as the mean of glucose results for a particular patient on a particular calendar day(26).
- Proportion of Adverse Glycaemic Days (AGD)

    - An AGD is defined as a day on which a participant experiences either hypoglycaemia (glucose < 4.0 mmol/L) or hyperglycaemia (glucose ≥ 15.0 mmol/L).
- Ward transfers to a high-dependency unit incidence
    - Defined as participants who were transferred to a high-dependency unit, including the Intensive Care Unit (ICU), Coronary Care Unit (CCU), and Respiratory Care Unit (RCU) from a hospital ward at least once in the course of their admission. This does not include participants who were admitted to a high-dependency unit from the emergency department or another hospital.

Exploratory secondary outcomes

Process

- Changes in diabetes therapy in response to hypoglycaemia or hyperglycaemia
- Appropriate in-hospital management of glucose-lowering medications e.g. peri-operative with-holding of metformin and/or SGLT2I medications.
- Changes in insulin therapy from pre-admission regimen
- New insulin therapy (including intravenous insulin infusions)
- Proportion of patients who received an Inpatient Diabetes Service (IDS) bedside diabetes review (BDR)
- Time from hypoglycaemia or hyperglycaemia to referral to inpatient diabetes service
- Time from hypoglycaemia to next blood glucose test.
- Time from hypoglycaemia to next blood glucose result in the normal range.

Glucometric

- Rate of level 1 (mild) hypoglycaemia with glucose < 4.0 mmol/L per patient-day
- Rate of level 2 (moderate) hypoglycaemia with glucose ≤ 3.0 mmol/L per patient-day
- Rate of level 3 (severe) hypoglycaemia with glucose ≤ 2.2 mmol/L per patient-day
- Mean patient-stay glucose
- Proportion of patient-day mean glucose values within target range (glucose 5.0 – 10.0 mmol/L)
- Proportion of patient-stay glucose values ≥ 15.0 mmol/L
- Interstitial glucose Area Under Curve (AUC) in patients who are monitoring with Continuous Glucose Monitoring (CGM)
- Glycosylated haemoglobin within 6 months following discharge

Clinical

- Inpatient Acute Coronary Syndrome (ACS) incidence
- Inpatient acute cerebrovascular accident and Transient Ischaemic Attack (TIA) incidence
- Delirium incidence
- Inpatient diabetic ketosis incidence (blood ketones > 1.5 mmol/L, pH > 7.30)
- Inpatient diabetic ketoacidosis incidence (blood ketones > 1.5 mmol/L, pH < 7.30)
- Acute kidney injury incidence (increase in creatinine by ≥ 50% from admission)
- Admission to a high-dependency unit i.e. Intensive Care Unit (ICU), Coronary Care Unit (CCU), Respiratory Care Unit (RCU) from the emergency department or from another hospital.
- Critical deterioration calls i.e. Medical Emergency Team (MET) and Code Blue calls
- Inpatient mortality
- Intensification or de-intensification of outpatient diabetes management.
- 30-day emergency department presentations and readmissions
- 90-day emergency department presentations and readmissions
- 30-day post-discharge morbidity and mortality

- 90-day post-discharge morbidity and mortality
- 30-day post-discharge infection incidence
- 90-day post-discharge infection incidence

Patient-centred

- Functional health and well-being (SF-12) and health utility (EQ-5D) at admission
- Functional health and well-being (SF-12) and health utility (EQ-5D) at 30 days post-discharge
- Functional health and well-being (SF-12) and health utility (EQ-5D) at 90 days post-discharge

Economic (Healthcare resource utilisation)

- Length of hospital stay
- Clinical costing
- Cost of the proactive diabetes care package
- Emergency and ambulatory care costs
- Treatment costs associated with diabetes-related complications
- Visits to general practitioners and other healthcare professionals

Pre-specified subgroups

The primary and key secondary outcomes will further be analysed as per the following pre-specified subgroups:

- Admission HbA1c ≥ 8.0%
- Admitted during the first 6 weeks of the intervention vs. remaining duration of intervention
- Diabetes type
- Administration of non-inhaled and non-topical glucocorticoids during the admission i.e. oral, intramuscular, intravenous, or intra-articular glucocorticoids
- Administration of supplemental or replacement therapeutic nutrition i.e. parenteral nutrition or enteral feeds administered via an enteral access tube e.g. nasogastric tube (NGT), percutaneous endoscopic gastrostomy (PEG) tube
- Participants diagnosed with an infection at the time of or within 48 hours of admission to hospital
- Participants diagnosed with an infection ≥ 48 hours after the time of admission to hospital
- Participants admitted with an Acute Coronary Syndrome (ACS)
- Participants admitted with an acute cerebrovascular accident or Transient Ischaemic Attack (TIA)
- Participants admitted on business days (Monday to Friday, excluding public holidays) vs. non-business days (Saturday, Sunday, and public holidays)
- Participants admitted during business hours (0800-1700 Monday to Friday, excluding public holidays) vs. non-business hours (all other times).

7. STUDY DESIGN

7.1 STUDY TYPE & DESIGN & SCHEDULE

Type

Prospective randomised controlled trial (RCT)

Design

Population

Adults admitted to a tertiary centre with either a diagnosis of diabetes recorded in the clinical record at the time of hospital admission or a random glucose result ≥ 11.1 mmol/L recorded during the admission. Further details on the population are provided in Section 7.

Location

Single centre design. The study site is The Royal Melbourne Hospital City Campus, 300 Grattan Street, Parkville Victoria 3050.

Aims and objectives

The study design will allow the aims to be achieved with a high level of evidence. Previous work in this area by our group used a cluster-randomised design(3). Participant-level individual randomisation, facilitated by the new Electronical Medical Record (EMR) will allow the intervention's effects to be assessed with a higher degree of granularity and certainty than previous studies. Data to assess the primary and secondary outcomes are readily collected using this study design.

Study procedures

Trial entry

All patients who are admitted to the RMH during the trial period will be assessed for eligibility for the trial. If they meet the inclusion criteria they will be randomised at the time of admission to the RMH to either the intervention or the control arm of the trial. Randomisation will occur automatically and electronically through the EMR software. Further details on randomisation are provided in Section 7.3. A waiver of consent will be sought for recruitment of participants into this trial. Further details on consent are provided in Section 8.3.

Proactive specialist care (intervention arm)

Participants randomised to specialist care will be automatically added to a remote review list hosted on the EMR. This list will allow ongoing identification and review of the participants by the Inpatient Diabetes Service (IDS).

First electronic review + Home team management

Within 24 hours of admission to hospital for business day admissions (Monday to Friday, excluding public holidays) and within 48 hours of admission to hospital for non-business day admissions (Saturday, Sunday, and public holidays) after entering the trial, a participant's EMR record for the admission will be reviewed electronically and remotely by a member of the IDS. A standardised Electronic Diabetes Review (EDR) document will be completed and entered into the clinical record. The participant's home team junior doctor will also be alerted of this review directly through the RMH's internal communications systems. No direct changes to the participant's inpatient management will be made during the first electronic review. The participant's home team will manage their diabetes and glucose as per their clinical judgement.

Ongoing electronic review + Home team management

Following the first electronic review a participant will remain on the remote review list. Their glucose and medication record will be reviewed at least every second business day for the duration of their participation in the trial. If a change in glycaemic management is indicated, the IDS team member will complete a follow-up EDR document enter this into the clinical record. If this occurs the participant's home team junior doctor will also be alerted of this review directly through the RMH's internal communications systems. No direct changes to the participant's inpatient management will be made during ongoing electronic reviews. The participant's home team will manage their diabetes and glucose as per their clinical judgement.

Indications for a change in management include glucose outside of the target range for that patient or a change in clinical circumstances that are likely to cause glucose to move outside of the target range e.g.

glucocorticoid commencement, patient fasting for surgery, and thus a proactive change in glycaemic management is required. The specific glycaemic range targeted for most individuals will be between 5.0 – 10.0 mmol/L as recommended by national and international inpatient diabetes guidelines but may differ for some individuals based on the clinical context(10, 12).

Escalation to Bedside Diabetes Review (BDR)

If any of the following criteria are met the participant will be escalated by an IDS team member for a Bedside Diabetes Review (BDR) by the IDS using a direct review EMR list:

- Request from the home team that the participant be reviewed directly by the IDS.
- A diabetes diagnosis type that is anything other than type 2 diabetes (T2DM) e.g. type 1 diabetes (T1DM), type 3c diabetes (T3cDM), Latent Autoimmune Diabetes in Adults (LADA).
- Commencement of a significant dose of oral glucocorticoids i.e. equal to or greater than prednisolone 5mg total daily dose or equivalent(27).
- If on oral glucocorticoids at the time of admission, an increase in dose above the regular outpatient dose.
- Commencement of supplemental or replacement therapeutic nutrition i.e. parenteral nutrition or enteral feeds administered via an enteral access tube e.g. nasogastric tube (NGT), percutaneous endoscopic gastrostomy (PEG) tube. This does not include supplemental nutrition that a participant ingests orally e.g. Fortisip® nutritional supplement, regardless of whether this is prescribed by a dietitian.
- A major hypoglycaemic event i.e. BGL ≤ 3.0 mmol/L.
- A major hyperglycaemic event i.e. BGL ≥ 20.0 mmol/L.
- Persistent hyperglycaemia i.e. 2 days on which there is any BGL ≥ 15.0 mmol/L or 3 days on which there is any BGL ≥ 12.0 mmol/L.
- HbA1c ≥ 8.0%.

Bedside Diabetes Review (BDR)

A BDR involves a member of the IDS performing an inpatient consultation at the participant's bedside. This may involve modification of the participant's inpatient management, communication with their home team, and communication with the treating nurse unit. The participant will be seen directly as frequently and as long as they continue to derive benefit from this intensity of management. This will be determined clinically by the IDS according to each individual's clinical context based on the criteria described below.

De-escalation to ongoing electronic review

At any point following the initial direct review an IDS team member may determine that the participant's diabetes and glucose management are stable and that they no longer require ongoing bedside review by the IDS. They will then de-escalate the participant to electronic review, which shall occur at least every second business day. Criteria for this de-escalation include:

- No major hypoglycaemic events i.e. BGL ≤ 3.0 mmol/L and fewer episodes of hypoglycaemia.
- No major hypoglycaemic events i.e. BGL ≥ 20.0 mmol/L and fewer episodes of hyperglycaemia.
- A greater proportion of glucose levels within the patient's individualised target range.

If following this the participant again meets criteria for escalation to direct IDS review, this re-escalation to bedside review will occur at that time. The criteria for re-escalation are:

- Request from the home team that the participant be reviewed directly by the IDS.
- Commencement of a significant dose of oral glucocorticoids i.e. equal to or greater than prednisolone 5mg total daily dose or equivalent(27).

- If on oral glucocorticoids at the time of admission, an increase in dose above the regular outpatient dose.
- Commencement of supplemental or replacement therapeutic nutrition i.e. parenteral nutrition or enteral feeds administered via an enteral access tube e.g. nasogastric tube (NGT), percutaneous endoscopic gastrostomy (PEG) tube. This does not include supplemental nutrition that a participant ingests orally e.g. Fortisip® nutritional supplement, regardless of whether this is prescribed by a dietitian.
- A major hypoglycaemic event i.e. BGL ≤ 3.0 mmol/L.
- A major hyperglycaemic event i.e. BGL ≥ 20.0 mmol/L.
- Persistent hyperglycaemia i.e. 2 days on which there is any BGL ≥ 15.0 mmol/L or 3 days on which there is any BGL ≥ 12.0 mmol/L.

Standard care (control arm)

Participants randomised to standard care will be automatically added to a list hosted on the EMR. This list will allow ongoing identification of the participants by the IDS. None of the following procedures described pertaining to standard care represent a departure from the management of diabetes in hospital inpatients as currently occurs at the RMH.

Home team management

The participant's home team will manage their diabetes and glucose as per their clinical judgement.

Escalation to IDS

If the home team believes they need additional advice or support in managing a participant's diabetes or glucose they can refer the participant to the IDS for review.

Bedside Diabetes Review (BDR)

A BDR involves a member of the IDS taking a referral from the home team and providing immediate phone advice. Depending on the clinical context the IDS will then perform an inpatient consultation at the participant's bedside at an appropriate time. This may involve modification of the participant's inpatient management, communication with their home team, and communication with the treating nurse unit. The participant will be seen directly as frequently and as long as they continue to derive benefit from this intensity of management. This will be determined clinically by the IDS according to each individual's clinical context.

De-escalation to home team management

At any point following initial IDS review an IDS team member may determine that the participant's diabetes and glucose management is stable and that they no longer require ongoing IDS review. They will then de-escalate the participant to home team management. Criteria for this de-escalation include:

- No major hypoglycaemic events i.e. BGL ≤ 3.0 mmol/L and fewer episodes of hypoglycaemia.
- No major hypoglycaemic events i.e. BGL ≥ 20.0 mmol/L and fewer episodes of hyperglycaemia.
- A greater proportion of glucose levels within the patient's individualised target range.

Trial exit

Participants will stop contributing glucose data and be considered to have exited the trial when one of the following events occur:

- Discharge from RMH City Campus
- Transfer to one of the following wards:
    - Palliative care ward

        - C 7W Palliative Care
    - Pre-discharge temporary ward
        - C Transit Lounge City Campus
    - Psychiatry ward
        - C Mntl Hlth Acute Inpatient Unit
        - C Mntl Hlth JC2ED
        - C Mntl Hlth JC2NP
    - Parkville campus ward
        - P Aged care 1
        - P Aged care 2
        - P Aged care 3
        - P Aged care 4
        - P Gardenview house
        - P Home dialysis service
        - P Rehabilitation
        - P RMH at Home SubAcute
        - P RPC Transit Lounge
        - P Transitional Care
- Transfer under one of the following admitting units:
    - Palliative care unit
        - PALL
    - Parkville campus-based unit
        - ASSM
        - RAMP
        - REHA
        - REHC
        - REHM
        - REHN
        - REHN2M
        - REHN3M
        - REHO
        - REHZ
        - REN
        - REST
        - RMED
        - RNEU
        - RORT
        - RRU
        - TRAN
    - Endocrinology specialist unit
        - DFU
        - ENDO
    - Patient's own home-based unit
        - HHIR
        - HHU
    - Psychiatry unit
        - NPSY
        - PSYC

- Non-RMH unit (bedcard of a patient admitted under a non-RMH precinct partner but currently physically located on a RMH ward)
  - MHICUPMHAE
  - MHICUPMMON
  - MHICUPMSONC
  - MONC
  - PMCU
  - PMHAE
  - PMMON
  - PMSONC
  - RWHGY
  - RWHOB
  - RWHON
- Length of stay of 15 days reached
- Death

If participants have exited the trial the IDS will communicate the relevant diabetes issues to the home team including the need for any ongoing specialist diabetes input. When the transfer destination is known, communication to the new unit/ward will be undertaken.

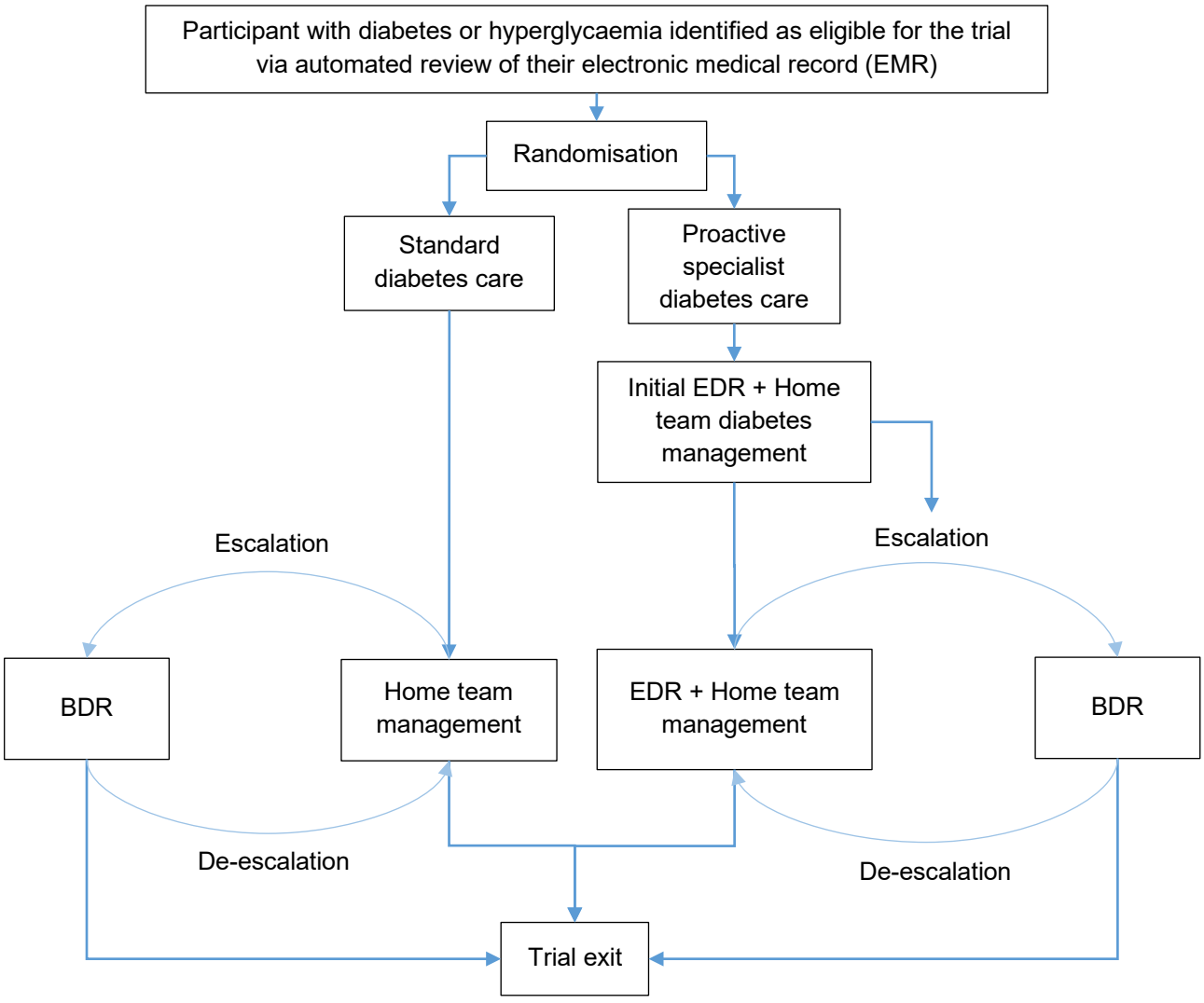


Figure 1: Participant flow through the trial. EDR = Electronic Diabetes Review. BDR = Bedside Diabetes Review

Multiple admissions

If a participant is admitted to the RMH multiple times during the study period and more than one of these admissions meets the inclusion criteria without any exclusion criteria being met, all such admissions can be included. If one of a participant's admissions meets the inclusion criteria without any exclusion criteria being met and a later admission meets the inclusion criteria but also meets an exclusion criterion, the earlier admission will still be included in the trial even though the latter admission will not.

Data

Identifiability

All data that is not marked as (*Identifier*) below will be collected and stored in a password-protected Research Electronic Data Capture (REDCap) project database against a randomly generated participant-specific study code. All data thus collected will be re-identifiable. All data marked as (*Identifier*) below will be collected and stored against the participant's study code in a password-protected Microsoft Excel file kept in the password-protected Endocrinology folder of the RMH network S: Drive (\\ssg.org.au\allfiles\SDrives). Only the principal investigator will have access to this identifier-containing document.

Trial entry

Trial entry occurs when a participant who meets the inclusion criteria is admitted to the RMH City Campus during the trial period.

Initial data points to be collected by review of the clinical record at trial entry include the following demographic and clinical information:

Demographics

- Unit record number (*Identifier*)
- Date of birth (*Identifier*)
- Age on date of admission
- Gender

Admission details

- Date of admission
- Admitting unit
- Admission ward
- Episode number (*Identifier*)
- Electronic Medical Record (EMR) Contact Serial Number (CSN) (*Identifier*)

Clinical details

- Primary diagnosis system
- Primary diagnosis specific
- CCI age in one of 5 categories
- CCI myocardial infarction
- CCI chronic heart failure
- CCI peripheral vascular disease
- CCI cerebrovascular event or Transient Ischaemic Attack (TIA)
- CCI dementia

- CCI Chronic Obstructive Pulmonary Disease (COPD)
- CCI connective tissue disease
- CCI peptic ulcer disease
- CCI chronic liver disease
- CCI diabetes mellitus
- CCI hemiplegia
- CCI Chronic Kidney Disease (CKD) moderate to severe
- CCI leukaemia
- CCI lymphoma
- CCI solid tumour
- CCI manifest Acquired Immunodeficiency Syndrome (AIDS) from Human Immunodeficiency Virus (HIV) infection
- Admitted with Acute Coronary Syndrome (ACS)
- Admitted with exacerbation of Chronic Heart Failure (CHF)
- Admitted with stroke or TIA
- Admitted with rheumatologic condition
- Admitted with asthma exacerbation
- Admitted with COPD exacerbation
- Admitted with Diabetic Ketoacidosis (DKA)
- Admitted with Hyperglycaemic Hyperosmolar State (HHS)
- Admitted with hypoglycaemia (primary diagnosis)
- Admitted with hyperglycaemia (primary diagnosis)
- Admitted with infection

Diabetes mellitus details

- Diagnosis of diabetes, uncomplicated vs. complicated
    - Type of diabetes
    - How long ago was the diagnosis of diabetes made
- History of Ischaemic Heart Disease (IHD)
- History of stroke or TIA
- History of Peripheral Vascular Disease (PVD)
- History of retinopathy
- History of nephropathy
- History of peripheral neuropathy
- History of gastroparesis
- History of erectile dysfunction
- History of Diabetic Ketoacidosis (DKA)
- History of Hyperglycaemic Hyperosmolar State (HHS)
- History of admission for hypoglycaemia

Medications on admission details

- Does the participant have any allergies
    - Allergy details
- Was the participant receiving oral glucocorticoids on admission
    - Admission glucocorticoid details
- Admit meds metformin presence
- Admit meds metformin details

- Admit meds sulphonylurea presence
- Admit meds sulphonylurea details
- Admit meds acarbose presence
- Admit meds acarbose details
- Admit meds TZD presence
- Admit meds TZD details
- Admit meds DPPIVI presence
- Admit meds DPPIVI details
- Admit meds SGLT2I presence
- Admit meds SGLT2I details
- Admit meds GLP1RA presence
- Admit meds GLP1RA details
- Admit meds insulin presence
- Admit meds insulin regimen
- Admit meds insulin details
- Admit meds statin presence
- Admit meds statin details
- Admit meds beta-blocker presence
- Admit meds beta-blocker details
- Admit meds ACEI/ARB presence
- Admit meds ACEI/ARB details
- Admit meds aspirin presence
- Admit meds aspirin details

Trial exit

Data points to be collected by review of the clinical record following trial exit include the following demographic and clinical information:

Discharge details

- Date of discharge
- Length of stay
- Discharge location e.g. death, transfer, home

Clinical details

- Admitted with infection

Infection at admission details

Infection at admission is defined as a sterile site positive culture, a non-sterile site positive culture with clinical action on this, or clinician adjudication of infection presence and commencement of empiric treatment. The positive culture must have been taken within 48 hours of admission or the clinician action must have been based on signs or symptoms that were recorded as being present within 48 hours of admission. These data points are only available in full at trial exit so are collected at this time point despite infection at admission definitional criteria potentially being met earlier.

- Infection type
- Nature of diagnosis, clinical or microbiologic
    - Type of positive microbiologic specimen
    - Details of positive microbiologic specimen

- Was the infection related to a healthcare intervention
    - Nature of the healthcare intervention
- Were intravenous antibiotics used
    - Intravenous antibiotic agents used
    - Duration of intravenous antibiotic use (to nearest half day)
- Were oral antibiotics used
    - Oral antibiotic agents used
    - Duration of oral antibiotic use (to nearest half day)
- Were antibiotics prescribed for continuation post discharge for the treatment of this infection
    - Planned duration of post-discharge antibiotic use
- Total duration of antibiotic use (inpatient + planned post-discharge)

Inpatient complications details

- Hospital-acquired ACS
- Hospital-acquired stroke or TIA
- Hospital-acquired fall
- Hospital-acquired Acute Kidney Injury (AKI)
- Hospital-acquired Diabetic Ketoacidosis (DKA)
- Hospital-acquired Hyperglycaemic Hyperosmolar State (HHS)
- Hospital-acquired Healthcare-Associated Infection (HAI)

Hospital-acquired HAI details

Hospital-acquired HAI is defined as a sterile site positive culture, a non-sterile site positive culture with clinical action on this, or clinician adjudication of infection presence and commencement of empiric treatment. The positive culture must have been taken at least 48 hours after admission or the clinician action must have been based on signs or symptoms that were first recorded as being present at least 48 hours after admission.

- Infection type
- Nature of diagnosis, clinical or microbiologic
    - Type of positive microbiologic specimen
    - Details of positive microbiologic specimen
- Were intravenous antibiotics used
    - Intravenous antibiotic agents used
    - Duration of intravenous antibiotic use (to nearest half day)
- Were oral antibiotics used
    - Oral antibiotic agents used
    - Duration of oral antibiotic use (to nearest half day)
- Were oral antibiotics prescribed for continuation post discharge for the treatment of this infection
    - Planned duration of post-discharge oral antibiotic use
- Total duration of antibiotic use (inpatient + planned post-discharge)

Inpatient therapies details

- Were glucocorticoids administered during the admission
    - Inpatient glucocorticoid details
- Was the patient treated with significant Total Parenteral Nutrition (TPN) or non-oral Enteral Nutrition (EN) e.g. via a Nasogastric Tube (NGT) or Percutaneous Gastrostomy (PEG)
    - What are the details of TPN/EN type and duration

Inpatient procedures details

These are significant procedures done in theatre or radiology i.e. not ward-based procedures like intubation or lumbar puncture, unless the LP was done in radiology.

- How many procedures did the participant have during the admission
    - Procedure details
    - Procedure date
- Was there a cancellation/delay of the inpatient procedure?
    - Cancellation/delay details
- Were there any inpatient complications of the inpatient procedures?
    - Complication details

Medications at discharge details

- Discharge meds metformin presence
- Discharge meds metformin details
- Discharge meds sulphonylurea presence
- Discharge meds sulphonylurea details
- Discharge meds acarbose presence
- Discharge meds acarbose details
- Discharge meds TZD presence
- Discharge meds TZD details
- Discharge meds DPPIV inhibitor presence
- Discharge meds DPPIV inhibitor details
- Discharge meds SGLT2 inhibitor presence
- Discharge meds SGLT2 inhibitor details
- Discharge meds GLP1RA presence
- Discharge meds GLP1RA details
- Discharge meds insulin presence
- Discharge meds insulin regimen
- Discharge meds insulin details
- Discharge meds statin presence
- Discharge meds statin details
- Discharge meds beta-blocker presence
- Discharge meds beta-blocker details
- Discharge meds ACEI/ARB presence
- Discharge meds ACEI/ARB details
- Discharge meds aspirin presence
- Discharge meds aspirin details

Process of care

- Which diabetes healthcare professionals reviewed the patient during the admission
- Was a follow-up plan documented
    - Follow-up plan details

Glucose details

- Glucose results throughout the admission. Glucose levels are tested by nursing staff as per hospital protocols with results automatically and immediately transmitted electronically to an electronic system where they are stored along with relevant meta-data. Glucose results will be analysed according to the

exclusion criteria detailed by Weinberg et. al. where results that have a repeat value taken either 5-60 minutes previously or within 5 minutes later are excluded(28).

Pathology details

- Last HbA1c result collected prior to the date of discharge and not more than 90 days prior to the date of admission.
    - Hba1c date
- Last haemoglobin result collected prior to the last HbA1c result
    - Haemoglobin date
- Last creatinine result collected prior to the last HbA1c result
- Last estimated Glomerular Filtration Rate (eGFR) result collected prior to the last HbA1c result
    - Creatinine/eGFR date

Timeframe

The study will run for approximately 12 months. Recruitment for the three trial populations may be staggered over this period to account for the availability of clinical staff to perform the trial procedures.

Home visits

No home visits are required for this study.

Student project

This protocol and the study it pertains to will contribute to the Doctor of Philosophy (PhD) candidature of the associate investigator Dr Rahul Barmanray.

Study table

Assessment/Procedure	Trial entry	First electronic review	Post-escalation	Trial exit
Trial entry data points: **-Demographics** **-Admission details** **-Clinical details** **-Medications on admission details** **-Diabetes mellitus details**	**x**			
Electronic Diabetes Review (EDR)		**x**		
Bedside Diabetes Review (BDR)			**x**	
Trial exit data points: **-Discharge details** **-Clinical details** **-Infection at admission details** **-Inpatient complications details** **-Hospital-acquired HAI details** **-Inpatient therapies details** **-Inpatient procedures details** **-Medications at discharge details** **-Glucose details**				**x**

-Pathology details				

Study phases

The study will be broken up into three concurrent and sequential recruitment phases based on type of diabetes and admitting unit. The 3 phases are:

1. Participants with a diagnosis of type 1 diabetes mellitus (T1DM)

2a. Participants admitted under a surgical admitting unit

2b. Participants admitted under a medical admitting unit

Patients with T1DM will be recruited for 24 months while recruitment into the other two study phases is ongoing. Each patient may only be randomised into one group with membership of group 1 taking priority (see 7.3 Randomisation). Patients admitted under a surgical unit will be recruited initially until numbers reached are sufficient to analyse the primary and first key secondary outcome with sufficient power (see 10.1 Sample size estimation, justification & power calculations). Thereafter, patients admitted under a medical unit will be recruited until numbers reached are sufficient to analyse the primary and first key secondary outcome with sufficient power (see figure 2).

While it is encouraged that admitted units refer patients with T1DM to the endocrinology team as a matter of course, auditing of consultation requests received by the endocrinology consults registrar in concert with discharge coding and data from other institutions shows that approximately half the patients with T1DM admitted to the RMH are referred to the endocrinology team. Thus it is anticipated that a prolonged period of recruitment will be required to be able to show or exclude a difference in management effects between the intervention and control arms in this phase.

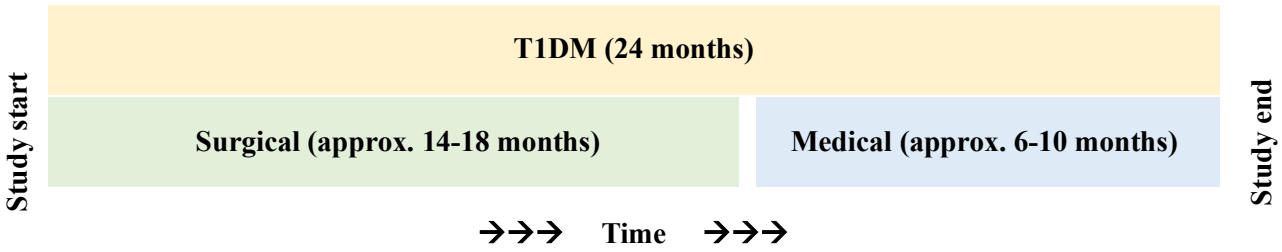


Figure 2: Indicative study phase timeline. T1DM = Type 1 Diabetes Mellitus.

Comparison with the RAPIDS trial

The RAndomised clinical trial of a Proactive Inpatient Diabetes Service (RAPIDS) parallel cluster randomised controlled trial (RCT) conducted at the Royal Melbourne Hospital (RMH) investigated the impact of a proactive model of diabetes care which consisted of early intervention for people with diabetes(3). This trial was conducted across 8 wards of the RMH at a time when the medical record was entirely paper-based. The STOIC-D trial by comparison will be conducted across all acute inpatient wards of the RMH in an environment when medical records are available electronically.

STOIC-D will thus have a wider scope with a larger and more heterogeneous patient population that will thus be more representative of the Australian tertiary hospital inpatient population. It will similarly provide an understanding of the benefits and place of proactive specialist diabetes care in the electronic medical

record environment, which is increasingly becoming the norm amongst Australian tertiary hospitals. STOIC-D will significantly build upon the groundwork laid by the RAPIDS trial.

COVID-19 considerations

It must be noted that this trial protocol has been devised during the contemporaneous COVID-19 pandemic. It is expected that with current experience in Victoria of COVID-19 and current projections of case numbers at the time of writing this protocol, there will be minimal impact upon this trial. The most pertinent risk to this trial posed by COVID-19 is that of staffing, if members of the IDS conducting the trial were re-deployed to other services or unable to work due to illness or self-isolation requirements. In these cases, the trial will be paused temporarily until the situation improves and it can be re-started.

7.2 STANDARD CARE AND ADDITIONAL TO STANDARD CARE PROCEDURES

Standard Care Procedures	
Procedure	**Trial arm**
Home team diabetes management	Standard care Proactive specialist care

Additional To Standard Care	
Procedure	**Trial arm**
First electronic review	Proactive specialist care
Ongoing electronic review	Proactive specialist care

7.3 RANDOMISATION

Randomisation will be performed immediately on identification of a potential participant as eligible for the trial via automated review of their electronic medical record (EMR). Randomisation will occur via the in-built software of the Epic EMR. Dynamic block randomisation with a single stratification factor (type 1 diabetes, medical admitting unit, surgical admitting unit) will be used. The 3 subgroups are:

1. Participants with a diagnosis of type 1 diabetes mellitus (T1DM)

2a. Participants admitted under a surgical admitting unit

2b. Participants admitted under a medical admitting unit

Membership of subgroup 1 takes precedence, i.e. participants with a diagnosis of type 1 diabetes mellitus will be block-randomised independent of their admitting unit. Membership of subgroups 2a and 2b is mutually exclusive. If a patient is admitted under a medical unit and then transferred to a surgical unit, they remain part of group 2a and the data they contribute be analysed as such.

7.4 BLINDING

Neither participants nor investigators will be blinded as to the allocation of study arm due to the impracticality of this under this clinical trial design.

Certain secondary outcomes will be adjudicated by an adjudicator blinded to the treatment allocation of the participants. These outcomes will include:

- Healthcare-associated infection (HAI) incidence
- Inpatient acute coronary syndrome incidence
- Inpatient acute cerebrovascular accident and transient ischaemic attack (TIA) incidence
- Inpatient diabetic ketosis incidence (blood ketones > 1.5 mmol/L, pH > 7.30)

- Inpatient diabetic ketoacidosis incidence (blood ketones > 1.5 mmol/L, pH < 7.30)

Blinded adjudication of the primary and other secondary outcomes is impractical as the presence of the outcome-defining events e.g. hyperglycaemia, hypoglycaemia, etc. will necessarily inform the intervention procedures. Furthermore, adjudication of most other outcomes is objective e.g. glucometric outcomes are defined by the glucose results taken by nursing staff not involved with the study, most clinical and all economic outcomes are reported upon by clinical coding and clinical costing staff not involved with the study, and thus independent blinded adjudication of these outcomes is not required.

7.5 STUDY METHODOLOGY

Clinical assessments and management advice and changes will be undertaken by the IDS while performing an EDR or BDR as per their clinical decision making. This will occur in a way that is no different to how such assessments and management decisions are currently made at the RMH in the absence of this clinical trial. Assessments and management decisions will be personalised to the individual participant's particular clinical scenario.

The IDS will aim to minimise hypoglycaemia (glucose < 4.0 mmol/L) and hyperglycaemia (glucose ≥ 15.0 mmol/L in all participants. The specific glycaemic range targeted for most individuals will be between 5.0 – 10.0 mmol/L as recommended by national and international inpatient diabetes guidelines but may differ for some individuals based on the clinical context(10, 12).

8. STUDY POPULATION

8.1 RECRUITMENT PROCEDURE

Participants will be identified electronically and automatically by the RMH's EMR software at the time of admission to the RMH. Clinical information is entered into a potential participant's clinical record by their treating medical team prior to a decision to admit is made. Upon a potential participant being admitted the EMR software reviews the information entered into their clinical record against the inclusion criteria. Further details on these criteria are provided in Section 7.2 and 7.3. If the software determines that the patient is eligible for the trial they are automatically recruited and randomised.

Participants cannot enter the trial through any means other than by being admitting to the RMH during the trial period and meeting the inclusion criteria and none of the exclusion criteria. As the method for identification and recruitment of potential participants into both the control and intervention arms is the same, the risk of recruitment bias is controlled.

8.2 INCLUSION CRITERIA

The inclusion criteria for eligibility to enter the trial are as follows:

- Admission to the Royal Melbourne Hospital City Campus during the study period
- Either:
    - a diagnosis of diabetes recorded in the clinical record at the time of hospital admission, or
    - a random glucose result ≥ 11.1 mmol/L recorded during the admission
- Age ≥ 18 years
- Non-pregnant
- Admission to a study ward, which includes:
    - C 2B Cardiology
    - C 2West
    - C 3S Surgery

    - C 3SW General Surgery
    - C 4S NSURG
    - C 4SE
    - C 5 North
    - C 5SE General Medicine
    - C 5SW General Medicine
    - C 6 South East
    - C 6B ICU
    - C 6SW Nephrology
    - C 7B Haematology and BMT
    - C 7SE Plastics
    - C 7SW Orthopaedic
    - C 8B NEUR
    - C 9E VIDS
    - C 9W Surgery
    - C AMU
- Admission under a study admitting unit, which includes:
    - AMU – Medical
    - ANPM – Medical
    - ANST – Medical
    - ASSM – Medical
    - BMTX – Medical
    - BOE – Surgical
    - CARD – Medical
    - CHNP – Surgical
    - CP – Medical
    - CPEU – Medical
    - CR – Surgical
    - CSUR – Surgical
    - EGS – Surgical
    - EMER – Medical
    - EPIL – Medical
    - FLXU – Surgical
    - GAST – Medical
    - HAEM – Medical
    - HB – Surgical
    - HNOE – Surgical
    - IMMU – Medical
    - MU1 – Medical
    - MU2 – Medical
    - MU3 – Medical
    - NEPH – Medical
    - NEPS – Surgical
    - NEUR – Medical
    - NSRI – Surgical
    - NSUR – Surgical
    - OMFS – Surgical
    - OPHT – Surgical

- ORTH – Surgical
- ORTM – Surgical
- ORTS – Surgical
- PLSA – Surgical
- PSR – Surgical
- PSRE – Surgical
- PSRI – Surgical
- RESP – Medical
- RHEU – Medical
- SCU – Medical
- TSUR – Surgical
- TT – Surgical
- UROI – Surgical
- UROL – Surgical
- VASC – Surgical
- VASI – Surgical
- VIDS – Medical

Wards and admitting units are periodically modified by the hospital administration for operational and administrative reasons. If this occurs during the study period, appropriate modification of the study protocol will be performed by the investigators.

All of the above criteria must be met for a potential participant to be eligible to enter the trial.

8.3 CONSENT

The investigators seek a waiver of consent for participants in this trial. The general reasons for this are that 1) trial participants are not being exposed to management procedures that are any different to those they would be exposed to were they admitted to the RMH outside of the study period, this trial is assessing whether and to what degree earlier intervention with specialist management is more effective than standard care; and 2) a substantially similar trial procedure has previously been approved by this human research ethics committee and granted a waiver of consent(3).

With reference to the National Health and Medical Research Council Statement on Ethical Conduct in Human Research – 2007 (Updated 2018)(29), the investigators believe this trial protocol meets the criteria for granting of a waiver of consent. Specifically with reference to section 2.3.10:

- a) – Involvement in the research carries negligible risk to participants over and above that which they are exposed to in the course of a hospital admission. The trial procedure involves standard care in the control arm and earlier specialist care in the intervention arm. Specialist care of inpatients is accepted as being safer than home team management in the Australian public healthcare system. Indeed, a referral to specialist care seeking input into a patient's management is made when the added expertise of a specialist team is expected to improve the safety and effectiveness of a patient's management during a hospital admission. The trial is assessing whether there is a benefit to earlier specialist care in addition to the accepted safety of this and thus the trial carries negligible risk to participants.
- b) – The research will answer an important question regarding the added benefits of earlier specialist care over standard care for hospital inpatients. Given there is no harm expected as per the response to point 2.3.10 a) above, the benefits from the research decidedly outweigh the negligible risk of harm.

- c) – It is impractical to obtain consent for this trial given that the study question requires recruited participants to be randomised from the time of admission to the RMH. Admissions are spread throughout the week and the majority thus occur after-hours. It would be impractical to either have investigators stationed at the various physical locations at which potential participants are admitted to the RMH, or to conduct the broad and ongoing training of the many staff members involved in admitting.
- d) – Given that the trial involves inpatients accessing earlier specialist care, which is a desired form of management, there is no reason for thinking that participants would not have consented if they had been asked.
- e) – Participants will be awarded the same privacy protections throughout the trial as they would have received were they not a trial participant. As with all hospital inpatients, the IDS will protect the privacy of the patients they have contact with through the course of the trial in the same way they do in regular clinical practice, as per the terms of their employment and their registration with the Australian Health Practitioner Regulation Agency.
- f) – Data confidentiality will be maintained throughout the trial. Further details on data confidentiality are provided in Section 11.
- g) – It is not expected the overall results from the trial will have any specific significance to the welfare of individual participants. While the potential application of the research findings, institution of early specialist care of inpatients at the RMH and other similar healthcare institutions, may be of interest to participants, this is not of welfare significance for participants now discharged from the RMH.
- h) – There is no expected commercial exploitation of data derivatives that may deprive participants of financial benefits to which they would be entitled.
- i) – There is no state, federal, or international law that the investigators are aware of that would prohibit a waiver of consent in this context.

9. PARTICIPANT SAFETY AND WITHDRAWAL

9.1 RISK MANAGEMENT AND SAFETY

It is not expected that participants will be exposed to any additional risk through participation in this trial. The trial procedure involves standard care in the control arm and earlier specialist care in the intervention arm. Specialist care of inpatients is accepted as being even safer than home team management in the Australian public healthcare system. Indeed, a referral to specialist care seeking input into a patient's management is made when the added expertise of a specialist team is expected to improve the safety and effectiveness of a patient's management during a hospital admission.

9.2 HANDLING OF WITHDRAWALS

No process for handling of withdrawals is required for this trial due to the waiver of consent obviating this.

9.3 REPLACEMENTS

The entire eligible population will be recruited and randomised for this trial. There is thus no need for the recruiting of replacements.

10. STATISTICAL METHODS

10.1 SAMPLE SIZE ESTIMATION, JUSTIFICATION & POWER CALCULATIONS

a. Infection rate estimates and mean patient-day glucose mean and sd estimates were obtained from Kyi et. al.(3).
b. To detect a difference in patient-day mean glucose, group sample sizes of 1102 (551 patients per treatment arm) achieve 80.037% power to reject the null hypothesis of equal means when the population mean difference is $\mu1 - \mu2 = 9.0 - 9.5 = -0.5$ with standard deviations of 2.7 for group 1 and 3.2 for group 2, and with a significance level (alpha) of 0.050 using a two-sided two-sample unequal-variance t-test. Assuming a 10% drop-out rate, 1226 (613 patients per treatment arm) will need to be recruited.
c. Additionally, to detect a difference in infection rates, group sample sizes of 658 (329 in intervention and 329 in control) would achieve 80.055% power to detect a statistically significant difference between the group proportions of 4.6% (2.7% vs. 7% in the control). The proportion in the intervention group is assumed to be 2.4% under the null hypothesis and 7% under the alternative hypothesis. The proportion in the control group is 7%. The test statistic used is the two-sided Z-Test with un-pooled variance. The significance level of the test is 0.0500. Assuming a 10% dropout rate, 732 patients would need to be recruited to achieve 80% power.
d. However, if we assume a conservative infection rate of 3% in the intervention group and 7% infection rate in the control group, by recruiting 1376 patients (accounting for a 10% drop-out rate), we would have 90% power to detect a different in infection rates between the intervention groups. Therefore this study aims to recruit 1376 patients, giving us sufficient power to detect a difference in mean patient-day glucose (the primary outcome) in addition to a difference in infection rates.'

10.2 STATISTICAL METHODS TO BE UNDERTAKEN

Primary analysis will be performed on an intention-to-treat basis with sensitivity analysis performed on a per-protocol basis to confirm the robustness of the findings.

Patient-day mean glucose is calculated by grouping all glucose results by patient-day and returning a mean value for each patient-day of all hospital admissions that comprise the study population.

A difference in patient-day mean glucose between treatment groups at a patient's exit from the study will be tested using a 2-sided t-test allowing unequal variance.

Patient day mean glucose will also be modelled using a Generalised Estimating Equation (GEE) with an autoregressive correlation structure - a model choice that assumes that the correlations between patient day mean glucose measurements taken on the same patient will decrease as the number of days between different measurements increases. The model will test whether a time-treatment interaction effect is present and include it in the primary analysis if the interaction effect is statistically significant. The primary outcome will otherwise be unadjusted. An adjusted model controlling for potential confounders including gender, baseline age, relative socioeconomic deprivation etc. will also be performed."

A difference in infection rates between the 2 groups will be tested using a two-sided test for proportions with un-pooled variance.

Continuous measures will be assessed for normality and log transformed where appropriate.

In case of participants missing the follow up assessment, appropriate imputation techniques will be employed in consultation with the study statistician.

Descriptive statistics and tables will be used to summarize relevant patient demographics and outcomes overall, by intervention groups. Continuous data will be reported as means (with standard deviations) if approximately normally distributed, and medians (inter-quartile range) and full [range] otherwise. Categorical data will be reported as frequencies and percentages and summarized as proportions with 95% confidence intervals as appropriate.

The baseline differences between study arms will be examined using a two-tailed T-test for continuous, normally distributed data, while the Wilcoxon rank-sum test will be used for skewed or ordinal data and either chi-2 or Fisher's exact for categorical data.

Multiplicity of testing will be acknowledged but for the primary and secondary endpoints, multiple statistical tests will be otherwise unadjusted.

To avoid overestimating hyperglycemia and hypoglycemia, multiple blood glucose measurements taken during the same hour will be handled according to Weinberg et. al.(28).

Adverse glycaemic days (AGDs), defined as the proportion of patient-days for which the BG level was below 4.0 mmol/L or above 15.0 mmol/L will be compared between the intervention and control group with a two-sided proportion test(30).

Data analyses will be carried out using the Statistical Package for the Social Sciences (IBM® SPSS® Statistics Premium Grad Pack Version 25.0) or Stata Corporation (Stata Statistical Software: Release 16. College Station, TX: StataCorp LP; 2019)."

11. STORAGE OF BLOOD AND TISSUE SAMPLES

11.1 DETAILS OF WHERE SAMPLES WILL BE STORED, AND THE TYPE OF CONSENT FOR FUTURE USE OF SAMPLES

There are no blood or tissue samples that will be taken specifically for this study.

12. DATA SECURITY & HANDLING

12.1 DATA COLLECTION METHODS

Data will be collected via the following methods:

- Direct manual review of the medical record
- Extraction of data from the medical record for patients who form the study population by Royal Melbourne Hospital Business Intelligence and/or the Connecting Care team
- Extraction of data from the NBGM glucose and ketone data storage system

12.2 DETAILS OF WHERE RECORDS WILL BE KEPT & HOW LONG WILL THEY BE STORED

Data will be collected and stored in a password-protected Research Electronic Data Capture (REDCap) project database against a randomly generated participant-specific study code. All data thus collected will be re-identifiable. All data marked as (*Identifier*) in Section 6.1 will be collected and stored against the participant's study code in a password-protected Microsoft Excel file kept in the password-protected Endocrinology folder of the RMH network S: Drive (\\ssg.org.au\allfiles\SDrives). Only the principal investigator will have access to this identifier-containing document.

Statistical analyses will be performed using the R project for statistical computing (R) on a computer owned by Melbourne Health (Department of Diabetes & Endocrinology). Results of these analyses will be kept electronically in the password-protected Endocrinology folder of the RMH network S: Drive (\\ssg.org.au\allfiles\SDrives).

Data will be stored in this location for the duration of the study and for a minimum of 5 years after study completion. If no longer required at this 5 years post study completion time point, the data will be destroyed by deletion.

Access to the data will be controlled through granting access to the Endocrinology folder of the RMH network S: Drive. Only those who have been given access by the head of the Department of Diabetes & Endocrinology, who is one of the investigators of this study, will be able to use their password to access the data in the folder where it is kept.

12.3 CONFIDENTIALITY AND SECURITY

Data will only be stored electronically in a de-identified form in order to preserve confidentiality. Measures to separate identifier and non-identifier fields are described in Section 11.1. Only the principal investigator will have access to the identifier-containing document.

12.4 ANCILLARY DATA

No ancillary data will be collected as part of this project and there will thus be no need to store and/or destroy such data.

13. APPENDIX

List of Attachments included:

Document Name	Version Number	Date (e.g. 18 January 2012)

14. REFERENCES

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