Flash glucose monitoring for Indigenous Australians with type 2 diabetes: a randomised pilot and feasibility study

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Abstract

Background:

Flash glucose monitoring (FGM) can improve diabetes management, but no randomised controlled trials (RCTs) of FGM have been undertaken in Indigenous Australian populations. This study aimed to assess the feasibility of performing a RCT of FGM in Indigenous Australians with type 2 diabetes.

Methods:

In this open-labelled pilot RCT, Indigenous adults with type 2 diabetes were randomised to FGM or standard care for 6 months. Eligible participants were being treated with injectable diabetes medications and had a glycosylated haemoglobin (HbA1c) ≥ 7.0%. The feasibility outcome was the proportion of participants completing the trial. The preliminary effective outcome was the change in HbA1c. Secondary effectiveness outcomes included a change in time spent in target blood glucose; safety (hypoglycaemic episodes); and quality of life (EuroQol 5-Dimension 3-Level (EQ-5D-3L) score).

Results:

Of 126 screened individuals, 74 were eligible, 40 (31.7%) were randomised and 39 (97.5%) completed the study. Participants’ baseline characteristics were similar between the FGM and usual care groups, except for sex and body mass index. There were no between-group differences for: change in HbA1c; percentage of time spent in target blood glucose, low glucose and high glucose; or EQ-5D-3L scores. No severe hypoglycaemic episodes occurred.

Conclusions:

This is the first pilot RCT of FGM in Indigenous Australians with type 2 diabetes. The results support a larger RCT, which is currently in progress.

Trial registration:

Australian New Zealand Clinical Trials Registry (ANZCTR12621000021875), retrospectively registered on 14 January 2021.

Key messages

What uncertainties existed regarding the feasibility?
• It was not known whether conducting a randomised controlled trial using diabetes technology in an Indigenous Australian population with diabetes would be feasible.

What are the key feasibility findings?

• It was feasible to conduct this trial in Indigenous Australians. However it is important to acknowledge that this trial was successful because it was led by Aboriginal researchers after extensive community consultation, and was performed in accordance with a Culturally Adaptive Governance Framework.

What are the implications of the feasibility findings for the design of the main study?

• It is feasible to conduct clinical trials in Indigenous populations. However to do so successfully, the research needs to be led by and conducted by Indigenous researchers and after community consultation.

Background

Diabetes mellitus contributes substantially to poor health outcomes [1] and disproportionately affects Indigenous Australians, in whom the prevalence is 3–4 times higher [2]. Indigenous Australians also experience diabetes complications more frequently and at an earlier age than non-Indigenous Australians [3]. Diabetes management in Indigenous populations has historically been suboptimal due to the interplay of social determinants of health including access to healthcare and medications, food insecurity, cultural losses, dispossession, and racial discrimination [4]. It is therefore imperative to find sustainable strategies that build on the many strengths of First Nations communities to improve their diabetes care. This study explored the potential of a specific strategy – of introducing a new diabetes technology that could improve the management of blood glucose levels.

Optimising blood glucose levels is essential to reducing diabetes complications [5–7]. Large, multicentre clinical trials have demonstrated that effective glucose-lowering therapies reduce the risk of micro- and macro-vascular complications [5–9]. Despite the availability of these therapies, a disproportionate number of Indigenous people with diabetes continue to experience significant hyperglycaemia and remain at risk of diabetes-related complications. Conversely, many individuals require insulin and/or sulphonylureas [3] which can cause hypoglycaemia that if severe, can precipitate macrovascular complications and/or death [10]. Safe and effective implementation of these therapies requires individuals check their blood glucose readings frequently.

Structured intensive self-monitoring of blood glucose (SMBG) can improve glycaemic levels [11]. However, there are barriers to successful implementation [12], especially in people receiving multiple insulin injections or pump therapy [13–16] who may experience diabetes distress from painful fingerprick glucose measurements [17]. SMBG readings also need to be initiated by the person with diabetes and only provide information at the time of measurement. Consequently, there is insufficient
data to identify patterns of blood glucose levels at particular times of the day (e.g., overnight) and over a longer period of time [18]. Since the development of continuous glucose monitoring (CGM) [19] and flash glucose monitoring (FGM), clear and comprehensive data can now be obtained with minimal user inconvenience [19, 20].

Real-time CGM/FGM in individuals with type 2 diabetes has been shown to reduce HbA1c without the intensification of treatment or an increased risk of hypoglycaemia [21]. This suggests that the availability of real-time glucose data results in behavioural and lifestyle changes [22, 23]. Yet CGM/FGM remain largely inaccessible due to cost (AUD$102/fortnight in 2023 [24]). In Australia, these technologies are subsidised for people with type 1 diabetes but not for people with type 2 diabetes on injectable therapies, including Indigenous Australians. Assisting Indigenous Australians with diabetes to use CGM or FGM technologies is a strategy that could not only improve diabetes care, but also facilitate greater independence for individuals managing this chronic disease.

International bodies have called for randomised controlled trials (RCTs) in people from diverse health literacy and socio-demographic backgrounds, to confirm the benefits of CGM/FGM in type 2 diabetes [18, 20, 25, 26]. The current study meets this call for action, as there are no studies of FGM in Indigenous Australians. Furthermore, this research directly addresses the Australian Government’s National Diabetes Strategy, which aims to reduce the impact of diabetes among Indigenous Australians.

This study was initiated after extensive consultation with the Rumbalara community (a First Nations community in regional Victoria), in response to the identified need to improve diabetes care and access to diabetes technology. This pilot study aimed to evaluate whether a RCT of FGM could be successfully undertaken in an Indigenous population with type 2 diabetes. The findings will guide the planning for a larger multicentre trial comparing FGM to SMBG in Indigenous Australians with type 2 diabetes on injectable therapies.

**Methods**

**Design**

Indigenous Australians with type 2 diabetes were recruited to a prospective, open-labelled, individually randomised controlled pilot study that compared FGM to standard care (SMBG) over 6-months. A wait-list design was utilised.

**Setting and participants**

Participants were recruited from three outpatient sites: the Rumbalara Aboriginal Co-operative (RAC), Goulburn Valley Health (GVH) and Austin Health. RAC is a Victorian Aboriginal Community Controlled Health Organisation in regional Victoria, which has one of the largest Aboriginal populations outside metropolitan Melbourne. Participants were initially recruited from RAC and GVH only, commencing March 2018. Recruitment was later extended to Austin Health in metropolitan Melbourne (October
Potential participants were identified through clinical databases at RAC and GVH and then contacted by study investigators.

Community engagement and consultation sessions were undertaken between 2016–2018 and involved community elders, RAC staff, Indigenous health workers and study investigators. Aboriginal researchers and health workers were integral to the study team. Several study investigators were in direct contact with participants and were familiar to and/or community members, which facilitated recruitment.

Eligible participants identified as Aboriginal and/or Torres Strait Islander, were aged $\geq 18$ years with type 2 diabetes, had suboptimal diabetes management (defined as glycosylated haemoglobin [HbA1c] $\geq 7.0\%$) and were on diabetes treatment including insulin and/or glucagon-like peptide-1 (GLP-1) agonists.

The exclusion criteria were: active illicit drug use or heavy alcohol use (> 4 standard drinks/day); active malignancy requiring chemotherapy; planning pregnancy/pregnant; known allergy to medical-grade adhesives; taking varying doses of corticosteroid therapy; using amphetamines, anabolic or weight-reducing therapies; significant renal impairment (defined as eGFR < 15ml/min/1.73m$^2$ or end-stage kidney disease); using erythropoiesis stimulating agents; or a known haemoglobinopathy.

**Trial intervention**

Participants were randomised to the intervention (FGM) or standard care (SMBG) for 6 months. Blinded CGM devices were also worn for 7–14 days by all participants at two time points - baseline (before randomisation) and 6-months. These blinded CGM systems were used to measure time spent in target glucose, low glucose and high glucose. Two systems (Medtronic iPro2 and Abbott Freestyle Libre Pro) were used, because the Freestyle Libre Pro - preferred because it was similar to the intervention device - only became available in August 2020. The first 19 participants used the iPro2 and the remaining 21 participants used the Freestyle Libre Pro.

**Intervention device (Flash glucose monitor - FGM)**

The Freestyle® Libre™ (Abbott Diabetes Care) is a single-use, factory-calibrated FGM sensor, that is worn for up to 14 days [20]. Real-time glucose data is obtained by scanning the sensor with the reader, which stores information from the preceding eight-hour period. Historical data in the reader can be uploaded to a computer to generate summary glucose reports for review by users or clinicians [20].

**Standard care (SMBG)**

This involved measuring blood glucose levels through capillary glucose testing with a glucometer and test strips. Participants were instructed to follow their usual diabetes care procedure as advised by their treating clinician. This included measuring blood glucose levels up to four times per day and when experiencing symptoms of hypoglycaemia/hyperglycaemia.

**Data collection**
Demographic and clinical characteristics and blood and urine tests were collected at baseline, 3 months and 6 months. These included measurements of: HbA1c, fasting or random glucose, lipid profile, urine albumin-to-creatinine ratio, full blood examination, electrolytes and liver function tests. Qualitative data were collected, the results of which are published elsewhere [27].

**Outcomes**

The feasibility outcome was whether participants could be recruited and retained in this RCT. The preliminary effective outcome was change in HbA1c from baseline to 6 months. HbA1c was measured on venous blood tested at National Association of Testing Authorities (NATA) accredited laboratories [28]. Secondary effectiveness outcomes were change in percentage of time spent in target blood glucose (4.0–10.0 mmol/L), low glucose (< 3.9 mmol/L), and high glucose (> 15.0 mmol/L). These data were collected from the blinded CGM systems.

Exploratory outcomes were change in percentage of time spent in CGM metrics as per the international consensus on time in range [29]: time above range [30] level 1 (glucose > 13.9 mmol/L), TAR level 2 (glucose = 10.1–13.9 mmol/L), time in range (glucose = 3.9–10.0 mmol/L), time below range [30] level 1 (glucose = 3.0-3.8 mmol/L), and TBR level 2 (glucose < 3.0 mmol/L). Further outcomes included changes in diabetes medications from baseline to 6 months for (a) the number of glucose-lowering medications, and (b) insulin usage and total daily dose.

The quality-of-life outcome was assessed by the change in EuroQol 5-Dimension 3-Level (EQ-5D-3L) score from baseline to 6 months. EQ-5D-3L index values were computed using the Australian value set developed by Viney et. al [31]. The safety outcome was the number and percentage of participants who experienced at least one severe hypoglycaemic event (defined as requiring third-party assistance). Adverse event occurrence was assessed at each study visit.

**Data management**

Study data (except data from the CGM and FGM devices) were collected and managed using REDCap electronic data capture tools hosted at The University of Melbourne [32, 33]. Device data from the blinded CGM devices were downloaded in an Excel (version 16.16.27) csv file.

**Randomisation, allocation and blinding**

Following baseline measurements, participants were randomised to the FGM (intervention) or SMBG (standard care) in a 1:1 ratio, using a computer-generated randomization list of randomly permuted blocks by an independent statistician. Individual study participant treatment codes were prepared in sequentially numbered opaque envelopes by independent support staff. Eligible participants learned their group allocation when opening these envelopes at randomisation. Participants, investigators, and study staff were not masked to group allocation because of the nature of the intervention. Study statisticians were blinded to the allocation until the database was cleaned and ready for analysis.

**Statistical methods**
The planned sample size was 40 participants, with 20 participants per arm. This was informed by the rule of thumb of 24 evaluable participants for the total sample size of a parallel-group two-arm pilot trial [34] and the available resources. Statistical analyses followed a prespecified statistical analysis plan (Supplementary file). Study participants were analysed according to their randomised treatment group (“as-randomised”) for the intention-to-treat population and actual treatment group (“as-treated”) for the safety population. A two-sided 95% confidence interval (CI) was obtained for the primary feasibility outcome using the Clopper-Pearson method. The preliminary effective outcome HbA1c was analysed using a likelihood-based longitudinal data analysis model, with response consisting of all values (baseline, 3- and 6-months) and the model including factors representing treatment group, time-point, and treatment group by time interaction. Due to the small sample size, restricted maximum likelihood estimation with a Kenward-Roger correction was applied. Secondary effectiveness outcomes were summarized by treatment group, and within each treatment group by blinded CGM device (iPro2 or Freestyle Libre Pro) using mean and standard deviation (SD) for symmetrical variables, or median and quartiles (25th and 75th percentile) for non-symmetrical variables. No statistical tests were performed for secondary effectiveness and exploratory outcomes. The EQ-5D-3L score was summarised by treatment group. The number and percentage of participants with at least one adverse event (including hypoglycaemic events) was reported by treatment group. Analyses were performed using Stata/SE software, version 17.0 (StataCorp).

Ethics

This study was approved by the GVH Human Research Ethics Committee (HREC), GVH 6–20(38 – 27) and Austin Health HREC/54334/Austin-2019. This trial was registered with the Australian and New Zealand Clinical Trials Registry (ACTRN12621000021875). All participants provided written informed consent using the National Health and Medical Research Council (NHMRC) Guidelines for Ethical Conduct in Aboriginal and Torres Strait Islander Health Research. This trial was completed in accordance with the Culturally Adaptive Governance Framework for Indigenous health research [35].

COVID-19

The COVID-19 pandemic occurred whilst the trial was underway which delayed recruitment and data collection (the latter extended until June 2022). The State of Victoria had extensive lockdowns during the COVID-19 pandemic and had cities with the highest number of days under lockdown. Furthermore, there were strict restrictions on research activity. Therefore COVID-19 pandemic had a major impact on the current trial. Study visit attendance also shifted from in-person to virtual (following a protocol amendment), which allowed participants to minimise interaction and adhere to public health measures. This change did not impact the recruitment target, which was achieved.

Results

Trial Participants
A total of 126 participants were assessed for eligibility between November 2017 to December 2021. Fifty-two individuals were ineligible after screening; five had type 1 or gestational diabetes, and 47 were not managed with injectable diabetes medications. Of the 74 eligible people, 42 participants were recruited, and 2 withdrew before randomization (see Fig. 1). Subsequently, 40 (54%) participants were randomised, with 20 allocated to FGM and 20 to standard care (SMBG). Two participants (1 from the FGM arm and 1 from the SMBG arm) did not receive the allocated intervention. Twenty-nine participants (72.5%) were recruited from the Rumbalara Aboriginal Health Service. Baseline demographic and clinical characteristics were similar between groups except sex, body mass index, and systolic blood pressure (see Table 1).
Table 1
Baseline demographic and clinical characteristics of participants and their medications by treatment group (Intention-to-treat population)

<table>
<thead>
<tr>
<th></th>
<th>Flash glucose monitoring</th>
<th>Self-monitored blood glucose</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N = 20</td>
<td>N = 20</td>
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</tbody>
</table>

**Demographic characteristics**

<table>
<thead>
<tr>
<th></th>
<th>N = 20</th>
<th>N = 20</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years), Mean (SD)</td>
<td>57.3 (13.9)</td>
<td>60.7 (11.1)</td>
</tr>
<tr>
<td>Male sex, n (%)</td>
<td>7 (35%)</td>
<td>12 (60%)</td>
</tr>
<tr>
<td>HbA1c (%)*, Mean (SD)</td>
<td>8.9 (1.1)</td>
<td>9.3 (1.3)</td>
</tr>
<tr>
<td>Body Mass Index, Mean (SD)</td>
<td>38.8 (8.3)</td>
<td>32.5 (7.8)</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg), Mean (SD)</td>
<td>138.6 (17.7)</td>
<td>127.0 (11.4)</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg), Mean (SD)</td>
<td>77.1 (12.7)</td>
<td>73.8 (9.1)</td>
</tr>
<tr>
<td>Diabetes duration (years), Median (IQR)</td>
<td>13.0 (6.0–20.0)</td>
<td>15.0 (10.0–23.0)</td>
</tr>
</tbody>
</table>

**Clinical characteristics**

<table>
<thead>
<tr>
<th>Significant medical history, n (%)</th>
<th>N = 20</th>
<th>N = 20</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke or transient ischaemic attack</td>
<td>1 (5%)</td>
<td>2 (11%)</td>
</tr>
<tr>
<td>Heart failure</td>
<td>3 (15%)</td>
<td>4 (20%)</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>2 (10%)</td>
<td>1 (5%)</td>
</tr>
<tr>
<td>Retinopathy</td>
<td>4 (20%)</td>
<td>3 (15%)</td>
</tr>
<tr>
<td>Chronic kidney disease</td>
<td>5 (26%)</td>
<td>7 (35%)</td>
</tr>
<tr>
<td>Peripheral neuropathy</td>
<td>4 (20%)</td>
<td>5 (25%)</td>
</tr>
<tr>
<td>Total cholesterol (mmol/L), Mean (SD)</td>
<td>4.0 (0.9)</td>
<td>4.1 (1.3)</td>
</tr>
<tr>
<td>Triglycerides (mmol/L), Median (IQR)</td>
<td>2.1 (1.4–3.0)</td>
<td>2.6 (1.8–3.0)</td>
</tr>
<tr>
<td>LDL-C (mmol/L), Mean (SD)</td>
<td>1.7 (0.6)</td>
<td>2.0 (1.1)</td>
</tr>
</tbody>
</table>

Abbreviations: SD = Standard Deviation; IQR = 25th to 75th percentile; LDL-C = Low density lipoprotein cholesterol; HMG-CoA = 3-hydroxy-3-methyl-glutaryl-coenzyme A; SGLT2 = Sodium–glucose co-transporter 2; GLP-1 = Glucagon-like peptide 1; DPP4 = Dipeptidyl peptidase 4; FGM = flash glucose monitoring; SMBG = self-monitored blood glucose.

*Among those randomised with a HbA1c assessment within 2 months before randomisation. 2 HbA1c values at baseline were excluded as a result.

1 participant in the intervention arm received SMBG instead of FGM, and 1 participant in the control arm received FGM instead of SMBG. These participants were included in the group ‘as randomised’.
<table>
<thead>
<tr>
<th>Demographic characteristics</th>
<th>Flash glucose monitoring</th>
<th>Self-monitored blood glucose</th>
</tr>
</thead>
<tbody>
<tr>
<td>N = 20</td>
<td>N = 20</td>
<td></td>
</tr>
</tbody>
</table>

### Creatinine (umol/L), Median (IQR)
- Flash glucose monitoring: 73.0 (59.0–89.0)
- Self-monitored blood glucose: 86.5 (71.0–119.5)

#### Estimated glomerular filtration rate (ml/min/1.73m²), n (%)

<table>
<thead>
<tr>
<th>Range</th>
<th>Flash glucose monitoring</th>
<th>Self-monitored blood glucose</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 60</td>
<td>16 (80%)</td>
<td>11 (55%)</td>
</tr>
<tr>
<td>45–59</td>
<td>1 (5%)</td>
<td>4 (20%)</td>
</tr>
<tr>
<td>25–44</td>
<td>2 (10%)</td>
<td>4 (20%)</td>
</tr>
<tr>
<td>&lt;25</td>
<td>1 (5%)</td>
<td>1 (5%)</td>
</tr>
</tbody>
</table>

#### Urine Albumin-to-Creatinine ratio (mg/mmol), n (%)

<table>
<thead>
<tr>
<th>Range</th>
<th>Flash glucose monitoring</th>
<th>Self-monitored blood glucose</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;30</td>
<td>13 (81%)</td>
<td>16 (89%)</td>
</tr>
<tr>
<td>30–299</td>
<td>2 (13%)</td>
<td>2 (11%)</td>
</tr>
<tr>
<td>≥300</td>
<td>1 (6%)</td>
<td>0 (0%)</td>
</tr>
</tbody>
</table>

### Medications

#### Cardiovascular medications, n (%)

- Antiplatelet: 12 (60%) Flash glucose monitoring; 11 (55%) Self-monitored blood glucose
- Renin-angiotensin system inhibitor: 12 (60%) Flash glucose monitoring; 12 (60%) Self-monitored blood glucose
- HMG-CoA reductase inhibitor: 16 (80%) Flash glucose monitoring; 16 (80%) Self-monitored blood glucose

#### Glucose-lowering therapy, n (%)

- Insulin: 15 (75%) Flash glucose monitoring; 13 (65%) Self-monitored blood glucose
- Metformin: 19 (95%) Flash glucose monitoring; 17 (85%) Self-monitored blood glucose

Abbreviations: SD = Standard Deviation; IQR = 25th to 75th percentile; LDL-C = Low density lipoprotein cholesterol; HMG-CoA = 3-hydroxy-3-methyl-glutaryl-coenzyme A; SGLT2 = Sodium–glucose co-transporter 2; GLP-1 = Glucagon-like peptide 1; DPP4 = Dipeptidyl peptidase 4; FGM = flash glucose monitoring; SMBG = self-monitored blood glucose.

*Among those randomised with a HbA1c assessment within 2 months before randomisation. 2 HbA1c values at baseline were excluded as a result.

1 participant in the intervention arm received SMBG instead of FGM, and 1 participant in the control arm received FGM instead of SMBG. These participants were included in the group ‘as randomised’.
### Feasibility Outcome

The primary outcome of the pilot study was feasibility. The feasibility outcome was the proportion of participants completing the trial. Thirty-nine (97.5%, 95% CI 87–100%) participants completed the study. One participant did not complete their final study visit due to hospitalisation for a diabetes complication unrelated to this trial.

### Effectiveness outcomes

The current trial was not powered to assess efficacy. Nevertheless, we examined effectiveness as a secondary outcome. The mean (SD) HbA1c decreased from 8.9% (1.1%) to 8.4% (1.8%) in the intervention group and from 9.3% (1.3%) to 8.4% (1.4%) in the control arm. No apparent difference was observed in the change in HbA1c values (mean between-group difference in change in HbA1c between FGM and SMBG at 6 months from baseline was −0.19%; 95% CI -1.20–0.81%) (see Table 2).
Table 2
– Primary effectiveness and quality of life outcomes by treatment group (Intention-to-treat population)

<table>
<thead>
<tr>
<th></th>
<th>Flash glucose monitoring</th>
<th>Self-monitored blood glucose</th>
<th>Treatment effect</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N = 20</td>
<td>N = 20</td>
<td>Mean difference (95% CI)</td>
</tr>
<tr>
<td><strong>Primary effectiveness outcome, Mean (SD)</strong>*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>8.9 (1.1)</td>
<td>9.3 (1.3)</td>
<td>-0.44 (-1.31, 0.42)</td>
</tr>
<tr>
<td>3 months</td>
<td>8.0 (0.9)</td>
<td>8.7 (1.1)</td>
<td>-0.19 (-1.20, 0.81)</td>
</tr>
<tr>
<td>6 months</td>
<td>8.4 (1.8)</td>
<td>8.4 (1.4)</td>
<td>-</td>
</tr>
<tr>
<td><strong>Quality of Life outcome, Median (IQR)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EQ-5D-3L score</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>0.7 (0.5–0.8)</td>
<td>0.7 (0.6–0.8)</td>
<td>-0.00 (-0.66, 0.66)</td>
</tr>
<tr>
<td>6 months</td>
<td>0.7 (0.5–0.8)</td>
<td>0.7 (0.7–0.8)</td>
<td>-</td>
</tr>
</tbody>
</table>

Abbreviations: SD = Standard Deviation; IQR = 25th to 75th percentile; CI = Confidence Interval; EQ-5D-3L = EuroQol 5-Dimension 3-Level; FGM = flash glucose monitoring; SMBG = self-monitored blood glucose.

*HbA1c and EQ-5D-3L values measured outside of the scheduled visit windows were excluded from the analysis. As a result, 2 HbA1c values at baseline, 4 at 3 months and 5 at 6 months follow-up were excluded. Similarly, 5 EQ-5D-3L values at baseline and 5 at 6 months follow-up were excluded.

1 participant in the intervention arm received SMBG instead of FGM, and 1 participant in the control arm received FGM instead of SMBG. These participants were included in the group ‘as randomised’.

There were no clear trends for changes in time in high glucose (> 15.0 mmol/L), target glucose (4.0–10.0 mmol/L) or low glucose (< 3.9 mmol/L) in either treatment arm (Fig. 2). Similarly, no clear trends emerged for changes in CGM metrics as per the international consensus on time in range [29] in either treatment arm (Appendix Fig. 1).

There was no change in the proportion of participants using insulin from baseline to 6 months in either group. The median total daily insulin dose increased from baseline to 6 months (Appendix Table 1). The number of participants in the control arm requiring three non-insulin glucose-lowering medications increased from baseline (n = 5, 25%) to 6 months (n = 6, 33%), but stayed unchanged in the intervention group (n = 5, 25%). There was no difference in EQ-5D-3L scores between groups at baseline and 6 months (see Table 2).
Safety outcomes

Eight participants (20%) experienced a serious adverse event [36], 3 (15%) from the FGM arm and 5 (25%) from the SMBG arm. There was no difference in the safety outcome of the current trial. All serious AEs involved hospital admission. No participant experienced a severe hypoglycaemic event. Six participants (30%) in the FGM arm had device-related AEs (pain, tenderness, or skin irritation). A total of 29 AEs (including serious AEs but excluding device-related AEs) were reported across both arms combined. See Table 3.

<table>
<thead>
<tr>
<th>Table 3</th>
<th>Number (%) of participants with at least one adverse event by treatment group (Safety population)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><strong>Flash glucose monitoring</strong></td>
</tr>
<tr>
<td>N = 20</td>
<td>10 (50%)</td>
</tr>
<tr>
<td>Adverse events</td>
<td>3 (15%)</td>
</tr>
<tr>
<td>Hospitalisation</td>
<td>3 (15%)</td>
</tr>
<tr>
<td>Death</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Device-related adverse events</td>
<td>6 (30%)</td>
</tr>
</tbody>
</table>

Adverse events excludes device-related adverse events. Serious adverse events include hospitalisation and death. Device-related adverse events included pain/irritation from sensor site and FGM sensor falling off prematurely.

FGM = flash glucose monitoring; SMBG = self-monitored blood glucose.

1 participant in the intervention arm received SMBG instead of FGM, and 1 participant in the control arm received FGM instead of SMBG. These participants were included in the group ‘as treated’.

Discussion

This is the first pilot RCT comparing FGM to SMBG in Indigenous Australians with type 2 diabetes. The primary outcome was feasibility and we demonstrated success with feasibility as the proportion of participants completing the trial was very high, with 39 out of 40 (97.5%, 95% CI 87–100%) participants completing the trial. The trial was successfully undertaken as demonstrated by the high completion and retention rates, despite a difficult COVID-19 period. This is a testament to Indigenous Australians and their communities, Aboriginal Health Services where the trial was conducted, and the depth of engagement between Indigenous people with diabetes, diabetes researchers and the dedication of the clinical trial staff. This is one of the very few RCTs involving Indigenous people with type 2 diabetes in Australia. This is significant because RCTs in Indigenous populations are uncommon and it has been suggested that recruitment of Indigenous people into RCTs may be difficult [37].
There were several reasons for why this RCT was so successfully completed in an Indigenous Australian population. Firstly, this trial was initiated in response to a community-identified need to improve diabetes management, and was conducted after extensive community consultation with the Rumbalara community. Secondly, the conduct of this trial and recruitment of participants was led by Aboriginal researchers and performed in accordance with a Culturally Adaptive Governance Framework which we developed [35]. The success of this approach are reflected by the study results, which showed that 29 of the 40 (72.5%) participants were patients of the RAC medical clinic. Both recruitment and follow-up of these participants occurred at the Aboriginal Health Service (AHS), which allowed participants to feel safe and comfortable as AHS are more culturally sensitive than non-Indigenous health services. Furthermore, the conduct of the study led by Aboriginal researchers and health workers at local Aboriginal health services and one of the trial nurses was also employed by RAC as a nurse in a clinical capacity, and this trust and familiarity may have facilitated recruitment. Moreover, extensive community consultation, with recruitment and conduct of the study led by Aboriginal researchers and health workers at local Aboriginal health services were crucial for the successful completion of this study.

This trial had a prolonged recruitment time, for several reasons. Firstly, this study was initially investigator-funded until a small grant was secured in 2019. From November 2017 until February 2019, first author AE performed all recruitment and follow-up at RAC whilst also undertaking full-time clinical work. When more funding became available, this enabled the sample size to be increased from 24 to 40 participants, as well as the employment of a trial nurse. A dedicated trial nurse commenced in the middle of 2019, improving the logistics of participant recruitment and follow-up. Secondly, diabetes management in the RAC clinic was better than anticipated [38], and there were insufficient eligible participants available for recruitment. Recruitment was then extended to include Austin Health to increase the availability of eligible participants. Thirdly, the COVID-19 pandemic occurred in 2020, and research activities were for paused for several months until amendments were made to allow virtual follow-up visits so participants could feel safe and adhere to public health measures. In 2021, there was a large COVID outbreak in Shepparton, near RAC, that affected staffing levels for basic services such as supermarkets, health services and hospitals. This impacted study visits and pathology collection. Despite all these challenges, the trial was successfully completed.

Participant completion of this trial was 97.5%. This suggests that the convenience of painlessly monitoring blood glucose levels was highly acceptable in this population and most people had a positive experience of using this technology [27]. The acceptability and convenience of FGM is similar to findings from an observational study of pregnant Aboriginal women [39]. These positive experiences occurred despite 30% of participants in the intervention group experiencing device-related adverse effects. The occurrence of AEs in both groups were similar. This not only reflects the multiple comorbidities of this population, but also suggests that the intervention did not increase the risk of AEs. Flash and continuous glucose monitoring are relatively expensive for people with type 2 diabetes, as its use is only subsidised for people with type 1 diabetes in Australia. Participation in this trial gave participants the opportunity to use this technology.
The pilot study had several limitations. The use of two different blinded CGM systems affected data quantity, as the iPro2 and Freestyle Libre Pro provided up to 7 and 14 days of data, respectively. Additionally, the iPro2 required calibration every 12 hours, otherwise the amount of interpretable data was reduced. The Freestyle Libre Pro was factory-calibrated, so data quantity was not limited by calibration. Consequently, participants using the iPro2 blinded CGM had less data available for analysis. CGM metrics were therefore analysed and reported by both treatment arm and blinded CGM device, to ensure consistency [40]. Whilst the option of using only the iPro2 blinded CGM would have improved data consistency, it was important to trial the preferred blinded CGM system in view of planning for a larger trial. This was a pilot trial with the primary outcome being feasibility and it was not powered to demonstrate efficacy. Nevertheless, we examined efficacy as a secondary outcome. Whilst the mean HbA1c decreased in both groups, the study was not powered to show a difference in HbA1c. There were no clear patterns in changes in time spent in target glucose, low glucose or high glucose or quality-of-life outcomes, but this was limited by sample size.

Research into and the use of CGM/FGM in diabetes is a rapidly evolving field. Many studies have shown CGM/FGM use improves HbA1c in type 1 diabetes [13, 14, 41–44], but few RCTs have shown improved HbA1c in type 2 diabetes [15, 16, 20, 45–50]. The Continuous Monitoring in Type 2 Diabetes Basal Insulin Users study [46] and Multiple Daily Injections and Continuous Glucose Monitoring in Diabetes [45] trial demonstrated improvements in HbA1c in people with insulin-treated type 2 diabetes [49, 51], and one RCT has shown FGM can improve HbA1c in non-insulin-treated type 2 diabetes [49]. There are increasing numbers of RCTs demonstrating that FGM/CGM use leads to improvements in diabetes management in type 2 diabetes without reducing HbA1c [15, 16, 20, 45–51]. However, until now, no RCT has evaluated FGM or CGM in Indigenous people with diabetes.

The success of this study was facilitated by extensive community consultation and performance in accordance with a Culturally Adaptive Governance Framework [35]. Notably, this study was not designed to demonstrate change in HbA1c, but to determine if a RCT using this technology could be successfully undertaken in an Indigenous Australian population. Larger studies are needed to evaluate the potential benefit of FGM and CGM in Indigenous people with diabetes. Following on from this pilot study, a larger multicentre RCT is underway across Australia (FlashGM study: NHMRC APP#1182464), and aims to recruit 350 participants. Progression criteria was not applied, but the success of this pilot study enabled a large grant to be secured to support a larger RCT.

**Conclusion**

This is the first randomised pilot study of FGM in Indigenous Australians with type 2 diabetes, and one of few RCTs in Indigenous Australians with diabetes. It confirms that a RCT of FGM can be successfully undertaken in an Indigenous Australian population, with a 97.5% retention rate. Extensive community consultation, with recruitment and conduct of the study led by Aboriginal researchers and health workers at local Aboriginal health services were crucial for the successful completion of this study. A larger
multicentre RCT in this population is currently in progress. It is hoped that findings from this and future studies will improve diabetes care and reduce the health gap in this population.

**Abbreviations**

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>FGM</td>
<td>Flash glucose monitoring</td>
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<tr>
<td>RCT</td>
<td>Randomised controlled trial</td>
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<tr>
<td>HbA1c</td>
<td>Glycosylated haemoglobin</td>
</tr>
<tr>
<td>EQ-5D-3L</td>
<td>EuroQol 5-Dimension 3-Level</td>
</tr>
<tr>
<td>SMBG</td>
<td>Self-monitoring of blood glucose</td>
</tr>
<tr>
<td>CGM</td>
<td>Continuous glucose monitoring</td>
</tr>
<tr>
<td>RAC</td>
<td>Rumbalara Aboriginal Co-operative</td>
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<tr>
<td>GVH</td>
<td>Goulburn Valley Health</td>
</tr>
<tr>
<td>GLP-1</td>
<td>Glucagon-like peptide-1</td>
</tr>
<tr>
<td>eGFR</td>
<td>Estimated glomerular filtration rate</td>
</tr>
<tr>
<td>TAR</td>
<td>Time above range</td>
</tr>
<tr>
<td>TBR</td>
<td>Time below range</td>
</tr>
<tr>
<td>HREC</td>
<td>Human Research Ethics Committee</td>
</tr>
<tr>
<td>NHMRC</td>
<td>National Health and Medical Research Council</td>
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<tr>
<td>CI</td>
<td>Confidence interval</td>
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<tr>
<td>SD</td>
<td>Standard deviation</td>
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<tr>
<td>AHS</td>
<td>Aboriginal Health Service</td>
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<td>AE</td>
<td>Adverse effect</td>
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**Declarations**

**Conflicts of Interest**

EIE’s institution has received funding which is unrelated to this study for clinical research from Novo Nordisk, Eli Lilly, Boehringer.

**Funding**

This trial was funded from grants from the Indigenous Research Initiative (University of Melbourne Hallmark Research Initiative) Seed Funding Scheme (2017) and a Melbourne Academic Centre for Health...
References


**Figures**
Figure 1: Consort diagram

Assessed for eligibility (n=126)

Eligible participants (n=74)
- Excluded (n=34)
  - Not meeting inclusion criteria (n=13)
  - Withdrew (n=2)
  - Declined to participate (n=11)
  - Did not respond to study invitation (n=8)

Randomized (n=40)

Allocated to flash glucose monitoring (n=20)
  - Received allocated intervention (n=19)*

Allocated to control (capillary glucose monitoring) (n=20)
  - Received allocated intervention (n=19)*

Follow-Up (3 months)
- Attended visit (n=20)
- Did not attend visit (n=0)
- Lost to follow-up (n=0)
- Discontinued intervention (n=0)

Follow-Up (6 months)
- Attended visit (n=19) - hospital admission
- Did not attend visit (n=1)
- Lost to follow-up (n=0)
- Discontinued intervention (n=0)

Analysis
- Analysed (n=20)
  - Excluded from analysis (n=0)

FGM = flash glucose monitoring; SMBG = self-monitored blood glucose.

*38 participants received the allocated intervention. 1 participant in the intervention arm received SMBG instead of FGM, and 1 participant in the control arm received FGM instead of SMBG.

Figure 1

See image above for figure legend.
Figure 2 – Secondary outcomes by treatment group and device (intention-to-treat population)

| A) Percentage time in glucose >15.0 mmol/L by Treatment Group and Device |
|-----------------------------|-----------------------------|
| **Figure A: Individual participant profiles** | **Table A: Median (25th and 75th percentile)** |
| | **Flash glucose monitoring (FGM)** | **Self-monitored blood glucose (SMBG)** |
| | Libre Pro | Libre iPro2 | Libre Pro | Libre iPro2 |
| | N=11 | N=9 | N=10 | N=10 |
| **Baseline** | 1.6 (0.6-17.7) | 5.2 (3.7-12.9) | 14.3 (4.1-22.8) | 0.8 (0.0-9.9) |
| **6-month** | 1.3 (0.6-13.8) | 7.3 (0.7-15.5) | 12.0 (1.2-21.1) | 10.5 (0.6-32.9) |

| B) Percentage time in glucose 4.0 – 10.0 mmol/L by Treatment Group and Device |
|-----------------------------|-----------------------------|
| **Figure B: Individual participant profiles** | **Table B: Median (25th and 75th percentile)** |
| | **Flash glucose monitoring (FGM)** | **Self-monitored blood glucose (SMBG)** |
| | Libre Pro | Libre iPro2 | Libre Pro | Libre iPro2 |
| | N=11 | N=9 | N=10 | N=10 |
| **Baseline** | 59.9 (39.3-78.3) | 47.9 (35.6-81.7) | 51.2 (16.0-86.6) | 62.3 (50.1-83.9) |
| **6-month** | 65.5 (43.7-79.1) | 52.3 (28.0-72.1) | 44.5 (21.7-73.8) | 60.5 (27.8-45.5) |

| C) Percentage time in glucose ≤3.9 mmol/L by Treatment Group and Device |
|-----------------------------|-----------------------------|
| **Figure C: Individual participant profiles** | **Table C: Median (25th and 75th percentile)** |
| | **Flash glucose monitoring (FGM)** | **Self-monitored blood glucose (SMBG)** |
| | Libre Pro | Libre iPro2 | Libre Pro | Libre iPro2 |
| | N=11 | N=9 | N=10 | N=10 |
| **Baseline** | 1.4 (0.0-2.9) | 0.0 (0.0-0.7) | 0.0 (0.0-3.1) | 0.0 (0.0-5.0) |
| **6-month** | 0.3 (0.0-0.7) | 0.5 (0.0-3.5) | 1.9 (0.0-4.9) | 0.1 (0.0-1.2) |

FGM = flash glucose monitoring, SMBG = self-monitored blood glucose.
Data are presented as median (25th to 75th percentile).
1 participant in the intervention arm received SMBG instead of FGM, and 1 participant in the control arm received FGM instead of SMBG. These participants were included in the group ‘at randomised’.
Data measured outside of the scheduled visit windows were excluded from the analysis. As a result, 1 participant data at baseline and 3 at 6 months follow-up were excluded.

Figure 2

See image above for figure legend.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.
- Appendix.docx
- PFSEquatorChecklist.doc
- SAPredacted.pdf