Comparison between Point of Care Haemoglobin A1C and Standard Laboratory Haemoglobin A1C at a Tertiary level Diabetic Clinic

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DECLARATION BY THE CANDIDATE

I, Ramadan Muftah Dabah, herewith declare that this report is the product of my own research and that it has not previously been submitted for any degree or examination either at the University of the Witwatersrand or at any other university.

Ramadan Dabah

Signature …….

Date …….

DEDICATION

To the soul of my father, who passed away in 2001.

ABSTRACT

Point of care testing (POCT) refers to medical testing that is performed at or near a patient at a convenient time. Recently, POCT HbA1c devices have gained renewed interest in the management of diabetes, particularly in the public-health sector where resources are limited. The benefits of POCT HbA1c for diabetes care are varied, but they are particularly pronounced for patients who cannot afford the cost of transport to standard laboratories to have blood drawn for testing or for return visits to a hospital or clinic. The results of tests performed with POCT HBA1c devices are available far sooner than results obtained from a laboratory. This speedy availability of results could help to improve diabetes management and contribute to more effective patient care.

For this study, which was conducted in a tertiary-level diabetic clinic, the precision, accuracy, ease of use and financial feasibility of using two widely available POCT devices were investigated, and the results compared with standard laboratory measurements. In addition, a survey to gauge participants' awareness and basic knowledge of glycaemic control using A1C was conducted.

The HbA1c of 100 type II diabetic patients was measured by means of the standard laboratory analyser (Dimension EXL with LM), and compared with measurements obtained by means of two POCT devices: (PTS Diagnostic A1C) A1C Now and Siemens DCA Vantage Analyzer. The laboratory results yielded a mean HbA1c of 8.59%; the AIC Now device had a mean of 9.17%, while the DC Vantage device produced a mean of 9.13.

The results indicate that the performance of the POCT devices AIC Now and DCA Vantage are acceptable, and that they can be used to ensure rapid and convenient measures of HbA1c, which, in turn, may enhance patient care.

In addition, the study revealed that in excess of 80% of the target population for this study were unaware of HbA1c as an indicator of long–term diabetic control which suggest that a concerted effort by health personnel is required to educate patients about HbA1c and the importance of glycaemic control.

Keywords: Point of care testing, sensitivity (in clinical tests), specificity (in clinical tests), correlation (in clinical tests), diabetes, glycated haemoglobin, Bland-Altman, confidence interval, limits of agreement

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ABBREVIATIONS

ADA	American Diabetes Association
CLSI	Clinical Laboratory Standard Institute
DCCT	Diabetes Control and Complications Trial
HbA1C	Haemoglobin A1 Concentration
HPLC	High Performance Liquid Chromatography
NGSA	National Glycohaemoglobin Standardization Program
OLS	Ordinary Least Square
POCT	Point of Care Testing
SEMDSA	Society for Endocrinology, Diabetes and Metabolism of South Africa
SMBG	Self-monitoring of blood glucose
TMP	Traceable Measurement Procedure
UKPDS	United Kingdom Prospective Diabetes Study

CHAPTER 1

OVERVIEW OF THE STUDY

1.1 Introduction

Across the globe, diabetic clinics have adopted point of care testing (HbA1c) measurements (POCT-HbA1c) in attempts to improve the quality of treatment given to patients suffering from diabetes (1). However, in recent years, questions have been asked about the performance of NGSP-certified POC instruments in comparison with testing in standard clinical laboratories. This means that the benefits of POCT-HbA1c should be considered very carefully in relation to potential limitations before it is applied comprehensively in publicsector tertiary environments.

The diabetic clinic at the Helen Joseph Academic Hospital is a tertiary-level centre where approximately 300 patients receive clinical care every month. Currently, many diabetic patients do not have HbA1c results available at the time of consultation, which means that there is a delay in management decisions regarding their condition and its treatment. This implies that use of POCT-HbA1c and the availability of speedy results may improve the standard of care provided to such patients.

1.2 Background

Diabetes mellitus is a metabolic condition characterised by hyperglycaemia produced by abnormalities in the production and/or utilisation of insulin in the body. There are two main types of diabetes: Type I which is an autoimmune condition in which pancreatic beta cells are destroyed and the body fails to produce enough insulin; type II diabetes is distinguished by hyperinsulinemia, resistance to the influence of insulin, and a reduced production of insulin. The majority of cases of diabetes are of the latter type.

Over the last few decades, Type II diabetes in particular, has reached epidemic proportions, with approximately twice as many cases occurring worldwide since 1980. The prevalence among adults has increased from 4.7% to 8.5%. The possibility of a heart attack or a stroke is substantially increased (2-4 times) for diabetics, and the disease accounts for 60% of all nontraumatic lower-limb amputations. In South Africa, diabetes is the primary cause of natural death among women, and is the second leading cause overall (after tuberculosis) (16). The

increasing global incidence of diabetes supports the need for effective management tools to improve the quality of treatment that patients receive.

Uncontrolled chronic hyperinsulinemia and hyperglycaemia associated with diabetes contribute to macrovascular complications involving the coronary, cerebral, and peripheral arteries, as well as microvascular complications that affect the eyes, kidneys, and nerves (3).

Haemoglobin A1C (HbA1c) is an indicator of long-term glycaemic control, and over the past two decades, it has been used to guide treatment decisions in medical practice. Its clinical significance arises from the identification of three-monthly average blood glucose levels corresponding to the half-life of red blood corpuscles (4).

In two comprehensive and random clinical trials, a convincing connection was shown between hyperglycaemia and the onset of microvascular complications caused by diabetes. So too have watershed trials such as the Diabetes Control and Complications Trial (DCCT) (14) for type I diabetes indicated that the onset of microvascular complications associated with the disease is contained by effective glycaemic control.

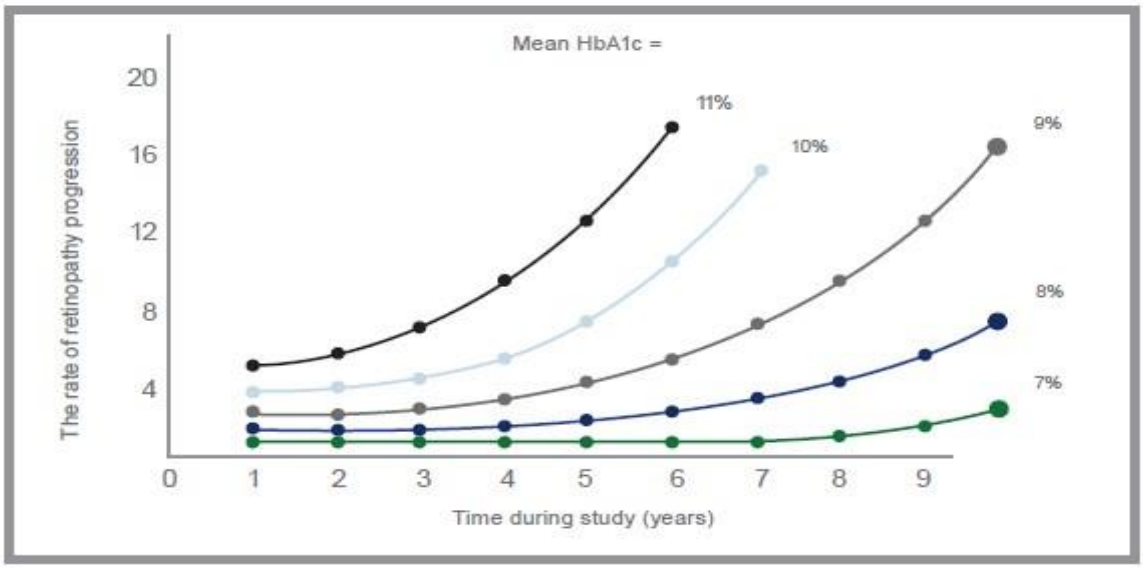

Figure 1.1: HbA1c and the risk of retinopathy in the DCCT (6)

The United Kingdom Prospective Diabetes Study (UKPDS) also showed that microvascular complications associated with type II diabetes might be reduced with increased glycaemic control (6).

The Society for Endocrinology, Diabetes and Metabolism of South Africa (SEMDSA) (7) recommends a twice-annual assessment of HbA1c among patients with steady glycaemic control and who are successfully approaching their glycaemic aims. A three-monthly test is preferable for patients whose glycaemic targets are not being reached and whose treatment has been adapted. In South Africa limited finances and problematic access to standard laboratory services in the public-health domain has led to a reliance on random blood glucose measurements for many therapeutic decisions.

Daramola et al. (3) found that a blood glucose level of 9.8 mmol/l with a sensitivity of 77% and a specificity of 75% best indicated the values at which diabetes is controlled (HbA1c <7%). Medical decisions that are made on the basis of random blood glucose measurements are likely to lead to incorrect assessment for approximately 25% of patients (3). For this reason, the availability of HbA1c is essential to guide therapeutic decisions in glycaemic control.

1.3 Limitations of HbA1c

HbA1c is dependent upon several genetic, lifestyle and hematologic factors, as well as factors associated with the disease itself. This dependence is shown in Table 1.1 below (5):

Table 1.1: Factors influencing HbA1c

Factor influencing HbA1C	**Increased HbA1C**	**Decreased HbA1C**	**Variable change in HbA1C**
Erythropoiesis	Iron deficiency, vitamin B12 deficiency, decreased erythropoiesis	Administration of erythropoietin, iron or vitamin B12, reticulocytosis, chronic liver disease	
Altered haemoglobin			Foetal haemoglobin, haemoglobinopathies, methaemoglobin
Glycation	Alcoholism, chronic kidney failure, decreased	Ingestion of aspirin, vitamin C, vitamin E;	Genetic determinants

	erythrocyte PH	certain haemoglobinopathies, increased erythrocyte PH	
Erythrocyte destruction	Increased erythrocyte lifespan: splenectomy	Reduced erythrocyte lifespan: haemoglobinopathies, splenomegaly, rheumatoid arthritis, medications such as antiretrovirals, ribavirin, and dapsone	
Assays	Hyperbilirubinemia, carbamylated haemoglobin, alcoholism, large quantities of aspirin, ongoing opiate use	Hypertriglyceridemia	Haemoglobinopathies

A variation in HbA1c and the results of a process of self-monitoring of blood glucose (SMBG) are likely to prompt a practitioner to takes the factors shown in Table 1 into account in his evaluation of a patient and as a result, may refer him or her to a laboratory to test for the possibility of haemoglobinopathy. HbA1c does not ascertain the incidence or seriousness of hypoglycaemia or glycaemic variability, which means that the results of the test should be explained and understood in relation to a patient's SMBG records and medical history.

1.4 Measuring HbA1c

Currently, HbA1c measurements are done by evaluating charge or structural differences between Hb components. Four fundamental methods are available for measuring HbA1c: immunoassay; ion-exchange high-performance liquid chromatography (HPLC); boronate affinity HPLC, and enzymatic assays (9). Immunoassays as a rule measure HbA1c, while

antibodies recognise the composition of the N-terminal glycated amino acids of the Hb β chain. Ion-exchange HPLC separates Hb species based on charge differences between HbA1c and other haemoglobins, and in boronate affinity HPLC, *m*-aminophenylboronic acid reacts with the cis-diol groups of glucose bound to Hb. In this way total glycated Hb, including HbA1c and Hb glycated in other areas, is measured and tends to show the lowest degree of intrusion by Hb variants and derivatives. The available enzymatic method ascertains HbA1c by means of an enzyme that splits the N-terminal valine (9).

1.5 Point of Care Testing (POCT)

Point of care testing (POCT) comprises basic medical diagnosis that takes place in close proximity to a patient, viz. in the home, sometimes at the bedside, and at a convenient time. From initially being supplementary to laboratory-based measurements, the use of POCT instruments has developed into a procedure that is essential for diagnostic and therapeutic monitoring purposes.

Assessment of POCT HbA1c shows that it holds potential benefits for treatment and management of diabetes. It can be used as an alternative to laboratory HbA1c measurements since it provides rapid test results, thereby expediting medical decision making. Devices typically require 0.4 – 10 ul from a finger-prick blood sample applied to a reagent cartridge, and produce results in 5-10 minutes, depending on the analyser. It stands to reason that the availability of rapid and reliable POCT HbA1c will facilitate access to HbA1c measurements for patients who live dispersed in rural or in outlying areas. Moreover, besides enhancing the quality of health care, it is also convenient for patients who will subsequently require fewer visits to laboratories or to health-care practitioners. The availability of rapid HbA1c test results, followed by ready decision making is known to improve glycaemic control (2, 8). The use of HbA1c POCT also improves communication between practitioner and patient on management and control of the disease, and it is known that patients generally prefer a quick finger-prick to a blood draw. Unlike the standard HbA1c testing which requires patients to travel twice every 3 months (first for blood testing and second, to obtain the results), POCT provides immediate results and may facilitate adherence to treatment. This, in turn, reduces patients' financial costs, besides reducing the need to apply for sick leave from work. In summary, the availability of

rapid and consistent POCT HbA1c results may therefore, promote the efficacy of diabetes-related health-care delivery.

1.6 Certification of POCT A1c devices

A POCT device must accurately measure the HbA1c of patients as well as replicate the actual HbA1c values. The National Glycohaemoglobin Standardization Program (NGSP) is responsible for establishing generally accepted regulations for HbA1c testing for both POCT and laboratory equipment to Diabetes Control and Complications Trial (DCCT). The NGSP specifies that devices must be certified annually by the manufacturer to ensure that they function effectively. A device is tested by means of a 40-sample comparison in relation to an NGSP secondary reference laboratory in a controlled environment (15). Certification is provided if at least 37 of the 40 samples fall within 6% of the NGSP secondary laboratory values. The strict criterion imposed by the NGSP and its alignment with DCCT results has meant that the American Diabetes Association (ADA) has endorsed the NGSP and proposed that laboratories should limit testing to NGSP-certified methods. According to Whitley et al., (15) by March 2014 only three NGSP-certified A1C POC devices were available, viz., Bayer (now Chek Diagnostics) A1CNow, Siemens DCA Vantage, and Axis-Shield Afinion.

1.7 Point of Care HbA1c testing in South Africa

Worldwide various POCT devices such as DCA Vantage, A1C Now+, Afinion, InnovaStar, Quo-Lab, Quo-Test, Cobas B101, B-analyst HbA1C and Hemocue HbA1C 501 system are available for measuring HbA1C. This study focuses on two devices used in South Africa: Siemens DCA Vantage and PTS Diagnostics A1CNow+. Both devices use an immunoassay based on antibodies binding to glycated haemoglobin molecules, and both have been certified by the National Glycohaemoglobin Standardization Program (NGSP), as well by as the International Federation of Clinical Chemistry and Laboratory Medicine.

Table 1.2: Comparison between key characteristics of A1cNow and DCA Vantage devices (15).

Characteristics	**PTS Diagnostic A1c Now+**	**Siemens DCA Vantage**
Physical size	• Disposable, portable, handheld • Dimensions Depth: 6.35cm(2.5in) Height: 1.0cm(0.4in) Width: 5.1cm (2.0 in) 0.18kg (0.4lb)	• Bench-top unit • Dimensions Depth:27.7cm(10.5in) Height: 25.4cm(9.0in) Width:28.7cm(11.5in) Weight:3.88kg(9lb)

Characteristics	**PTS Diagnostic A1c Now+**	**Siemens DCA Vantage**
Assay methodology	Immunoassay	Immunoassay (latex agglutination inhibition)
Blood sample size (µL)	5	1
Analysis time (min)	5	6
Reporting A1C range (%)	4.0-13.0	2.5-14.0
Source of interference (24)	HbF (when level is 10-15%) HbC HbS	HbF (when level is >20%)
Other quantitative tests (moderate complexity requiring quarterly proficiency testing)	None	• Albumin: creatinine ratio • Creatinine • Microalbumin

Storage	• Refrigerate the test kit (2-8°) until expiry date or store at room temperature (1525º) for not more than 4 months • Use the test cartridge within 2 minutes once the foil pouch has been opened	• Refrigerate the test kit (2-8º) until expiry date or store at room temperature (15-25º) for not more 3 months • Use the test cartridge within 5 minutes once the foil pouch has been opened
Features	• Memory capacity: none • Display: black and white, non-touch • Power supply: battery • Calibration: none • Separate test cartridge and sampling device • Data export: none • Accessories: one	• Memory capacity: 4000 patient and control records • Colour touch display • Power supply: AC/DC adapter • Calibration: lot specific calibration card • Separate test cartridge
Characteristics	**PTS Diagnostic A1c Now+**	**Siemens DCA Vantage**
		and sampling device • Data export USB flash drive Ethernet port Accessories: barcode scanner, on-board printer
Company Internet address	http://www.ptsdiagnostics.co.za	http://www.siemens.co.za

1.8 Evidence of performance of Point of Care HbA1c testing

In 2010, Lenters-Westra et al. (10) assessed the performance of 8 POCT HbA_{1c} devices by subjecting them to performance rules formulated by the Clinical Laboratory Standard Institute (CLSI). Only the DCA Vantage from Siemens and Afinion from Axis-Shield conformed to the NGSP-specified criteria of a coefficient of variation of < 3% and error criterion of ± 0.85% (10).

Further evaluations of various POCT instruments conducted in 2014 (11) by the same group indicated a much enhanced analytical performance when compared with the previous results. The DCA Vantage device met the criteria in the diagnostic range, but indicated a high CV>8.0%. Consequently, users of DCA Vantage were discouraged from adjusting treatment as a result of small differences in the values of two consecutive HbA1c when the HbA1c>8.0%. Regarding the use of POCT HbA1c devices for diagnostic purposes, in 2011 the ADA stated that POCT HbA1c assays lacked accuracy. In 2014, the ADA pointed out that despite POCT HbA1c assays being NGSP-certified, proficiency testing is not required for conducting tests, and consequently using these assays for diagnosis of diabetes could have limited value. Based on these concerns, The Society for Endocrinology, Metabolism and Diabetes of South Africa (7) does also not recommend the use of POCT HbA1c testing for diagnosing diabetes.

1.8.1 Evidence of the effect of Point of Care HbA1c testing in clinical care

In a recent study conducted by Tanyanyiwa et al. (13), who researched the use of POCT in the diabetic clinic at Chris Hani Baragwanath Hospital, support was shown for the use of POCT-HbA1c in a primary-health facility. The results revealed a moderate correlation between random glucose levels and levels of HbA1c. The random glucose tests indicated that 41% of the patients lacked adequate glycaemic control, whereas HbA1c revealed that inadequate glycaemic control was apparent among 74% of the patients. Venous and capillary blood in HbA1c revealed a positive correlation, while there was also a very strong correlation in HbA1c

when measured by the standard laboratory analyser, Multichannel Analyzer 917 and the POCT device DCA Vantage. The results confirmed the effectiveness of using the POCT DCA Vantage to monitor glucose control and to manage diabetes in South Africa.

1.8.2 Evidence of cost implications of introducing Point of Care HbA1c testing in Clinical practice

A study by Mash et al. (12) that took place at two control and two intervention centres in a sub-district focused on the cost and implications of introducing POCT for HbA1c among patients with type 2 diabetes at local clinics in the Western Cape. The DCA Vantage analyser was used at the intervention centres for one year. The results showed that although the POCT provided immediate feedback to the patients, test coverage, intensified treatment and glycaemic control remained unchanged. Furthermore, an additional cost of R21.10 per test was required, which could have been reduced if the HbA1c cartridges had been bought in large numbers. This study therefore, did not favour the use of POCT for HbA1c in primary health-care facilities in the public domain.

1.11 Aims and objectives of the study

1.11.1 Aims

This study has the following aims:

to

a) review the correlation between POCT-HbA1c devices (A1CNow+ and DCA Vantage) and a laboratory analyser (Dimension EXL with LM-HbA1c) in type I and type II diabetic patients who receive treatment at the diabetic clinic at Helen Joseph Hospital
b) assess patients' knowledge of glucose control, and
c) evaluate the cost implications of introducing Point of Care HbA1c testing compared with standard laboratory measurements.

1.11.2 Objectives

The following objectives are identified for the study:

To

a) describe the cohort of diabetic patients included in the study and to assess their knowledge of glucose control, and

b) Compare the effectiveness of the POCT A1CNow+ and DCA Vantage devices with the laboratory analyser (Dimension EXL with LM-HbA1c) in HbA1C testing.

1.12 Justification for the study

The increasing incidence of diabetes in South Africa means that there is a growing need for rapid, reliable, cost-effective and accurate HbA_{1c} testing to monitor glycaemic control. According to Tanyanyiwa et al. (13), the prevalence of the disease in South Africa is about 5.5% in people 30 years and older, and is rising among black South Africans. The prevalence of the disease among South Africa's Indian population is 17.1%, and among people of mixed decent it is 10.8%. The results of tests performed by experienced technologists at the point of manufacture suggest that certification obtained under ideal conditions may not reflect the performance of these devices in clinical settings. For this reason, validating and comparing the POCT devices in relation to standard laboratory analysers is essential.

CHAPTER 2

METHODOLOGY

2.1 Introduction

For a POCT device to be approved as replacement for laboratory testing, evidence of agreement between the two methods of testing should be evaluated and approved. Such method-comparison studies are used to assess the relative agreement between methods that measure the same substance (HbA1c), primarily to assess the performance of a new method of measurement. The correlation and least square regression, coefficient of variation (CV), independent sample t-test and Bland-Altman graphs were used in this research to assess the levels of agreement between the measurements obtained from the laboratory and from the POCT-HbA1c devices.

This chapter elaborates on the research design, the data used, sampling design, variables considered, the measurement process that was applied, and how the data were analysed.

2.2. Research design

In this study a cross-sectional research design was applied to achieve the objectives as outlined in the first chapter. Participants in the project were selected from among patients attending the diabetic clinic at the Helen Joseph Academic Hospital, Johannesburg, South Africa.

2.3. Sample population

The study aimed to recruit 100 standardised type I or type II diabetes patients undergoing treatment at the diabetic clinic at the Helen Joseph Hospital between 01 March and 31 May 2017.

2.4. Method of sample recruitment

Patients who had not had a recent HbA1c at the time of consultation were prioritised. Verbal and written consent was obtained from each patient prior to the start of the project. Patient who were willing to participate in the project were requested to complete a simple patient questionnaire, after which they underwent both POCT analysis and laboratory HbA1c analysis performed within 24 hours of each other.

2.5. Inclusion criteria

Patients attending the diabetic clinic at the Helen Joseph Hospital who consented to participate in the study and who had not had an HbA1c measured in the three months prior to the study were included in the project.

2.6. Exclusion criteria

Patients who did not consent to participate in the study or who had had an HbA1c in the previous three months were excluded from the project.

2.7. Data collection

Finger-stick blood samples were collected by clinic technicians after which HbA1c levels were measured using the POCT devices according to guidelines provided by the manufacturers. Venous blood samples were collected in EDTA tubes containing an anticoagulant. POCT HbA1c measurements were compared with those determined by HPLC in the central laboratory (Dimension EXL).

The following information was obtained from each participant's medical record:

- Biographic details (age, gender, level of education)
- Clinical information (type of diabetes, duration of diabetes, weight).

A copy of the data collection form is given in Appendix VI of this report.

The laboratory staff and physician performing the HPLC and POCT assays respectively, were not shown the results of the other assay.

2.8. Sampling technique

Patients who participated in the study were randomly selected by means of a simple random sampling technique from among patients at the diabetic clinic who had initially agreed to participate in the study.

2.9. Statistical method and data analysis

Data obtained from the laboratory and the POCT HbA1c devices were first recorded and then captured in Excel. The captured data were then imported into the R software version 3.3.3 for analysis. Variables were recorded in order to be readily included in the software using a codebook. Both descriptive and inferential statistics were applied in the analysis and

interpretation of the data. Descriptive statistics were employed to describe what the data showed in terms of measures such as mean, standard deviation, and minimum and maximum for numerical variables, and frequencies and graphs were used to depict categorical variables. In turn, inferential statistics were used to draw inferences from the data that were collected during the research. Pearson's correlation and simple linear regression were used to assess the level of correlation between the results obtained from the laboratory and results obtained from the POCT-HbA1c devices. Differences between the results obtained from the two methods of measuring the HbA1c were determined by means of the paired-sample t-test, while the Bland-Altman plot was employed to analyse agreement between the laboratory results and results obtained via the POCT-HbA1c device.

2.10. Ethics

Ethical approval to conduct this study was obtained from the Human Research Ethics Committee of the University of the Witwatersrand in July 2016 (Appendix III: Clearance certificate number M160509) before the process of data collection began.

2.11. Consent

Each participant in the study was required to provide written consent to take part and completed a patient information sheet (Appendix IV). Patient information sheets and consent forms were available in English only, but nurses were requested to translate the content of the forms into vernacular languages if patients had difficulty understanding the contents of the forms.

2.12. Cost analysis

The costs of the tests were analysed in relation to the cost of all the materials used by the two POCT devices and by the standard laboratory analyser. The cost of performing the POCT testing and the cost of taking blood samples were not included in the cost analysis since these procedures were done by the researcher. A comparative analysis was used to determine the cost.

CHAPTER 3

RESULTS

3.1. Biographic background of the patients

A total of 102 participants met the entry criteria for the study. However, only 100 had data for the laboratory HbA1c that could be used in the analysis. Of the 100 participants, 39 (38.2%) were males and 63 (61.8%) were females as shown in Table 3.1. Forty (40%) participants had type 1 diabetes; 32 (32%) had type II diabetes, while 28 (28%) did not know their sub-type of diabetes. Forty-three (43%) had had diabetes for more than 10 years; 29 (29%) had the disease for fewer than 5 years, while 28 (28%) had suffered from diabetes for 5 to 10 years.

The frequency with which participants visited the diabetic clinic is presented in Table 3.1. From the data available, 14 (13.7%) of the participants visited the diabetic clinic monthly; 56 (54.9%) visited every 3 months; 18 (17.7%) visited every 4 months, and 14 (13.7%) of the total number of participants visited the diabetic clinic every 6 months.

Table 3.1: Biographic information of the patients (100).

		Percentage
Gender	Male	39
	Female	61
Type of diabetes mellitus	Type I	40
	Type II	32
	Don't know	28
Duration of diabetes mellitus	Less than 5 years	29
	Between 5 and 10 years	28
	In excess of 10 years	43
Visit to diabetic clinic	Monthly	14

	Every 3 months	55
	Every 4 months	18
	Every 6 months	13
Education level	No education	11
	Attended school	55
	Completed grade 12	22
	Attended university or technical college	12

3.2. Knowledge of HbA1c among the patients

The graph below shows the distribution of awareness of HbA1c among the participants: 19 (19%) of the total number of participants indicated that they were aware of HbA1c, while 81(81%) did not know the meaning of HbA1c.

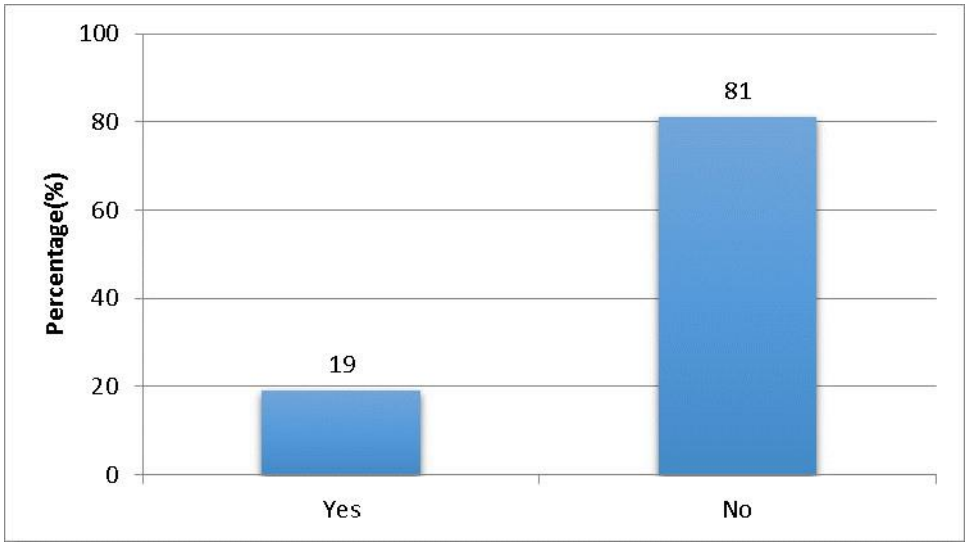

Figure 3.1: Awareness of HbA1c

3.3 Summary statistics

The performance of the POCT devices, AIC Now+ and DCA Vantage, was compared with HPLC reference results. The mean and standard deviations for the results are shown in Table 3.2. The mean HbA1c for the AIC Now+, DCA Vantage and standard laboratory measurements

were 9.17, 9.13 and 8.59 respectively. Comparison of the results shows that on average HbA1c measured by both POCT devices was marginally higher than the results of the laboratory-based measurements.

The AIC Now+ results were 0.6% higher, and the DCA Vantage measurements 0.5% higher overall. The HbA1c range was 5.2% to 12.6% for laboratory readings; 5% to 19.4% for the AIC Now+, and 4% to 14% for the DCA Vantage device.

Table 3.2: Summary statistics for the laboratory and the AIC Now and DCA Vantage devices

	Mean ±SD	**Range**
Lab HbA1c	8.59% ±1.87	5.2-12.6%
A1C Now+	9.17%±2.72	5-19.4%
DCA Vantage	9.13%±2.67	4-14%

3.4 Analysis of the bias of POCT results in relation to HPLC references

The mean bias for both POCT devices versus the standard laboratory measurements as well as the correlation coefficient are shown in Table 3.3. Both POCT devices showed a small, non-significant positive bias from the laboratory results. The 95% CIs for the range of the differences (i.e. the upper and lower limits of agreement) were 0.765% to 0.887% for the A1c Now+ and 0.824%-0.916% for the DCA Vantage.

Table 3.3: Mean bias between laboratory results and results of the POCT-HbA1c devices

Analyte	**Lab HbA1c versus**	**Correlation coefficient**	**Mean bias**	**Mean bias (%)**	**95% CI for correlation coefficient**
HbA1c	AIC Now+	0.836	0.577	6.7	0.765-0.887
	DCA Vantage	0.878	0.541	6.3	0.824-0.916

Linear regression graphs of HbA1c for both POCT devices compared with the laboratory device are shown in Figures 3.2 and 3.3. All HbA1c measurements by means of the POCT devices correlated significantly (p-value<0.0001) with the laboratory results. There was a strong

correlation between A1C Now+ and DCA Vantage measurements versus laboratorybased measurements (r=0.836 and 0.878 respectively).

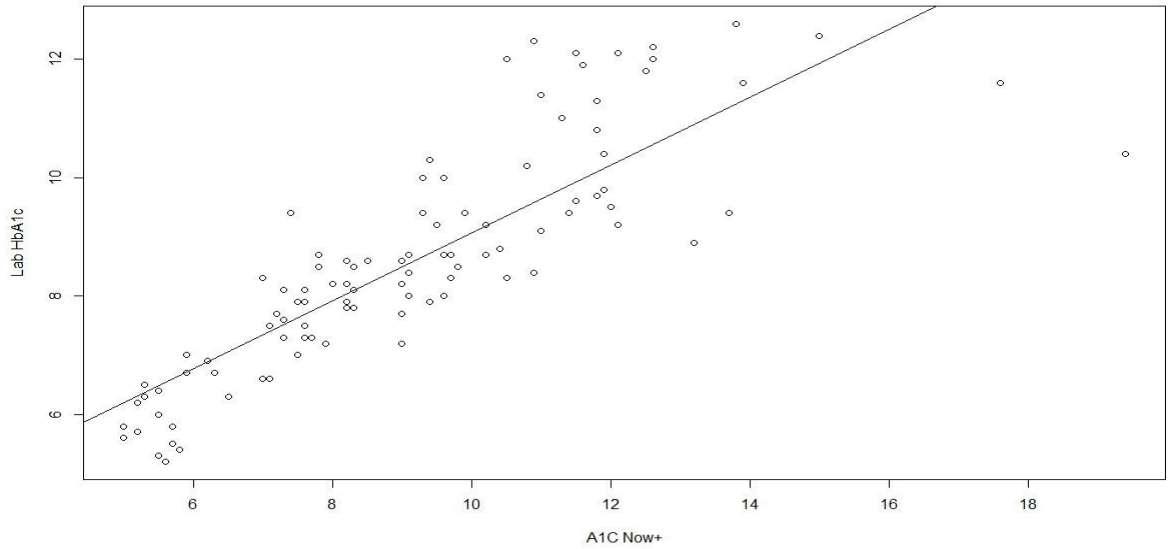

Figure 3.2: Linear regression graph of HbA1c measured by POCT device AIC Now compared with laboratory results

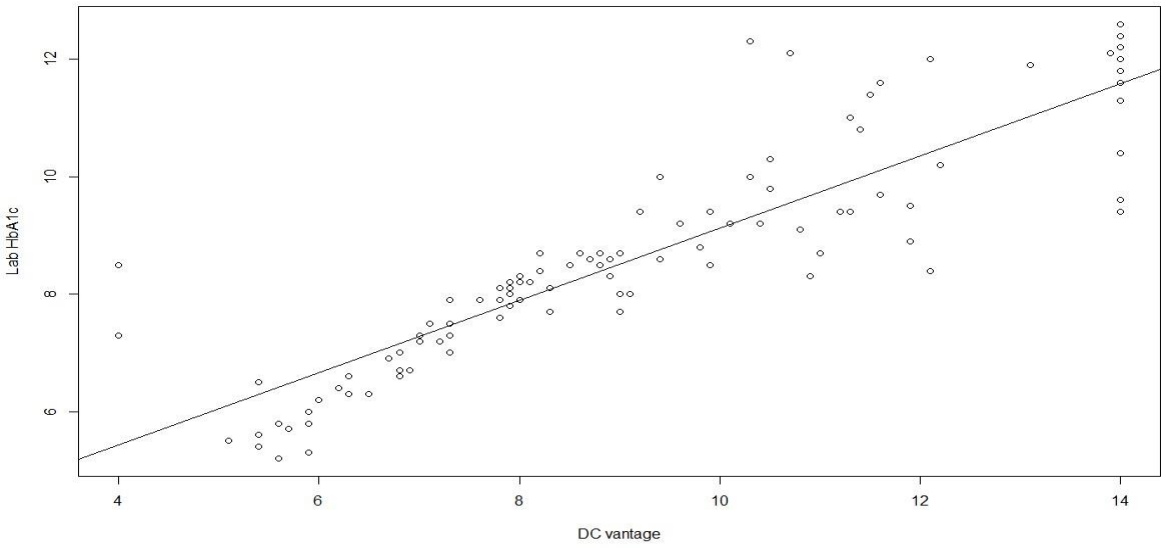

Figure 3.3: Linear regression graph of HbA1c measured by POCT device DCA Vantage compared with laboratory results.

3.5 Sensitivity and specificity analysis (in clinical tests)

In most cases, glycaemic therapy should be intensified in patients with HbA1c >7%.

The results obtained from the POCT devices were compared with those from the laboratory at a 7% HbA1c threshold. These are shown in Tables 3.4 and 3.5 for each of the POCT devices. The sensitivity of the POCT device AIC Now+ was 98.8% and specificity was 89.5%. In this research, 1.2% of the patients whose HbA1c laboratory results were greater than 7% were not identified correctly by the POCT device, and 10.5% of the patients whose HbA1c laboratory results were lower than 7% were recorded to be above 7% by the POCT device. The false negative ratio was 0.012 and the false positive ratio was 0.11. The positive predictive value was 0.98, while the negative predictive value was 0.94.

Table 3.4: Sensitivity and specificity of HbA1c of the POCT device AIC Now at 7% compared with laboratory test results

		Laboratory	
A1C Now+		HbA1c≥7 (%)	HbA1c < 7(%)
	HbA1c≥7	80	2
	HbA1c < 7	1	17
	Total	81	19

The sensitivity of the POCT device DCA Vantage was 96.3% and specificity was 100%. Three point seven percent (3.7%) of the patients whose HbA1c results were greater than 7% from the laboratory results were identified to be lower than 7% by the DCA Vantage, while all the patients whose HbA1c results were lower than 7% from the laboratory results were correctly identified by the DCA Vantage device. The false negative ratio was 0.037. The positive predictive value was 100 and the negative predictive value was 0.86.

Table 3.5: Sensitivity and specificity of HbA1c of the POCT device DCA Vantage at 7% compared with laboratory test results

		Laboratory	
		HbA1c≥7 (%)	HbA1c < 7(%)
	HbA1c≥7	78	0
	HbA1c < 7	3	19

DCA Vantage	Total	81	19

3.6 Results of the t-test

To test the null hypothesis of non-equivalence (a difference of ±1% in HbA1c) between the methods, the paired equivalence t-test was applied to ascertain whether the HbA1c value from the POCT equaled the value produced in the laboratory test. The result of the t-test for the POCT device A1C Now+ gave a test statistic of 1.7473 with 175.29 degrees of freedom and a p-value of 0.08234. Because the p-value was greater than 0.05, the null hypothesis of no difference in the mean HbA1c results between the laboratory results and the POCT device AIC Now+ was not rejected. We concluded that the mean HbA1c results from the laboratory and the results obtained from the POCT device were not statistically different at a 95% confidence level.

The result of the t-test for the POCT device DCA Vantage gave a test statistic of 1.662 with 177.36 degrees of freedom and a p-value of 0.09825. From these results, the null hypothesis of no difference was not rejected in the mean HbA1c results obtained from the laboratory and the POCT device DCA Vantage. Statistically, the mean HbA1c obtained from the two methods was not significantly different using the 95% confidence level.

3.7 The Bland-Altman plot

Bland and Altman proposed a method of comparing the agreement between two methods of measurement in which graphical techniques and uncomplicated calculations were considered. The Bland-Altman plot (Figure 3.4 and 3.5) shows the difference in HbA1c measurements (laboratory results less the POCT device results) on the vertical axis in relation to the average of the two measurements, which is regarded as a more acceptable approximation of the actual HbA1c than would be the case with measurement done separately by the different devices. Hence, the Bland-Altman plot makes it possible to view the relation between the difference in measurements and the size of HbA1c. It is not a statistical test, but aims to show typical differences between the measures as well as any patterns such differences might reveal. The Bland-Altman plot shows four horizontal lines (Figure 3.4 and 3.5). The thin black line that crosses the vertical axis at zero represents no difference between laboratory measurements of HbA1c and measurements obtained by the POCT device.

In Table 3.6 the average difference between the laboratory results and those obtained by means of the POCT device A1C is -0.577. This mean difference implies that the A1C device on average measures the HbA1c values 0.577 higher than the results obtained from the laboratory. Similarly, the average difference between laboratory results and the DCA Vantage device is -0.541. This implies that the DCA Vantage on average measures the HbA1c 0.541 higher than the results obtained from the laboratory. The bias (-0.577) between the laboratory results and the POCT device AIC results is indicated by the space between the X axis corresponding to the zero differences and the parallel line to the X axis at -0.577 as shown in Figure 3.5.

Similarly, the bias (0.541) between the results from the laboratory and the DCA Vantage device is indicated by the space between the X axis corresponding to the zero differences and the parallel line to the X axis at -0.541 (see Figure 3.4). The confidence intervals, as shown in Table 3.7, indicate that results measured in the laboratory may be 3.7% below or 2.5% higher than results obtained from the AIC device, while the results from the laboratory may be 3.3% below or 2.2% higher than the results obtained from the DCA Vantage device. Table 3.6: The Bland-Altman plot statistics

	Difference mean	**Standard deviation**	**Lower limit**	**Upper limit**
Lab and A1C Now+	-0.577	1.549379	-3.675759	2.521759
Laboratory and DCA vantage	-0.541	1.360117	-3.261234	2.179234

In this study, most of the points were below the line of no difference. This shows that for the majority of patients, measurements of HbA1c in the POCT device DCA Vantage exceeded the laboratory results. The measurements in DCA Vantage were greater than the laboratory results by an average of 0.541%. The broad blue line (B) on the Bland-Altman plot immediately below the line of no difference indicates this.

The standard deviation of the differences (laboratory results less the DCA Vantage) in HbA1c was 1.360117. For about 95% of the patients, the difference in HbA1c was within two standard deviations of the mean difference. This interval is (-0.541−1.96 (1.360117)) to (0.541+1.96(1.360117)), which equals -3.261234 to 2.179234. The broad blue lines (A, B, and C) on the plot depict this interval. The limits of this interval are known as the limits of

agreement. On the plot the limits are depicted by the blue lines (A and C) which are the interval of two standard deviations of the measurement differences on both sides of the mean difference.

The average readings between the laboratory results and the POCT device DCA Vantage increased from 5.3 to 13.1 and the difference between the two readings increased from -4.4 to 4.5. From Figure 3.4, it is evident that the laboratory results are lower than the results obtained from the DCA Vantage device for an average greater than 8. The laboratory values are lower than the POCT device DCA Vantage results from 8 to 13.1 on the average scale. There was a significant but minor difference between the two devices for average values greater than 8. There seems to be good agreement between the two readings for average values below 8, with only two readings which are too far removed from the zero difference horizontal line. The laboratory result for those two points are far greater than the results obtained from the DCA Vantage device.

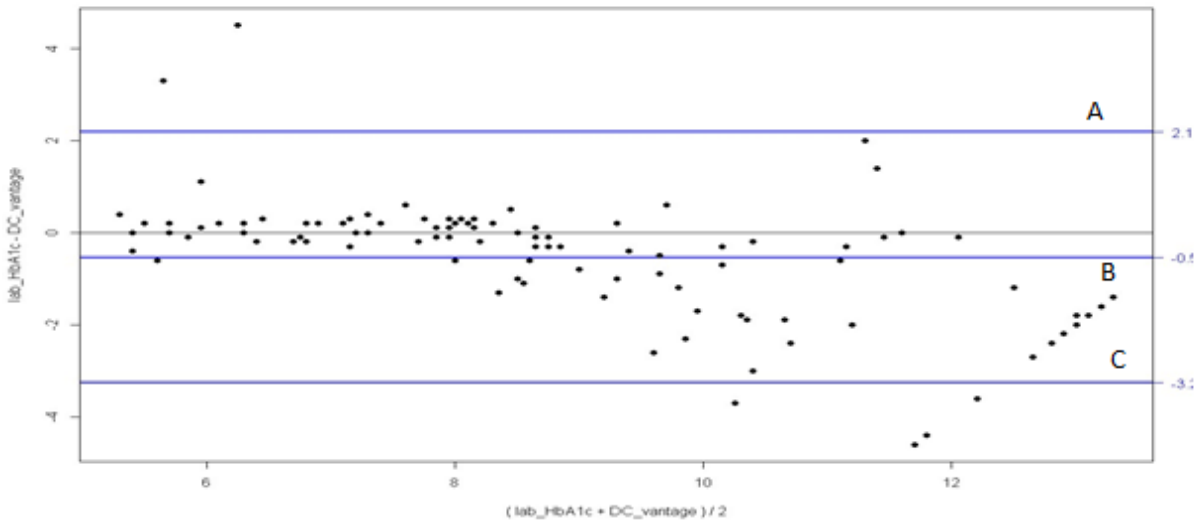

Figure 3.4: The Bland-Altman plot with limits of agreement (laboratory and POCT device DCA Vantage)

In this study, most of the points were below the line of no difference, which shows that for most of the patients measurements of HbA1c in POCT device A1C Now+ exceeded the results obtained from the laboratory. The measurements in A1C Now+ exceeded the laboratory results by an average of 0.577%. The broad blue line (D) on the Bland-Altman plot immediately below the line of no difference shows this difference. The standard deviation of the differences (laboratory results less AIC Now) in HbA1c was 1.549379. For about 95% of the patients, their difference in HbA1c falls within two standard deviations of the mean difference. This interval is (-0.577−1.96 (1.549379)) to (-0.577+1.96(1.549379)) which equals -3.675759 to 2.521759.

The broad blue lines (D and E) on the plot depict this interval. The limits of this interval are known as the limits of agreement. On the plot the limits are represented by the blue lines (D and E). This is the interval of two standard deviations of the measurement differences on either side of the mean difference.

From the Bland-Altman plot in Figure 3.5, it is apparent that the average reading between the laboratory results and the A1C Now+ results starts from 5.3 to 14.9, while the difference between the results starts from -9 to 2. There appears to be an acceptable agreement between the two readings for average values below 8. However, below the 8 average mark, most of the laboratory results are greater than the readings recorded by the POCT A1C, since the majority of the points lie above the zero horizontal line. For the average values between 8 and 14.9, there seems to be a significant difference between the two readings since most of the points are positioned away from the zero horizontal line. The laboratory values are lower than the POCT device A1C results from 8 to 14.9 on the average scale. There seems to be a significant difference between the two devices for average values above 8%.

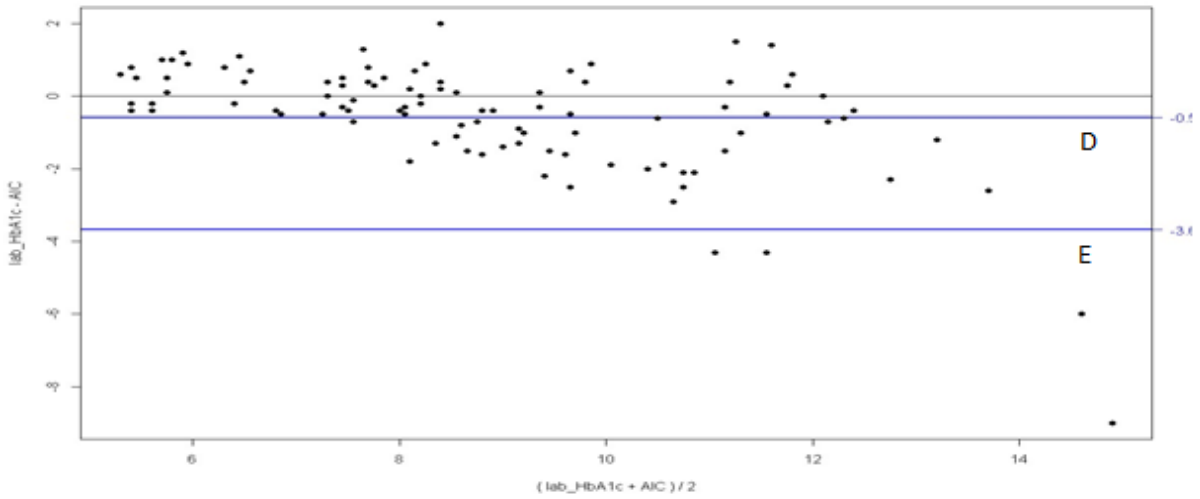

Figure 3.5: The Bland-Altman plot with limits of agreement (laboratory and POCT device A1C Now+)

3.8 Cost analysis

Table 3.7 shows the cost of a single HbA1c test with POCT devices, A1C Now+ and DCA Vantage, versus standard laboratory measurements, based on most recent market rates. The cost of electricity to run each modality was excluded from the analysis. It should be noted that

although the cost of the DCA Vantage analyser is presented, it was not included in the final cost analysis.

The cost of performing the test in the laboratory was found to be lower than tests by both the POCT devices: by an average of R3.35 per test in comparison with the DCA Vantage (excluding the cost of the analyser), and by R24.31 as compared with the A1c Now+.

Table 3.7: Comparison of cost between PTS Diagnostic A1C Now+, DCA Vantage HbA1c and Laboratory HbA1c (Dimension EXL with LM-HbA1c)

Item	**PTS Diagnos A1C Now+**	**DCA Vantage HbA1c**	**Laboratory HbA1c (Dimension EXL with LM-HbA1c)**
POC test analyser	Included in the cartridge price	R28000.00, but it can be free of charge if high volume of cartridges used.	R73.87 per test, including all items
Cartridge	R95.19	R74.23	
Lancet	R2.28	R2.28	
Cotton swab	R0.60	R0.60	
Webcols	R0.11	R0.11	
Syringe	NA	NA	
Needles	NA	NA	
Blood test tube	NA	NA	
Total	R98.18 per test	R77.22 (analyser excluded)	

CHAPTER 4

DISCUSSION, STRENGTHS AND LIMITATIONS OF THE STUDY, AND SOME RECOMMENDATIONS

4.1 Discussion

The use of POCT devices for recording HbA1c is on the increase, and therefore validations and evaluations of these devices should be undertaken. Results from measuring HbA1c using POCT devices are available almost immediately, which therefore enhances monitoring glycaemic control among diabetic patients. This enables such patients to seek early medical attention for optimal management of the condition. The devices are portable and some are powered by batteries which makes them easy to use in rural areas and in outreach programs where the availability of electricity is not guaranteed.

Statistical techniques, namely correlation coefficient and simple linear regression, sensitivity and specificity analysis, independence t-test and the Bland-Altman plot methods were used to assess the performance of the two POCT-HbA1c devices used in this study. Although the mean measurements obtained from the two devices were slightly higher than those obtained from laboratory analyses, there was no difference that could be regarded as statistically significant. The linear regression graph indicated a very close correlation between the POCT device results and the laboratory analysis, with correlation coefficients of 0.835 and 0.878 for A1c Now+ and DCA Vantage respectively.

This indicates that the measurements from the devices correlated with the laboratory results generally, although on average the POCT devices had higher results compared with the laboratory results. The Bland-Altman graphs indicated good agreement between the laboratory results and the POCT devices, although some of the measurements lay outside of the confidence interval. Most of the HbA1c laboratory measurements that exceeded 7% were correctly measured by the AIC Now and DCA Vantage devices. This also applied to those below 7%. The study validated the use of the two POCT devices AIC Now and DC Vantage for the measurement of HbA1c in a tertiary-level health-care facility in South Africa.

A major concern is the finding that the majority of diabetic patients (81%) who participated in the study were unaware of HbA1c. They were also unaware of the importance of HbA1c as a measure of glycaemic control. This could be due to the limited number of clinicians and

diabetic educators at the clinic who must attend to a large number of patients. In addition, the standard of education of most patients was low, with 11% of the patients having no formal education, while 22% had not completed Grade 12.

The mean HbA1c in this study was 8.59% ±1.87, highlighting the challenge of sub-optimal glycaemic control in diabetic patients. A concerted effort will therefore have to be made to educate patients about HbA1c and the importance of glycaemic control.

Although the study validated the use of POCT devices for HbA1c, poorly functioning POCT devices and incorrect techniques may affect the analysis of HbA1c when these devices are used. Limitations at the NHLS laboratory in terms of rejection of blood samples due to gatekeeping (HbA1c done in the last three months), and clotted and/or insufficient samples are also ongoing challenges. From the results of the cost analysis, it was established that laboratory testing was more cost effective compared with testing by both POCT devices. The implementation of POCT in primary-health facilities is limited by the lack of reimbursement for POCT services by the national government. Hence, at present, cost is a major factor limiting their widespread use in the public-health sector. However, this factor should be assessed in relation to the indirect financial advantages of the POCT devices, viz. provision of timeous results for patients and enabling practitioners to make early decisions to manage the condition. In addition, it means fewer visits to a health centre, and hence a reduction in costs to patients in the long term. The cost of travelling to and from the hospital can affect the total cost of measuring HbA1c using the laboratory device.

In summary, the AIC Now and DCA Vantage devices provided accurate and reliable HbA1c measurements. It can therefore, be concluded that in comparison with standard laboratory measurements, the performance of the POCT devices is acceptable and that these devices represent a speedy point of care method for measuring HbA1c for clinicians and other practitioners, which in turn, may contribute to improved patient care.

4.2 Strengths and limitations of the study

The study involved patients who represent various South African ethnic groups with type I and II diabetes mellitus.

Point of care measurements were performed by two trained medical personnel, which limited the potential for sampling errors. However, the sample size was relatively small, which reduces the significance of the study and may have negatively influenced margins of error.

4.3. Recommendations

NGSP-certified POCT devices offer a reliable means of monitoring glycaemic control in diabetic patients. In view of the high burden of this condition and the benefits of POCT, greater accessibility in the public-health sector is recommended.

Educational lectures and workshops should be organised where patients can be informed about HbA1c and the importance of glycaemic control. A focus on diabetic education will enable patients to assume greater control of their condition, and assist them to effectively manage their health on a daily basis. Sound health education may significantly affect health outcomes and improve patients' quality of life.

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APPENDICES

Appendix I: Approval of the research proposal

UNIVERSITY OF THE WITWATERSRAND JOHANNESBURG

Private Bag 3 Wits, 2050
Fax: 027117172119
Tel: 02711 7172076

Reference: Mrs Sandra Benn
E-mail: sandra.benn@wits.ac.za

06 January 2017
Person No: 1013692
PAG

Dr RMN Dabah
Unit 10 Clachan Complex
Kemp Avenue
2195
South Africa

Dear Dr Dabah

Master of Medicine: Approval of Title

We have pleasure in advising that your proposal entitled *Comparison between point of care haemoglobin A1C and standard laboratory haemoglobin A1C at a tertiary level diabetic clinic* has been approved. Please note that any amendments to this title have to be endorsed by the Faculty's higher degrees committee and formally approved.

Yours sincerely

Mrs Sandra Benn
Faculty Registrar
Faculty of Health Sciences

Appendix II: Ethical clearance letter

Human Research Ethics Committee (Medical)

Research Office Secretariat: Senate House Room SH 10005, 10th floor.
Medical School Secretariat: PV Tobias Building 2nd Floor.
Private Bag 3, Wits 2050, www.wits.ac.za
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20 June 2016

To Whom It May Concern

SUBJECT: **CONFIRMATION OF STUDY APPROVAL**

Protocol Ref No: M160509

Protocol Title: Comparison between Point of Care HbA1c and Standard HbA1c at a Tertiary Level Diabetic Clinic

Principal Investigator: Dr Ramadan Dabah

Department: Internal Medicine

This letter serves to confirm that the Human Research Ethics Committee (Medical) has received an ethics application for the abovementioned study. In order for a clearance certificate to be issued, the researcher is required to submit written approval to conduct the study in your district/institution.

The researcher has been informed that this study cannot commence without your approval and receipt of the Clearance certificate from the HREC (Medical).

Should you have any queries, you may contact me at tel: 011 717 1234/2700/2656 or by email Rhulani.Mkansi@wits.ac.za

Yours Faithfully,

.....

Mr Rhulani Mkansi
Administrative Officer
Human Research Ethics Committee (Medical)

UNIVERSITY OF THE WITWATERSRAND
OFFICE OF THE DEPUTY VICE CHANCELLOR RESEARCH
20 JUN 2016
RESEARCH OFFICE HREC (Medical)
JOHANNESBURG

Appendix III: Ethical clearance certificate

R14/49 Dr Ramadan Dabah

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M160509

NAME: (Principal Investigator)	Dr Ramadan Dabah
DEPARTMENT:	Internal Medicine Helen Joseph Hospital
PROJECT TITLE:	Comparison between Point of Care HbA1c and Standard HbA1c at a Tertiary Level Diabetic Clinic
DATE CONSIDERED:	27/05/2016
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Tasneem Mohamedy
APPROVED BY:	Professor P. Cleaton-Jones, Chairperson, HREC (Medical)
DATE OF APPROVAL:	07/07/2016

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office Secretary in Room 10004,10th floor, Senate House/2nd floor, Phillip Tobias Building, Parktown, University of the Witwatersrand. I/We fully understand the the conditions under which I am/we are authorised to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated,from the research protocol as approved, I/we undertake to resubmit to the Committee. **I agree to submit a yearly progress report**. The date for annual re-certification will be one year after the date of convened meeting where the study was initially reviewed. in this case, the study was initially review in May and will therefore be due in the month of May each year.

Principal Investigator Signature Date

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

Appendix IV: Consent form

Diabetic Clinic

Helen Joseph Hospital

Perth road

Auckland Park

Dear patient

My name is Dr Ramadan Dabah and I am attached to the Department of Internal Medicine at the University of the Witwatersrand. We are conducting a study to compare different ways of assessing your sugar control at the Diabetic Clinic. We would like you to take part in the study and we hope that the study will allow us to better manage our diabetic patients. If you agree to take part in the study, please sign below and take a few minutes to answer the questions on the next page.

Thank You

Dr Ramadan Dabah

I, _____, agree to take part in the study.

_____ _____

Signature **Date**

Appendix V: Questionnaire

Please read through the following questions and circle the most appropriate answer. If you do not understand any question, please feel free to ask any staff member for assistance.

Question 1:

How long have you had Diabetes (Sugar)?
A: Less than 5 years
B: Between 5 – 10 years
C: More than 10 years

Question 2:
Do you have Type 1 or type 2 Diabetes?
A: Type 1 Diabetes
B: Type 2 Diabetes

Question 3:
How often do you attend the diabetic clinic?
A: Every month
B: Every 3 months
C: Every 4 months
D: Every 6 months

Question 4:
What is your highest education level?
A: Did not attend school
B: Attended Primary or High school
C: Completed Matric
D: Attended University or technical college

Question 5:
For good sugar control, what should your fasting sugar be?
A: <5 mmol/l
B: <7 mmol/l
C: < 9 mmol/l
D: <12 mmol/l
E: <15 mmol/l

Question 6:
Do you know what HbA1c is?
A: Yes
B: No

Question 7:

If yes, what does it measure?

A: It measures daily sugar control

B: It measures sugar control over the last 3 months

C: It measures sugar control over the last year

Question 8:

What should your HbA1c level be?

A: <6 %

B: <6.5 %

C <10 %

D: <15 %

E: >15 %

Appendix VI: Data Collection form

Comparison between Point of Care Haemoglobin A1C and Standard Laboratory Haemoglobin A1C at a Tertiary level Diabetic Clinic

Data collection form

Biographic information										
Date of data collection	y	y	y	y	m	m	d	d		
Date of birth (Participant number)	y	y	y	y	m	m	d	d		
Gender (male=1, female=2, missing=9)										
Weight (kg) (missing=999)										
Type of Diabetes (type 1=1, type 2=2, missing=99)										
Patient Questionnaire										
How long have you had Diabetes (High Sugar)? (< 5 years=1, 5 – 10 years= 2, >10 years=3, Do not know= 4, missing=99)										
Do you have Type 1 or type 2 Diabetes? (type 1=1, type 2=2, Do not know=3, missing=99)										
How often do you attend the diabetic clinic? (Monthly=1, 3 months= 3, 4 months=4, 6 months= 6, missing=99)										

What is your highest education level? (Did not attend school=1, Attended school=2, Completed matric= 3, Attended University or technical college=4, missing=99)			
For good sugar control, what should your fasting sugar be? (< 5=1, < 7=2, < 9=3, < 12=4, < 15=5, Do not know=6, missing=99)			
Do you know what HbA1c (glycated haemoglobin) is? (Yes = 1, No = 2, missing=99)			
If yes, what does it measure? (Daily control = 1, 3 monthly control = 3, 6 monthly control = 6, Yearly control = 12, Do not know = 0, missing=99)			
What should your HbA1c level be? (< 6.5 %=1, < 7 %=2, < 10 %=3, < 15 %=4, >15 %=5, Do not know=6, missing=99)			
Lab HbA1c			
Point of Care: A1C Now+			
Point of Care: DC Vantage			
Random HGT			