UNIVERSITEIT VAN PRETORIA
UNIVERSITY OF PRETORIA
YUNIBESITHI YA PRETORIA

The effect of a structured self-monitoring blood glucose regimen on glycaemic control for type 2 diabetes patients using insulin

by

Kerry Leigh Kalweit
u10056042

Submitted in partial fulfilment of the requirements for the degree
Master of Science in Clinical Epidemiology

In the Faculty of Health Sciences
University of Pretoria
October 2016

Supervisor: Professor Paul Rheeder
Co-supervisor: Professor Daniel G. van Zyl

Abstract

Background: Self-monitoring of blood glucose (SMBG) can inform on the timing of hyperglycaemia; however there is currently no standardised approach to utilise these data to improve glycaemic control in type 2 diabetes patients.

Aims: To assess the efficacy of structured blood glucose testing in guiding an insulin titration algorithm in poorly controlled, insulin-treated type 2 diabetes patients. The secondary aim was to compare change in HbA1c between the study subjects and matched controls receiving standard treatment.

Methods: This six-month prospective intervention recruited 39 poorly controlled (HbA1C ≥ 8.5% or 69.4 mmol/mol), type 2 diabetes subjects using twice-daily biphasic insulin from two public hospitals in Tshwane, South Africa. Patients were asked to perform structured SMBG over 4 weeks and return monthly for consultations where physicians titrated insulin doses using a standardised algorithm guided by the data collected. Post-hoc analysis was performed to assess glycaemic control of study participants compared to those receiving standard treatment.

Results: It was found that mean HbA1c decreased over the study period by 1.89% (95% CI: -2.46 to -1.33, p-value<0.001). Mean SMBG and mean fasting plasma glucose (FPG) decreased by 1.6 mmol/L (95% CI: -2.5 to -0.6 mmol/L, p-value: 0.002) and 1.5 mmol/L (95% CI: -2.2 to -0.2 mmol/L, p-value: 0.024), respectively. Hypoglycaemic event rate (≤3.9 mmol/L) was 33.08 events per patient-year. Total daily insulin use increased by a mean 40.12 units.day^{-1} (SE: 7.7, p-value<0.001); weight increased by an average 3.98 kg (95% CI: 2.56 to 5.41, p-value <0.001) over the study period. Study participants were found to have a greater mean (SE) reduction of 0.777% (0.404) in HbA1c compared to patients receiving standard care, which fell short of statistical significance (95% CI: -1.569 to 0.015%, p-value: 0.054) due to lack of power (56.5%) in the post-hoc comparison.

Conclusion: A structured SMBG programme that advises monthly algorithmic insulin titration can improve glucose control in type 2 diabetes patients using insulin, with moderate hypoglycaemic events and weight gain.

Keywords: Type 2 diabetes; structured self-monitoring blood glucose; insulin titration algorithm; HbA1c; South Africa

Table of contents

List of tables

List of figures

Abbreviations

ADA	American Diabetes Association
AM	Morning
BMI	Body Mass Index
CADTH	Canadian Agency for Drugs and Technologies in Health
CGM	Continuous glucose monitoring
CI	Confidence interval
DCCT	Diabetes Control and Complications Trial
DoH	Department of Health
DTSQ	Diabetes Treatment Satisfaction Questionnaire
DvZ	Professor Danie van Zyl (co-supervisor)
FPG	Fasting plasma glucose
GLMM	Generalised linear mixed modeling
HbA1c	Glycated haemoglobin
HCPs	Health care professionals
IDF	International Diabetes Federation
IQR	Interquartile range
KK	Miss Kerry Kalweit (primary investigator)
n	Number
NHLS	National Health Laboratory Service
NICE	National Institute for Health and Care Excellence
NPH	Neural Protamine Hagedorn
OHAs	Oral hypoglycaemic agents
PM	Evening
PPG	Post-prandial glucose
PR	Professor Paul Rheeder (supervisor)
QoL	Quality of life
RCT	Randomised control trial
SD	Standard deviation
SE	Standard error
SEMDSA	Society for Endocrinology, Metabolism and Diabetes of South Africa
SMBG	Self-monitoring of blood glucose
TIA	Transient ischemic attack

Declaration

I hereby declare that this dissertation presented to the University of Pretoria for the Masters of Science in Clinical Epidemiology degree is my own work and has not been previously submitted for a degree to any other tertiary institution.

_____

Kerry Kalweit

Ethics approval

The author, whose name appears on the title page of this dissertation, has obtained, for the research described in this work, the applicable research ethics approval (reference number: 432/2014) on 30 October 2014, see Appendix H. The trial was registered with the Department of Health on the South African National Research Register (reference number: DOH-27-0115-4949) on 02 December 2014.

The author declares that she has observed the ethical standards required in terms of the University of Pretoria's Code of ethics for researchers and the Policy guidelines for responsible research.

Proposed publication

The study is proposed to be submitted to *Diabetes Care*, a journal of the American Diabetes Association for publication, and for oral presentation at the Society for Endocrinology, Metabolism and Diabetes of South Africa (SEMDSA) Congress 2017.

Acknowledgements

Authorship

First author: Miss Kerry L Kalweit

Second authors: Professor Paul Rheeder (supervisor)

Professor Daniel G. van Zyl (co-supervisor)

Editing

I wish to sincerely thank Ms Gila Carter for giving up many of her Saturdays to guide me in writing and editing this thesis. I wish to thank Professor David Segal for his critique of the clinical significance of findings herein. Appreciation goes to Mr Marcel du Plessis for grammatical editing.

Funding

The financial assistance of the National Research Foundation (NRF) towards this research is hereby acknowledged. Opinions expressed and conclusions arrived at are those of the author and are not necessarily to be attributed to the NRF. Appreciation also goes toward the School of Health Systems and Public Health and the School of Medicine, University of Pretoria for their funding contribution of this project. I would also like to thank Roche Products (South Africa) for their enormous generosity of financial and product contributions that made this project possible.

Personal

I sincerely wish to express my gratitude to the patients enrolled in this study and to the doctors at Kalafong Hospital. I learnt invaluable skills from my clinical experience at the diabetes clinics, and was inspired to direct my future career towards endocrinology. I would also like to thank my mom for her continuous, unwavering support, especially in these last two years.

1. Literature review

1.1. Introduction

The Diabetes Atlas report by the International Diabetes Federation (IDF) reports that South Africa currently has more than 2.3 million adults living with diabetes, with an additional estimated 1.4 million people that remain undiagnosed. The report also cites that in 2015, 16.3% of all deaths in people aged 20 to 79 years were diabetes-related, demonstrating how this chronic condition is severely affecting the working class of our society.[1] Local studies demonstrate that prevalence of diabetes is higher than reported by the IDF: the Durban Diabetes Study found the age-standardised prevalence of diabetes to be 12.9% (95% CI: 11.0-14.9%)[2], which was similar to the prevalence found in Cape Town of 13.1% (95% CI: 11.0-15.1%)[3], both within an urban black South African population. In a landmark study, the Diabetes Control and Complications Trial (DCCT) Research Group showed that reduction in glycated haemoglobin (HbA1c) can be used as a biomarker to assess risk for diabetes-related complications, including all-cause mortality[4], which has major cost implications for the national health system.[1]

1.2. HbA1c: issues with the gold standard

Since the DCCT, HbA1c has become the gold standard for assessing glycaemic control. HbA1c is measured primarily to identify the average plasma glucose concentration, where blood glucose levels from the preceding 30, 30 to 90, and 90 to 120 days contribute 50%, 40% and 10%, respectively.[5] Attaining HbA1c targets is the primary goal in diabetes management as a biomarker for improved prognosis and the delay or prevention of diabetes-related complications.[2] There are, however, numerous caveats associated with HbA1c.

Limitations include (i) the non-linear relationship between HbA1c and mean blood glucose due to patient biological variation, including age[6]; (ii) unreliable results for patients with haemoglobinopathies, such as haemolytic anaemia or sickle-cell disease[7]; and (iii) the inability of HbA1c to account for glycaemic variability.[8]

Research studies have shown that glycaemic variability, measured as pre- and postprandial blood glucose excursions, is an independent indicator for quantifying risk

of diabetes complications, regardless of HbA1c measurement. The Diabetes Epidemiology: Collaborative analysis Of Diagnostic criteria in Europe (DECODE) study found that postprandial hyperglycaemia was an independent factor in the development of macrovascular complications[9], such as cardiovascular disease[10] and that fasting plasma glucose variability is able to predict the incidence of retinopathy.[11,12]

Monnier, Lapinski and Colette (2003) conducted a study to quantify the contribution of glucose variability to overall glycaemic control and thus relate fluctuations in glucose values to HbA1c.[13] The results showed that postprandial glucose excursions were the predominant contributor to overall hyperglycaemia for patients who were fairly to moderately well controlled (HbA1c <8.4%, <68 mmol/mol). Whereas, for patients with increasingly poor control (HbA1c ≥8.4%, ≥68 mmol/mol), overall hyperglycaemia was predominantly attributed to fasting blood glucose excursions. Thus medication titration should be targeted at hyperglycaemia at specific times of the day according to HbA1c, emphasising the need to have this data available in the consultation.

Within the South African public healthcare sector, an additional issue to consider when using HbA1c as a measure of glycaemic control is that the National Health Laboratory Service (NHLS) only allows for HbA1c to be tested once per year. These blood test results are routinely processed up to eight weeks later. After such time, patients' HbA1c values have changed.[4] Therapy adjustments are therefore made based on outdated patient information and cannot be made within the current clinical consultation time. A common solution to this is to send patients for blood tests two weeks prior to the consultation. As can be seen, HbA1c is far from an ideal gold standard in assessing glycaemic control. Routine blood glucose monitoring may be able to offset these limitations.

1.3. SMBG in South Africa

Self-monitoring of blood glucose (SMBG) is an alternative tool in the assessment of diabetes control.[14] The purpose of SMBG is for the patient to collect detailed information about glucose levels across various intervals each day and take

appropriate action should those levels be outside the desired range.[15] For example, insulin up titrated if hyperglycaemia occurs.

The literature shows that SMBG has a number of advantages over traditional HbA1c as a measurement of glycaemic control. A major benefit is the ability to detect blood glucose excursions and thus capture glycaemic variability, which is not adequately portrayed by HbA1c.[6] Moreover, data gathered can be used for adjusting medications, dietary content and physical activities.[16] Through SMBG, patients are made aware of the effect of food and/or exercise on their blood glucose which in turn may provide enhanced motivation for behavioural changes.[17]

Despite the obvious benefits, SMBG has some disadvantages. A patient may feel that their quality of life (QoL) is negatively affected by the use of SMBG due to the increased level of perceived diabetes-related burden. Since patients are increasingly aware of hypo- or hyperglycaemia, this may also lead to anxiety or even self-blame.[17]

In the context of the South African healthcare sector, availability of blood glucose meters and test strips is limited and unreliable as these resources are not included in the Essential Medicines List.[18] Hospitals must therefore carry the costs of test strips. In addition, there is currently no standardised approach to utilise SMBG data to improve glycaemic control for patients who receive home blood glucose monitoring equipment. Current practise is that patients who receive test strips are advised to test their blood glucose levels once or twice a day, with most patients choosing to test fasting plasma glucose (FPG) levels. This does not allow health care professionals (HCPs) to obtain accurate glycaemic information over the course of the day. Structured SMBG regimens may serve as a solution, whereby patients receive guidance on the timing and frequency of SMBG.

1.4. Recommended SMBG regimes

Two popular structured SMBG approaches emerge from current literature: the 7-point regimen and staggered or meal-based SMBG method.

1.4.1. Seven-point regimen

Kato, Cui and Kato (2013) conducted a randomised controlled trial (RCT) in Japan to investigate if the 7-point, 3-day SMBG regimen was effective for insulin-using diabetes patients.[19] Patients were requested to perform SMBG before and two hours after each meal and an additional blood glucose test before bed for three consecutive days directly before their monthly clinical visit resulting in a total of 21 tests (Figure 1).

Week before consultation with physician	Breakfast		Lunch		Dinner		
	Before	2 hours after	Before	2 hours after	Before	2 hours after	Bedtime
Sunday							
Monday							
Tuesday							

Figure 1: An example of the 7-point structured SMBG regimen with a total of 21 tests performed per month. Shaded blocks indicate where SMBG should be performed.

Patients visited the clinic monthly and their therapy was adjusted based on the SMBG results. After six months, results indicated that there was a significant reduction in HbA1c for the intervention arm compared to the control arm (–0.4%; p-value: 0.002). After the intervention, patients in the structured SMBG group were given the choice to continue with the structured SMBG or return to usual treatment.[19] Fifty-five percent of patients in the intervention arm elected to continue structured testing; no reasons were listed for why the remaining sample chose not to continue with the 7-point structured testing. The trial states that limitations included small sample sizes (n=83) and the use of only one clinic.

In the Structured Testing Program (STeP) study, the researchers also employed a 7-point 3-day routine in type 2 diabetics treated with oral hypoglycaemic agents (OHAs).[20] Patients were seen at three month intervals to adjust therapy where structured SMBG was conducted in the week prior to clinical consultations. The intervention group achieved a –0.3% greater reduction in HbA1c than the control group

(p=0.04). The researchers added OHAs to the patients' regimens, thus the reduction in HbA1c could not be solely attributed to the SMBG alone.

An area of concern in the above studies is that the frequency and timing of these structured methods are often impractical and difficult to implement, thus reducing compliance. Patients may also perceive this routine to be taxing and decrease their perceived QoL. It can be expected that a bias may have also played a role in these studies, whereby patients take medication and eat correctly on days of SMBG, but may not have done so on other days. In addition, these studies did not specify the SMBG goals used to titrate medication, or how therapy changes were determined.

1.4.2. Paired testing

An alternative structured SMBG approach is the 2-point paired testing method where the patient only performs a pre-prandial and two hour postprandial (PPG) test for one meal a day. This is usually done three times a week covering breakfast, lunch and dinner (Figure 2).

	Day of the week	Breakfast		Lunch		Dinner		Bedtime
		Before	2 hours after	Before	2 hours after	Before	2 hours after	
Week 1	Monday							
	Tuesday							
	Wednesday							
Week 2	Friday							
	Saturday							
	Sunday							

Figure 2: An example of the paired testing structured SMBG regimen with a total of 12 tests performed per month. Shaded blocks indicate where SMBG should be performed.

In a RCT by Franciosi, Lucisano, Pellegrini *et al.* (2011), type 2 diabetes patients on OHAs were instructed to report the content of each meal, together with pre- and post-meal blood glucose readings for one meal three times a week and this was repeated for two weeks every month.[21] These results were communicated to nursing staff who

then administered medical nutrition education to the patient. If mean SMBG values exceeded pre-defined thresholds, a physician adjusted OHA doses following a predefined algorithm. The study found a 0.5% greater HbA1c reduction in the intervention arm (p-value: 0.04). They also observed very good compliance with the self-monitoring schedule – 93.4% of required measurements. A limitation of this study was that no bedtime readings were recorded with follow-up SMBG the next morning to monitor overnight glycaemia. The algorithm used to titrate doses was also not specified, and thus the study cannot be repeated.

As can be seen, there are many approaches to structured SMBG currently in circulation, thus it was deemed necessary to examine guidelines and consensus statements on this topic.

1.5. SMBG guidelines

The IDF suggest that the intensity and frequency of SMBG should be individualised to each patient's specific clinical requirements whilst taking the data required by the HCP to identify patterns of glycaemic variability into account.[22] Guidelines issued for frequency of SMBG for type 2 diabetes patients by the American Diabetes Association (ADA) specify the frequency of testing be determined according to insulin treatment.[23] The ADA advise that patients on intensive basal-bolus insulin therapy perform SMBG "prior to meals and snacks, occasionally postprandially, at bedtime, prior to exercise and when they suspect low blood glucose" (page S33). For patients on less intensive biphasic or basal insulin therapy, the ADA states that frequency of SMBG is unclear due to insufficient evidence.[23]

For type 2 diabetes patients using insulin, the Canadian Agency for Drugs and Technologies in Health (CADTH) found that those who perform a higher frequency of SMBG must attain higher HbA1C reductions to achieve more favourable cost-effectiveness estimates. Specific frequency of SMBG could not be advised due to the low quality of studies identified in the review.[24] In their 2012 Guideline for the Management of Type 2 Diabetes, the Society for Endocrinology, Metabolism and Diabetes of South Africa (SEMDSA) state that "in those individuals injecting insulin two to four times per day, testing should be undertaken at least three times per day.

In those individuals on once-daily insulin, with or without OHAs, once-daily testing at variable times is recommended" (page S21).[23]

From the above, there is no single recommended SMBG regimen for type 2 diabetes patients and none that advise specific treatment changes that should accompany SMBG results. Once adequate data can be collected, interpretation and use of the results by patients and diabetes HCPs is crucial.

1.6. Usage of SMBG data

A thorough search of the literature was performed for dosing regimens of different types of insulin available on tender in the public healthcare system. These included neutral protamine Hagedorn (NPH), biphasic insulin 70/30, and rapid acting human insulin.[18] Articles on basal analogue insulin were not considered since these insulins are not available in government hospitals. The Cochrane Library systematic review within the category of "Diabetes: glycaemic control type 2 (drug treatments)" was used as a starting point and analysed for articles providing evidence of dosing regimens.[26] A total of 20 articles were deemed relevant. Of these, 2 were review articles and were searched similarly for non-duplicated original articles.[27,28] Seven guidelines were also reviewed for insulin titration recommendations, including The National Institute for Health and Care Excellence (NICE) guideline[29], IDF guideline 2005[30], ADA standard treatment guideline 2015[23], ADA and EASD position statement[31], SEMDSA 2012 guideline[25], CADTH recommendations[32], and the Canadian Diabetes Association 2013 clinical practice guidelines.[33]

NICE describes an evidence-based approach for the initiation of new medication, guidelines for glycaemic targets and advice on "stopping criteria" for OHAs and insulin.[29] The IDF has presented a treatment algorithm for patients with type 2 diabetes that shows which medications are considered first line treatment, how HCPs should progress through different treatment options, and alternative treatment options should the recommended therapy not be suitable or effective.[30]

Most patients who are unable to achieve SMBG goals using maximum tolerated OHAs are candidates for insulin therapy.[31] Since only biguanide and sulfonylurea drug classes are available in government hospitals[18], triple OHA therapy is not an option.

Unless the patient is markedly hyperglycaemic (HbA1c ≥12% or 108 mmol/mol), initial insulin therapy is typically basal insulin.[32] A once-daily bedtime dose of NPH is commonly used to reduce endogenous glucose output during the night-time hours and to specifically target FPG levels.[28] Basal analogue insulins, such as glargine or detemir, can also be used. Although associated with moderately less nocturnal hypoglycaemia and less weight gain, basal analogue insulins are more expensive and have been shown to reduce HbA1c significantly less than NPH.[33]

Once initiated on basal insulin, the patient must be monitored for the need for prandial insulin to address PPG excursions. Use of sulfonylureas must be reviewed if frequent hypoglycaemia occurs.[34] Basal insulin is titrated primarily against the FPG, generally irrespective of the total insulin dose.[35] Although these guidelines detail which classes of medication to use, no information on the titration of OHAs or insulin doses is given.

The success of a structured SMBG routine would be minimal if it was not accompanied by a medication dose titration strategy to target specific hyperglycaemic patterns identified. Several RCTs have validated forced insulin titration schedules in both type 1 and type 2 diabetes patients; however, many of these studies have not published the algorithms used, and often only state that “insulin was titrated at the investigator’s discretion” or that insulin was titrated to reach certain glycaemic targets.[36-42] Only 7 studies provided data on titration algorithms used.

1.6.1. Insulin titration algorithms

Available titration algorithms were analysed individually for applicability to the South African public healthcare system according to type of insulin used, regularity of titration, and sample demographics (including mean age, baseline HbA1c, duration of diabetes and ethnicity). Study validity was assessed based on study design and loss to follow-up. Clinical utility was gauged on reduction in HbA1c and FPG achieved, hypoglycaemia event rate, weight change, whether study subjects were insulin naïve, and concomitant OHAs used.

Three RCTs assessed the titration of NPH where titration schedules were published.[43-45] The titration schedule used by Riddle, Rosenstock, Gerich *et al.* was seen to have the highest hypoglycaemic event rate of 12.9 events per patient year at a level <4.0

mmol/L.[43] A wide range of concomitant OHAs were also being used by the study sample that are not available in state healthcare, including pioglitazone and rosiglitazone. Hermansen, Davies, Derezinski *et al.* evaluated twice-daily NPH dosing, which is not recommended as first-line insulin therapy.[23,31] Also, baseline HbA1c levels for the study population seemed relatively low (8.51 ± 0.76%) compared to the typical HbA1c of type 2 diabetes patients starting insulin in public healthcare.[44] The titration algorithm from Eliaschewitz, Calvo, Valbuena *et al.* was thus deemed the most appropriate and effective.[45] The sample achieved a mean HbA1c reduction of −1.44 ± 1.33% with only 7.2 mild hypoglycaemic events per patient year (defined as blood glucose values of 2.8–4.2 mmol/L). Baseline HbA1c was more representative (9.2 ± 0.9%), and the only concomitant medication used was 4 mg/day of glimepiride.

Once-daily NPH is considered insufficient to control glycaemia when average pre-dinner blood glucose values >10.0 mmol/L, frequent hypoglycaemia occurs despite average SMBG >6.5 mmol/L, recurrent nocturnal hypoglycaemia occurs, pattern of total elevated blood glucose observed, or if the patient experiences elevated 2-hour PPG values ≥12.0 mmol/L.[44]

Most type 2 diabetes patients maintain some endogenous insulin secretion even in late stages of disease and thus the more complex and intensive dosing strategies of type 1 diabetes are not typically necessary.[46] The effectiveness of basal bolus regimens in T2DM is also not well established.[47] For these reasons, biphasic insulin is considered the next line of treatment when glycaemic goals are not reached with NPH alone.[29, 30]

Biphasic insulins can be used for a greater reduction in HbA1c compared to basal insulin alone by targeting both FPG and PPG excursions; and should particularly be considered if HbA1c ≥9.0% (75 mmol/mol).[47] When transitioning from NPH to twice-daily biphasic insulin, the new regimen should be started 18-24 hours after the last basal dose was given.[28] It should be noted that hypoglycaemia event rate and weight gain will be slightly increased. [47] Pre-breakfast and pre-dinner doses should be titrated using pre-dinner and FPG glucose levels respectively.[49]

Seven RCTs from the literature published their titration algorithms used for biphasic insulin aspart 30 (BIAsp, 30% aspart, 70% protaminated aspart). Table 1 compares the outcomes for different titration algorithms available. Comments on the applicability of each algorithm follows below.

Riddle, Rosenstock, Vlajnic *et al*. (2014) achieved a large reduction in HbA1c (−2.0 ± 0.12%) over 60 weeks with weekly titration of insulin doses and concomitant use of Pioglitazone.[48] This algorithm was deemed unfeasible due to the high frequency of titration that is resource intensive and because Pioglitazone is not available within the South African public healthcare system.[18] Additionally, the large drop-out rate of 27% points to bias and few ethnic populations were included in the sample.

Holman, Thorne, Farmer *et al*. (2007) achieved a moderate reduction in HbA1c (-1.3 ± 1.1%), with maximal reduction occurring by 24 weeks which then remained stable for the remainder of the year.[49] Only 17% of the 235 patients achieved the target HbA1c of ≤ 6.5%, which was deemed to be too stringent a target for patients in South Africa due to the sole availability of biphasic insulins in the public health sector for targeting prandial hyperglycaemia, which would lead to excessive hypoglycaemia.[18] Raskin, Allen, Hollander *et al*. (2005) achieved a massive HbA1c reduction of -2.79 ± 0.11% in 28 weeks, but also allowed for concomitant use of Pioglitazone and set target HbA1c at ≤6.5%.[50]

Yang, Ji, Zhu *et al*. (2008) achieved an impressive reduction in HbA1c (-2.48 ± 0.07%) in just 24 weeks, but titration was performed weekly, again not indicating long-term feasibility within the South African context.[51] In the study, Yang *et al*. discontinued all OHAs, contradicting international guidelines to continue biguanide therapy with the initiation of insulin;[30] however, this did allow for an accurate evaluation of how insulin titration independently reduced HbA1c. The investigators also gave subjects diet and lifestyle advice which may have contributed to the achieved reduction in HbA1c.

Garber, Wahlen, Wahl *et al*. (2006) tested the success of once, twice- and three-times daily biphasic insulin injections in a non-randomised, single group trial.[52] Patients who achieved glycaemic targets with once-daily dosing were deemed to have completed the study, and removed; the rest of the patients moved to twice- and thrice-daily

biphasic injections after 15 week intervals for each phase. The short duration of time required to achieve the glycaemic targets per phase required an aggressive insulin titration regimen that was suspected to have caused the excessive hypoglycaemia rate of 22.4 events per patient year.

Janka, Plewe, Riddle *et al*. (2005) achieved a reduction in HbA1c of -1.34 [95% CI, -1.17 to -1.44], with moderately frequent hypoglycaemia (9.87 events per patient year at a glucose level <3.3mmol/L).[53] Patients were insulin naïve, which is not representative of clinical practise, since NPH insulin is used as a first-line insulin treatment prior to starting any prandial-based insulin as per international guidelines.[29, 31] We can thus expect a more modest reduction in HbA1c when using this algorithm for patients previously treated with NPH.

Liebl *et al*. (2009) was the only study that incorporated some patients who had previously used insulin.[49] An HbA1c reduction of -1.23% was achieved over 26 weeks; however, patients who were previously treated with insulin only achieved a -0.75% reduction in HbA1c. Insulin was titrated weekly for the first six weeks, and thereafter more gradual optimisation continued until patients reached glycaemic targets. This is more realistic to implement in the public healthcare setting, where insulin can be titrated monthly over a longer duration. Hypoglycaemia was seen to be very low (1.92 events per person year at a glucose level of <3.1mmol/L). Like Yang *et al*., Liebl *et al*. stopped all OHAs. It is thus expected that HbA1c and weight gain may be ameliorated when adding concomitant biguanide therapy as per international guidelines.[29, 31]

From the above analysis, it was decided that the titration protocol used by Liebl *et al*. (2009, page 47)[47] with aspects from the CADTH [24] and Canadian Diabetes Association clinical guidelines[32] would be most suitably paired with a structured SMBG routine for the South African context. This algorithm is outlined in Figure 3.

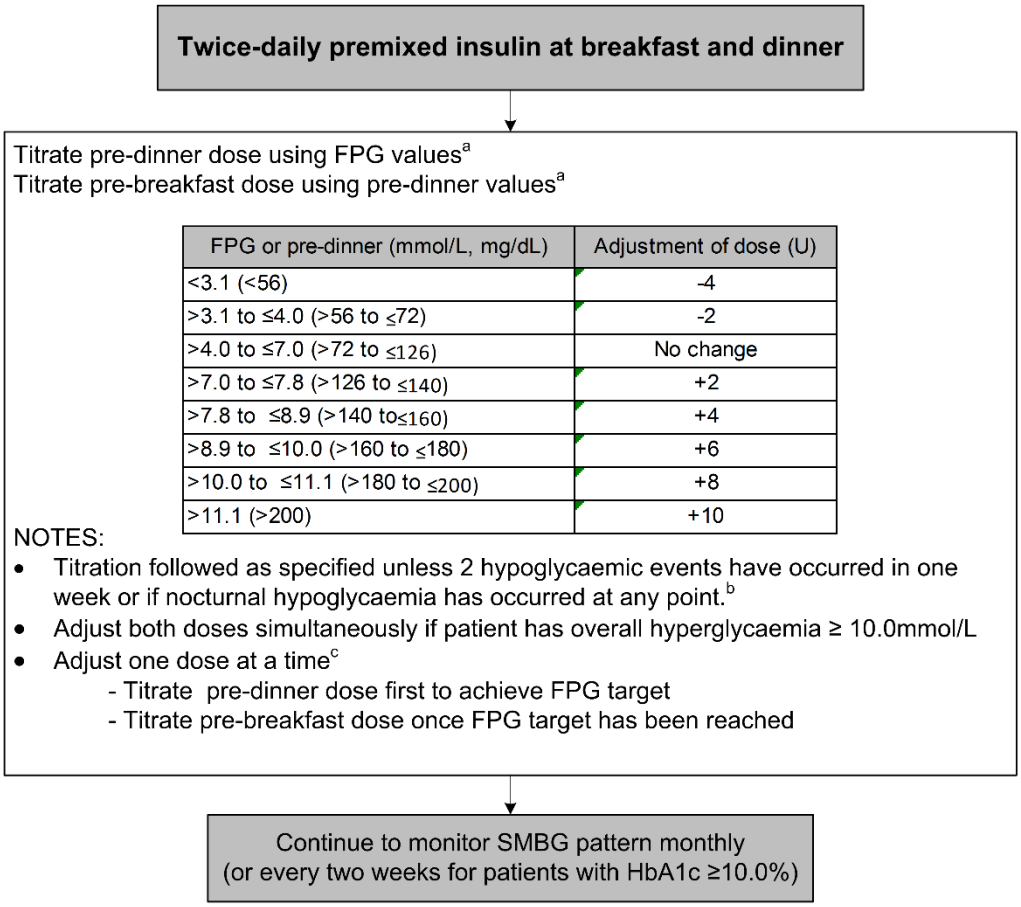
1.7. Summary

It is the combination of structured SMBG and algorithmic insulin titration that are proposed to achieve a maximum glucose lowering effect. Guidance on the timing and frequency of SMBG for patients will allow HCPs an overall view of hyperglycaemic

patterns experienced, and thus better inform insulin and OHA adjustments. The lack of consensus for how best to utilise SMBG data to guide medication titration for type 2 diabetes patients within a low-resource setting represents a gap in the literature than needs to be further explored.

Table 1: Comparison of outcomes from various clinical trials that made use of insulin titration algorithms

Researchers	Study design	Study duration (weeks)	Sample size	Loss to follow-up %	Frequency of titration	Concomitant medication	Change in glycaemic control	Hypoglycaemia (events per patient-year)	Insulin naïve	Mean (SD) change in insulin (units.day^{-1})	Change in weight (kg)
Riddle *et al* (2014)	Multicentre Open-label Randomised	60	194	27	Weekly	Metformin Pioglitazone Sulphonylurea	HbA1c: −2.0 (0.12)% FPG: −3.4 (4.0) mmol/L	1.9 at <2.8 mmol/L	Y	+110 (82.3)	+6.9 (6.9)
Holman *et al* (2007)	Multicentre Randomised	52	235	5.5	At visits 2, 6, 12, 24, 38, and 52 weeks with interim phone calls	Metformin Sulfonylureas	HbA1c: -1.3 (1.1)% FPG: -2.5 (3.1) mmol/L	5.0 at <3.1 mmol/L	Y	+48 (IQR: 30-71)	+4.7 (4.0)
Raskin *et al* (2005)	Multicentre Open-label Randomised	28	117	15	Weekly for the first 12 weeks, then bimonthly thereafter	Metformin Pioglitazone	HbA1c: -2.79 (0.11)% FPG: -6.9 (4.1) mmol/L	3.4 at <3.1 mmol/L	Y	+78.5 (39.5)	+5.4 (4.8)
Yang *et al* (2008)	Multicentre Randomized Open-label	24	160	7.5	Weekly	All OHAs stopped	HbA1c: -2.48 (0.07)% FPG: not available	1.28 at <2.8 mmol/L	Y	+56.6 (19.3)	+3.87 (0.28)
Garber *et al* (2006)	Single group Open label	30	68	-	Self-titration under supervision every 3-4 days	Metformin	HbA1c: -1.9 (1.0)% FPG: -2.8 (3.3) mmol/L	22.4 at <3.1 mmol/L	N	+117.9	5.0
Janka *et al* (2005)	Multinational Multicentre Open label	24	187	15	Weekly for the first 8 weeks, then bimonthly thereafter	All OHAs stopped	HbA1c: -1.31% FPG: -2.2 mmol/L	9.87 at <3.3 mmol/L	Y	+ 64.5 (17.1)	2.1 (4.2)
Liebl *et al* (2009)	Multinational Multicentre Randomized Open label	26	178	9.5	Weekly for first 6 weeks; then less frequent until at target	All OHAs stopped	HbA1c: -1.23% FPG: - 2.9 mmol/L	1.92 at <3.1 mmol/L	N	+30.5	2.1 (4.0)



[a]. Liebl A, Prager R, Binz K, et al. Comparison of insulin analogue regimens in people with type 2 diabetes in the PREFER study: a randomized controlled trial. Diabetes Obes Metab 2009;11:45–52.
[b]. Canadian Diabetes Association Clinical Practice Guidelines Expert Committee. Canadian Diabetes Association 2008 clinical practice guidelines for the prevention and management of diabetes in Canada. Can J Diabetes 2008; 32: S95-S98.
[c]. Canadian Agency for Drugs and Technologies in Health (CADTH). Optimal use recommendations for second and third-line therapy for patients with type 2 diabetes. Ottawa (ON): Canadian Agency for Drugs and Technologies in Health (CADTH); 2013 Jul. 19 p. http://www.guideline.gov/content.aspx?f=rss&id=47068#Section420

Figure 3: Titration algorithm suitable for the South African public health context.

2. Rationale

The IDF estimates the prevalence of diabetes within urban areas of South Africa at 8.47% (95% CI: 4.47 – 17.05%)[1] as compared to the prevalence in rural areas at 4.23% (95% Ci: 1.87 – 8.69%) in local studies, such as the study conducted in the Ubombo district of rural northern KwaZulu-Natal. [55] The city of Tshwane currently houses approximately 2.9 million residents, of which 71.9% are between the ages of 15 to 64 years, and 4.9% are over the age of 65 years.[54] This population was chosen due to the proximity of existing academic hospitals with available data records on patients with type 2 diabetes.

Clinicians agree that medication doses should be adjusted far more frequently than routine clinic visits allow, recommending titration every 1-4 weeks.[56] Patients treated at public healthcare institutions visit the facilities every month to collect their medication in South Africa. In order to target patients who have poor glycaemic control, physicians could take advantage of these regular visits to increase the frequency of clinical consultations, thereby facilitating more regular medication titration.

It is theorised that a greater reduction in HbA1c can be achieved by more frequent clinical visits with an adjustment of medication by HCPs based on SMBG values, rather than less regular consultations and doses adjusted by the patient. This method may also be able to be applied to a wider range of patients, including those with low levels of health literacy.

Many previous RCTs have focused on teaching patients how to adjust their own medication according to patterns in their blood glucose levels.[57-60] However, such interventions are predicted to have little success in the South African public healthcare system due to the low health literacy rates of patients and the lack of diabetes educators to teach these concepts to the patients.[61, 62] Specific diabetes education programs are not currently a priority for the National DoH since financial resources are very limited to employ staff solely dedicated to this task.[63] Structured SMBG regimens that stipulate patterns of home glucose testing may give HCPs a better picture of diabetes control.

Due to the different contributions of FPG and PPG to HbA1c cited earlier[13], patients who present with high HbA1c (≥8.4%, or ≥68 mmol/mol) need to first reduce FPG as opposed to patients with better control who need to target PPG excursions.

For a variety of conditions, such as HIV or tuberculosis, outcomes under standardised pathways or dose titration protocols are superior to those achieved by individualization of care.[28] This may be true for type 2 diabetes as hesitation of physicians to initiate and/or titrate insulin due to concerns about severe hypoglycaemia and weight gain are common.[62]

A comparison of glycaemic control in patients before and after implementing structured SMBG with insulin titration can assess the effects of the intervention in controlling type 2 diabetes. Should this method prove effective, the authors wish to present the intervention to the DoH to promote policy change regarding a national tender for glucometers and testing strips to ensure all patients using insulin are provided with SMBG resources.

3. Aim

The primary aim of the study was to assess the efficacy of a structured SMBG schedule in combination with an insulin titration algorithm in controlling blood glucose levels of type 2 diabetes patients.

The secondary aim of the study was post-hoc retrospective analysis of participants receiving the intervention in comparison to those receiving standard treatment over the same period of time.

4. Hypothesis and endpoints

4.1. Evaluation of the intervention

4.1.1. Efficacy assessments

The primary efficacy endpoint of the study was change in HbA1c from baseline to three months and six months for insulin-treated type 2 diabetes patients.

An absolute mean change in HbA1c was expected to be ≥1.0% after six months adherence to the structured SMBG protocol with the application of the titration schedule. Additional efficacy endpoints included: proportion of patients reaching an HbA1c target <7.0%; change in mean fasting plasma glucose (FPG) and mean post-prandial glucose (PPG); changes in glycaemic variability; change in insulin dose and rate of compliance to SMBG routine.

4.1.2. Safety assessments

Safety was assessed by reporting adverse events and hypoglycaemic episodes. Change in weight from baseline to end-of-study was also assessed.

4.1.3. Quality of life assessments

The impact of the SMBG routine and treatment algorithm on quality of life (QoL) perceived by the patients was measured. This was performed in order to predict the likelihood of patients continuing with the SMBG regimen after the study.

4.2. Comparison to standard treatment

Changes in glycaemic control in the study participants (intervention group) were compared to changes in glycaemic control in a matched control group of patients who were receiving standard diabetes care.

5. Methodology

5.1. Study design

This study was a prospective, non-randomised, single-group trial. Intervention duration was six months, with patient visits occurring monthly. The study received ethical approval from the main research ethics committee of the University of Pretoria (432/2014). Approval from Academic Advisory Committee of the School of Health Systems and Public Health (SHSPH) was also obtained. The trial was registered with the Department of Health on the South African National Research Register (DOH-27-0115-4949).

5.2. Study setting

This research was conducted in an outpatient setting in the diabetic clinics at Steve Biko Academic Hospital and Kalafong Hospital located in Tshwane, Gauteng. Permission for this study was obtained from hospital management from both of these facilities.

5.3. Study participants

5.3.1. Recruitment

Patients were recruited from the diabetes clinics at Steve Biko and Kalafong by assessing patient records at each of the facilities. Patients diagnosed with type 2 diabetes, with an HbA1c result ≥8.5% (69 mmol/mol) in the preceding six months and who were currently using insulin were telephonically invited to attend a screening visit. Patients without a recorded HbA1c measurement in the six month window were also invited to maximise the number of screened patients.

5.3.2. Inclusion and exclusion criteria for the sample

Sample patients included in the study had to:

- have had type 2 diabetes mellitus for a duration of more than one year
- be between 18 and 75 years of age
- be taking at least one insulin injection per day
- have voluntarily signed the informed consent document.

Exclusion criteria were:

- Type 1 diabetes mellitus diagnosis
- No insulin treatment at the start of the study
- Prior participation in any other research protocol within the last 30 days
- Current use of oral hypoglycaemic agents other than Metformin
- History of cancer within the last 5 years
- Currently treated with chemotherapy or radiation therapy
- Plans to relocate or travel extensively during the next 6 months
- Pregnant or breast feeding
- Females planning on pregnancy within the next 6 months
- Severe depression or other severe psychological conditions
- History of chronic kidney disease
- History of heart failure where cardiovascular status was unstable
- History of hypo-unawareness
- One or more severe hypoglycaemic episodes within the previous 6 months
- Patients with manual or visual disability that required dependency on others to give insulin or documenting blood glucose values
- Current drug or alcohol abuse
- Any severe concomitant disease that may affect glucose control
- Undergone a medical procedure in the previous 4 weeks or had planned surgery during the study
- Current use of oral corticosteroids

Reasoning that informed exclusion criteria were the following: less stringent HbA1C goals (<8%, 64 mmol/mol) may not be appropriate for patients with a history of severe hypoglycaemia, limited life expectancy, and advanced microvascular or macrovascular complications;[23] older patients (>75 years) are more likely to be compromised by hypoglycaemia that may result in falls and fractures;[64] individuals with chronic kidney disease are at increased risk for hypoglycaemia since insulin is eliminated slower with prolonged activity profiles, meaning dose reductions may be necessary.[65]

5.3.3. Amendments to inclusion criteria

Due to the slow recruitment rate, an amendment was made to the age range of participants included in the study. It was also found that the average age of diabetic patients at Steve Biko and Kalafong was older than originally anticipated. We included patients aged ≥ 18 years to ≤ 75 years (the original range was 18-70 years).

Due to recent changes in the national government tender in provision of sulfonylureas, it could not be guaranteed that patients would have access to Gliclazide for the duration of the study. Thus the study elected to exclude patients using any sulfonylurea. This change also simplified the intervention protocol since Gliclazide use was to be reviewed if recurrent hypoglycaemia occurred.

5.3.4. Screening visit

At the screening appointment, patients received an information leaflet explaining the purposes of the study (Appendix A). Researchers explained to patients that participation in the study was completely voluntary and confidential. Patients were also informed that their transport costs would be covered by the study.

If the patient agreed to participate in the study, investigators obtained written informed consent, recorded demographics, collected relevant medical history/lifestyle activities, assessed baseline QoL, and documented all current medications, including vitamins and supplements from the participant (Appendix B). A 5 µl blood sample was taken using a finger prick test in order to measure HbA1c on-site using the Cobas B101 (Roche Products, Johannesburg, South Africa), which meets acceptance criteria for lot-to-lot reproducibility and precision according to the National Glycohemoglobin Standardization Program and Clinical and Laboratory Standards Institute guidelines.[66] Patients who were found to have an HbA1c ≥8.5% (69 mmol/mol), and who met all other inclusion criteria were enrolled in the trial.

Participants received a blood glucose meter (Accu-Chek® Active blood glucose meter system, Roche Products, Johannesburg, South Africa) and were thoroughly trained in its operation with the use of visual aids for those with low health literacy levels (Appendix C). Research staff also provided participants with blood glucose test strips, a blood glucose diary (Appendix D) and an appointment card. Participants were

instructed on how to appropriately record blood glucose values and medication according to the structured SMBG routine. Participants were also educated in the use of metered dosing flex pens to administer accurate insulin doses. Participants were compensated for their transport costs for which they signed a receipt book.

No diabetes-related treatment changes occurred during this visit. Baseline assessment of QoL was conducted using the Diabetes Treatment Satisfaction Questionnaire (DTSQ, Appendix E).

5.4. Intervention

Week	Day of the week	Breakfast		Lunch		Dinner		Bedtime
		Before	2 hours after	Before	2 hours after	Before	2 hours after	
1	Sunday	■	■			■		■
	Monday	■				■	■	■
	Tuesday	■				■	■	■
2	Friday	■	■	■				■
	Saturday	■		■	■			■
	Sunday	■		■	■			■
3	Wednesday	■	■			■		■
	Thursday	■				■	■	■
	Friday	■				■	■	■
4	Monday	■	■	■				■
	Tuesday	■		■	■			■
	Wednesday	■		■	■			■

Figure 4: The newly designed structured SMBG routine with a total of 48 tests performed per month. Shaded blocks indicate where SMBG was performed.

5.4.1. Frequency and structure of SMBG

Participants were asked to perform four blood glucose tests for three consecutive days of each week as shown in Figure 4 above. On each of the SMBG days, a fasting breakfast and bed-time glucose test was performed. Each alternative week, the patient also performed either a fasting lunch time or fasting dinner time glucose test. For the fourth test each day, the patient alternated between one post-breakfast, and two post-

lunch or two post-dinner glucose tests. SMBG testing was staggered on different days of the week throughout the month to cover both weekdays and weekends. This resulted in a total of 48 blood glucose tests per month. Participants saw their diabetes physician once a month for medication adjustments based on SMBG values according to the validated insulin titration schedule (see Figure 3).

5.4.2. Utilisation of SMBG results by physicians

Professors Paul Rheeder (PR) and Danie van Zyl (DvZ) served as the treating physicians at Steve Biko and Kalafong Hospitals, respectively. At each consultation the participant's weight was measured, any technical complaints about their glucometer recorded, medication compliance assessed (by self-reported insulin and/or OHA doses missed), blood glucose diary collected, and any adverse events (AEs) or hypoglycaemic events recorded. Injection sites were inspected, and the participant advised to rotate sites if lipodystrophy and/or scarring were present. SMBG results were downloaded using the Accu-chek SmartPix software (Roche Products, Johannesburg, South Africa). The overall pattern of glycaemia was classified in the following categories: "Fasting elevated glucose", "Post-prandial elevated glucose", "Total elevated glucose", "Meal-specific elevated glucose", "Frequent hypoglycaemia", or "Other".

SMBG results and targets were discussed with the patient, emphasising the timing of hyperglycaemia. Insulin doses were titrated according to the titration algorithm; however, if deemed inappropriate by the physician, reasons for not using the algorithm were recorded. The start and end-time of each consultation was documented to calculate accurate appointment duration. If patients had experienced hypoglycaemic events in the prior month, identification and treatment of low blood glucose was also discussed.

Participants with an HbA1c ≥10.0% (86 mmol/mol) were telephonically contacted by trial staff between monthly clinical consultations (2 weeks after each consultation). The participants were asked to state their blood glucose readings from the preceding 2 weeks, where upon their insulin dose was titrated. As soon as it had been established that such a participant's HbA1c had decreased below 10.0% (86 mmol/mol), these interim phone call sessions were stopped.

Insulin was titrated to achieve the glycaemic goals shown in Table 2. Once this was achieved, participants continued to be monitored in order to assess the stability and robustness of their euglycaemia.

Table 2: Targets for blood glucose measurements used to guide insulin titration

BG measurement	Target
Fasting/pre-prandial (mmol/L)	5.0 - 7.2
2-h post-prandial (mmol/L)	<10.0
HbA1c (%)	<7.0
Average SMBG values (mmol/L)	<8.6

5.5. Data collection

All participants were recruited using a standard screening document, and subsequent clinical consultations recorded with monthly clinic forms (Appendix F). Patients were issued with a diary each month in which to record their blood glucose value and medication – data which would be entered into a Microsoft Access database created specifically for the project. Data entries had validation limits to ensure the soundness of data entered. The database was saved on a virtual cloud to prevent loss and corruption of the data.

Each month, the participants' blood glucose meters were tested with two control solutions to ensure accuracy of SMBG data. If values were outside the control limits, participants were issued immediately with a new machine. Participants were also changed to metered-dose insulin pens, as opposed to vials and syringes, to ensure administration of accurate insulin doses.

The optical quality of the Cobas B101 machine (Roche Products, Johannesburg, South Africa) was checked weekly to ensure accurate HbA1c readings. Control samples were assessed for each new lot number of HbA1c test cartridges.

Data for matched controls were retrieved from the Kalafong patient database with the assistance of DvZ. Patients were filtered according to the same inclusion and exclusion criteria as participants who had received the intervention. Patients were

excluded sequentially for the following: lack of two recorded HbA1c results (n=296), baseline HbA1c <8.5 (n=119), use of OHAs other than Metformin (n=12), enrolled in the intervention (n=15), and age >75 years (n=4). This left 54 patients, which were then matched to study participants to according to sex, race, age (within a median of 4 years), and baseline HbA1c (within a mean of 0.5%) whilst blinded to follow-up HbA1c values.

5.6. Statistical analysis

Data distribution was analysed using the Shapiro–Wilk test and histograms. Parametric tests were used for data deemed normally distributed and non-parametric tests applied to skewed data. All data were analysed using Stata 12 software.[67]

5.6.1. Sample size

The study was designed to have a 90% power to detect an absolute mean HbA1c percentage difference of 1.0% over 6 months within patients that received the intervention. This was determined by using the GLIMMPSE online power and sample size software for repeated measures and longitudinal designs using Hotelling Lawley Trace test.[68] A mean HbA1c of 9.0% (75 mmol/mol) at baseline was assumed. Correlation of repeated HbA1c measurements was estimated to monotonely decrease by 0.5 for every three months. The base correlation between successive HbA1c measurements was assumed to be 0.8. The standard deviation of HbA1c measurements between participants was estimated at 2.2% according to HbA1c data from the Steve Biko Diabetes Clinic. A type 1 error rate of 0.05 was selected. According to these specifications, a sample size of 32 participants with complete data was needed. However, to account for missing data and loss to follow up, a 20% drop-out rate was assumed, resulting in a final sample size of 40 participants receiving the intervention.

Use of a formal control group was not feasible due to budgetary constraints. According to GLIMMPSE, the same analysis using two arms (intervention versus control) would have required a sample size of 368 in each arm to have a 90% power to detect an absolute mean HbA1c percentage difference of -1.0% between groups. After

accounting for loss to follow up, a total sample size of 884 participants would have been required.

In addition, a randomised control trial was beyond the scope of this degree. However, some measure of comparison was warranted, thus post-hoc retrospective analysis of patients receiving standard treatment over the same time period was performed for the secondary aim of this study. Controls were matched to participants based on age, sex, race and baseline HbA1c.

5.6.2. Change in HbA1c

The analysis of trends in HbA1c was performed using generalised linear mixed modelling (GLMM) using the XTMIXED command in STATA to see changes between 3 time periods, namely: baseline, three months, and six months.

GLMM is an extension of linear mixed modelling that includes both fixed and random effects, and is particularly useful when analysing longitudinal data with repeated measures.[69] Fixed effects factors are variables with values that are clearly represented in the dataset, and are thought to refer to the population-average. In contrast, random-effect factors are variables with values that are taken at random for a larger population of values. These factors are useful for explaining excess variability in the dependent variable, and are thought to capture subject-specific effects.[70]

Control variables included: participant age, gender, and race as fixed effects; with visit number and subject as random effects. Random intercept and random slope were modelled for all dependent variable analyses. This allowed the model to predict an independent baseline value per patient, and allowed different rates of change in the dependent variable over the time intervals for each individual. Based on the mixed model, the least square estimates of the time interval differences were obtained and tested for statistical significance. No missing data were imputed.

Sensitivity analysis was conducted for participants with a baseline HbA1c ≥10% (86 mmol/mol), participants who were deemed compliant (see section 5.6.7), and for those using Metformin.

5.6.3. Mean SMBG

GLMM analysis was used for assessing changes in mean SMBG per monthly visit over six time periods. The mean of all 48 blood glucose values for each month was captured from downloaded SMBG data at each monthly clinical consultation. Participant age, gender, race and number of SMBG tests performed were set as fixed effects; and visit number and subject as random effects. Random intercept and random slope were modelled. No missing data were imputed.

Mean SMBG was also correlated to HbA1c using spearman rank correlation coefficient to assess how accurately SMBG captured true glycaemia.

5.6.4. Mean FPG and PPG analysis

GLMM analysis was used for assessing changes in mean FPG and PPG per monthly visit over six time periods. The mean of all 12 FPG values, and 12 paired pre- and post-meal BG values for each month was captured from downloaded SMBG data at each monthly clinical consultation. Participant age, gender, race and number of FPG or PPG tests performed were set as fixed effects; and visit number and subject as random effects. Random intercept and random slope were modelled. No missing data were imputed.

5.6.5. Glycaemic variability analysis

5.6.5.1. Overall variability

Standard deviation (SD) around mean glucose values remains the gold standard for assessing glucose variability. This information was extracted at each clinical consultation from downloaded SMBG data from the previous 30 days using the Accu-chek Smart Pix software (Roche Products, Johannesburg, South Africa).

5.6.5.2. Intraday variability

Several tools for assessing intraday glycaemic variability exist, but almost all such measures require the use of continuous glucose monitoring systems or are difficult to interpret due to the complexity of the formulas used. Thus, in an attempt to capture intraday variability, the following two components were utilised:

(i) Trend in FPG standard deviation over six months using GLMM analysis. The SD of all 12 FPG values for each month was captured from downloaded

SMBG data at each monthly clinical consultation. No missing data were imputed.

(ii) Trend in PPG standard deviation over six months using GLMM analysis. This was measured by determining the SD of absolute differences in the 12 paired pre- and post-meal BG values for each month. No missing data were imputed; if values were missing, the pairing was excluded.

5.6.6. Insulin titration analysis

Change in morning and evening insulin doses were analysed using paired t-test analysis with equal and unequal variance, respectively. Qualitative analysis was undertaken for situations where the insulin titration algorithm was deemed inappropriate.

5.6.7. Compliance

Compliance was analysed as a categorical variable where patients were divided into quartiles according to the total number of SMBG tests performed out of a maximum of 288 throughout the study period.

5.6.8. Appointment duration

The start and end-time of each monthly clinical consultation for participants was recorded to estimate the duration of the sessions. Median appointment duration was reported per month of the intervention.

5.6.9. Adverse and hypoglycaemic events

An adverse event was defined as serious if the incident was fatal, life-threatening, resulted in persistent or significant disability/incapacity, or required hospitalisation. All events were recorded at monthly clinical consultations and are discussed separately in the results section.

The incidence rate of hypoglycaemic events (defined as blood glucose value ≤3.9 mmol/L) was calculated as [(total number of events across all participants) / (total duration of treatment in years across all participants)]. A subset analysis was conducted to determine the nocturnal hypoglycaemic rate wherein hypoglycaemia occurred while the participant was sleeping. Nocturnal hypoglycaemic rate was

calculated as [(total number of nocturnal events across all participants) / (total duration of treatment in years across all participants)]. Median number of hypoglycaemic episodes (total and nocturnal) were also reported, as well as the number of participants to whom the majority of the hypoglycaemic events could be attributed.

5.6.10. Weight changes

Change in weight was calculated using a t-test of differences in baseline and final mass of the participants.

5.6.11. QoL data

5.6.11.1. DTSQ analysis

Analysis of change in QoL was carried out on the three dependent variables within the DTSQ form. Change in treatment satisfaction was calculated as the sum of items 1, 4-8 on the DTSQ, and differences in pre- and post-intervention evaluated using the sign rank test. Change in perceived hyperglycaemia (item 2 on the DTSQ), and change in perceived hypoglycaemia (item 3 on the DTSQ) were evaluated using t-tests for pre- and post-intervention scores.

5.6.11.2. Qualitative analysis of QoL

Participants were issued with a questionnaire at the end of the study to gain in-depth qualitative information about how they perceived the intervention (see Appendix G). Participants were asked to comment on which aspects of the intervention they enjoyed during the trial, what aspects they disliked, what suggestions or comments they had regarding the intervention, what they had learnt by participating in the study, and whether or not they would continue with the structured SMBG program. Answers for open-ended questions were categorised into common themes and reported on. The proportion of patients willing to continue with the regimen was also reported.

5.6.12. Comparison to standard care

As part of the secondary aim, differences in HbA1c change, from baseline to six months, between participants and matched controls were calculated using GLMM. Patients were matched based on age, sex, race and baseline HbA1c. The Student's t-test was used to evaluate if statistically significant baseline differences occurred between the two arms. Treatment group was the only variable included as a fixed

effect factor since other variables were matched. Subject was included as the random effect factor. Random intercept was used in the model, but random slope could not be used due to the existence of only two time point data available for the matched controls.

Analysis of power was performed using the GLIMMPSE online software to evaluate whether the comparison was sufficiently powered to detect significant differences between the two groups.

5.7. Research funding

Roche Products South Africa (Pty) Ltd funded glucometers, test strips, lancets, Smart Pix software, HbA1c tests cartridges (to the total value of R91 409.99), as well as R48 000.00 in cash for this study. The University of Pretoria's School of Medicine funded the project R 11 675.90, and the SHSPH funded the project R8 000.00. The financial assistance of the National Research Foundation (NRF) towards this research is hereby also acknowledged for tuition and living expenses of the primary investigator KK.

6. Results

6.1. Introduction

For the primary aim of this study, patients were recruited from Steve Biko Academic Hospital and Kalafong Hospital during the period of January to April 2015. Each patient was followed up for six months afterwards, therefore follow-up took place between February and October 2015. Results for these participants will be discussed from Sections 6.2 to 6.5.

For the secondary aim of the study, retrospective data (for the period January to December 2015) from the Kalafong database was analysed to match patients who received the intervention with patients who had received standard care. Comparison of the two groups will be discussed in Section 6.6.

6.2. Description of the sample

A total of 59 patients were screened for the study. Patients were not included in the trial due to: HbA1c below inclusion rate (n=11); severe hypoglycaemic episode in the last 6 months (n=1); inability to travel to the clinic every month (n=2); weary of insulin titration (n=1); major surgery scheduled within the next 6 months (n=2); and personal reasons (n=2). Figure 5 summarises the patient flow within the study.

A total of 40 patients were enrolled into the study; 35 were treated at Kalafong Hospital, and five were treated at Steve Biko Academic Hospital. One patient was lost to follow-up due to their relocation to a different province after three weeks in the study. No insulin titration was made, thus the patient's results are excluded from all calculations.

None of the participants were insulin naïve, though duration of insulin use was not available. Frequency of insulin doses was not changed except in one patient (0043) at Visit 5 due to extreme hyperglycaemia over lunch time, where DvZ elected to add an additional lunch dose of biphasic insulin. No new insulins or OHAs were added, thus keeping medication regimen constant throughout the trial; only doses of current biphasic insulin were titrated. Table 3 describes baseline demographic and clinical characteristics of the 39 patients who completed the trial.

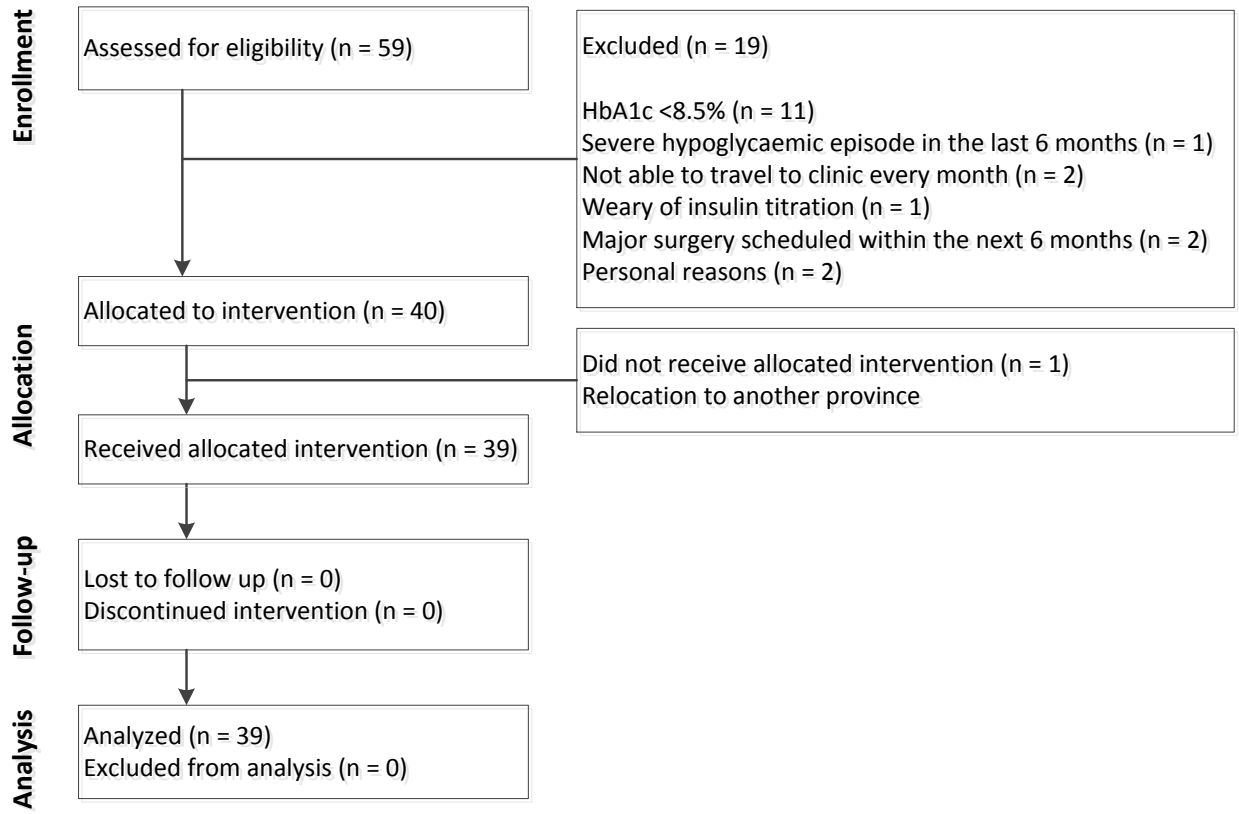


Figure 5: Patient flow within the study. Parentheses indicate number of patients.

Table 3: Baseline demographic and clinical characteristics of the study participants

Characteristic	Study sample
Patient age: mean (SD) age (years)	58.8 (6.5)
Male: n (percentages)	13 (33.3)
Ethnicity: n (percentages)	
Black	28 (71.8)
White	4 (10.2)
Coloured	4 (10.2)
Indian	3 (7.7)
HbA1C: mean (SD) (%)	10.69 (1.69)
BMI: mean (SD) (kg/m^2)	34.9 (7.6)
Diabetes duration: mean (SD) (years)	17.6 (8.2)
Smoking status: n (percentages)	
Never	29 (74.4)
Ex-user	9 (23.1)
Current	1 (2.5)
Number of hypertensives: n (percentage)	37 (94.9)
Hypertension duration: mean (SD) (years)	14.7 (9.3)

6.3. Efficacy endpoints

6.3.1. HbA1c findings

GLMM analysis revealed that a mean reduction of 1.89% (SE: 0.289) in HbA1c level was achieved over the six month intervention (95% CI: -2.46 to -1.33, p-value<0.001). Patients decreased from baseline 10.69% (SD: 1.69%; Range: 8.5 – 14.0%) to 8.8% (73 mmol/mol; SD: 1.42%; Range: 6.7 – 12.1%) at the end of the study. Figure 6 shows the trend in HbA1c at baseline (Visit 0), 3 and 6 months. A total of 10.25% (n=4) patients achieved a target HbA1c of <7.0% (53 mmol/mol).

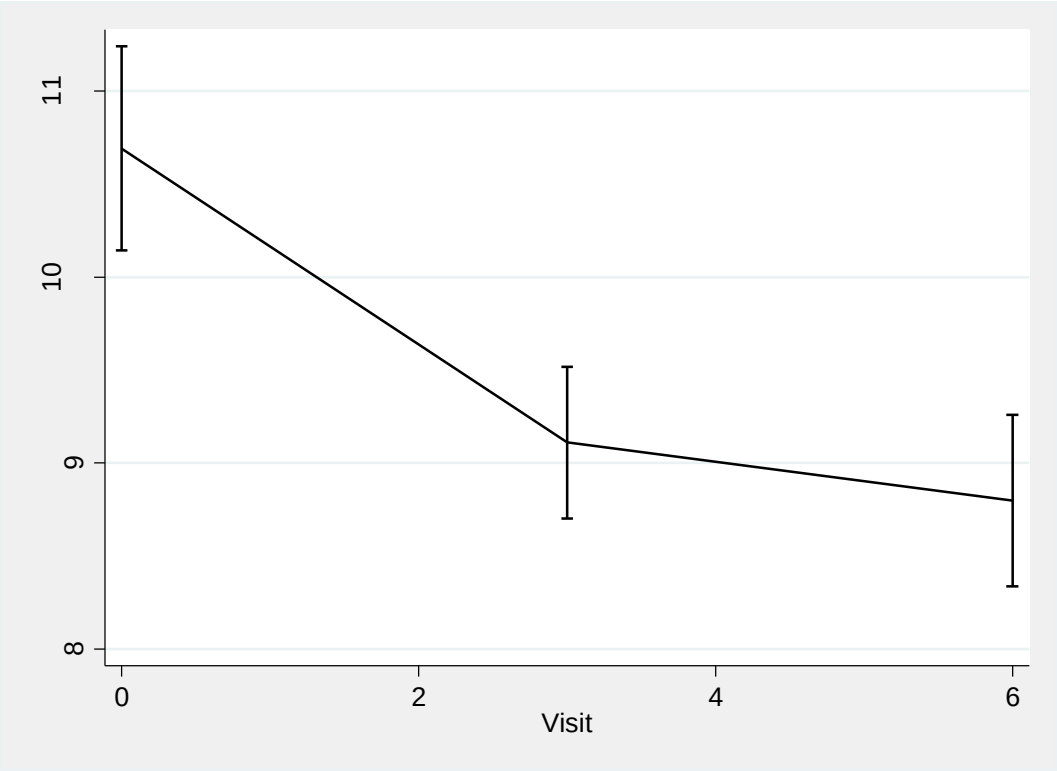


Figure 6: Graph showing mean HbA1c data with 95% CI error bars for the sample at baseline (Visit 0), 3 months and 6 months of the study.

The majority of HbA1c reduction was achieved in the first three months of the intervention. The mean difference between baseline HbA1c and three months was -1.582% (SE: 0 .338%, 95% CI: -0.91 to -2.25%, Range: -6.1 to +1.2%), as compared to a difference of HbA1c between three months and six months that was found to be -0.3102% (SE: 0.304, 95% CI: -0.92 to +0.3%, Range: -1.5 to +1.4%). As can be seen from the ranges of these comparisons, HbA1c values for some patients increased; this is shown in more detail in Figure 7.

Sensitivity analysis was performed on patients with baseline HbA1c ≥10.0% (86 mmol/mol). A larger, statistically significant reduction in HbA1c of 0.381% (0.071) per month was found, resulting in total mean decrease of -2.29% (p-value <0.001, 95% CI: -3.1 to -1.5 mmol/L, GLMM) for these patients as compared to -1.26% reduction for patients with a baseline HbA1c <9.9% (85 mmol/mol). This can be seen in Figure 6. Patients using Metformin (in addition to insulin) were found to have a slightly larger, though statistically non-significant, mean reduction in HbA1c of 1.98% (SE: 0.306, p-value: 0.885, GLMM) over the study compared than those using only insulin (n=6). No

statistically significant difference in HbA1c reduction was found for patients allocated to different compliance quartiles (p-value: 0.062, GLMM).

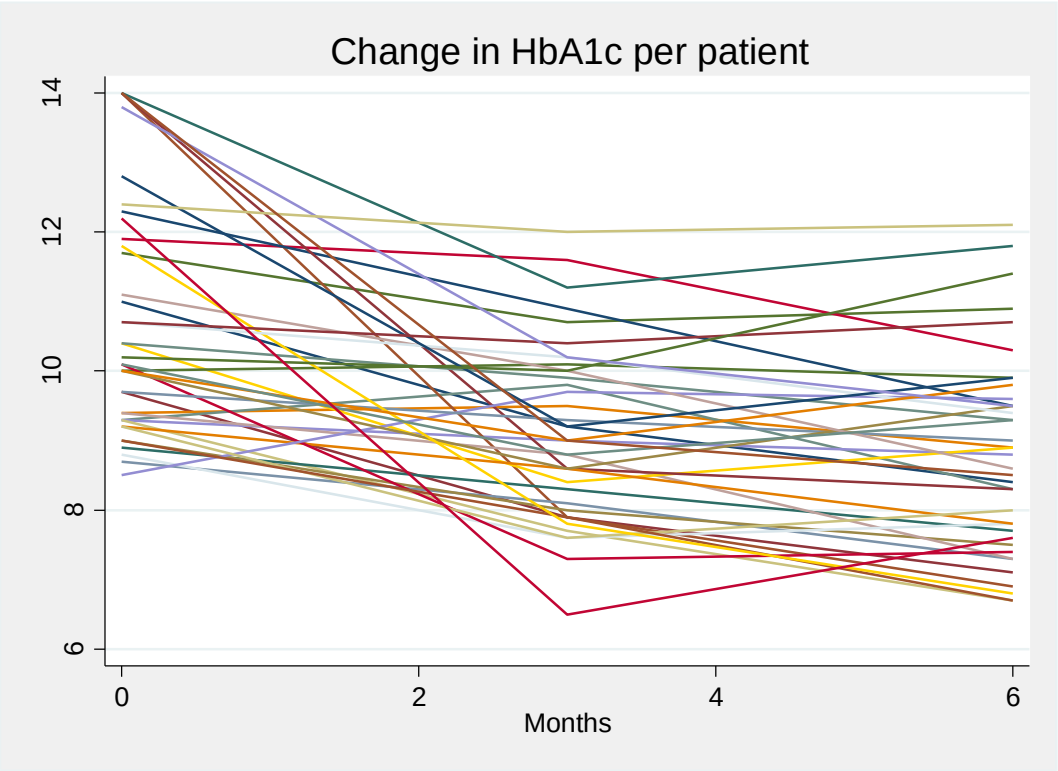


Figure 7: Graph showing trend in HbA1c for each patient in the sample at baseline (Visit 0), 3 months and 6 months of the study.

Pearson's correlation between successive HbA1c tests was found to be significant for all comparisons. Table 4 shows the correlation coefficients and associated p-values for all comparisons.

Table 4: Pearson's correlation between successive HbA1c measurements with p-values over the study period. "Visit 0" indicates baseline measurement.

Visit	0	3	6
0	1.000		
3	0.3269 p-value: 0.0423	1.000	
6	0.3228 p-value: 0.0450	0.8410 p-value <0.001	1.000

6.3.2. Mean SMBG

Mean (SD) SMBG at baseline was 10.9 (2.0) mmol/L; six months later, mean (SD) SMBG was 9.6 (1.2) mmol/L. GLMM analysis confirmed this reduction whilst controlling for age, sex, race, and random patient effects by demonstrating that mean SMBG decreased significantly over the study period by 1.6 mmol/L (p-value: 0.002, 95% CI: -2.5 to -0.6 mmol/L). Figure 8A shows the trend in mean SMBG with associated 95% CI for the duration of the study period. Mean SMBG was significantly correlated to HbA1c with a correlation coefficient of 0.5251 (p-value< 0.001, Spearman's rank correlation).

Further investigation was done into the first month of SMBG to get a more accurate baseline SMBG since titrations occurred for 41% of patients (n=16) at Week 2 via an interim telephone call according to the protocol. Table 5 describes SMBG statistics per week of the first month of the trial. This shows that the mean SMBG before any titrations were made (Week 1 and 2) was 11.7 mmol/L, thus true mean SMBG decreased by 2.1 mmol/L over six months of intervention.

Table 5: Mean SMBG and number of glucose tests performed per week during the first month after enrolment into the trial

Week	Mean SMBG (SD) (mmol/L)	Median (IQR) number SMBG performed
1	11.80 (2.933)	10 (8-12)
2	11.59 (3.374)	9 (7-12)
3	10.36 (2.629)	8 (5-12)
4	10.36 (2.714)	7 (5-10)

6.3.3. FPG and PPG findings

It was shown that mean FPG decreased significantly from 9.5 mmol/L to 8.5 mmol/L over the study period, resulting in a reduction of 1.0 mmol/L (p-value for change in FPG: 0.024, 95% CI: -2.2 to -0.2 mmol/L). Further investigation of the first two weeks of the intervention (prior to any titrations), mean FPG was found to be 10.0 mmol/L (SD: 3.35 mmol/L), demonstrating a total reduction of 1.5 mmol/L over the study period.

Analysis of change in mean PPG failed to show significance as starting PPG was recorded as an absolute change of 3.64 mmol/L from pre-prandial to post-prandial levels, and by the end of the trial was 3.63 mmol/L, showing a reduction in 0.01 mmol/L (p-value for change in PPG: 0.765, 95% CI: -0.801 to 1.089 mmol/L). Figure 8B and 6.4C shows the trend in mean FPG and mean PPG with associated 95% CI over the six month intervention, respectively.

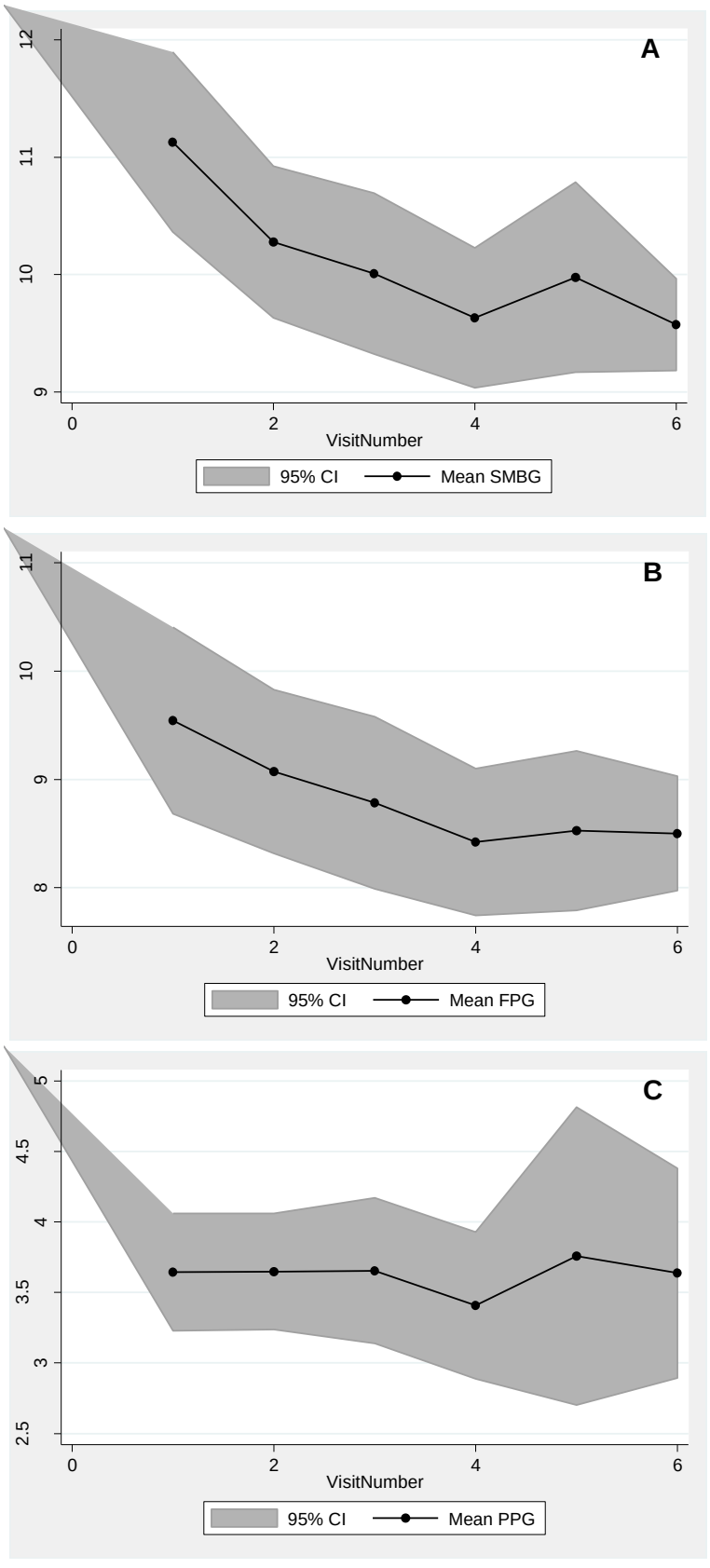


Figure 8: Changes in (A) mean SMBG, (B) mean FPG, and (C) mean PPG over the six month study period.

6.3.4. Glycaemic variability changes

Change in overall glycaemic variability (measured as standard deviation of SMBG) was not found to significantly change over the study period (p-value: 0.904, 95% CI: -0.596 to 0.527 mmol/L, GLMM). Table 6 demonstrates the median monthly change in SMBG standard deviation, where the reduction in variation was greatest within the first three months, where after this effect was largely lost.

Change in FPG and PPG standard deviation also failed to show any significance (p-value: 0.766, 95% CI: -0.4 to 0.6 mmol/L, GLMM) (p-value: 0.480, 95% CI: -0.715 to 0.336 mmol/L, GLMM), respectively.

Table 6: SMBG standard deviation per month

Visit	Median SMBG SD	Median FPG SD	Median PPG SD
1	4.32	2.91	2.60
2	3.47	2.76	2.26
3	3.50	2.33	2.22
4	3.72	2.68	2.60
5	3.71	2.61	2.19
6	3.94	3.07	2.25

6.3.5. Insulin titration findings

The mean baseline morning dose was 42.69 units.day^{-1} (SD: 16.33 units.day^{-1}; range: 16 to 88 units.day^{-1}) as compared with a final mean morning dose of 66.23 units.day^{1} (SD: 20.70 units.day^{-1}; range: 16 to 108 units.day^{-1}). The mean baseline dinner dose was 25.07 units.day^{-1} (SD: 9.35 units.day^{-1}; range: 8 to 45 units.day^{-1}), with a mean dinner dose of 41.66 units.day^{-1} (SD: 24.32 units.day^{-1}; range: 3 to 96 units.day^{-1}) at the end of the intervention.

Paired t-test analysis indicated that both mean pre-breakfast and pre-dinner insulin doses increased significantly over the 6 month study period by 23.53 units.day^{-1} (SE: 4.22, p-value<0.001) and 16.59 units.day^{-1} (SE: 4.17, p-value<0.001) respectively. Mean total daily insulin was found to increase from 67.76 to 107.89 units.day^{-1}, showing a total increase of 40.12 units.day^{-1} (37.19% increase) over the duration of the intervention (SE: 7.7, p-value<0.001, unequal paired t-test). Table 7 shows the

mean monthly adjustments made for morning and evening insulin doses. Note that dose titrations were not made at the last visit (Visit 6).

Table 7: Mean morning (AM) and evening (PM) insulin adjustments made per month. Standard deviations are shown in parentheses.

Visit	Mean (SD) Insulin AM titration in units.day^{-1}	Mean (SD) Insulin PM titration in units.day^{-1}
1	6.35 (5.8)	3.64 (6.3)
2	5.97 (5.2)	4.10 (7.1)
3	5.12 (4.4)	4.61 (5.8)
4	3.15 (4.4)	1.59 (3.6)
5	2.92 (4.4)	2.64 (5.3)

Throughout the study period, a total of 234 consultations with insulin titration were performed. Of those visits, 22 consultations (9.4%) occurred where it was deemed inappropriate to use the insulin titration algorithm. Reasons for these decisions were grouped into the following: insufficient data to make informed titration decisions (n=11); patient not taking new prescribed doses recommended at the previous visit (n=4); patient taking insulin doses at the incorrect time (n=3); SMBG showed excessive intraday variability (n=4); patient placed on separate regimens for day/night shifts (n=2); and patient diagnosed with renal failure requiring decreased doses (n=1).

At baseline, 24 of the participants had an HbA1c ≥10.0% (86 mmol/mol); at three months when HbA1c was re-evaluated, 11 patients continued to have elevated readings. As per the protocol, these patients were contacted telephonically between visits in order to titrate their insulin doses in the interim. However, many patients could not be reached, and thus not all eligible patients had their insulin titrated between visits. Table 8 shows the number of patients contacted for each visit.

Table 8: Patients contacted for interim insulin titration

		Interim call				
		1	2	3	4	5
Patients eligible to be called		24	24	11	11	11
Insulin titrated	Yes	16	14	9	6	5
	No	8	10	2	5	6

The titration algorithm did not allow for sufficient reduction in insulin doses when frequent hypoglycaemia occurred, rather advising that there be no insulin adjustment if two hypoglycaemic events occurred in one week or if nocturnal hypoglycaemia had occurred during any point in the previous month. Moreover, patients never had mean FPG or pre-dinner values of ≤4.0 mmol/L (see Figure 3). For this reason, it was deemed appropriate to reduce insulin dose by 2 units if three or four hypoglycaemic episodes had occurred at the same SMBG time point during the previous month. Insulin was reduced by 4 units if five or more hypoglycaemic episodes had occurred at the same SMBG time point during the previous month.

6.3.6. Compliance findings

All patients in the sample attended 100% of the seven clinical visits. Mean patient compliance was greater than 70% at each month. Post-dinner readings were the most commonly missed SMBG (60.15%) and FPG was the most regularly recorded (83.26%). Three patients were categorised as performed between 25-50% of total SMBG tests throughout the study period. Eighteen patients were classified as having performed 50-75% of all prescribed SMBG, and another 18 patients fell in the upper quartile of >75% of all SMBG tests. Table 9 shows the median number of SMBG tests performed per month according to the structured SMBG regimen. Note that if a patient tested outside the regimen, these tests were not counted. ANOVA analysis of baseline HbA1c for different compliance quartiles showed that those who performed greater number of SMBG tests had a lower baseline HbA1c (p-value: 0.0148). Patients in the second compliance quartile (having performed 25-50% of SMBG) had a baseline HbA1c 2.22% higher than those in the fourth quartile (having tested >75% of prescribed SMBG).

Table 9: Number of SMBG tests performed each month according to the structured regimen out of a maximum of 48 tests per month.

Visit	Median (IQR) SMBG tests performed	Percentage compliance (%)
1	35 (26-41)	72.9
2	38 (31-44)	79.1
3	40 (32-43)	83.3
4	36.5 (31-40)	76.0
5	35 (27-40)	72.9
6	36 (25-43)	75.0

Participants were asked to self-report the number of missed insulin injections and OHAs doses. Table 10 describes the number of patients and the doses missed during each month of the study. As is evident from the data, participants were more likely to miss insulin doses than OHA doses. Surprisingly, the patients who missed ≥12 insulin doses in months 3 and 4, still had a >1.0% reduction in HbA1c over the study period.

Table 10: Number of participants who missed one or more insulin injections or OHA doses for each month.

Visit	Missed insulin injections		Missed OHA doses	
	Doses	Participants	Doses	Participants
1	1	4	2	1
	2	2	15	1
2	1	1	2	1
	2	3	4	1
	3	1		
	4	1		
3	1	2	1	1
	2	1		
	3	2		
	12	1		
4	1	2	7	1
	2	1	14	1
	14	2		
5	1	2	1	2
	2	4	7	1
6	1	2	3	1

6.3.7. Appointment duration

Median appointment duration was found to be 14 minutes (IQR: 10-17 minutes) over the study. Table 11 shows summary statistics for appointment duration for each visit of the intervention.

Table 11: Median appointment duration and interquartile range (IQR) for each visit.

Visit	Median appointment duration (IQR)
1	17 (14-22)
2	16 (13-19)
3	16 (13-20)
4	11 (9-16)
5	10 (8-12)
6	11 (8-14)

6.4. Safety endpoints

6.4.1. Adverse events

A total of five patients were hospitalised during the study due to: cataract surgery (n=1); observation due to suspected transient ischemic attack (n=1); uncontrolled hypertension with arrhythmia (n=1); diagnosis of new onset renal failure (n=1); and diabetic ketoacidosis (n=1).

6.4.2. Hypoglycaemia

During the six months of the study, no severe hypoglycaemic events were reported. The incidence of hypoglycaemia (defined as ≤3.9 mmol/L) based on downloaded SMBG data, was 33.08 events per patient-year, with a median (IQR) of 13 (3-26) events per patient over the six month intervention. A total of 20.51% of the sample (n=8) contributed to 52.71% of all hypoglycaemic events. Each of these patients had at least one month where they experienced ≥10 hypoglycaemic episodes. When hypoglycaemia was defined as <3.1 mmol/L, the incidence of hypoglycaemia reduced to 12.92 events per patient-year, with a median of 6.5 events per patient over the 6 month intervention.

Figure 9 shows the total number of hypoglyaemia episodes for different visits. The majority of the low blood glucose levels occurred in the last three months of the trial. Most hypoglycaemic episodes were recorded within the specified SMBG regimen time points. Table 12 describes the number of patients contributing to total hypoglycaemic episodes each visit.

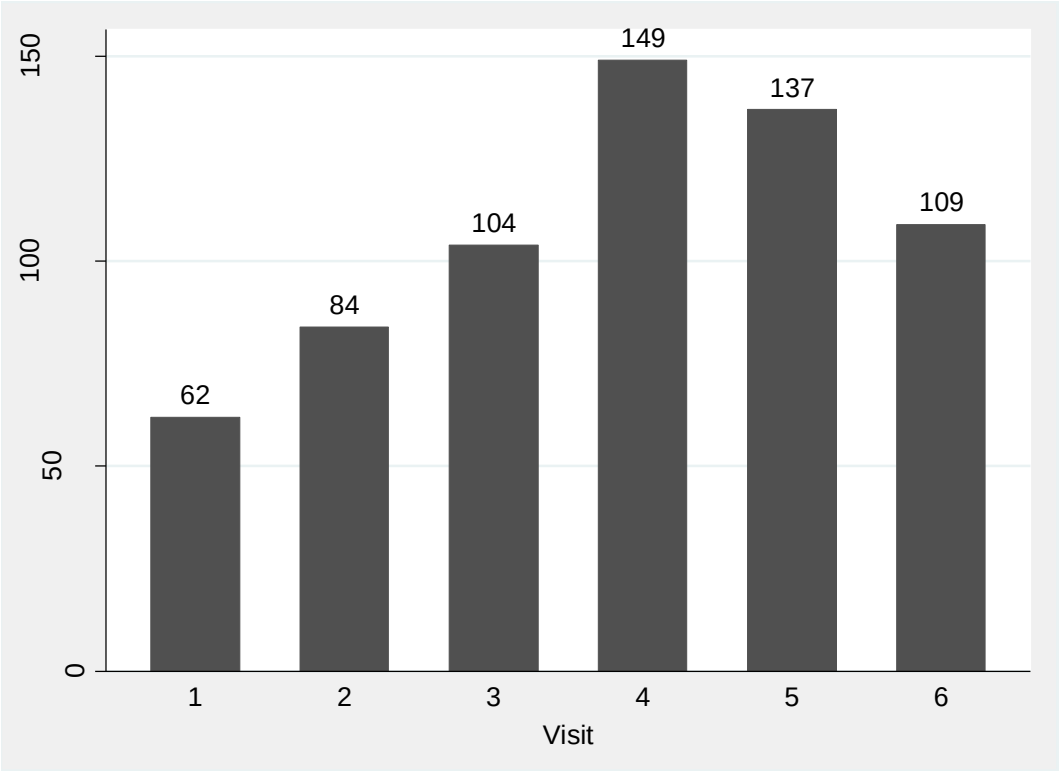


Figure 9: Bar graph of the number of hypoglycaemic episodes over different visits throughout the study.

The incidence of nocturnal hypoglycaemia was found to be 2.82 events per patient-year, with a median of 2.0 events per patient over the 6 months. Only 12.8% of the sample (n=5) contributed to 67.3% of all nocturnal hypoglycaemic events.

Table 12: Median number of hypoglycaemic events and the number of patients contributing towards this count per visit.

Visit	Median (IQR) number of hypoglycaemic events	Number of patients
1	0 (0 – 4)	19
2	1 (0 – 4)	22
3	2 (0 – 4)	23
4	2 (0 – 6)	27
5	2 (0 – 6)	25
6	2 (1 – 4)	31

6.4.3. Weight changes

Mean weight increased by 3.98kg (95% CI: 2.56 to 5.41, p-value <0.001, GLMM) over the study period. Sensitivity analysis was performed for patients using Metformin in addition to insulin doses, but found an nonsignificant difference of -0.09kg (p-value: 0.090, GLMM) less weight gain.

6.5. Quality of life endpoints

Median treatment satisfaction scores were found to be 30 at both baseline (IQR: 28-32) and at the end of the study period (IQR: 27-33) the difference of which was found to be non-significant (p-value: 0.2717, Wilcoxon signed-rank test). Mean (SD) perceived hyperglycaemia scores were 3.59 (1.55) and 3.05 (1.26) at baseline and end of study respectively, the difference of which was found to be non-significant (p-value: 0.1156, paired t-test). Mean (SD) perceived hypoglycaemia scores were 1.95 (1.39) and 2.56 (1.39) at baseline and end of study respectively, the difference of which was found to be significant (p-value: 0.0251, paired t-test).

From the questionnaire issued at the end of the trial, 69.23% of participants indicated that they would continue to follow the structured SMBG regimen. Comments about what participants enjoyed from the trial were grouped into the following categories: being aware of BG levels (n=12), better BG control (n=8); benefits of travel money, regular test strips and new meters (n=3); diabetes education on insulin injections and diet (n=9); recognising hypoglycaemia (n=2); increased attention and care (n=5). Comments about what participants learnt from the study were grouped into the

following: adherence to medication and timing of insulin injections (n=24); dietary effects on BG levels (n=9), SMBG as a tool for diabetes management (n=5).

Participants listed the following as aspects of the trial they did not like: weight gain (n=1), testing too often (n=5), recording BG levels in the patient diary (n=1). These issues were listed by 30.77% (n=12) of the sample as reasons for not wanting to continue with the regimen. Two major issues suggested by respondents were that post-dinner testing was too close or overlapped with bedtime tests and that the 10 day waiting period between week one and two of the month was too long.

6.6. Comparison to standard treatment

Changes in glycaemic control for patients who received standard care during the data collection period was compared to study participants. Patients were matched based on sex, ethnicity, age and baseline HbA1c in a 1:1 ratio of study participants to standard treatment patients. Not all baseline demographics could be collected for the standard treatment patients: data was missing for BMI (n=2), smoking (n=5), duration of diabetes (n=2) and duration of hypertension (n=2). The absence of hypertension was greater in the standard treatment group (n=8) compared to the study participant group (n=2), but this was found to be non-significant (p-value: 0.087, Fischer's exact test). Significant differences between the two groups were found to be baseline BMI and the number of hypertensives, with study participants found to be 4.0 kg/m^2 heavier and more likely to have hypertension than patients receiving standard care (p-value: 0.043, and 0.025 respectively, Fischer's exact test). Table 13 shows the comparison of baseline characteristics and their associated p-values between patients in the study group and those receiving regular treatment.

Table 13: Comparison of baseline demographic and clinical characteristics of the study participants and patients who received standard care. Asterisk indicates significant p-value.

Characteristic	Intervention	Standard care	P-value
Patient age: mean (SD) age (years)	58.8 (6.5)	57.5 (8.05)	0.433
Male: n (percentages)	13 (33.3)	13 (33.3)	1.000
Ethnicity: n (percentages)			0.217
Black	28 (71.8)	35 (89.8)	
White	4 (10.2)	1 (2.5)	
Coloured	4 (10.2)	1 (2.5)	
Indian	3 (7.7)	2 (5.2)	
HbA1C: mean (SD) (%)	10.69 (1.69)	10.49 (1.43)	0.569
BMI: mean (SD) (kg/m^2)	34.9 (7.7)	30.94 (6.7)	0.043*
Diabetes duration: mean (SD) (years)	17.6 (8.2)	14.8 (7.9)	0.141
Smoking status: n (percentages)			0.197
Never	29 (74.4)	30 (88.2)	
Ex-user	9 (23.1)	3 (8.8)	
Current	1 (2.5)	1 (2.9)	
Number of hypertensives: n (percentage)	37 (94.9)	29 (78.4)	0.025*
Hypertension duration: mean (SD) (years)	14.7 (9.3)	15.6 (7.5)	0.683

Mean HbA1c for patients receiving standard treatment was 10.49% (87 mmol/mol; SD: 1.43%; Range: 8.6 – 15.3%) at baseline, and then observed to be 9.37% (79 mmol/mol; SD: 1.66%; Range: 6.4 – 13.9%) six months later. A significant reduction of 1.12% in HbA1c was achieved over the observation time period by these patients (95% CI: -1.67 to -0.561%; p-value< 0.001, GLMM).

A comparison of glycaemic control between patients receiving the intervention and those receiving standard care using GLMM was made. Participants in the structured SMBG arm were found to have a greater mean (SE) reduction of 0.777% (0.404) in HbA1c, which fell just short of statistical significance (95% CI: -1.569 to 0.015%, p-value: 0.054). Analysis of power using GLIMMPSE software found this comparison between the two groups to have a power of 56.5%, which may explain the lack of statistical significance. Figure 10 shows the change in HbA1c for patients receiving the intervention and those receiving standard treatment over the duration of 6 months.

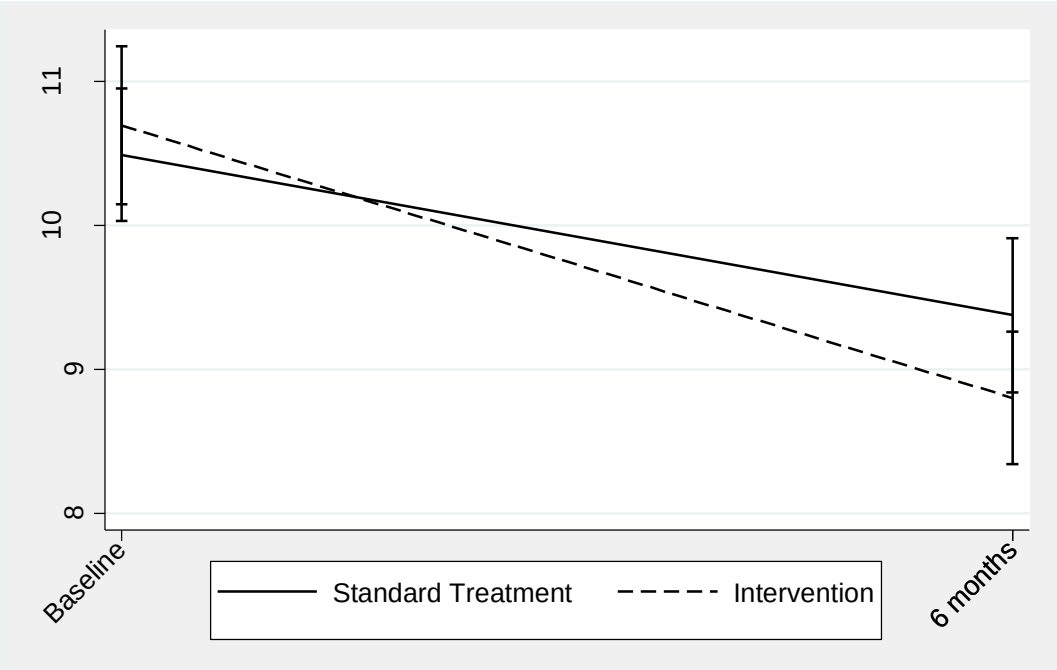


Figure 10: Change in HbA1c from baseline to 6 months for patients in the intervention (dotted line) and those receiving standard treatment (solid line).

6.7. Summary of findings

The primary aim of this study was to evaluate the efficacy of a novel structured SMBG regimen paired with algorithmic insulin titration for type 2 diabetes patients. The results show a statistically significant mean reduction of 1.89% in HbA1c over 6 months (International Federation of Clinical Chemistry conversion not applicable). This reduction is attributed to the 1.6 mmol/L reduction in mean SMBG levels, and more specifically the 1.2 mmol/L reduction in mean FPG levels achieved over the study period. Glycaemic improvement was greater in patients who had a baseline HbA1c ≥10.0% (86 mmol/mol). Moderate frequency of hypoglycaemia occurred, at 33.08 events per patient-year. Patients gained a mean of 3.98 kg over the 6 month trial period. Perceived burden of hypoglycaemia increased marginally from baseline to the end of the study.

The secondary aim of this study was a comparison of the intervention with a matched control group receiving standard treatment. An additional mean reduction in HbA1c of 0.77% was found in patients receiving the intervention as compared to those receiving standard treatment.

7. Discussion

7.1. Sample baseline demographics

Looking at baseline demographic and clinical characteristics from Table 3, average age in the sample group was slightly older than expected. This may be due to younger type 2 diabetes patients being treated with only oral hypoglycaemic agents (OHAs), and thus attending local clinics, rather than district/tertiary hospitals, as is required when a patient commences insulin.[18] Age serves as a risk factor for the development of type 2 diabetes.[71] In addition, the current guidelines recommend delaying the initiation of insulin for the treatment of type 2 diabetes, proposing OHAs as first line treatment.[29-31]

The predominantly female sample may be due to sampling bias; however, based on the 500 type 2 diabetes patients within the Kalafong Hospital Diabetes database, 70.4% of patients are female. This is closely mimicked by the 66.7% female patients in the sample. It is postulated that this may be an effect of fewer males within 55-74 year old subdivision of the Gauteng general population, with more males dying at a younger age, leaving 54.43% females within this age category.[72] Due to a lack of data on the prevalence of diabetes, it cannot be assessed if ethnic subdivisions of this sample are representative of those living with diabetes in South Africa. However, if assumed to mirror those of the general population, the sample is closely representative.[72]

Study participants had poorer baseline glucose control than anticipated with a mean 10.69% (93 mmol/mol) as compared to the estimated 9.0% (75 mmol/mol) HbA1c. This may be due to the hesitancy of HCPs to titrate insulin aggressively in the fear of hypoglycaemia and/or weight gain.[61] In addition, HCPs lack data to make informed decisions regarding medication titration. As alluded to in the literature review, results from laboratory reports are often delayed, forcing clinicians to make adjustments to insulin whilst blinded to glycaemic outcomes.

The mean participant BMI of 34.9 kg/m^2 was predicted owing to obesity being a risk factor for type 2 diabetes.[71] The sample had a high prevalence of hypertension as a

co-morbidity. This was anticipated due to the close association of diabetes and high blood pressure.[71]

The mean 17.6 years duration of diabetes for the sample was envisaged since type 2 diabetes is a progressive disease where complete insulin deficiency may evolve over a number of years.[73]

7.2. Mean HbA1c reduction

Patients achieved a mean reduction of 1.89% in HbA1c over the 6 month intervention primarily due to the significant reduction in mean SMBG and FPG resulting from increased frequency of insulin titrations.

As cited in the literature review, Monnier *et al*. (2003) found that in patients with HbA1c ≥8.4% (≥68 mmol/mol), overall hyperglycaemia was predominantly attributed to FPG excursions.[13] The mean SMBG at Visit 1 (10.9 mmol/L) did not correlate to a mean baseline HbA1c of 10.1% (87 mmol/mol). Further analysis of the mean SMBG per week within the first month of the intervention showed that the first two weeks were decidedly elevated (11.7 mmol/L) in comparison to mean SMBG for the month (10.9 mmol/L). This is due to 16 patients that were titrated after two weeks by interim call due to their elevated baseline HbA1c levels. In addition, patients may have made behaviour, lifestyle and/or dietary changes within this period due to their enrolment in the study.

The notion that mean SMBG actually decreased greater than 2.1 mmol/L is supported by the fact that four participants had maximum recordable HbA1c values at baseline (>14% or 130 mmol/L), yet only one patient had a mean SMBG at the first visit to warrant such high glycated haemoglobin levels (Patient 0012: mean of 18.9 mmol/L in the first two weeks). The other three patients may not have been compliant in taking their insulin doses prior to enrolling into the trial, thus when enrolled, adhered to their medication.

The majority of HbA1c reduction was attributed to the first three months of the intervention as seen in Figure 6. During this time, insulin doses were aggressively titrated by using larger (even maximum) dose increments permitted within the

algorithm as compared to later dose adjustments (Table 7). The latter three months can be seen as a period of fine-tuning of insulin doses. It follows that, if resources are severely limited in a clinical setting, it may be beneficial to enrol patients into this intervention for a three month period and still achieve significant glycaemic reductions whilst promoting medication adherence.

Additional factors that may be attributed to large glycaemic improvement in the first three months are: more frequent clinical consultations with greater patient interaction, increased use of free meters and strips, and the practise of downloading SMBG data. These variables are in line with improved patient compliance in taking insulin regularly due to the knowledge of being enrolled in a study (also known as the Hawthorn effect).[74] This notion is supported by data from Table 4 where correlation of baseline and three month HbA1c readings were weakly correlated (r^2=0.3228), yet correlation of HbA1c of months 3 and 6 were strongly correlated (r^2=0.8410). The data suggest that elevated baseline HbA1c levels were not only related to insufficient insulin doses, but due to other factors such as poor compliance and diet (among others), and that these factors may have been corrected or somehow indirectly addressed within the first three months of the intervention.

Patients with a baseline HbA1c ≥10.0% (86 mmol/mol) achieved a larger reduction in HbA1c (-2.29%) as compared to participants who had better baseline glycaemic control (-1.26%). This was assumed to occur because these patients had a larger range over which to improve glycaemic control before reaching blood glucose targets. This regression toward to the mean may have also been perpetuated by the “ceiling effect” of the Cobas B101 measurement of HbA1c: since glycated haemoglobin could only be measured to a maximum of 14.0% (130 mmol/mol), the ceiling or “level above which variance in an independent variable is no longer measured”, may have disturbed the central tendency of the data, since these patients may have in fact had a larger decrease in true HbA1c.

The UKPDS team that assessed intensive glycaemic control in type 2 diabetes patients found that a reduction of 0.9% in HbA1c was comparable to a 25% reduction in microvascular endpoints, including retinopathy requiring photocoagulation, vitreous haemorrhage, and/or fatal or non-fatal renal failure.[75] By extrapolation, the 1.89%

reduction in HbA1c achieved in the study sample may have reduced each patient's risk of microvascular complications by approximately 50%. This is a notable decrease in clinical risk if the patient did not yet have such complications. Nevertheless, many of the microvascular and macrovascular complications of type 2 diabetes are already present when the diagnosis is first made, particularly retinopathy, erectile dysfunction, nephropathy and/or atherosclerotic vascular disease.[76] Thus this benefit would only apply to patients who were free from such complications at the start of the intervention.

Reduction in HbA1c was greater than was achieved by Liebl *et al*. (-1.23%), Holman *et al*. (-1.3%) and Janka *et al*. (-1.31%). Decrease in glycaemia was very similar to that achieved by Garber *et al*. (-1.9%); however, was less impressive than the outcomes achieved by Riddle *et al*. (-2.0%), Yang *et al*. (-2.48%) and Raskin *et al*. (-2.79), see Table 1.

7.3. Changes in mean SMBG, FPG and PPG

Mean SMBG was significantly correlated to HbA1c but at a lower coefficient than previous research. The international A1C-Derived Average Glucose (ADAG) trial used approximately 2 700 glucose measurements over three months per HbA1c measurement in 507 adults with type 1, type 2, and without diabetes.[77] The correlation between HbA1c and average glucose was found to be 0.92 in their research. In contrast, average SMBG results from this study demonstrated a weaker correlation to HbA1c (spearman's rank r^2=0.5251) since only 144 glucose measurements per HbA1c measurement were used. This can be confirmed since mean SMBG at the end of the trial (9.6 mmol/L) was not reflected in the same relative reduction in HbA1c (8.8% or 73 mmol/mol). According to the ADAG study, an HbA1c of 8.8% should have yielded a mean SMBG of 11.4 mmol/L.[77] It is thus assumed that total glucose variations were therefore not captured.

In secondary data analysis of the ADAG study, Wei, Zheng, and Nathan (2014) established SMBG values throughout the day associated with HbA1c outcomes. The researchers found that specific FPG levels needed to achieve an HbA1c <7% (53 mmol/mol) were significantly less stringent than targets set forth by current international guidelines seen in Table 1 of the Literature Review.[78] The study

demonstrated that for patients who had achieved an HbA1c of 8.0 to 8.5% (64 to 69 mmol/mol), mean (95% CI) FPG was estimated as 9.9 (9.1 to 10.7) mmol/L. This may explain why a relatively small decrease in FPG (1.5 mmol/L) in the current study produced large changes in HbA1c. FPG was also the most accurately recorded of all SMBG time points, therefore its accuracy is thought to be improved in comparison to mean SMBG. Reduction in FPG (-1.5mmol/L) was smaller than that achieved by Liebl *et al* (-2.9 mmol/L), and other studies listed in Table 1.

7.4. Glycaemic variability

Several tools for assessing intraday glycaemic variability exist, but almost all such measures require the use of continuous glucose monitoring (CGM) systems. Due to the limited number of SMBG tests performed each month, the SD or any other measure of glycaemic variability, may not be representative of the true glucose fluctuations experienced by the patient, thus comments on changes in glycaemic variations are invalid, as seen in Table 6.

Biphasic insulin has the potential to slightly decrease glycaemic variability due to the prandial insulin component[49], but it was not expected to significantly reduce variability over the course of study. Instead, data capturing on variability was performed to monitor whether glycaemic variability did not fortuitously increase due to the intervention.

The majority of glycaemic variability is known to be attributed to the timing of insulin administration, use of analogue insulin compared to human insulin,[46] quantity and glycaemic index of carbohydrates eaten, and background insulin at the time of the meal.[79]

7.5. Insulin titrations

The magnitude of insulin titration was unforeseen, with patients increasing their total daily dose by 37.18% by the end of the study period. NICE indicates that theoretically there is no upper limit to insulin doses.[29] From this observation, it is speculated that patients receiving standard care are substantially under-dosed on current insulin regimens, which should be addressed in future research.

Dose increments were largest during the first three months of the study (Table 7). This is expected since the titration algorithm allows for smaller adjustments as patients achieve SMBG levels closer to target, correlating to the larger reduction in HbA1c achieved in the first half of the study.

It can also be seen from Table 7 that larger insulin titrations were needed for morning insulin doses compared to insulin given at dinner time. This is expected as throughout the day, patients need to compensate for carbohydrate eaten at meal times. Due to night time fasting, patients needed less insulin to correct blood glucose levels between dinner and breakfast.

Increase in mean daily insulin dose in the current study (40.1 units.day^{-1}) was 10.4 units greater than seen in the Liebl *et al.* study (30.5 units.day^{-1}). However, increases in insulin dose were remarkably greater in the other six studies listed in Table 1. This may be explained by the fact that in these other studies, patients were insulin naïve.

At most consultations (>90%), the insulin titration algorithm was applied appropriately. Visits where use of the algorithm was deemed inappropriate, were due to patient-related issues beyond the investigators' control.

Patients who required interim calls were difficult to contact, did not always carry or update their blood glucose diary, and may not always have been truthful about their blood glucose readings. All of these factors imply that insulin may have been titrated on unreliable information. This shows that the practise of interim calls is unrealistic to apply to the clinical setting due to low reliability as well as staff and resource shortages.

7.6. Compliance

Compliance did not seem to influence HbA1c, as participants who were more compliant did not achieve a greater reduction in HbA1c. In fact, participants that were deemed to be non-compliant were still able to achieve HbA1c reductions. This effect may be explained due to the high compliance rate the research team achieved with all study participants, as can be seen in Table 9. The advantage of such a high degree

of compliance is that titration of insulin was based on accurate data as per the SMBG regimen.

Self-reporting of missed insulin injections and OHA doses is fraught with bias owing to the fact that patients may feel intimated, or pressured to be perfectly compliant, thus would rather omit the true number of doses missed. This variable was therefore not used in determining compliance, yet it was interesting to note that participants felt it more detrimental to omit OHA doses than to miss insulin doses, as is evident by the frequency of non-compliance of the two medications in Table 10.

7.7. Appointment duration

As is shown in Table 11, appointment duration decreased as the intervention continued. This may be related to researchers becoming more familiar with paperwork and assessments performed, thus speeding up consultation time. Visits 3 and 6 were expected to take slightly longer since HbA1c was evaluated during these sessions.

It is concerning that this intervention could place a burden on the diabetes clinic to see patients on a monthly basis. However, many of the protocols followed in the visits will not be necessary should this intervention be applied to clinical practise, thus shortening the consultations (including use of control solutions, completing extensive trial paperwork, explanation of blood glucose diaries and issuing of travel fees). As an illustration, if the mean appointment time was 10 minutes per patient (allowing 5 minutes between patients), one clinician could see up to 24 patients a day between the hours of 08:00 to 14:00. Patients with the highest baseline HbA1c values could be prioritised to be enrolled into the intervention first. As stated in Section 7.2.1., clinics could enrol patients into the intervention for only three months to further limit the burden on staff.

7.8. Adverse events

A total of five patients were hospitalised during their participation in the study, but none appeared associated or caused by the intervention.

Patient 0015 had surgical removal of an existing cataract from their left eye. No complications arose, thus it was decided to keep the patient in the study since improved glucose control would assist in healing.[80] Patients with type 2 diabetes are at higher risk of eye complications due to abnormally high glucose concentrations in the aqueous humour converted into sorbitol via the polyol pathway which promotes oxidative stress and cataract formation.[81]

Patient 0035 was hospitalised for diabetic ketoacidosis due to self-reported non-adherence to insulin injections. The patient said that he and his family had gone on holiday and thus he could not collect his insulin from the hospital causing him to be without insulin supply for five days. The complete lack of insulin resulted in severe hyperglycaemia and ketoacidosis. The patient was also using hydrochlorothiazide, known to promote hyperglycaemia.[82]

Patient 0032 was hospitalised for observation due to recurring dizziness and pain in the upper left shoulder. HCPs suspected a transient ischemic attack (TIA). Baseline clinical data that increased the patient's risk for possible TIA included: high BMI (34.7 $kg.m^{-2}$), long standing diabetes (11 years), and dyslipidaemia (Total cholesterol: 5.1 mmol/L).[83] Brain scans showed normal cerebral function; however Doppler scans of the carotid arteries showed evidence of arteriosclerosis. Aggressive management of diabetes and dyslipidaemia were recommended, therefore the patient was kept in the study as it was considered an opportunity for improved blood glucose control.

Patient 0029 experienced new onset renal failure. He was originally hospitalised due to gastritis with sudden weight loss, diarrhoea and nausea. Gastroscopy and biopsy of the oesophagus and stomach were performed to rule out suspected neoplasm. He was subsequently diagnosed with early renal failure which caused hypotension and large reduction in insulin requirements due to excessive damage to the glomerular basement membrane. Existing determinants of renal failure present in this patient at baseline were the following: age (64 years), high baseline blood pressure (170/64 mmHg), long duration of diabetes and hypertension (11 and 8 years, respectively), with the presence of existing retinopathy and elevated serum creatinine for a duration of >12 months.[75] This indicates that damage to the glomerular basement membrane was likely to have already occurred prior to enrolment.

Patient 0045 was hospitalised due to uncontrolled hypertension with arrhythmia. Baseline risk factors included: obesity (BMI: 36.1 $kg.m^{-2}$), ex-smoker, long duration of hypertension and diabetes (both 13 years), and raised urine Albumin: Creatinine ratio for more than 12 months. Concomitant medication included Perindopril, Hydrochlorothiazide, Isosorbide-mononitrate, Glyseryltrinitrate, Diclofenac, Simvastatin, Salbutamol inhaler, Beclomethazone inhaler, Nifedipine and Bezafibrate. Evidence points toward long-standing, poorly controlled hypertension as the precipitating factor of this event.

7.9. Hypoglycaemia

A large proportion of hypoglycaemic events were recorded when patients were scheduled to perform SMBG, thus the risk for hypoglycaemia is likely to be underreported. Additionally, blood glucose levels were not measured during the night, a period when participants were at risk due to the peak of biphasic insulin action occurring 2-4 hours after dinner.[84]

A large proportion of hypoglycaemic events were attributed to only 8 patients. Nevertheless, these patients were not found to have any shared characteristics.

As can be seen in Figure 9, the frequency of hypoglycaemia doubled in the fourth month and thereafter remained elevated for the duration of the intervention. This could be due to regression towards glycaemic targets and therefore patients are at greater risk for hypoglycaemia. Incidence of hypoglycaemia was significantly increased as compared to other studies; however, as it can be seen in Table 1, all of these studies did not use the conventional definition of <4.0 mmol/L. When hypoglycaemia was defined as <3.1 mmol/L in the current study, rates were slightly more comparable, yet still elevated. This is hypothesised to be an effect of poor compliance in taking insulin regularly or due to erratic insulin adsorption caused by lipodystrophy.

7.10. Weight changes

The weight gain during the intervention was predictable as is seen when increasing insulin doses due to a decrease in basal metabolic rate, a decrease in glycosuria, and

increased caloric intake for the treatment of hypoglycaemia.[85] Insulin as an anabolic hormone prevents lipolysis, increases the storage of glucose as glycogen, and increases de novo lipogenesis, all of which contribute toward weight increases. A concern is that the mean 3.98 kg gain may have a significant impact on increasing risk for cardiovascular disease such as myocardial infarctions and coronary artery disease.[59]

The change in weight seen in this study (+3.89 kg) was 1.8 kg greater than seen in the Liebl *et al*. and Janka *et al*. studies (both +2.1 kg). Weight gain was very similar to Yang *et al*. (3.87 kg). However, weight gain was markedly less than the remaining four studies described in Table 1.

7.11. Impact on QoL

The DTSQ identified an increase in perceived burden of hypoglycaemia. This is expected since increased SMBG frequency may reveal asymptomatic hypoglycaemia and contribute to increased awareness of glucose fluctuations.[22] As noted in section 7.9, patients are expected to experience more frequent hypoglycaemia as they approach glycaemic targets.

A frequent issue associated to measurement of QoL is the relatively high level of patient satisfaction with pre-trial treatment. Patients are inclined to make the best of their current treatment and only become aware of its drawbacks when they can compare it with something better.[86] This leaves those participants who were already very satisfied beforehand with little or no room to show improved satisfaction later.[87] This may be one explanation for the quantitative lack of improvement in patient satisfaction. The open-ended trial experience questionnaire revealed that two-thirds of patients reported that they would continue with the new structured SMBG regimen due to the benefits they had experienced during the intervention.

Another inference that can be made from results from the open-ended trial experience questionnaire is that the support of additional factors influencing reduction in HbA1c other than insulin titrations. A total of 19 patients listed indirect effects associated with

their enrolment in a clinical trial, rather than the intervention *per se*, as reasons for benefiting from the study.

7.12. Comparison to standard treatment

It was unexpected that the matched control group experienced such a large reduction in HbA1c (-1.16%) over six months of standard care. Patients whose treatment is not changed or intensified are expected to have gradual rising HbA1c levels.[88] Unfortunately no data on changes in insulin or OHA doses were available, thus it cannot be elucidated as to how these patients improved their glycaemic control. A number of reasons may be responsible for this observation: HCPs who routinely follow up patients are expected to respond to poorly controlled blood glucose values by adjusting medication regimens by adding OHAs or increased the frequency of medication; HCPs may have subjectively titrated doses according to HbA1c; patients may have been initiated on insulin during the period of observation; or patients may have been referred to dieticians for modification of their diets during the six month period.

Despite the significant reduction in HbA1c among matched controls, there was still a clinically notable, albeit statistically non-significant, greater HbA1c reduction in patients receiving the intervention compared to those receiving standard care (-0.77%). It was demonstrated that this comparison was underpowered to detect statistically significant differences between the two groups. To confirm the true benefit of this intervention, it is recommended that a sufficiently powered RCT be conducted where controls are to receive no change in therapy. This was, however, beyond the scope of this project and outside budgetary limitations.

Baseline differences in BMI and prevalence of hypertension between the two groups are assumed to be an artefact of sampling bias. Previous data for diabetes patients receiving care within Tshwane demonstrated an average BMI of 31.0 kg.m-2 and 78.7% prevalence of hypertension.[89] It is anticipated that a larger cohort would eliminate these differences between intervention and control groups. It is not expected that the higher BMI and proportion of hypertensives in the study participants

contributed to the improved glycaemic control as compared to the group receiving standard care.

7.13. Limitations

There were several limitations to the study. Firstly, the lack significant difference in change of HbA1c between study participants and the matched group signifies that we cannot explicitly state that this intervention truly improved glycaemic control. Secondly, we could not confirm that the recommended insulin titration changes actually occurred. Thirdly, we cannot assess whether improvement of glycaemic control was maintained after the intervention. Fourthly, no duration of insulin use was recorded, thus we cannot comment on the appropriateness of baseline insulin doses. Lastly, the QoL assessment was at risk for information bias due to the researcher being present when patients answered the questions. This was primarily done due to the low literacy levels of the patients who needed clarification on the items contained within the questionnaire.

7.14. Recommendations

7.14.1. Adjustments to intervention

From the results and discussion above, there are a number of changes to both the SMBG regimen and titration algorithm that are recommended. Failure to capture true glycaemic fluctuations by the SMBG regimen, as well as the lack of reduction in glycaemic variability provide reasoning to remove all 12 PPG SMBG tests in the structured testing. None of these results were utilised by the titration algorithm to adjust insulin doses, and patients also found it difficult to remember to test their blood glucose levels two hours after eating. Additionally, biphasic insulin is unable to effectively alter PPG excursions, and these glucose fluctuations contribute less to overall hyperglycaemia in patients with high HbA1c values.[13]

Titration of insulin only required 50% of SMBG to be performed to have sufficient data to inform insulin adjustments. This was shown by equivalent HbA1c reductions in patients in the second and third quartile of compliance compared to those with improved compliance. It was also noted that patients complained of too many SMBG tests, thus reducing the total number prescribed may increase compliance.

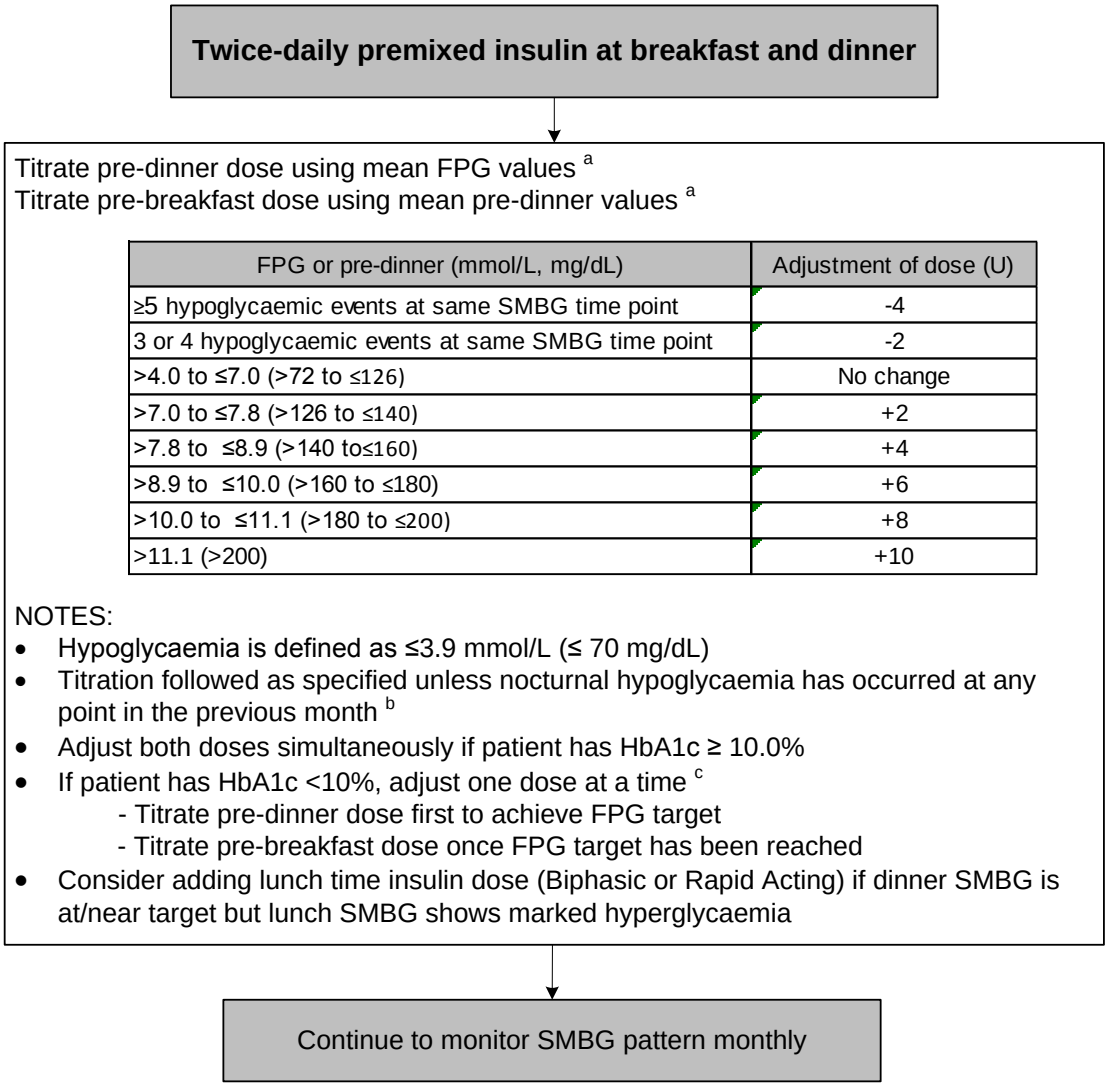
From these points, the researchers recommend that the structured SMBG regimen be reduced to a total of 16 tests over a period of 4 days prior to, and one FPG test on the day of the patient's clinical consultation and/or collection of medication according to Figure 11. This will allow sufficient data on which to titrate insulin doses, accounting for a 70-80% compliance rate. The FPG on the day of the consult will encourage patients to inject morning insulin and to eat breakfast prior to visiting the clinic, thus reducing hypoglycaemic events while waiting to be seen by physicians. It can be argued that patients will behave differently over these four days, adhering to medication and dietary advice, but this ensures titration occurs on the lowest SMBG readings, thus ensuring safety from hypoglycaemia.

Days prior to consultation or medication collection	Before breakfast	Before lunch	Before dinner	Bedtime
4				
3				
2				
1				
0				

Figure 11: Recommended adjustments to structured SMBG routine with a total of 17 tests performed per month. Shaded blocks indicate where SMBG is to be performed.

The titration algorithm from Liebl *et al*. was found to be effective in reducing HbA1c during the intervention; however, it did not allow for appropriate dose reductions for frequent hypoglycaemia experienced over similar time intervals (see Section 6.3.5.). Another consideration that needs to be addressed is when to consider altering insulin regimen by adding a lunch time insulin dose. From experience gained in the study, the authors recommend that an additional dose of insulin (biphasic human insulin or rapid acting insulin) be added at lunch when the patient is achieving/near dinner SMBG targets but shows considerable hyperglycaemia over lunch, as was seen in patient 0043. It is also recommended to abandon the practise of interim telephone calls

between monthly titrations due to resource shortages. From these points, it is recommended that the following changes be made to the titration algorithm (Figure 12):



[a]. Liebl A, Prager R, Binz K, et al. Comparison of insulin analogue regimens in people with type 2 diabetes in the PREFER study: a randomized controlled trial. Diabetes Obes Metab 2009;11:45–52.
[b]. Canadian Diabetes Association Clinical Practice Guidelines Expert Committee. Canadian Diabetes Association 2008 clinical practice guidelines for the prevention and management of diabetes in Canada. Can J Diabetes 2008; 32: S95-S98.
[c]. Canadian Agency for Drugs and Technologies in Health (CADTH). Optimal use recommendations for second and third-line therapy for patients with type 2 diabetes. Ottawa (ON): Canadian Agency for Drugs and Technologies in Health (CADTH); 2013 Jul. 19 p. http://www.guideline.gov/content.aspx?f=rss&id=47068#Section420

Figure 12: Recommended adjustments to insulin titration algorithm.

7.14.2. Application in clinical practice

This intervention would be most suitable to patients with a high HbA1c (≥10%, 86 mmol/mol) and/or high risk for diabetes-related complications. Patients can be put onto

the intensive intervention for six months and reviewed. The adjusted algorithm will take rates of hypoglycaemia into account in order to reduce side effects.

The advantage of this intervention is that an insulin titration algorithm is easy to follow for HCPs who have limited experience with diabetes, whilst not reducing the physician's autonomy to override the recommendation set forth. The consistency of care will assist a diabetes clinic to efficiently reach glycaemic targets for the majority of patients.

Since this study did not enrol patients with concomitant sulfonylurea OHAs, the authors recommend caution when applying this titration algorithm to such patients. The use of the sulfonylurea should be reviewed if frequent hypoglycaemia occurs with the use of insulin.[31]

7.14.3. Implication for public health practice

This study was based on a pragmatic cohort design whereby an approach to the identified gap in the literature was dealt with in a realistic way. This methodology took the challenges within the public healthcare setting of South Africa into account, rather than basing it on ideal, theoretical considerations. An example of this is the timing of clinical consultations: a month may be too long a wait for the titration of a sub-optimal insulin dose; however, contacting patients more frequently would put great strain on the financial and personnel resources of hospitals already overloaded with patients. As demonstrated in Section 6.3.5., it was not feasible to contact patients with high baseline HbA1c levels in order to titrate insulin more frequently. This research aimed for sustainable efficacy, rather than faster, optimal achievement of glycaemic targets.

Structured SMBG regimen combined with regular insulin titration was effective in reducing HbA1c. The authors therefore make a recommendation to the National DoH for glucose test strips to be made consistently available to patients with type 2 diabetes who are using insulin. The availability of these resources is paramount to ensure the safety of patients on insulin who are at risk for hypoglycaemia.

7.14.4. Future research

This was an exploratory study that can be up-scaled into a cluster RCT in order to ensure generalisability of results. In order to assess the contribution of insulin titration as separate from other influences of HbA1c (as noted in Section 7.2), it is recommended that titrations be conducted by pharmacists. Patients can have their SMBG data downloaded, analysed by an automatic, computerised algorithm and a recommended dose change printed. This eliminates influence of dietary or lifestyle advice from physicians, and limits the Hawthorne effect. In order to motivate patients to comply with the structured SMBG regimen, researchers could create a “fast-track” queue to collect medication. Those who have completed >80% of SMBG can avoid long lines and extended waiting times to collect their monthly medication. The researchers recommend that future research include a follow-up recording of HbA1c six months after the conclusion of the intervention to assess if improved glycaemic control is maintained.

8. Conclusion

In conclusion, structured SMBG that advises monthly algorithmic insulin titration can improve glucose control in type 2 diabetes patients using twice-daily biphasic insulin by aggressively targeting mean SMBG and FPG excursions with moderate hypoglycaemic events, weight gain and decrease in QoL. Glycaemic improvement achieved here has the potential to delay or reduce diabetes-related microvascular complications. The intervention may allow greater confidence in HCPs to safely titrate insulin doses. It is recommended to assess this study in a cluster RCT in order to ensure accuracy and generalisability of results.

9. List of References

1. International Diabetes Federation [Internet]. IDF Diabetes Atlas, 7th ed. Brussels, Belgium: International Diabetes Federation; [updated 2015; cited 2016 Oct 06]. Available from: http://www.diabetesatlas.org
2. Hird TR, Pirie FJ, Esterhuizen TM, O'Leary B, McCarthy MI, Young EH, Sandhu MS, Motala AA. Burden of diabetes and first evidence for the utility of HbA1c for diagnosis and detection of diabetes in urban black South Africans: the Durban diabetes study. PloS one. 2016 Aug; 11(8):e0161966.
3. Peer N, Steyn K, Lombard C, Lambert EV, Vythilingum B, Levitt NS. Rising diabetes prevalence among urban-dwelling black South Africans. PloS one. 2012 Sep; 7(9):e43336.
4. The Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. N Engl J Med. 1993 Sep 30; 329(14): 977-986.
5. Goldstein DE, Little RR, Lorenz RA, Malone JI, Nathan D, Peterson CM, et al. Tests of glycemia in diabetes. Diabetes Care. 2004 Jul; 27(7):1761-1773.
6. Chalew S, Hempe J. Caveats regarding the use of HbA1c for prediction of mean blood glucose. Diabetologia. 2008;51 (5):903-904.
7. Little RR, Roberts WL. A review of variant hemoglobins interfering with hemoglobin A1c measurement. J.Diabetes Sci.Technol. 2009 May 1; 3 (3):446-451.
8. Ceriello A, Colagiuri S, Gerich J, Tuomilehto J. Guideline for management of postmeal glucose. Nutr Metab Cardiovasc Dis. 2008; 18(4):S17-S33.
9. DECODE Study Group: the European Diabetes Epidemiology Group. Glucose tolerance and cardiovascular mortality: comparison of fasting and 2-hour diagnostic criteria. Arch Intern Med. 2001 Feb 12; 161(3):397-405.
10. Cavalot F, Petrelli A, Traversa M, Bonomo K, Fiora E, Conti M, et al. Postprandial blood glucose is a stronger predictor of cardiovascular events than fasting blood glucose in type 2 diabetes mellitus, particularly in women: lessons from the San Luigi Gonzaga Diabetes Study. J Clin Endocrinol Metab. 2006; 91(3):813-819.

11. Gimeno-Orna JA, Castro-Alonso FJ, Boned-Juliani B, Lou-Arnal LM. Fasting plasma glucose variability as a risk factor of retinopathy in Type 2 diabetic patients. J Diabetes Complications. 2003; 17(2):78-81.
12. Nalysnyk L, Hernandez-Medina M, Krishnarajah G. Glycaemic variability and complications in patients with diabetes mellitus: evidence from a systematic review of the literature. Diabetes Obes Metab. 2010; 12(4):288-298.
13. Monnier L, Lapinski H, Colette C. Contributions of fasting and postprandial plasma glucose increments to the overall diurnal hyperglycemia of type 2 diabetic patients: variations with increasing levels of HbA (1c). Diabetes Care. 2003 Mar; 26(3):881-885.
14. Benjamin EM. Self-monitoring of blood glucose: the basics. Clin Diabetes. 2002; 20(1):45-47.
15. Institute of Health Economics [Internet]. Consensus statement on self-monitoring in diabetes. Alberta, Canada: Institute of Health Economics [updated 2006; cited 2015 Jan 9]. Available from: http://www.ihe.ca/documents/consensus_statement_complete_nov17_0.pdf.
16. Sheu WH. Addressing self-monitoring of blood glucose: Advocating paired glycemic testing for people with type 2 diabetes. J Diabetes Investig. 2012; 3(4):337-338.
17. Peel E, Parry O, Douglas M, Lawton J. Blood glucose self-monitoring in non-insulin-treated type 2 diabetes: a qualitative study of patients' perspectives. Br J Gen Pract. 2004 Mar; 54(500):183-188.
18. National Essential Drugs List Committee. Chapter 9: Endocrine System, Diabetes mellitus. Standard Treatment Guidelines and Essential Drugs List. South Africa: Pudifin D; 2008.
19. Kato N, Cui J, Kato M. Structured self-monitoring of blood glucose reduces glycated hemoglobin in insulin-treated diabetes. J Diabetes Invest. 2013 September; 4(5):450-453
20. Polonsky WH, Fisher L, Schikman CH, Hinnen DA, Parkin CG, Jelsovsky Z, et al. Structured self-monitoring of blood glucose significantly reduces A1C levels in poorly controlled, noninsulin-treated type 2 diabetes: results from the Structured Testing Program study. Diabetes Care. 2011 Feb; 34(2):262-267.

21. Franciosi M, Lucisano G, Pellegrini F, Cantarello A, Consoli A, Cucco L, et al. ROSES: role of self-monitoring of blood glucose and intensive education in patients with Type 2 diabetes not receiving insulin. A pilot randomized clinical trial. Diabetic Med. 2011; 28(7):789-796.
22. IDF Clinical Guidelines Taskforce and SMBG International Working Group. Global guideline on self-monitoring of blood glucose in non-insulin treated type 2 diabetes. Brussels, Belgium: International Diabetes Federation; 2009.
23. American Diabetes Association. Standards of medical care in diabetes. Diabetes Care. 2015 Jan; 38, (Suppl 1): S33-41
24. Canadian Optimal Medication Prescribing and Utilization Service. Cost-Effectiveness of Blood Glucose Test Strips in the Management of Adult Patients with Diabetes Mellitus. Canadian Agency for Drugs and Technologies in Health. 2009 May; 3(3).
25. Amod A, Ascott-Evans B, Berg G. The 2012 SEMDSA guideline for the management of type 2 diabetes. JEMDSA. 2012; 17: S1-S95.
26. Gorter KJ, de Laar FAv, Janssen PGH, Houweling ST, and Rutten GEHM. Diabetes: glycaemic control in type 2 (drug treatments). Clin Evid. 2012;1 0(609).
27. Rafoth RJ. Standardizing sliding scale insulin orders. Am J Med Qual. 2002 Sep-Oct; 17(5):175-178.
28. Hirsch IB, Bergenstal RM, Parkin CG, Wright E, Buse JB. A real-world approach to insulin therapy in primary care practice. Clin Diabetes. 2005; 23(2):78-86.
29. Sibal L, Home PD. Management of type 2 diabetes: NICE guidelines. Clin Med. 2009 Aug; 9(4):353-357.
30. IDF Clinical Guidelines Task Force. Global guideline for Type 2 diabetes. Brussels: International Diabetes Federation; 2005.
31. Inzucchi SE, Bergenstal RM, Buse JB, Diamant M, Ferrannini E, Nauck M, et al. Management of hyperglycemia in type 2 diabetes: a patient-centered approach: position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetes Care. 2012 Jun; 35(6):1364-1379.
32. Harper W, Clement M, Goldenberg R, Hanna A, Main A, Retnakaran R. Canadian Diabetes Association 2013 Clinical Practice Guidelines for the Prevention and Management of Diabetes in Canada: pharmacologic management of type 2 diabetes. Can J Diabetes. 2013; 37(Suppl 1):S61-S68.

33. Kilo C, Mezitis N, Jain R, Mersey J, McGill J, Raskin P. Starting patients with type 2 diabetes on insulin therapy using once-daily injections of biphasic insulin aspart 70/30, biphasic human insulin 70/30, or NPH insulin in combination with metformin. J Diabetes Complications. 2003; 17(6):307-313.
34. Esposito K, Ciotola M, Maiorino MI, Gualdiero R, Schisano B, Ceriello A, et al. Addition of neutral protamine lispro insulin or insulin glargine to oral type 2 diabetes regimens for patients with suboptimal glycemic control: a randomized trial. Ann Intern Med. 2008; 149(8):531-539.
35. Roach P, Trautmann M, Arora V, Sun B, Anderson JH, Mix50 Study Group. Improved postprandial blood glucose control and reduced nocturnal hypoglycemia during treatment with two novel insulin lispro-protamine formulations, insulin lispro Mix25 and insulin lispro Mix50. Clin Ther. 1999; 21(3):523-534.
36. Boehm B, Home P, Behrend C, Kamp N, Lindholm A. Premixed insulin aspart 30 vs. premixed human insulin 30/70 twice daily: a randomized trial in type 1 and type 2 diabetic patients. Diabetic Med. 2002; 19(5):393-399.
37. Malone JK, Kerr LF, Campaigne BN, Sachson RA, Holcombe JH, Lispro Mixture-Glargine Study Group. Combined therapy with insulin lispro Mix 75/25 plus metformin or insulin glargine plus metformin: a 16-week, randomized, open-label, crossover study in patients with type 2 diabetes beginning insulin therapy. Clin Ther. 2004; 26(12):2034-2044.
38. Roach P, Trautmann M, Arora V, Sun B, Anderson JH, Mix50 Study Group. Improved postprandial blood glucose control and reduced nocturnal hypoglycemia during treatment with two novel insulin lispro-protamine formulations, insulin lispro Mix25 and insulin lispro Mix50. Clin Ther. 1999; 21(3):523-534.
39. Kazda C, Hülstrunk H, Helsberg K, Langer F, Forst T, Hanefeld M. Prandial insulin substitution with insulin lispro or insulin lispro mid mixture vs. basal therapy with insulin glargine: a randomized controlled trial in patients with type 2 diabetes beginning insulin therapy. J Diabetes Complications. 2006; 20(3):145-152.
40. Hirao K, Arai K, Yamauchi M, Takagi H, Kobayashi M, Japan Diabetes Clinical Data Management Study Group. Six-month multicentric, open-label, randomized trial of twice-daily injections of biphasic insulin aspart 30 versus multiple daily

injections of insulin aspart in Japanese type 2 diabetic patients (JDDM 11). Diabetes Res Clin Pract. 2008; 79(1):171-176.

41. Pan C, Sinnassamy P, Chung K, Kim K. Insulin glargine versus NPH insulin therapy in Asian Type 2 diabetes patients. Diabetes Res Clin Pract. 2007; 76(1):111-118.
42. Jacober S, Scism-Bacon J, Zagar A. A comparison of intensive mixture therapy with basal insulin therapy in insulin-naïve patients with type 2 diabetes receiving oral antidiabetes agents. Diabetes Obes Metab. 2006; 8(4):448-455.
43. Riddle MC, Rosenstock J, Gerich J, Insulin Glargine 4002 Study Investigators. The treat-to-target trial: randomized addition of glargine or human NPH insulin to oral therapy of type 2 diabetic patients. Diabetes Care. 2003 Nov; 26(11):3080-3086.
44. Hermansen K, Davies M, Derezinski T, Martinez Ravn G, Clauson P, Home P. A 26-week, randomized, parallel, treat-to-target trial comparing insulin detemir with NPH insulin as add-on therapy to oral glucose-lowering drugs in insulin-naive people with type 2 diabetes. Diabetes Care. 2006 Jun; 29(6):1269-1274.
45. Eliaschewitz FG, Calvo C, Valbuena H, Ruiz M, Aschner P, Villena J, et al. Therapy in type 2 diabetes: insulin glargine vs. NPH insulin both in combination with glimepiride. Arch Med Res. 2006; 37(4):495-501.
46. Bergenstal RM, Johnson M, Powers MA, Wynne A, Vlajnic A, Hollander P, et al. Adjust to target in type 2 diabetes: comparison of a simple algorithm with carbohydrate counting for adjustment of mealtime insulin glulisine. Diabetes Care. 2008 Jul; 31(7):1305-1310.
47. Liebl A, Prager R, Binz K, Kaiser M, Bergenstal R, Gallwitz B. Comparison of insulin analogue regimens in people with type 2 diabetes mellitus in the PREFER Study: a randomized controlled trial. Diabetes Obes Metab. 2009; 11(1):45-52.
48. Riddle MC, Rosenstock J, Vlajnic A, Gao L. Randomized, 1-year comparison of three ways to initiate and advance insulin for type 2 diabetes: twice-daily premixed insulin versus basal insulin with either basal-plus one prandial insulin or basal-bolus up to three prandial injections. Diabetes Obes Metab. 2014 May 1; 16(5):396-402.

49. Holman RR, Thorne KI, Farmer AJ, Davies MJ, Keenan JF, Paul S, et al. Addition of biphasic, prandial, or basal insulin to oral therapy in type 2 diabetes. N Engl J Med. 2007; 357(17):1716-1730.
50. Raskin P, Allen E, Hollander P, Lewin A, Gabbay RA, Hu P, et al. Initiating insulin therapy in type 2 Diabetes: a comparison of biphasic and basal insulin analogs. Diabetes Care. 2005 Feb; 28(2):260-265.
51. Yang W, Ji Q, Zhu D, Yang J, Chen L, Liu Z, et al. Biphasic insulin aspart 30 three times daily is more effective than a twice-daily regimen, without increasing hypoglycemia, in Chinese subjects with type 2 diabetes inadequately controlled on oral antidiabetes drugs. Diabetes Care. 2008 May; 31(5):852-856.
52. Garber A, Wahlen J, Wahl T, Bressler P, Braceras R, Allen E, et al. Attainment of glycaemic goals in type 2 diabetes with once-, twice-, or thrice-daily dosing with biphasic insulin aspart 70/30 (The 1-2-3 study). Diabetes Obes Metab. 2006; 8(1):58-66.
53. Janka HU, Plewe G, Riddle MC, Kliebe-Frisch C, Schweitzer MA, Yki-Jarvinen H. Comparison of basal insulin added to oral agents versus twice-daily premixed insulin as initial insulin therapy for type 2 diabetes. Diabetes Care. 2005 Feb; 28(2):254-259.
54. Statistics South Africa [Internet]. City of Tshwane. South Africa: Statistics South Africa; [updated 2011; cited 2016 Oct 06]. Available from: http://www.statssa.gov.za/?page_id=1021&id=city-of-tshwane-municipality
55. Motala AA, Esterhuizen T, Gouws E, Pirie FJ, Omar MA. Diabetes and other disorders of glycemia in a rural South African community prevalence and associated risk factors. Diabetes care. 2008 Sep 1; 31(9):1783-8.
56. Bashan E, Herman WH, Hodish I. Are glucose readings sufficient to adjust insulin dosage? Diabetes Technol Ther. 2011; 13(1):85-92.
57. Yki-Jarvinen H, Juurinen L, Alvarsson M, Bystedt T, Caldwell I, Davies M, et al. Initiate Insulin by Aggressive Titration and Education (INITIATE): a randomized study to compare initiation of insulin combination therapy in type 2 diabetic patients individually and in groups. Diabetes Care. 2007 Jun; 30(6):1364-1369.
58. Esposito K, Ciotola M, Maiorino MI, Gualdiero R, Schisano B, Ceriello A, et al. Addition of neutral protamine lispro insulin or insulin glargine to oral type 2 diabetes regimens for patients with suboptimal glycemic control: a randomized trial. Ann Intern Med. 2008; 149(8):531-539.

59. Gerstein HC, Riddle MC, Kendall DM, Cohen RM, Goland R, Feinglos MN, et al. Glycemia treatment strategies in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial. Am J Cardiol. 2007; 99(12):S34-S43.
60. Yki-Järvinen H, Kauppinen-Mäkelin R, Tiikkainen M, Vähätalo M, Virtamo H, Nikkilä K, et al. Insulin glargine or NPH combined with metformin in type 2 diabetes: the LANMET study. Diabetologia. 2006; 49(3):442-451.
61. Steyn K, Levitt D, Patel M, Fourie J, Gwebushe N, Lombard C, et al. Hypertension and diabetes: poor care for patients at community health centres. S Afr Med J. 2008; 98(8):618-622.
62. Daniels A, Biesma R, Otten J, Levitt NS, Steyn K, Martell R, et al. Ambivalence of primary health care professionals towards the South African guidelines for hypertension and diabetes. S Afr Med J. 2000; 90(12):1206-1211.
63. Asmall S, Mahomed O. Integrated chronic diseases management manual. South Africa: National Department of Health of South Africa. 2011.
64. Nelson JM, Dufraux K, Cook PF. The relationship between glycemic control and falls in older adults. J Am Geriatr Soc. 2007; 55(12):2041-2044
65. Moen MF, Zhan M, Walker LD, Einhorn LM, Seliger SL, Fink JC. Frequency of hypoglycemia and its significance in chronic kidney disease. Clin J Am Soc Nephrol. 2009 Jun 1; 4(6):1121-7.
66. COBAS CB. Enhancing patient care at the point of need with combined HbA1c and lipid panel testing [Internet]. Roche Diagnostics International Ltd. [cited 2017 Jan 16]. Available from: https://www.cobas.com/content/dam/cobas_com/pdf/product/cobas-b-101-system/cobas_b101_gpsp_12pg_EURO.pdf
67. StataCorp. 2011. Stata Statistical Software: Release 12. College Station, TX: StataCorp LP.
68. Kreidler SM, Muller KE, Grunwald GK, Ringham BM, Coker-Dukowitz ZT, Sakhadeo UR, et al. GLIMMPSE: Online Power Computation for Linear Models with and without a Baseline Covariate. J Stat Softw. 2013; 54(10).
69. Institute for Digital Research and Education [Internet]. Introduction to Generalized Linear Mixed Models. United States of America: UCLA Statistical Consulting Group; [updated 2006; cited 2016 Oct 06]. Available from: http://www.ats.ucla.edu/stat/mult_pkg/glmm.htm

70. Wolfinger R, O'Connell M. Generalized linear mixed models a pseudo-likelihood approach. J Stat Comput Simul. 1993 Dec 1; 48(3-4):233-43.
71. Lyssenko V, Jonsson A, Almgren P, Pulizzi N, Isomaa B, Tuomi T, et al. Clinical risk factors, DNA variants, and the development of type 2 diabetes. N Engl J Med. 2008 Nov 20; 359(21):2220-32.
72. Census 2011: Population Dynamics. Statistics South Africa. Pretoria: Statistics South Africa. 2012.
73. Turner RC, Cull CA, Frighi V, Holman RR, UK Prospective Diabetes Study (UKPDS) Group. Glycemic control with diet, sulfonylurea, metformin, or insulin in patients with type 2 diabetes mellitus: progressive requirement for multiple therapies (UKPDS 49). JAMA. 1999 Jun 2; 281(21):2005-12.
74. McCarney R, Warner J, Iliffe S, Van Haselen R, Griffin M, Fisher P. The Hawthorne Effect: a randomised, controlled trial. BMC Med Res Methodol. 2007 Jul 3; 7(1):1.
75. UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). Lancet. 1998 Sep 12; 352(9131):837-53.
76. Manley SM, Meyer LC, Neil HA, Ross IS, Turner RC, Holman RR. Complications in newly diagnosed type 2 diabetic patients and their association with different clinical and biochemical risk factors. UKPDS 6. Diabetes Res. 1990 Jan;13(1):1-1.
77. Nathan DM, Kuenen J, Borg R, Zheng H, Schoenfeld D, Heine RJ. A1c-Derived Average Glucose Study Group. Translating the A1C assay into estimated average glucose values. Diabetes Care. 2008; 31:1473-1478.
78. Wei N, Zheng H, Nathan DM. Empirically establishing blood glucose targets to achieve HbA1c goals. Diabetes Care. 2014 Apr; 37(4):1048-51.
79. Monsod TP, Flanagan DE, Rife F, Saenz R, Caprio S, Sherwin RS, Tamborlane WV. Do sensor glucose levels accurately predict plasma glucose concentrations during hypoglycemia and hyperinsulinemia? Diabetes Care. 2002 May 1; 25(5):889-93.
80. Falanga V. Wound healing and its impairment in the diabetic foot. Lancet. 2005 Nov 18; 366(9498):1736-43.

81. Chung SS, Ho EC, Lam KS, Chung SK. Contribution of polyol pathway to diabetes-induced oxidative stress. J Am Soc Nephrol. 2003 Aug; 14(8 Suppl 3):S233-6.
82. Gress TW, Nieto FJ, Shahar E, Wofford MR, Brancati FL. Hypertension and antihypertensive therapy as risk factors for type 2 diabetes mellitus. N Engl J Med 342:905–912, 2000
83. Khare S. Risk factors of transient ischemic attack: An overview. J Midlife Health. 2016 Jan; 7(1):2.
84. Hermansen K, Colombo M, Storgaard H, OStergaard A, Kolendorf K, Madsbad S. Improved postprandial glycemic control with biphasic insulin aspart relative to biphasic insulin lispro and biphasic human insulin in patients with type 2 diabetes. Diabetes Care. 2002 May; 25(5):883-888.
85. Mäkimattila S, Nikkilä K, Yki-Järvinen H. Causes of weight gain during insulin therapy with and without metformin in patients with type II diabetes mellitus. Diabetologia. 1999 Mar 1; 42(4):406-12.
86. Bradley C. Psychological issues in clinical trial design. Ir J Psychol. 1997 Jan 1; 18(1):67-87.
87. Pouwer F, Snoek FJ, Heine RJ: Ceiling effect reduces the validity of the Diabetes Treatment Satisfaction Questionnaire. Diabetes Care. 1998, 21(11):2039-2039.
88. Brown JB, Nichols GA, Perry A. The burden of treatment failure in type 2 diabetes. Diabetes care. 2004 Jul 1; 27(7):1535-40.
89. Webb EM, Rheeder P, Van Zyl DG. Diabetes care and complications in primary care in the Tshwane district of South Africa. Primary care diabetes. 2015 Apr; 9(2):147-54.

10. Appendices

10.1. Appendix A: Patient information leaflet

PATIENT / PARTICIPANT'S INFORMATION LEAFLET & INFORMED CONSENT FORM

TRIAL TITLE: The effect of a structured self-monitoring blood glucose regimen on glycaemic control for type 2 diabetes patients using insulin

Principal Investigator: Miss Kerry Kalweit
Institution: University of Pretoria

DAYTIME AND AFTER HOURS TELEPHONE NUMBER(S):
Daytime numbers: 060 310 9835
Afterhours: 060 310 9835

DATE AND TIME OF FIRST INFORMED CONSENT DISCUSSION:

			:
dd	**Mmm**	**Yyyy**	**Time**

Dear Patient

INTRODUCTION

You are invited to volunteer for a research study. This information leaflet is to help you to decide if you would like to participate. Before you agree to take part in this study you should fully understand what is involved. If you have any questions, which are not fully explained in this leaflet, do not hesitate to ask the investigator. You should not agree to take part unless you are completely happy about all the procedures involved. In the best interests of your health, it is strongly recommended that you discuss with or inform your personal doctor of your possible participation in this study, wherever possible.

WHAT IS THE PURPOSE OF THE RESEARCH TRIAL?

Since you have been diagnosed with Type 2 diabetes and are currently using insulin, the investigator would like you to consider taking part in the research of self-monitoring blood glucose routines where you will test your blood glucose at home at specific times and days. We are assessing if a structured routine for monitoring blood glucose at home will help your doctor adjust your diabetes medication doses to reduce HbA1c. HbA1c is a measure of your average blood glucose over the past 3 months. Research has shown that decreasing your HbA1c helps to reduce your risk for diabetes complications.

WHAT IS THE DURATION OF THIS TRIAL?

If you decide to take part you will be one of approximately 40 patients. The study will last for up to 6 months. You will be asked to visit the diabetes clinic once a month during this time.

DESCRIPTION OF PROCEDURES

Screening procedures

If you decide to take part in this trial you will be asked to sign this informed consent form. The trial clinic staff will interview you and examine you in order to find out if you meet the criteria for participating in the trial. At the interview you will be asked some general questions about your personal data including smoking habits, your diabetes and other medical conditions and the medications you are currently taking. It is important that you let the investigator know of any medicines (both prescription and over-the-counter medicines), alcohol or other substances that you are currently taking.

You will have your height, weight, blood pressure and pulse measured. You should avoid exercise and caffeine for at least 30 minutes before your blood pressure and pulse is measured, and if you smoke, you must refrain from this for at least 30 minutes beforehand. You will also go through a general examination of your body and blood samples will be taken will be taken to check your health status and to see if you are suitable for the trial. A blood glucose meter to be used in the trial and a participant diary will be handed out to you. You will be instructed how to use both.

Your trial doctor will go through the results of your tests and let you know if you are suitable to participate in the trial. If you are suitable for participating in the trial, you will be invited by the trial clinic staff to your next trial visit one month later.

General procedures that you must perform throughout the trial
At all times you must comply with the instructions provided by the trial clinic staff. You will be asked to test your blood glucose 4 times a day for 3 days of the week. We will ask you to record your blood glucose values in the diary, as well as what you ate during that day. You will also be asked to test your blood glucose anytime that you feel it is too low.

At your monthly visit to the diabetes clinic, you will need to register at the hospital to collect your hospital file as you normally do. Research staff at the diabetes clinic will ask you about any changes in medication during the last month and about any adverse events such as hospitalisation or low blood glucose episodes. Your doctor will then discuss your blood glucose values from the past month. The doctor will make changes to your insulin and/or Metformin doses. For the next month, you must take your medication as prescribed by your doctor. Your doctor will ask you about how many times you skipped your insulin injections or other medication and also look at the site where you inject your insulin. Your HbA1c will be measured again 3 months and 6 months later after you enter the trial.

After each clinic visit you will receive a new diary and test strips to monitor your blood glucose for a month. The date of your next appointment will be written on an appointment card that also reminds you of your new medication doses. For each clinic visit, you will also receive R150.00 to reimburse you for your travel expenses and inconvenience of taking part in the trial.

If you are female, who is able to become pregnant, you need to use contraception throughout the trial.

HAS THE TRIAL RECEIVED ETHICAL APPROVAL?

This clinical trial Protocol was submitted to the Faculty of Health Sciences Research Ethics Committee, University of Pretoria, telephone numbers 012 3541677 / 012 3541330 and written approval has been granted by that committee. The study has been structured in accordance with the Declaration of Helsinki (last update: October 2008), which deals with the recommendations guiding doctors in biomedical research involving human/subjects. A copy of the Declaration may be obtained from the investigator should you wish to review it.

WHAT ARE YOUR RIGHTS AS A PARTICIPANT IN THIS TRIAL?

Your participation in this trial is entirely voluntary and you can refuse to participate or stop at any time without stating any reason. Your withdrawal will not affect your access to other medical care. The investigator retains the right to withdraw you from the study if it is considered to be in your best interest. If it is detected that you did not give an accurate history or did nor follow the guidelines of the trial and the regulations of the trial facility, you may be withdrawn from the trial at any time.

Whether you complete the trial or stop early, your trial doctor will discuss your future diabetes treatment with you. The trial will not continue to supply you with test strips after your final clinical consultation, but you may keep the glucose meter given to you.

IS ALTERNATIVE TREATMENT AVAILABLE?

Alternative treatment in the form of random blood glucose monitoring is often used to assess control in Type 2 diabetes. If you decide not to take park in this study, it is possible that your doctor may treat you with this or another suitable glucose monitoring routine.

MAY ANY OF THESE TRIAL PROCEDURES RESULT IN DISCOMFORT OR INCONVENIENCE?

Hypoglycaemic episodes (too low blood glucose)

Since your trial doctor may increase your insulin dose or other oral diabetic medication, it has the potential to cause hypoglycaemic episodes (too low glucose). This type of side effect is usually mild and may include symptoms such as: cold sweat, hunger, headache, nausea, feeling sick, changes in vision, light-headedness, feeling sleepy, nervous, anxious and confused, fast heartbeat, slight shaking, weakness and difficulties in concentrating. In rare cases, hypoglycaemic episodes may be more severe ad may lead to unconsciousness and even death.

If you experience hypoglycaemic episodes, you should eat sugar, sweets or sugar-containing juice such as Coca-Cola. Your trial doctor will help you understand how to treat hypoglycaemic episodes.

Hyperglycaemia (too high blood glucose)

In case of too little insulin or too little oral diabetic medication, hyperglycaemia (too high blood glucose) may occur. Symptoms include increased urination, feeling thirsty, losing your appetite, nausea or vomiting, feeling drowsy or tired, flushed, dry skin, dry mouth and a fruity smell of the breath. If not treated, these symptoms may develop into a serious condition called diabetic ketoacidosis which may even lead to death.

Other inconveniences

Blood testing (finger-prick and laboratory blood sampling) is part of normal diabetes care, but there might be some discomfort due to more frequent blood testing during the trial. Laboratory blood sampling may cause bruising and infection but the risk of this occurring in the trial is not higher than for normal laboratory blood sampling.

If you experience any of these side effects, you should report it to your trial doctor.

WHAT ARE THE BENEFITS TO YOU

The benefits of participating in this trial may be an improvement in your overall blood glucose control, however this cannot be guaranteed. The information gained during the trial can benefit society by gaining useful information on the future treatment of Type 2 diabetes.

ARE THERE ANY WARNINGS OR RESTRICTIONS CONCERNING MY PARTICIPATION IN THIS TRIAL?

If you are a female who can become pregnant you must use suitable contraceptive measures during the trial, as the safety of this blood glucose testing pattern during pregnancy has not been established. The following birth control methods will be considered acceptable to prevent pregnancy during your participation in the study: Oral hormonal birth control such as the pill, eg. Triphasil, Dianne, etc; injectable birth control; intra-uterine devices/loop; barrier methods such as male and female condoms; spermicides and cervical diaphragms; tubal ligation and abstaining from sex. If you have any questions about birth control options, please ask your trial clinic staff.

If you should become pregnant during your participation in the trial, you must inform your trial clinic staff as soon as possible. You will be withdrawn from the trial and the trial clinic staff will discuss with you the best alternatives for your future diabetes care.

SOURCE OF ADDITIONAL INFORMATION

For the duration of the trial, you will be under the care of Dr/Prof _____. If at any time between your visits you feel that any of your symptoms are causing you any problems, or you have any questions during the trial, please do not hesitate to contact him/her or the trial contact person.

CONFIDENTIALITY

All information obtained during the course of this trial is strictly confidential. Data that may be reported in scientific journals will not include any information which identifies you as a patient in this trial. Your trial data will be identified only by a participant number to make sure that your identity remains confidential. All blood samples will be identified in the same way.

TERMINATION OF PARTICIPATION

It is up to you to decide whether or not to participate in this trial. If you decide not to take part you do not need to give a reason and this will not affect your future treatment.

If you decide to take part you will be asked to sign and date this participant information/informed consent form. Since your participation is voluntary you are free to withdraw your consent at any time without giving a reason. Your discontinuation will not affect the standard of care that you receive.

TRIAL RESULTS

A description of this clinical trial will be available on http://www.clinicaltrials.gov as required by law. This web site will not include information that can identify you. At most, the website will include a summary of the results of the trial. You can search this website at any time.

CONTACT DETAILS

If you require further information, please feel free to ask any questions. Below is the name, address and telephone number of the trial contact person.

Name: Kerry Kalweit
Address: 9 Bophelo Road, Prinshof Campus, Pretoria
Tel number: 060 310 9835
Email: k.kalweit@live.com

INFORMED CONSENT

I hereby confirm that I have been informed by the investigator about the nature, conduct, benefits and risks of the clinical trial “The Effect of a Structured Self-Monitoring Blood Glucose Regimen on Glycaemic Control for Type 2 Diabetes Patients using Insulin”. I have also received, read and understood the above written information (Patient Information Leaflet and Informed Consent) regarding the clinical trial.

I am aware that the results of the trial, including personal details regarding my sex, age, date of birth, initials and diagnosis will be anonymously processed into a trial report.

I may, at any stage, without prejudice, withdraw my consent and participation in the trial. I have had sufficient opportunity to ask questions and (of my own free will) declare myself prepared to participate in the trial.

Patient's name _____
(Please print)

Patient's signature _____ Date _____

I, _____ herewith confirm that the above patient has been informed fully about the nature, conduct and risks of the above trial.

Investigator's name _____
(Please print)

Investigator's signature _____ Date _____

Witness's name _____
(Please print)

Witness's signature _____ Date _____

VERBAL PATIENT INFORMED CONSENT

I, the undersigned, _____, have read and have explained fully to the patient, named _____ and/or is/her relative, the patient information leaflet, which has indicated the nature and purpose of the trial in which I have asked the patient to participate. The explanation I have given has mentioned both the possible risks and benefits of the trial and the alternative treatments available for his/her illness. The patient indicated that he/she understands that he/she will be free to withdraw from the trial at any time for any reason and without jeopardizing his/her subsequent injury attributable to the drug(s) used in the clinical trial, to which he/she agrees.

I hereby certify that the patient has agreed to participate in this trial.

Patient's Name _____
(Please print)

Investigator's Name _____
(Please print)

Investigator's Signature _____ Date _____

Witness's name _____
(Please print)

Witness's signature _____ Date _____

10.2. Appendix B: Screening form

Visit 0: Screening Form

Date: _____ Patient Number: _____

Subject Initials: _____

Informed consent was discussed by:

Name: _____

The discussion was conducted in (list language/s): _____

Date and time Informed consent was signed:

Date: _____ Time: __ __ : __ __

Informed consent process completed according to SOP. If not please add comment below:

_____

_____

_____

Hospital: ☐Steve Biko Academic
☐Kalafong Hospital

Treating physician: _____

Next Appointment Date (Visit 2): _____

Informed Consent obtained by:

_____ _____
Investigator Signature Date

Date: _____ Patient Number: _____

Subject Initials: _____

Contact details:

Primary cellphone number:_____

Work phone number: _____

Other contact number: _____

Address: _____

_____

_____

_____

Demography:

Date of Birth: __ __ __ __ / __ __ / __ __ Age: _____ (years)

Gender: ☐Male ☐Female ☐Other: _____

Race /Ethnic Group: ☐ Black ☐ White ☐ Coloured ☐ Indian

☐ Asian ☐ Other: _____ ___

Smoking Habits: ☐ Current ☐ Ex-User ☐ Never Smoked

Vitals:

Height: _____ cm

Weight: _____ _kg

HbA1c (on-site): _____ %

Blood pressure: _____ / _____mmHg

Total cholesterol: _____mmol/L

_____ _____

Investigator Signature Date

Date: _____ Patient Number: _____

Subject Initials: _____

Medical History past and current (specifically ask about any neoplasms)

Condition	Start date	Current (Yes/No)	End date
Type 2 diabetes			

Concomitant Medication

Trade Name and Strength	Total Dosage	Frequency	Start date	Stop Date

_____ _____

Investigator Signature Date

Date: _____ Patient Number: _____

Subject Initials: _____

Diabetes complications, have any of the following occurred:

Neuropathy	☐ Unknown	☐ Yes	☐ within last 12 months ☐ >12 months ago	☐No
Retinopathy (any)	☐ Unknown	☐ Yes	☐ within last 12 months ☐ >12 months ago	☐No
Urine albumin creatinine ratio >3mg/mmol	☐ Unknown	☐ Yes	☐ within last 12 months ☐ >12 months ago	☐No
Serum creatinine >100µm/L	☐ Unknown	☐ Yes	☐ within last 12 months ☐ >12 months ago	☐No
Stroke	☐ Unknown	☐ Yes	☐ within last 12 months ☐ >12 months ago	☐No
Myocardial infarction	☐ Unknown	☐ Yes	☐ within last 12 months ☐ >12 months ago	☐No
Ischemic heart disease	☐ Unknown	☐ Yes	☐ within last 12 months ☐ >12 months ago	☐No
Heart failure	☐ Unknown	☐ Yes	☐ within last 12 months ☐ >12 months ago	☐No
Amputation	☐ Unknown	☐ Yes	☐ within last 12 months ☐ >12 months ago	☐No

_____ _____

Investigator Signature Date

Date: _____ Patient Number: _____

Subject Initials: _____

Inclusion and exclusion criteria:

Type 2 diabetes?		☐ Yes	☐ No
Full dose Metformin?		☐ Yes	☐ No
Using any sulfonylurea?		☐ Yes	☐ No
Participated in a research protocol within the last 30 days?		☐ Yes	☐ No
Plans to relocate or travel extensively during next 6 months?		☐ Yes	☐ No
Pregnant or breast feeding?	☐ N/A	☐ Yes	☐No
Planning on pregnancy within the next 6 months?	☐ N/A	☐ Yes	☐No
Severe depression or other severe psychological conditions?		☐ Yes	☐ No
History of hypo-unawareness?		☐ Yes	☐ No
One or more severe hypoglycaemic episodes within last 6 months?		☐ Yes	☐ No
Dependency on others to give insulin?		☐ Yes	☐ No
Current drug or alcohol abuse?		☐ Yes	☐ No
Undergone a medical procedure within last 4 weeks or has planned major surgery within the next 6 months?		☐ Yes	☐ No
Currently using insulin pens with metered-dose		☐ Yes	☐ No

_____ _____

Investigator Signature Date

10.3. Appendix C: Accu-Chek Active visual training

HOW TO USE YOUR BLOOD GLUCOSE METER

- Insert a test strip.
- This turns the meter on.
- Without bending, gently push the strip into place until it locks into place.
- The blood symbol will show.

- Push the top of the lancet until it clicks so that the button on the side appears yellow.
- Hold the lancet against the side of your finger.
- Push the yellow button to prick your finger.
- Get a drop of blood.

- Apply your blood to the centre of the orange block.
- Wait 5 seconds.

- The result will be shown.
- Record this in your diary.
- Pull out the strip and throw it away.

10.4. Appendix D: Blood glucose diary

The Effect of a Structured Self-Monitoring Blood Glucose Regimen on Glycaemic Control for Type 2 Diabetes Patients using Insulin

DIARY ___

TO BE COMPLETED BY TRIAL STAFF

PARTICIPANT NUMBER: _____

NEXT VISIT

Date: _____

Time: __ __ : __ __

PHONE CALL (if applicable)

Date: _____

Time: __ __ : __ __

DIARY REVIEWED AFTER RETURN:

_____

Date and trial staff signature

Contents

Reminders for this diary

You will get a new diary at each clinic visit that will be used until the next clinic visit. **You** must be the person who completes this diary.

Please remember to:

- Keep the diary as complete as possible
- Use a pen when you fill in the diary
- Hand this diary over to your trial staff at your next clinic visit
- Do not use Tippex

Instructions

This diary is for you to keep a record of your blood sugars during the trial.

The coloured-in squares in the diary show on which days and times you will need to test your blood sugars.

On those days, you need to record the food you eat at breakfast, lunch and dinner, including any alcohol.

WEEK 1 – Day 1

BLOOD GLUCOSE DATE: _____

Meal	Time	Blood glucose	Food eaten
Before breakfast	__ __:__ __		
2-hours after breakfast	__ __:__ __		
Before lunch	__ __:__ __		
Before bedtime	__ __:__ __		

If a blood glucose value is **below or equal to 3.9mmol/L**, please fill this in on the 'Low Blood Glucose' form at the back of this diary.

INSULIN AND OTHER DIABETES MEDICATION

Medication	Time taken	Number of tablets taken or units of insulin
	__ __:__ __	
	__ __:__ __	
	__ __:__ __	
	__ __:__ __	
	__ __:__ __	
	__ __:__ __	
	__ __:__ __	

Comments for the day: _____
_____
_____

10.5. Appendix E: DTSQ

The Diabetes Treatment Satisfaction Questionnaire: DTSQ

Patient number: _____ Date: _____

The following questions are concerned with treatment for your diabetes (including insulin, tablets and/or diet) and your experience over the past few weeks. Please answer each question by circling a number on each of the scales.

1. How satisfied are you with your current treatment?

Very satisfied	6	5	4	3	2	1	0	Very dissatisfied

2. How often have you felt that your blood sugars have been unacceptably high recently?

Most of the time	6	5	4	3	2	1	0	None of the time

3. How often have you felt that your blood sugars have been unacceptably low recently?

Most of the time	6	5	4	3	2	1	0	None of the time

4. How convenient have you been finding your treatment to be recently?

Very convenient	6	5	4	3	2	1	0	Very inconvenient

5. How flexible have you been finding your treatment to be recently?

Very flexible	6	5	4	3	2	1	0	Very inflexible

6. How satisfied are you with your understanding of diabetes?

Very satisfied	6	5	4	3	2	1	0	Very dissatisfied

7. Would you recommend this form of treatment to someone else with your kind of diabetes?

Yes, I would definitely recommend the treatment	6	5	4	3	2	1	0	No, I would definitely not recommend the treatment

8. How satisfied would you be to continue with your present form of treatment?

Very satisfied	6	5	4	3	2	1	0	Very dissatisfied

Please make sure that you have circled one number for each of the questions.

10.6. Appendix F: Monthly clinic data collection form

Clinic visit Form

Date: _____ Patient Number: _____ Visit: _____

Subject Initials: _____

Appointment Start time: __ __ : __ __

Vitals:

Weight: _____ _kg

HbA1c (on-site): _____ %

Technical Complaints:

_____

_____

_____

_____

Subject Compliance:

Number of SMBG tests done: _____

Self-reported missed insulin injections: _____

Self-reported missed OHA doses: _____

_____ _____

Investigator Signature Date

Date: _____ Patient Number: _____ Visit: _____

Subject Initials: _____

Have you changed any medication since your last clinic visit

Trade Name	Dosage	Frequency	Start date	Stop Date

Any adverse events (such as flu, infection, etc)
For hypoglycaemia, check patient diary

Onset date	AE diagnosis	Is this AE serious?	Date recovered

_____ _____

Investigator Signature Date

Date: _____ Patient Number: _____ Visit: _____

Subject Initials: _____

SMBG results:

Diary handed in? ☐Yes ☐ No

Diary completeness: ☐80 – 100% ☐ 50 – 80% ☐< 50%

Meter accuracy with control solution:

Test 1 result: _____ mmol/L

Test 2 result: _____ mmol/L

Test 3 result: _____ mmol/L

Meter downloaded? ☐Yes ☐ No

Overall glycaemic pattern observed:

☐ Fasting elevated glucose
☐ Post-prandial elevated glucose
☐Total elevated glucose
☐ Meal-specific elevated glucose
☐ Frequent hypoglycaemia
☐ Normal glycaemia
☐ Other: _____

Discussed SMBG results and targets with patient? ☐Yes ☐ No

Discussed identification and treatment of hypoglycaemia? ☐Yes ☐ No

Injection sites: ☐Adequate ☐ Poor, advised to rotate

HbA1c target discussed: ☐N/A ☐ Yes ☐No

Prompt patients to set reminder for post-prandial SMBG: ☐Yes ☐ No

_____ _____

Investigator Signature Date

Date: _____ Patient Number: _____ Visit: _____

Subject Initials: _____

Treatment algorithm:

Used algorithm to titrate doses? ☐Yes ☐ No

If not, describe reasoning: _____

_____

Insulin Dose Adjustment:

Insulin type	Adjustment			
	Pre-breakfast	Pre-lunch	Pre-dinner	Bedtime

_____ _____

Investigator Signature Date

Date: _____ Patient Number: _____ Visit: _____

Subject Initials: _____

Next appointment:

New diary issued:	☐Yes	☐ No
Reimbursement issued:	☐Yes	☐ No
Appointment card issued with new doses:	☐Yes	☐ No
Testing strips issued:	☐Yes	☐ No

Length of time taken for appointment: _____ minutes

End time: __ __ : __ __

_____ _____

Investigator Signature Date

10.7. Appendix G: End-of-study questionnaire

Date: _____ Patient Number: _____ Subject Initials: _____

PATIENT QUESTIONNAIRE ON TRIAL EXPERIENCE

Please answer these questions as honestly as possible. This is based on your experience participating in the "Structured SMBG" Trial. Your opinions will help us for future research trial designs.

Q1: Did you find participating in this trial beneficial to you?

☐ Yes ☐No ☐ I don't know

Q2: What did you <u>like</u> about participating in this trial?

_____

_____

_____

Q3: Did you learn anything about diabetes from this trial?

☐ Yes ☐No ☐ I don't know

If yes, please describe below:

_____

_____

_____

Q4: Did you find participating in this trial harmful in anyway?

☐ Yes ☐No ☐ I don't know

Q5: What did you <u>not like</u> about participating in this trial?

_____

_____

_____

Q6: What would you like to change in the way you were asked to test your blood glucose levels?

_____

_____

_____

Q7: Would you like to continue with the same pattern of testing your blood glucose levels?

☐ Yes ☐No ☐ I don't know

Thank you for participating in this study.

10.8. Appendix H: Ethical approval certificate

UNIVERSITEIT VAN PRETORIA
UNIVERSITY OF PRETORIA
YUNIBESITHI YA PRETORIA

Faculty of Health Sciences Research Ethics Committee

30/10/2014

Approval Certificate
New Application

Ethics Reference No: 432/2014

Title: The effect of a Structured Self-Monitoring Blood Glucose Regimen on Glycaemic Control for type 2 Diabetes Patients using Insulin.

Dear Miss Kerry Kalweit

The **New Application** as supported by documents specified in your cover letter for your research received on the 26/09/2014, was approved by the Faculty of Health Sciences Research Ethics Committee on the 29/10/2014.

Please note the following about your ethics approval:
- Ethics Approval is valid for 1 year.
- Please remember to use your protocol number (**432/2014**) on any documents or correspondence with the Research Ethics Committee regarding your research.
- Please note that the Research Ethics Committee may ask further questions, seek additional information, require further modification, or monitor the conduct of your research.

Ethics approval is subject to the following:
- The ethics approval is conditional on the receipt of 6 monthly written Progress Reports, and
- The ethics approval is conditional on the research being conducted as stipulated by the details of all documents submitted to the Committee. In the event that a further need arises to change who the investigators are, the methods or any other aspect, such changes must be submitted as an Amendment for approval by the Committee.

We wish you the best with your research.

Yours sincerely

*** Kindly collect your original signed approval certificate from our offices, Faculty of Health Sciences, Research Ethics Committee, H W Snyman South Building, Room 2.33 / 2.34.*

Dr R Sommers; MBChB; MMed (Int); MPharMed.
Deputy Chairperson of the Faculty of Health Sciences Research Ethics Committee, University of Pretoria

The Faculty of Health Sciences Research Ethics Committee complies with the SA National Act 61 of 2003 as it pertains to health research and the United States Code of Federal Regulations Title 45 and 46. This committee abides by the ethical norms and principles for research, established by the Declaration of Helsinki, the South African Medical Research Council Guidelines as well as the Guidelines for Ethical Research: Principles Structures and Processes 2004 (Department of Health).

☎ 012 354 1677 🖷 0866516047 deepeka.behari@up.ac.za http://www.healthethics-up.co.za
✉ Private Bag X323, Arcadia, 0007 - 31 Bophelo Road, HW Snyman South Building, Level 2, Room 2.33, Gezina, Pretoria