FreeStyle *Lite*

Meter and test strips designed for glucose self-measurement manufactured by Abbott Diabetes Care Inc.

Report from an evaluation organised by

SKUP

The evaluation was ordered by Abbott Norge AS

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The organisation of SKUP

Scandinavian evaluation of laboratory equipment for primary health care, *SKUP*, is a co-operative commitment of NOKLUS [1] in Norway, "Afdeling BFG"[2] in Odense, Denmark and EQUALIS [3] in Sweden. SKUP was established in 1997 at the initiative of laboratory medicine professionals in the three countries. SKUP is led by a Scandinavian *steering committee* and the secretariat is located at NOKLUS in Bergen, Norway.

The aim of SKUP is to produce reliable, objective and independent information about analytical quality and user-friendliness of laboratory equipment for primary healthcare. This information is generated by organising *SKUP evaluations*.

SKUP offers manufacturers and suppliers evaluations of equipment for primary healthcare and also of devices for self-monitoring. Provided the equipment is not launched onto the Scandinavian market, it is possible to have a confidential pre-marketing evaluation. The company requesting the evaluation pays the actual testing costs and receives in return an impartial evaluation.

There are *general guidelines* for all SKUP evaluations and for each evaluation a specific *SKUP protocol* is worked out in co-operation with the manufacturer or their representatives. SKUP signs *contracts* with the requesting company and the evaluating laboratories. A *complete evaluation* requires one part performed by experienced laboratory personnel as well as and one part performed by the intended users.

Each evaluation is presented in a *SKUP report* to which a unique *report code* is assigned. The code is composed of the acronym SKUP, the year and a serial number. A report code, followed by an asterisk (*), indicates a special evaluation, not complete according to the guidelines, e.g. the part performed by the intended users was not included in the protocol. If suppliers use the SKUP name in marketing, they have to refer to www.skup.nu and to the report code in question. For this purpose the company can use a logotype available from SKUP containing the report code.

SKUP reports are published at www.skup.nu. A detailed list of previous SKUP evaluations is included in this report.

[1] NOKLUS (Norwegian Quality Improvement of Primary Care Laboratories) is an organisation founded by Kvalitetsforbedringsfond III (Quality Improvement Fund III), which is established by The Norwegian Medical Association and the Norwegian Government. NOKLUS is professionally linked to "Seksjon for Allmennmedisin" (Section for General Practice) at the University of Bergen, Norway.

[2] "Afdeling for Biokemi, Farmakologi og Genetik" (Afdeling BFG) is the Department for Clinical Chemistry at the University Hospital in Odense, Denmark. Afdeling BFG in Odense and the national "Fagligt Udvalg vedrørende Almen Praksis" (Professional Committee for General Practice) have through an agreement created "the SKUP-division in Denmark". "Fagligt Udvalg vedrørende Almen Praksis"is a joint committee for "PLO", "Praktiserende Lægers Organisation" (General Practioners Organisation) and "Sygesikringens Forhandlingsudvalg" (Committee for Negotiations within the General Health Insurance System).

[3] EQUALIS AB (External quality assurance in laboratory medicine in Sweden) is a limited company in Uppsala, Sweden, owned by "Sveriges Kommuner och Landsting" (Swedish Association of Local Authorities and Regions), "Svenska Läkaresällskapet" (Swedish Society of Medicine) and IBL (Swedish Institute of Biomedical Laboratory Science).

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1. Summary

Background
FreeStyle Lite blood glucose meter and FreeStyle Lite test strips are designed for glucose self-measurements performed by diabetes patients. The meter and the test strips are produced by Abbott Diabetes Care Inc. and are supplied in Scandinavia by Abbott. FreeStyle Lite blood glucose meter and FreeStyle Lite test strips was launched onto the Norwegian market the 1st of October 2007. In order to give reimbursement for the test strips in Norway, the Norwegian Labour and Welfare Organisation (NAV) requires from the companies to carry out an evaluation that includes a user-evaluation among diabetes patients. The evaluation of FreeStyle Lite was done under the direction of SKUP from May to June 2007.

The aim of the evaluation
The aim of the evaluation of FreeStyle Lite is to

- reflect the analytical quality under standardised and optimal conditions, performed by biomedical laboratory scientists in a hospital environment
- reflect the analytical quality by the intended users
- compare the analytical quality among trained and un-trained diabetes patients
- compare the analytical quality among diabetes patients before and after three weeks of practice
- check the variation between three lots of test strips
- examine if hematocrit interferes with the measurements
- evaluate FreeStyle Lite regarding user-friendliness
- evaluate the FreeStyle Lite user guide

Materials and methods
82 diabetes patients took part in the evaluation. Half of the diabetes patients had two consultations (the "training group") and the rest of them had one consultation (the "mail group"). The diabetes patients in the "training group" were given a standardised instruction about FreeStyle Lite before they did a finger prick and performed two measurements on the meter. The biomedical laboratory scientist also collected capillary samples from the diabetes patients and measured twice on FreeStyle Lite. In addition, two capillary samples were taken for measurements with a designated comparison method. The diabetes patients in the "mail group" received FreeStyle Lite by mail and no training was given. Both groups of diabetes patients used the equipment for approximately three weeks at home, before they were called for a final consultation. The blood glucose sampling and measurement procedures at the first consultation were repeated, and in addition a sample for hematocrit was taken. Three different lots of test strips were used in the evaluation. All the participants answered questionnaires about the user-friendliness and the user guide of FreeStyle Lite.

Results

- The precision of FreeStyle Lite was good. The repeatability CV was between 2 and 3 % under standardised and optimal measuring conditions and approximately 4 % when the measurements were performed by the diabetes patients.
- The trueness of FreeStyle Lite was acceptable. For glucose values < 7 mmol/L no significant bias between FreeStyle Lite and the comparison method was pointed out. For

glucose values > 7 mmol/L there was a small, but statistically significant bias between FreeStyle Lite and the comparison method. FreeStyle Lite gave glucose values approximately 0,3 mmol/L lower than the comparison method for glucose values 7 – 10 mmol/L and approximately 0,8 mmol/L lower than the comparison method for glucose values > 10 mmol/L.

- The agreement with a designated comparison method was good. The quality goal set in ISO 15197 was achieved under standardised and optimal measuring conditions. When handled by the diabetes patients, FreeStyle Lite also showed accurate results. These results were within the "adjusted ISO-goal" and also within the quality goal set in ISO 15197.
- Two of the three lots of test strips used in this evaluation gave significantly lower values than the comparison method. The third lot of test strips gave significantly higher values than the comparison method. The deviations are small, but statistically significant.
- Glucose measurements on FreeStyle Lite did not seem to be affected by hematocrit in this study. Hematocrit outside the range 31 – 48 % has not been tested.
- The diabetes patients summarised the FreeStyle Lite device as easy to use. Most of them were pleased with the device. Most of the diabetes patients that had used the user guide were satisfied with the guide.

Conclusion

The analytical quality of FreeStyle Lite was good. The precision of FreeStyle Lite was good. The results were accurate and within the quality goal for the total error set in the ISO-guide 15197. The glucose results did not seem to be affected by hematocrit in this study. The users found the FreeStyle Lite device easy to use and they were quite satisfied with the device.

Comments from Abbott

There is no additional information from producer attached to the report.

2. Analytical quality specifications

There are different criteria for setting quality specifications for analytical methods. Ideally the quality goals should be set according to the medical demands the method has to meet. For glucose it is natural that the quality specification is set according to whether the analysis is used for diagnostic purpose or for monitoring diabetes. FreeStyle Lite is designed for monitoring blood glucose, and the quality goals must be set according to this.

Precision
For glucose meters designed for monitoring blood glucose one should point out the need of a method with good precision [1]. According to the American Diabetes Association (ADA) the imprecision (CV) of new glucose devices must be less than 5 % [2]. Other authors also recommend an imprecision of 5 % or less [3].

Accuracy
According to ADA the total error for meters designed for self monitoring and point of care testing of glucose should not exceed 10 % in the range 1,67 – 22,2 mmol/L. The quality goal from ADA must be seen as an optimal goal for the analytical quality of these meters.

The quality goal for the total error of FreeStyle Lite is derived from ISO 15197, *In vitro diagnostic test systems – Requirements for blood glucose monitoring systems for self-testing in managing diabetes mellitus* [4]. The ISO-guide is an international protocol for evaluating meters designed for glucose monitoring.

ISO 15197 gives the following minimum acceptable accuracy requirement:
Ninety-five percent (95 %) of the individual glucose results shall fall within ± 0,83 mmol/L of the results of the comparison method at glucose concentrations < 4,2 mmol/L and within ± 20 % at glucose concentrations ≥ 4,2 mmol/L.

This is a quality goal for measurements made by trained laboratory staff. Ideally, the same quality requirements should apply to measurements performed by the diabetes patients. Previous investigations under the direction of the NOKLUS-project "Diabetes-Self-measurements" in 1997 [3,5] showed that few of the self-monitoring glucose meters tested at the time met the ISO-requirements. Subsequent SKUP-evaluations confirmed these findings. As a consequence, the results achieved by the diabetes patients have been discussed towards a *modified* goal suggested by NOKLUS, with a total error of ± 25 %. This modified goal has wide, and not ideal, limits. The intention was to tighten up the modified requirements for the diabetes patients over time, as the meters would hopefully improve due to technological development. More recent evaluations performed by SKUP [6] clearly show that the quality goals set by ISO 15197 now can be achieved also by the diabetes patients. But for the time being, the quality demands adjusted to the diabetes patients' self-measurements, still apply.

Quality demands, adjusted to the diabetes patients self-measurements:
Ninety-five percent (95 %) of the individual glucose results shall fall within ± 1,0 mmol/L of the results of the comparison method at glucose concentrations < 4,2 mmol/L and within ± 25 % at glucose concentrations ≥ 4,2 mmol/L.

3. Materials and methods

3.1. FreeStyle Lite

FreeStyle Lite is a blood glucose monitoring system based on coulometric electrochemical biosensor technology. The system consists of a meter, FreeStyle Lite, and dry reagent test strips, FreeStyle Lite. The system is designed for capillary blood glucose testing performed by persons with diabetes or by health care professionals. FreeStyle Lite reports plasma glucose values. The system does not require calibration by the user. The test principle of FreeStyle Lite is as follows: Glucose dehydrogenase converts glucose to gluconolactone. The coenzyme in the reaction is pyrroloquinolone quinone (PQQ).

$$\text{Glucose} + \text{Mediator}_{\text{Oxidized}} \xrightarrow{\text{PQQ Glukose Dehydrogenase}} \text{Gluconolactone} + \text{Mediator}_{\text{Reduced}}$$

The test strips are packed in a plastic bottle with flip-top closure and desiccant. The system requires a blood volume of 0,3 µL. The blood is automatically drawn into the test strip. If the amount of blood is insufficient, more blood can be applied within 60 seconds. The result is shown in approximately 5 seconds, dependent on the glucose concentration. According to the user guide alternative site testing is possible with FreeStyle Lite. The meter has the capacity of storing 400 results in the memory. Technical data from the manufacturer is shown in table 1.

Table 1. Technical data from the manufacturer

Technical data for FreeStyle Lite	
Optimal operating temperature	4 – 40 °C
Sample volume	0,3 µL
Measuring time	Approximately 5 seconds
Measuring range	1,1 – 27,8 mmol/L
Hematocrit	Not affected by hematocrit values from 15 to 65 %
Memory	400 test results
Power source	One 3-volt lithium battery (CR2032)
Operating time	Approximately 500 tests
Humidity	5 – 90 %
Dimensions	40 mm x 74 mm x 17 mm
Weight	39,7 g (including the battery)

3.1.1. Product information, FreeStyle Lite

FreeStyle Lite blood glucose meter system

Manufactured by:
Abbott Diabetes Care Inc.
Alameda
CA 94502 USA

Suppliers of FreeStyle Lite in the Scandinavian countries:

Denmark:	Norway:	Sweden:
Abbott Laboratories A/S	Abbott Norge AS	Abbott Scandinavia AB
Abbott Diabetes Care	Abbott Diabetes Care	Abbott Diabetes Care
Smakkedalen 6	Pb 1, 1330 Fornebu	BOX 509
2820 Gentofte		169 29 Solna
Phone: +45 80 81 53 54	Phone: +47 800 87 100	Phone: +46 020-190 11 11
www.medisense.dk		www.abbott-diabetes.se

84 FreeStyle Lite blood glucose meters were used in this evaluation. Serial no. DBMK091-C0171 (called meter A) and serial no. DBMK091-C0025 (called meter B) were used by the biomedical laboratory scientists. Attachment 1 gives serial numbers for the 82 meters used by the diabetes patients.

FreeStyle Lite test strips:

Lot 0707142	Expiry 2009-03
Lot 0707202	Expiry 2009-03
Lot 0707140	Expiry 2009-03

FreeStyle Control:

Control Low	Lot 6F1N03	Expiry 2008-04
Control High	Lot 6F3N03	Expiry 2008-04

3.2. The designated comparison method

Definition
A designated comparison method is a fully specified method, which, in the absence of a Reference method, serves as the common basis for the comparison of a field method.

Verifying of trueness
The comparison method should be a plasma method, hexokinase by preference. The method has to show traceability equivalent to that of an internationally accepted reference solution, such as the standards supplied by the National Institute of Standards & Technology, NIST. The NIST-standard SRM 965a consists of ampoules with human serum with certified concentrations of glucose (and their given uncertainties) at four levels. The uncertainty is defined as an interval estimated to have a level of confidence of at least 95 %. The SRM 965a materials cover a glucose concentration range from 1,9 to 16,2 mmol/L [7] and was used in this evaluation. In addition, freshly frozen, human serum controls from NOKLUS with glucose concentrations at two levels were analysed. The NOKLUS-controls have target values determined with an isotope-dilution gas chromatography/mass spectrometry method on a Reference laboratory in Belgium; Laboratory for Analytical Chemistry, University of Gent, Belgium [8]. The results are summarized in chapter 5.1.2.

The designated comparison method in this evaluation
In this evaluation, the routine method for quantitative determination of glucose in human serum and plasma (e.g. lithium heparin) on the Laboratory at Haraldsplass Diaconal Hospital (HDH) was used as the designated comparison method. The method will be called *the comparison method* in this report. The comparison method is a photometric enzymatic method, utilising hexokinase and glucose-6-phosphate dehydrogenase enzymes. The method is used on Architect *ci*8200 System from Abbott Laboratories, with reagents and calibrators from Abbott Laboratories. The measuring principle is as follows: Glucose is phosphorylated by hexokinase in the presence of ATP and magnesium ions. The glucose-6-phosphate that is formed is oxidised in the presence of glucose-6-phosphate dehydrogenase causing the reduction of NAD to NADH. The NADH produced absorbs light at 340 nm and can be detected spectrophotometrically as an increased absorbance.

Internal quality assurance of the comparison method during the evaluation period
The Autonorm Human Liquid Control Solutions at two levels from Sero AS were included in all the measuring series in this evaluation. The controls were measured as the first and the last samples in all the series. The results are summarised in table 5.

3.2.1. Product information, the comparison method

Designated comparison method on Architect ci8200
Manufactured by Abbott Laboratories Serial no. C800890

Reagents
Glucose Reagent Kit, Ref. 3L82-20 and 3L82-40
Lot 45004HW00 Expiry 2007-07-31

Calibrator
Multiconstituent Calibrator, List No. 1E65

Lot 42395M100	Expiry 2007-05-31	Reference value, cal 1 = 5,44 mmol/L
		Reference value, cal 2 = 24,64 mmol/L
Lot 47140M100	Expiry 2007-09-30	Reference value, cal 1 = 5,38 mmol/L
		Reference value, cal 2 = 23,53 mmol/L

Internal quality controls
Seronorm Autonorm Human Liquid 1 and 2, Sero AS

Liquid 1: Value = 3,4 ± 0,24 mmol/L	Lot 609470	Expiry 2008-01-30
Liquid 2: Value = 16,1 ± 1,12 mmol/L	Lot 509415	Expiry 2007-10-31

NOKLUS controls
Reference value from Laboratory for Analytical Chemistry, University of Gent, Belgium; ID-GCMS method
Level 1: Value = 7,43 ± 0,06 mmol/L
Level 2: Value = 10,40 ± 0,08 mmol/L

NIST standards
Standard Reference Material® 965a, National Institute of Standards & Technology
Level 1: Value = 1,918 ± 0,020 mmol/L
Level 2: Value = 4,357 ± 0,048 mmol/L
Level 3: Value = 6,777 ± 0,073 mmol/L
Level 4: Value = 16,24 ± 0,19 mmol/L

Blood sampling device
Medlance lancets Expiry 2012-01

Tubes used for sampling for the designated comparison method
Microvette CB 300 LH (lithium-heparin) manufactured by Sarstedt AS
Lot 7070301 Expiry 2009-12

Centrifuge used for samples for the designated comparison method
Eppendorf Centrifuge 5415D Serial no. 0057100

Pipette
Eppendorf automatic pipette 100 µl

3.3. Planning of the evaluation

The FreeStyle Lite-system is produced by Abbott Diabetes Care Inc. and supplied by Abbott. The system was launched onto the Norwegian market the 1st of October 2007. Jorun K. Holst from Abbott Norge AS applied to SKUP in October 2006 for an evaluation of the glucose meter FreeStyle Lite with FreeStyle Lite test strips. SKUP agreed with Abbott Norge AS to start the evaluation in January 2007. Due to late delivery of the test strips from Abbott, the evaluation was postponed. A contract was set up between Abbott Norge AS and SKUP in May 2007. In April 2007 a preliminary suggestion regarding how to organise the evaluation of FreeStyle Lite was sent to Abbott. The protocol for the evaluation was accepted in May 2007. The Laboratory at HDH accepted to carry out the analytical part of the evaluation dealing with the samples for the comparison method. SKUP carried out the user-evaluation of FreeStyle Lite from May to June 2007.

SKUP evaluations are based upon the guidelines in the book "*Evaluation of analytical instruments. A guide particularly designed for evaluations of instruments in primary health care*" [9]. The evaluation of a self-monitoring blood glucose device follows the guidelines in the book, but the evaluation in primary health care is replaced by a user-evaluation conducted among diabetes patients, based on the model by the NOKLUS-project "*Diabetes-Self-measurements*" [10]. This model is basis for the quality specifications used when NAV decides whether or not to give reimbursement for glucose test strips [11].

The evaluation comprises the following studies:

- An examination of the analytical quality under standardised and optimal conditions, performed by biomedical laboratory scientists in a hospital environment
- An examination of the analytical quality among approximately 80 diabetes patients
- An examination of the agreement between FreeStyle Lite and a designated comparison method
- A comparison of the analytical quality among diabetes patients with and without a training programme
- A comparison of the analytical quality among diabetes patients before and after three weeks of practise
- An examination of the variation between three lots of test strips
- An examination to see if hematocrit interferes with the measurements
- An evaluation of the user-friendliness of FreeStyle Lite
- An evaluation of the user guide of FreeStyle Lite

After the evaluation, the diabetes patients returned the FreeStyle Lite device to the project.

3.3.1. Evaluation sites and persons involved

The blood sampling of the diabetes patients and the measurements on FreeStyle Lite under standardised and optimal conditions, were done by Kari Fischaa Nilsson and Torun Gravning, biomedical laboratory scientists, SKUP/NOKLUS. Three biomedical laboratory scientists, Henriette Mohn Soldal, Kjersti Østrem and Grete H. Solsvik, were given the responsibility for the practical work with the comparison method on the Laboratory at HDH. The statistical calculations and the report writing are done by Marianne Risa, SKUP/NOKLUS in Bergen.

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3.4. The evaluation procedure

3.4.1. The model for the evaluation

The practical work with the evaluation was carried out during 6 weeks from May to June 2007 at Østfold Hospital Trust, Fredrikstad, Norway. The practical work was done by the biomedical laboratory scientists Kari Fischaa Nilsson and Torun Gravning.

The evaluation consisted of two parallel parts. One part of the evaluation was done under standardised and optimal conditions in a hospital laboratory. This part of the evaluation was done by laboratory educated personnel, in exact accordance with the protocol and the user guide and after having received thorough training. All possibilities for disturbance of, and interference with, the measurements were tried kept at a minimum. The evaluation under standardised and optimal conditions documents the quality of the system under as good conditions as possible. The other part of the evaluation was done by diabetes patients. In order to determine the analytical quality of FreeStyle Lite by the users, 82 diabetes patients tested their blood glucose using FreeStyle Lite. The diabetes patients were divided into two groups (random distribution). 43 diabetes patients received personal training in how to use the blood glucose meter, here called the "training group". The others received the blood glucose meter and instructions by mail, here called the "mail group". Dividing the diabetes patients into a "training group" and a "mail group" reflects the actual market situation regarding training when diabetes patients acquire blood glucose meters [10]. The model for the evaluation is shown in figure 1.

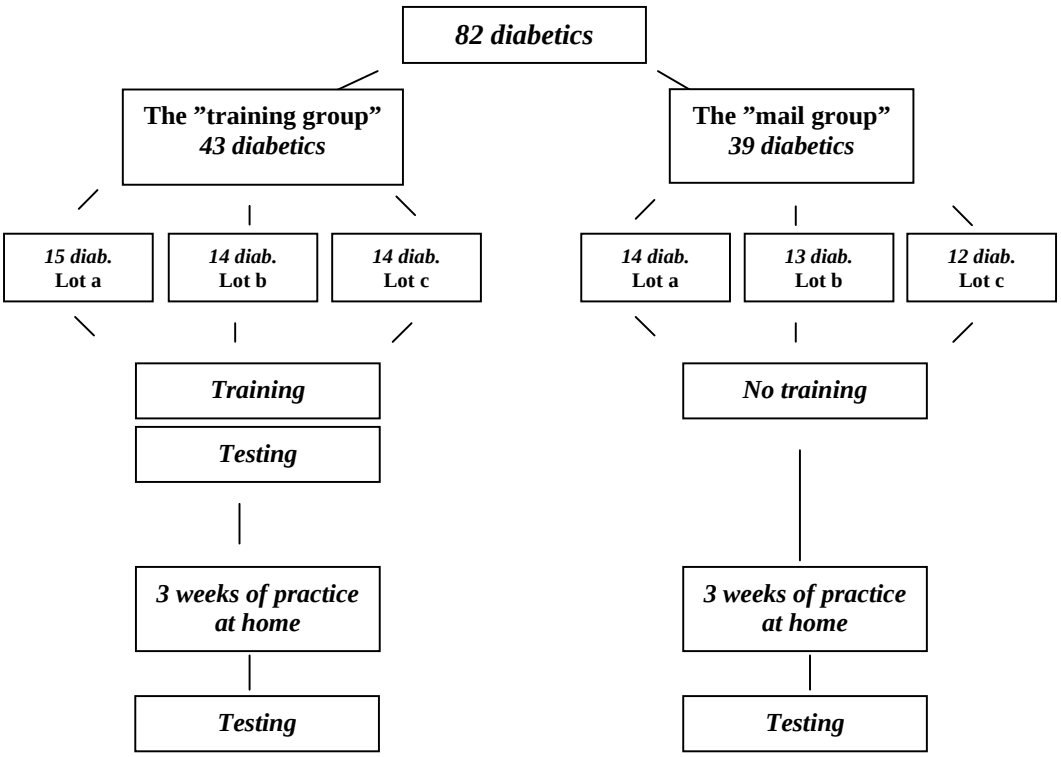

Figure 1. Model for the evaluation

3.4.2. Recruitment of the diabetes patients

The FreeStyle Lite glucose meter was tested in use by 82 diabetes patients. The diabetes patients were recruited through an advertisement in the daily press, a brochure and by mail inquiry sent to members of the local branch of the Norwegian Diabetes Association. The group of diabetes patients was representative for diabetes patients who carry out self-monitoring of blood glucose (SMBG). The group included diabetes patients from across a range of self-monitoring frequencies, i.e. diabetes patients who perform self-monitoring often (once or more a day) and those who perform self-monitoring less frequently (once a week). Characteristics of the diabetes patients are shown in table 2.

Table 2. Characteristics of the diabetes patients (n=82)

		Number of diabetes patients
Total		82
Sex	Men	44
	Women	38
Age, median in years (range)		62 (19 – 74)
Diabetes	Type 1	26
	Type 2	56
Treatment	Insulin	34
	Insulin and tablets	9
	Tablets	33
	Diet	6
Frequency of SMBG	Less than weekly	4
	1 – 3 per week	12
	4 – 6 per week	6
	7 – 10 per week	17
	> 10 per week	43

The SMBG-devices that the diabetes patients used regularly were:
Accu-Chek (model not specified) (5), Accu-Chek Aviva (5), Accu-Chek Compact/Compact Plus (27), Accu-Chek Sensor/Accutrend Sensor (5), Ascensia (model not specified) (1), Ascensia Breeze/Dex (8), Ascensia Contour (14), Ascensia Elite (1), FreeStyle Mini (5), OneTouch Ultra/Ultra 2/Easy (8), Precision Xceed/Xtra (2), unregistered (1). Some of the diabetes patients used more than one SMBG-device at home, but only one device is registered here.

3.4.3. The "training group" at the first consultation

The 43 diabetes patients that were selected to participate in a training programme were invited in pairs for training. They received the FreeStyle Lite device along with test strips, lancet pen, lancets, user guide (in Norwegian), and an instruction letter with explanations regarding what to do with the FreeStyle Lite device during the period at home. The instruction letter is attached to the report (in Norwegian), see attachment 2. The responsibility for the training programme was undertaken by SKUP. Kari Fischaa Nilsson and Torun Gravning were in charge of the training of the diabetes patients, after having been trained themselves by a representative from Abbott.

Training programme

The training programme covered a simple demonstration of how to use FreeStyle Lite, with an explanation of the display and error messages, insertion of the test strips, blood sampling and drawing of the blood into the test strip, as well as precautions for storage and the shelf-life of test strips, etc. The training programme was standardised to make sure that all the diabetes patients received the same instruction.

Blood sampling

After having been trained, the 43 diabetes patients made duplicate blood glucose tests on FreeStyle Lite. These results were registered for the evaluation. The biomedical laboratory scientists collected samples for the evaluation under standardised and optimal conditions (see chapter 3.4.7.). Afterwards the diabetes patients brought the FreeStyle Lite home to use it over a three-week period. After this period they attended a final consultation (see chapter 3.4.6).

3.4.4. The "mail group"

The 39 diabetes patients in the "mail group" received the FreeStyle Lite device by mail, along with test strips, lancet pen, lancets, user guide (in Norwegian) and an instruction letter with explanations regarding what to do with the FreeStyle Lite device during the period at home. No training was given. They used the meter over a three-week period at home. After this period they attended a final consultation (see chapter 3.4.6).

3.4.5. Use of FreeStyle Lite by the diabetes patients at home

The diabetes patients used FreeStyle Lite at home for three weeks. The length of this practice period ought not to exceed three weeks by more than a few days. Most users read the user guide at once when they receive the meter. As the diabetes patients should evaluate the user guide at the final consultation, it would be unfortunate if the practice period at home was too long. During the practice period the diabetes patients used FreeStyle Lite in addition to their own glucose meter and they continued to carry out self-measurements with their own meter as normal.

The first and the second week

The diabetes patients familiarised themselves with the new device during the first two weeks. Each diabetes patient used approximately 25 test strips to measure his/her blood glucose with FreeStyle Lite. They could choose when to do the measurements themselves. Fasting was not necessary. If more convenient to them, they could perform the measurements at the same time as they performed measurements with their own meter.

The third week
During the third week the diabetes patients performed duplicate measurements on FreeStyle Lite on five different days. The results were recorded on a provided form. They pricked a finger and made two consecutive measurements with blood from the same prick. If necessary they pricked another finger for the second measurement. They were free to choose when to perform the measurements, and it was not necessary to be fasting. They could choose whether to use the lancets provided for the evaluation, or the lancets they use ordinarily.

Internal quality control
The diabetes patients are not familiar with control solutions for glucose self-measurements. Therefore they were not instructed to use the control solutions on FreeStyle Lite in the evaluation. To document correct functioning of the FreeStyle Lite meters used by the diabetes patients during the test period, the biomedical laboratory scientists in charge of the practical work checked the meters with the control solutions when the diabetes patients met at the consultations.

3.4.6. The final consultation

Blood sampling
After the three-week practice period at home, 79 of the 82 diabetes patients met, one by one, for a final consultation. Three of the diabetes patients were not able to meet. Each diabetes patient brought their assigned FreeStyle Lite and the remaining test strips to the consultation. Before the samples were collected, the FreeStyle Lite device was equilibrated to room temperature while the diabetes patients filled in the two questionnaires. Then the diabetes patients made duplicate blood glucose tests on their assigned meter. These results were registered for the evaluation. The biomedical laboratory scientist collected samples for the evaluation under standardised and optimal conditions. Finally, a venous sample for hematocrit was taken.

Evaluation of the user-friendliness and the user guide
Before the blood samples were collected and the measurements on FreeStyle Lite were done, the diabetes patients filled in two questionnaires. The first questionnaire deals with the user-friendliness of FreeStyle Lite; the second covers the user guide. The questionnaires (in Norwegian) are attached to the report.

3.4.7. Evaluation under standardised and optimal conditions

The biomedical laboratory scientists used two FreeStyle Lite blood glucose meters for the evaluation (meter A and B). On meter A one lot of test strips was used for all the measurements. Meter B was used for the same three lots as distributed among the diabetes patients. The variation between the three lots, or more precisely, the agreement of the three lots to the comparison method, was assessed. The number of samples for each lot of test strips measured under standardised and optimal conditions is shown in table 3.

Table 3. The number of samples (n) for each lot of strips measured under standardised and optimal conditions

FreeStyle Lite		Lot 0707142 (n)	Lot 0707202 (n)	Lot 0707140 (n)
Meter A	1st consultation	43 x 2		
	2nd consultation	79 x 2		
Meter B	1st consultation	12 x 2	13 x 2	18 x 2
	2nd consultation *	31 x 2	26 x 2	20 x 2
Total		165 x 2	39 x 2	38 x 2

* For two of the consultations the lot used on meter B was not specified

Blood sampling
Meter A and B were checked by means of the manufacturer's control solutions every day they were used. The biomedical laboratory scientists measured one of the two internal quality controls on the diabetes patient's meter at each consultation.

All the samples for FreeStyle Lite, as well as the samples for the comparison method, were collected from finger capillaries.

The blood sampling and analysis were done in the following order:

1. The biomedical laboratory scientist took a first sample for the comparison method
2. The biomedical laboratory scientist took samples and analysed on meter A, B, A and B
3. The diabetes patient took duplicate samples for his/her assigned meter
4. The biomedical laboratory scientist took a second sample for the comparison method

In order to reduce the possibility for a change in the glucose concentration during the sampling sequence, the sampling time ought not to exceed 10 minutes. The stability of the glucose concentration during the sampling in the evaluation is supervised. A more detailed explanation of the matter is found in the paragraph "*Analysing the samples for the comparison method*" and in section 5.1.3.

The order of meter A and B was changed between each diabetes patient, but the blood samples for the comparison method were always taken first and last in accordance with ISO 15197. The biomedical laboratory scientist registered whether the diabetes patients used correct cleaning, drying, and skin puncture procedures, applied the blood sample correctly to the test strip, and otherwise followed manufacturer's instructions for performing a blood glucose test. At the final consultation a venous sample for hematocrit determination was taken. Hematocrit may influence blood glucose readings, especially in meters designed for self-monitoring. The product insert of FreeStyle Lite test strips and the user guide states that measurements on FreeStyle Lite are not affected by hematocrit values from 15 to 65 %.

Handling of the samples for the comparison method
The samples for the comparison method were taken from a finger capillary using Microvette Li-heparin tubes from Sarstedt. The samples were centrifuged immediately for three minutes at 10000 g, and plasma was separated into sample vials. The plasma samples were frozen directly and stored at minus 80 °C. The samples were transported under cold storage to NOKLUS where they were kept at minus 80 °C until the analysis took place [7].

Analysing the samples for the comparison method
The samples were analysed on an Architect instrument. Recommended minimum volume for analysis of glucose on Architect in this evaluation was 120 µL plasma. The samples were thawed at NOKLUS just before they were analysed. For each sampling sequence two samples for the comparison method were collected. The first and the second sample for the comparison method, taken at the start and at the end of each blood sampling sequence, reflect the stability of the glucose concentration during the sampling time. When the paired measurements gave agreeable glucose concentrations on the comparison method, the mean of the two results was looked upon as the estimate of the true value of the sample. Basically, the difference between the first and the second comparative reading must not be more than 4 % or 0,22 mmol/L (per ISO 15197 Section 7.3.2.). If the difference between any paired results exceeded these limits, the samples were re-analysed. If the results from the re-run confirmed the difference, the difference was looked upon as a real difference in the glucose concentration in the two samples. Deviations > 10 % were regarded as not acceptable and such results were excluded. As a consequence of this, the matching FreeStyle Lite results were excluded before assessment of accuracy and calculation of trueness. Differences between 4 and 10 % are discussed and included in the calculations (see chapter 5.1.3.). If the deviation between the two results was not confirmed by the re-run, the result from the re-run was used as the accepted result. All the samples for the comparison method were analysed within a two-week period.

Evaluation of the user-friendliness and the user guide
The biomedical laboratory scientists evaluated the user-friendliness of FreeStyle Lite and the user guide. The biomedical laboratory scientists provided a description in the form of key words and looked for any defects and deficiencies or whether there was anything with the system that did not function optimally.

3.4.8. Evaluation of analytical quality

The following sets of data give the basis for the evaluation of the analytical quality:

1. Results from 43 diabetes patients in the “training group” who had participated in the training programme, but not practiced using the blood glucose meter at home
2. Results from 40 of the same diabetes patients after they had practiced using FreeStyle Lite at home for three weeks
3. Results from 39 diabetes patients in the “mail group” who had not participated in the training programme, but who had practiced using FreeStyle Lite at home for three weeks
4. Results from 122 measurements in duplicate under standardised and optimal conditions
5. Results from 122 measurements in duplicate from the comparison method

The results from the diabetes patients with and without training were compared (item 2 and 3) as well as the results from the diabetes patients with and without practice at home (item 1 and 2). All the diabetes patients’ measurements were evaluated against the results achieved under standardised and optimal conditions. All the measurements were compared with the results from the comparison method.

The three lots of test strips were distributed evenly between the diabetes patients in the group with and without training (random distribution in each group). Each lot was used by approximately 13 diabetes patients in each group (see figure 1).

4. Statistical expressions and calculations

4.1. Statistical terms and expressions

4.1.1. Precision

The often used terms within-series imprecision and between-series imprecision are often misinterpreted. Especially the terms between-series and between-day imprecision are often not precisely defined. In this report, the terms are replaced by *repeatability* and *reproducibility*. Repeatability is the agreement between the results of consecutive measurements of the same component carried out under identical measuring conditions (within the measuring series). Reproducibility is the agreement between the results of discontinuous measurements of the same component carried out under changing measuring conditions over time. The reproducibility includes the repeatability. The two terms are measured as imprecision. Precision is descriptive in general terms (good, acceptable, poor e.g.), whereas imprecision is expressed by means of the standard deviation (SD) or coefficient of variation (CV). SD is reported in the same unit as the analytical result and CV is usually reported in percent. The imprecision will be summarised in tables.

4.1.2. Accuracy

Accuracy is the closeness of agreement between the result of one measurement and the true value. Inaccuracy is a measure of the deviation of a single measurement from the true value, and implies a combination of random and systematic error (analytical imprecision and bias). Inaccuracy, as defined by a single measurement, is not sufficient to distinguish between random and systematic errors in the measuring system. Inaccuracy can be expressed as total error. The inaccuracy will be illustrated by difference-plots with quality goals for the total error shown as deviation limits in percent.

4.1.3. Trueness

Trueness is the agreement between an average value obtained from a large number of measuring results and a true value. Trueness is measured as bias (systematic errors). Trueness is descriptive in general terms (good, poor), whereas bias is the estimate, reported in the same unit as the analytical result or in %. The bias at different glucose concentration levels will be summarised in tables.

4.2. Statistical calculations

4.2.1. Number of samples

82 diabetes patients participated in the evaluation. 79 of them completed the evaluation. 40 of the diabetes patients in the "training group" met at two consultations while three of the diabetes patients just met at the first consultation. The 39 diabetes patients in the "mail group" met at one consultation. Blood samples were taken at each consultation. The total number of samples is: [(43 x 2 (duplicates)) + (40 x 2) + (39 x 2)] x 4 (meter A, meter B, diabetes patient's meter, comparison method) = 976 samples.

4.2.2. Statistical outliers

The criterion promoted by Burnett [12] was used for the detection of outliers. The model takes into consideration the number of observations together with the statistical significance level for the test. The significance level is often set to 5 %, so also in this evaluation. The segregation of outliers was made with repeated truncations. All the results were checked. Where the results are classified according to different glucose concentration levels, the outlier-testing is done at each level separately. Statistical outliers are excluded from the calculations. Possible outliers will be commented on under each table.

4.2.3. Missing or excluded results

Besides the statistical outliers, some results are missing or excluded for other reasons. They are summarized and explained here:

- ID 38 and ID 117 were not able to complete the evaluation and are missing from the final consultation as well as from the home measurements.
- ID 81 was not able to meet at the final consultation and is missing from this consultation, but has performed home measurements as well as answered the questionnaires.
- ID 98, ID 115 and ID 140 (at the final consultation) had a difference > 10 % between the paired results on the comparison method. The difference was confirmed by a rerun. As a consequence, these results are excluded when FreeStyle Lite is compared with the comparison method (accuracy and trueness) and from the calculation regarding the influence of hematocrit. The results are included in the calculations of the imprecision of FreeStyle Lite because each set of duplicate measurements on FreeStyle Lite is completed in less than a minute.
- ID 147 is excluded from the calculation of variation between the three lots of test strips because the lot used was unspecified. Lot used was also unspecified on ID 140. This result is excluded because of a difference > 10 % between the paired results on the comparison method.
- In the calculation of repeatability based on the diabetes patients' measurements at home quite a number of measurements are missing. Some of the diabetes patients had not performed five duplicate measurements and some had not fully understood or followed the instructions. Totally 40 results are missing from this calculation.
- ID 80 at the final consultation was classified as an outlier according to Burnett in the calculation of repeatability on meter B and is excluded from the calculation of lot variation.

4.2.4. Calculations of imprecision based on duplicate results

Two capillary samples were taken of each diabetes patient for meter A, meter B, the diabetes patient's meter and for the comparison method at each consultation. The imprecision was calculated by use of paired measurements [13, 14], based on the following formula:

$SD = \sqrt{\frac{\sum d^2}{2n}}$, d = difference between two paired measurements, n = number of differences

Even if this formula is based on the differences between the two parallel measurements of every duplicate, the calculated standard deviation is still a measure of the imprecision of single values, and completely comparable with the more commonly used calculation based on repeated measurements of only one sample. The assumption for using this formula is that no systematic difference between the 1st and the 2nd measurement of the duplicate is acceptable. Table 4 shows that in four of the six t-tests no systematic difference was pointed out. The difference for glucose concentrations of 7 – 10 mmol/L on meter A and for low glucose concentrations on meter B are slightly significant and may have appeared by chance. For the total set of data the conclusion is that there is no systematic difference between the paired measurements.

Table 4. Comparison of the 1st and the 2nd measurement. T-test for paired values

		Glucose level mmol/L	Mean 1st measurement mmol/L	Mean 2nd measurement mmol/L	Mean difference 2nd – 1st measurement mmol/L	95 % CI for the mean difference, mmol/L	n
FreeStyle Lite	Meter A	< 7	5,6	5,7	0,02	-0,03 – 0,07	36*
		7 – 10	8,4	8,5	0,09	0,01 – 0,16	48
		> 10	13,2	13,3	0,17	-0,02 – 0,35	36
	Meter B	< 7	5,6	5,7	0,08	0,03 – 0,14	36**
		7 – 10	8,5	8,5	0,05	-0,07 – 0,16	47
		> 10	13,2	13,1	-0,08	-0,22 – 0,06	38

* Two outliers (ID 85 and ID 90 1st consultation) according to Burnett (two truncations)

** One outlier (ID 80 final consultation) according to Burnett

4.2.5. Calculation of trueness

To assess the trueness of the results on FreeStyle Lite, the average bias at three glucose concentration levels is calculated based on the results obtained under standardised and optimal measuring conditions. A paired t-test is used with the mean values of the duplicate results on the comparison method and the mean values on FreeStyle Lite meter A. The mean difference is shown with a 95 % confidence interval.

4.2.6. Calculation of accuracy

To evaluate the accuracy of the results on FreeStyle Lite, the agreement between FreeStyle Lite and the comparison method is illustrated in difference-plots. In the plots the x-axis represents the mean value of the duplicate results on the comparison method. The y-axis shows the difference between the first measurement on FreeStyle Lite with three lots and the mean value of the duplicate results on the comparison method.

5. Results and discussion

5.1. Analytical quality of the designated comparison method

5.1.1. The precision of the comparison method

The best estimate of the repeatability of a method is achieved by using patient samples. By doing so, the matrix effects in artificially produced materials are avoided. In this evaluation, though, the diabetes patient samples for the comparison method can not be used for this purpose. The blood sampling for the comparison method was certainly done in duplicate, but with small blood volumes and a time gap between the first and the second sample for each diabetes patient. Because of the small blood volumes each sample was analysed only once. Because of the time gap, the paired measurements reflect the stability of the glucose concentration during the sampling time, and not the precision of the method (see 5.1.3). To get a good estimate of the repeatability of the comparison method, the results from the documentation of trueness were used. Both the NIST-standards and the NOKLUS controls are genuine patient materials with no additives, and the standards and the controls have been analysed repeatedly.

The repeatability of the comparison method is shown in table 6 and table 7. The results are obtained with the SRM 965a standards supplied by the National Institute of Standards & Technology, NIST, and freshly frozen, human serum controls from NOKLUS.

The reproducibility of the comparison method is shown in table 5. The results are obtained with internal quality control solution at two levels of glucose concentrations. The controls were analysed in the beginning and at the end of each series of samples. All the results were inside the limits of the target values for the controls.

The raw data is shown in attachment 3.

Table 5. The comparison method – Reproducibility (results with internal quality control solutions)

Control Solution	Target value glucose (mmol/L)	Mean value glucose (mmol/L)	n	Outliers	CV % (95 % CI)
Autonorm 1	3,4 ± 0,24	3,3	25	0	1,1 (0,8 – 1,5)
Autonorm 2	16,1 ± 1,12	15,8	25	0	0,8 (0,7 – 1,2)

Discussion

The precision of the comparison method is good. The repeatability CV is below 1,0 % (see table 6 and 7) and the reproducibility CV is approximately 1,0 %.

5.1.2. The trueness of the comparison method

In order to demonstrate the trueness of the comparison method, the SRM 965a standards supplied by the National Institute of Standards & Technology, NIST, were analysed. The agreement between the comparison method and the NIST-standards is shown in table 6.

Table 6. The comparison method – Standard Reference Material (SRM 965a) measured on the comparison method

SRM 965a	Date	Certified glucose concentration mmol/L (uncertainty)	Mean value glucose (mmol/L)	n	Combined CV % (95 % CI)	% deviation from target value
Level 1	08.06.07	**1,918** (1,898 - 1,938)	1,91	5	0,6 (0,4 – 1,1)	-0,6
	29.06.07		1,86	5		-2,9
	Total		**1,88**	**10**		**-1,8**
Level 2	08.06.07	**4,357** (4,309 - 4,405)	4,42	5	0,9 (0,6 – 1,6)	1,4
	29.06.07		4,28	5		-1,7
	Total		**4,35**	**10**		**-0,1**
Level 3	08.06.07	**6,777** (6,704 - 6,850)	6,85	5	0,3 (0,2 – 0,6)	1,1
	29.06.07		6,65	5		-1,8
	Total		**6,75**	**10**		**-0,3**
Level 4	08.06.07	**16,24** (16,05 - 16,43)	16,51	5	0,6 (0,4 – 1,1)	1,7
	29.06.07		16,09	5		-0,9
	Total		**16,30**	**10**		**0,4**

To verify the trueness of the comparison method, freshly frozen, human serum controls from NOKLUS with glucose concentrations at two levels were analysed. The agreement with target values from the Reference laboratory in Belgium is shown in table 7.

Table 7. The comparison method – Control samples from NOKLUS's External Quality Assessment program, measured on the comparison method during the evaluation period

Control solution	Date	Target value glucose (mmol/L)	Mean value glucose (mmol/L)	n	Outliers	Combined CV% (95% CI)	% deviation from target value
NOKLUS control 1	07.06.07	7,43	7,46	5	0	0,4 (0,3 – 0,8)	0,4
	27.06.07		7,24	5	0		-2,6
	Total		**7,35**	**10**	**0**		**-1,1**
NOKLUS control 2	07.06.07	10,40	10,38	5	0	0,7 (0,5 – 1,3)	-0,2
	27.06.07		10,11	5	0		-2,8
	Total		**10,25**	**10**	**0**		**-1,5**

Discussion
The trueness of the comparison method is satisfactory.

5.1.3. Stability of the glucose concentration during the sampling time

The first and the second sample for the comparison method, taken at the start and at the end of each blood sampling sequence, reflect the stability of the glucose concentration during the sampling time (see chapter 3.4.7, *Analysing the samples for the comparison method*). In this evaluation, deviations > 10 % were regarded as not acceptable and such results were excluded without further discussion. This applies to ID 98, ID 115 and ID 140 at the 2nd consultation. For further explanation, see chapter 4.3. 24 of 122 paired results on the comparison method gave deviations between 4 and 10 %. For 13 of these 24 samples the deviation was less than 6 %. After a general evaluation of all the results, the paired measurements with differences between 4 and 10 % are included in the calculations in this evaluation. The summing up in table 13 has been done with and without these 24 results. The percentage number of results that falls within the different quality limits is not dependent on keeping or excluding these results.

5.2. Analytical quality of FreeStyle Lite

5.2.1. The precision of FreeStyle Lite

The FreeStyle Lite-meters in the user evaluation were checked with the manufacturer's control solutions by the biomedical laboratory scientists. All the results were inside the limits of the controls.

All the results from the calculation of the precision are discussed at the end of this chapter.

Repeatability under standardised and optimal measuring conditions
The repeatability obtained under standardised and optimal conditions with capillary blood samples from the diabetes patients, is shown in table 8. The table gives the results from the biomedical laboratory scientists' measurements at the first and the final consultation together.

The raw data is shown in attachment 4.

Table 8. FreeStyle Lite – Repeatability (results with blood samples from the diabetes patients) measured under standardised and optimal conditions

FreeStyle Lite	Glucose level (mmol/L)	Mean value glucose (mmol/L)	n	Outliers	CV % (95 % CI)
Meter A	< 7	5,7	36	2*	1,9 (1,5 – 2,5)
Meter B	< 7	5,6	36	1**	2,3 (1,9 – 3,0)
Meter A	7 – 10	8,5	48	0	2,3 (1,9 – 2,8)
Meter B	7 – 10	8,5	47	0	3,2 (2,7 – 4,0)
Meter A	> 10	13,2	36	0	3,0 (2,5 – 4,0)
Meter B	> 10	13,2	38	0	2,3 (1,8 – 2,9)

* Two outliers (ID 85 and ID 90 1st consultation) according to Burnett (two truncations)
** One outlier (ID 80 final consultation) according to Burnett

Repeatability obtained by the diabetes patients
The repeatability obtained by the diabetes patients with capillary blood samples is shown in table 9. The table gives the results from the measurements at the first and the second consultation for the "training group", the results from the measurements at the consultation for the "mail group" and the results the diabetes patients obtained at home. The results obtained at home have, of course, a higher degree of uncertainty since it is impossible to check what has actually been done. The reporting of these home-values also reveals that some of the diabetes patients did not quite understand the instruction on how to perform and report the five duplicate measurements they were supposed to carry out.

The raw data from the diabetes patients' measurements at NOKLUS is shown in attachment 5.
The raw data from the diabetes patients' measurements at home is shown in attachment 6.

Table 9. FreeStyle Lite – Repeatability (results with diabetic samples) measured by the "training group" and the "mail group"

FreeStyle Lite	Consultation/ diabetic group	Glucose level (mmol/L)	Mean value glucose (mmol/L)	n	Outliers	CV % (95 % CI)
At NOKLUS	1st/training group	< 7	5,6	16	0	4,3 (3,2 – 6,6)
	2nd/training group	< 7	5,7	12	0	3,6 (2,5 – 6,1)
	The mail group	< 7	6,0	11	0	3,5 (2,4 – 6,1)
At home**		< 7	5,7	139	5	4,6 (4,1 – 5,2)
At NOKLUS	1st/training group	7 – 10	8,4	14	0	2,7 (1,9 – 4,3)
	2nd/training group	7 – 10	8,5	13	0	3,5 (2,5 – 5,7)
	The mail group	7 – 10	8,7	16	0	4,4 (3,3 – 6,9)
At home**		7 – 10	8,2	151	1	6,0 (5,4 – 6,8)
At NOKLUS	1st/training group	> 10	13,0	13	0	6,6* (4,7 – 10,9)
	2nd/training group	> 10	13,0	15	0	4,4 (3,3 – 7,0)
	The mail group	> 10	12,7	12	0	4,6 (3,3 – 7,9)
At home**		> 10	12,8	72	2	6,2 (5,3 – 7,4)

* See comment below

** 40 home measurements are missing and 8 statistical outliers among the home measurements are excluded

Comment

The CV for glucose level > 10 mmol/L in the training group at the first consultation is 6,6 %. This relative weak CV is mainly affected by the results of ID 150. The difference between the two measurements of ID 150 is 3,7 mmol/L. The difference is still not segregated as a statistical outlier according to Burnett. After visual inspection the result is clearly an atypical result. The actual CV is 3,8 % without this result.

Reproducibility with Internal Quality Control Solutions

The reproducibility is assessed with FreeStyle Control Low and FreeStyle Control High. The measurements are carried out on meter A and meter B during the whole evaluation period. The reproducibility of FreeStyle Lite on meter A and meter B is shown in table 10.

Table 10. FreeStyle Lite – Reproducibility (results with FreeStyle Control Low and Control High) measured by the biomedical laboratory scientists on meter A and meter B

FreeStyle Lite	QC	Target value (mmol/L)	Mean value glucose (mmol/L)	n	Outliers	CV % (95 % CI)
Meter A	Low	3,1 (2,2 – 3,9)	2,9	17	0	2,8 (2,1 – 4,2)
	High	18,6 (14,9 – 22,3)	18,1	14	0	2,2 (1,6 – 3,6)
Meter B	Low	3,1 (2,2 – 3,9)	3,0	21	0	4,6 (3,5 – 6,6)
	High	18,6 (14,9 – 22,3)	18,3	19	0	2,7 (2,0 – 3,9)

Internal Quality Control on the diabetes patients' meters

The control measurements on the diabetes patients' meters (totally 82 meters) were performed with FreeStyle Control Low and FreeStyle Control High. Artificially produced control materials have other matrix effects than whole blood, and may therefore give other results than achieved with blood. All the control measurements are performed by the biomedical laboratory scientists with the test strips that were distributed to each diabetes patient (three different lots of test strips). The control solutions were kept according to the instructions in the product insert through out the evaluation period. The reproducibility on the meters of the diabetes patients is shown in table 11.

The raw data from the measurements with the internal quality control is shown in attachment 7.

Table 11. FreeStyle Lite – Reproducibility (results with FreeStyle Control Low and Control High) measured by the biomedical laboratory scientists on the diabetes patients' meters

FreeStyle Lite	QC	Target value (mmol/L)	Mean value glucose (mmol/L)	n	Outliers	CV % (95 % CI)
1st consultation						
The diabetes patients' meters	Low	3,1 (2,2 – 3,9)	3,0	24	0	3,3 (2,5 – 4,6)
	High	18,6 (14,9 – 22,3)	17,9	19	0	3,8 (2,9 – 5,6)
2nd consultation						
The diabetes patients' meters	Low	3,1 (2,2 – 3,9)	3,0	43	0	4,3 (3,6 – 5,5)
	High	18,6 (14,9 – 22,3)	18,1	36	0	5,3 (4,3 – 6,9)

Discussion
The overall precision of FreeStyle Lite was good. The repeatability CV obtained under standardised and optimal conditions was between 2 and 3 %. The repeatability CV obtained at NOKLUS when the measurements were performed by the diabetes patients was approximately 4 %. The CVs for the diabetes patients with and without training programme (the "training group" and the "mail group") were not significantly different. The CVs for the diabetes patients with and without practise at home (1st and 2nd training) were not significantly different either. This indicates that FreeStyle Lite is a robust system, easy to use, and that training is not essential for a good result. The results at home show that the diabetes patients had been practising with the new system according to the instructions, but one should not make a point of the calculated CV values.

The reproducibility on FreeStyle Lite was acceptable when measured with internal quality control solutions. The CV was between 2 and 5 %.

5.2.2. The trueness of FreeStyle Lite

The trueness of FreeStyle Lite is calculated from the results achieved by the biomedical laboratory scientists at the final consultation (the "training group" and the "mail group"). The calculations are based on measurements on meter A and are shown in table 12. All the measurements on meter A are performed with lot 0707142.

The raw data from the comparison method is shown in attachment 8.

Table 12. Mean difference between FreeStyle Lite and the comparison method. Results under standardised and optimal conditions from the final consultation

	< 7 mmol/L		**7 – 10 mmol/L**		**> 10 mmol/L**	
	The comparison method	**Meter A**	**The comparison method**	**Meter A**	**The comparison method**	**Meter A**
Mean glucose, mmol/L	5,7	5,7	8,5	8,2	13,7	12,9
Mean deviation from the comparison method, mmol/L (95 % CI)	0,01 (-0,08 – (+0,10)		-0,26 (-0,35 – (-0,16))		-0,81 (-1,09 – (-0,54))	
n	20		29		26	
Outliers	0		1*		0	

* One outlier (ID 157) according to Burnett

Discussion

Table 12 shows that no significant bias between FreeStyle Lite and the comparison method was pointed out for glucose values < 7 mmol/L. For glucose concentrations > 7 mmol/L the glucose measurements on FreeStyle Lite were systematic lower than the measurements on the comparison method. The deviation increases with increasing glucose concentration. The negative bias was small but statistically significant. For glucose values 7 – 10 mmol/L FreeStyle Lite gave glucose values approximately 0,3 mmol/L lower than the comparison method. For glucose values > 10 mmol/L FreeStyle Lite gave glucose values approximately 0,8 mmol/L lower than the comparison method.

5.2.3. The accuracy of FreeStyle Lite

To evaluate the accuracy of the results on FreeStyle Lite, the agreement between FreeStyle Lite and the comparison method is illustrated in two difference-plots. The plots show the deviation of single measurement results on FreeStyle Lite from the true value, and give a picture of both random and systematic deviation, reflecting the total measuring error on FreeStyle Lite. The total error is demonstrated for the first measurements of the paired results, only. On meter A only one lot of test strips was used. On meter B three different lots were used. The same three lots were randomly distributed between the diabetes patients. The limits in the plots are based upon the quality goals discussed in chapter 2 in this report. Under standardised and optimal measuring conditions the ISO-goal at ± 20 % is used. For the diabetes patients' self-measurements the "adjusted ISO-goal" at ± 25 % is used.

The accuracy, FreeStyle Lite meter B, under standardised and optimal measuring conditions, at the final consultation is shown in figure 2. The accuracy, FreeStyle Lite, as measured by the diabetes patients at the final consultation is shown in figure 3. The accuracy is summarised in table 13 and discussed afterwards.

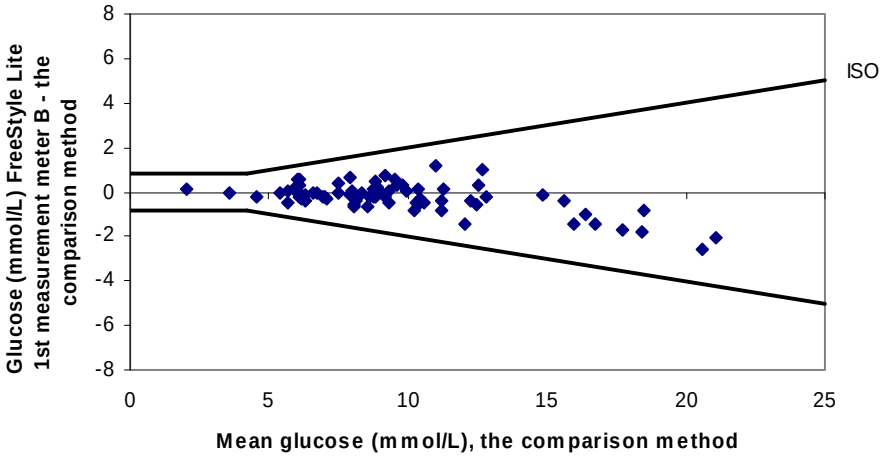

Figure 2. Accuracy. FreeStyle Lite meter B (three lots of test strips) under standardised and optimal measuring conditions at the final consultation. The x-axis represents the mean value of the duplicate results on the comparison method. The y-axis shows the difference between the first measurement on FreeStyle Lite and the mean value of the duplicate results on the comparison method, n = 76

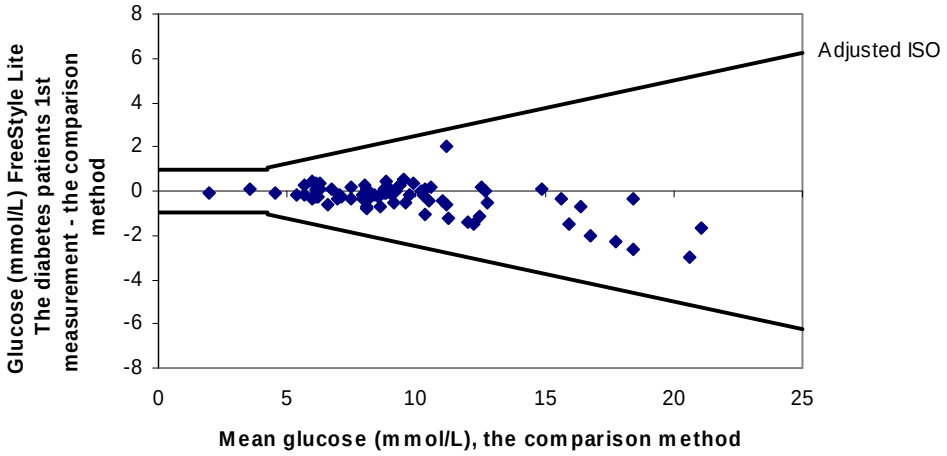

Figure 3. Accuracy. The diabetes patients' self-measurements at the final consultation. Three lots of test strips. The x-axis represents the mean value of the duplicate results on the comparison method. The y-axis shows the difference between the first measurement on FreeStyle Lite and the mean value of the duplicate results on the comparison method, n = 76

Table 13. Total error of FreeStyle Lite results compared to the comparison method. Percentage FreeStyle Lite results within the limits

Measurements done by	Consultation	Meter	n	Number of results (%)			Shown in figure
				< ADA < ± 10 %	**< ISO** < ± 20 % (and < ± 0,83 mmol/L at concentrations ≤ 4,2)	**< "adjusted ISO"** < ± 25 % (and < ± 1,0 mmol/L at concentrations ≤ 4,2)	
Biomedical laboratory scientists	1st ****	A* 1st measurement	43	95	98		
		B 1st measurement	43	93	100		
Biomedical laboratory scientists	2nd	A 1st measurement	76	93	100		
		B** 1st measurement	76	96	100		2
Diabetes patients at NOKLUS	1st ****	1st *** measurement	43	88	98	100	
	2nd	1st measurement	76	88	100	100	3

* In connection with the calculation of repeatability on meter A, ID 85 and ID 90 were classified as outliers according to Burnett. With regard to accuracy, ID 85 (1st measurement) is within the ISO-goal while ID 90 falls outside the limit.

** In connection with the calculation of repeatability on meter B, ID 80 was classified as an outlier according to Burnett. With regard to accuracy, ID 80 (1st measurement) is within the ISO-goal.

*** In connection with the calculation of repeatability, ID 150 had a difference between the two measurements of 3,7 mmol/L. The difference was still not segregated as a statistical outlier according to Burnett. After visual inspection the result was clearly an atypical result. With regard to accuracy, ID 150 (1st measurement) falls outside the ISO-limit.

**** ID 81 and ID 85 had only one sample for the comparison method. The result of this sample is used as the estimate of the "true value".

Discussion

The figures show that the FreeStyle Lite-results was lower than the comparison method for glucose concentrations > approximately 10 mmol/L.

Figure 2 shows that all the results obtained under standardised and optimal measuring conditions at the final consultation are within the ISO-limits. The summing up in table 13 shows that 98 % of the first measurements on meter A and all the first measurements on meter B at the first consultation are within the ISO-limits. At the final consultation all the first measurements are within the ISO-limits.

Figure 3 shows that all the diabetes patients' first self-measurements at the final consultation are within the "adjusted ISO-goal". The summing up in table 13 shows that all the diabetes patients' first self-measurements at the first and the final consultation are within the "adjusted ISO-goal". 98 % of the first measurements at the first consultation and all the first measurements at the final consultation are also within the ISO-goal.

Assessment of accuracy
The FreeStyle Lite device fulfils the quality goal set in ISO 15197 when used under standardised and optimal conditions. The "adjusted ISO-goal" as well as the ISO-goal is also met by the measurements of the diabetes patients.

5.3. Variation between three lots of test strips

All the measurements on meter A were performed with one lot of test strips. The measurements on meter B were performed with three different lots of test strips, with samples from three different groups of diabetes patients. The three lots can not be compared with each other directly because the mean glucose concentrations in the three groups of diabetes patients are different. To measure the variation between the three lots, the mean glucose results on FreeStyle Lite obtained under standardised and optimal conditions on meter B were compared with the mean of the paired values from the comparison method (paired t-test). The results are shown in table 14.

Table 14. Variation between three lots of test strips. T-test for paired values between three lots on meter B and the comparison method under standardised and optimal conditions at the final consultation

	The comparison method	**Meter B Lot 0707142**	**The comparison method**	**Meter B Lot 0707202**	**The comparison method**	**Meter B Lot 0707140**
Mean glucose, mmol/L	9,2	8,8	10,1	9,7	9,2	9,4
Mean deviation from the comparison method, mmol/L (95 % CI)	-0,41 ((-0,64) – (-0,18))		-0,35 ((-0,58) – (-0,12))		0,25 ((+0,05) – (+0,44))	
n	31		25		17	
Outliers	0		0		1*	

* One outlier (ID 150) according to Burnett

Discussion
Lot 0707142 and lot 0707202 gave significantly lower values than the comparison method.
Lot 0707140 gave significantly higher values than the comparison method.
The deviations are small, but statistically significant.

5.4. Effect of hematocrit

The product insert of FreeStyle Lite test strips states that the measurements are not affected by hematocrit values from 15 to 65 %. To measure the effect of hematocrit on FreeStyle Lite, a hematocrit sample was taken of the diabetes patients at the second consultation.

The investigation of the effect of hematocrit is based on the measurements on FreeStyle Lite (meter A with one lot of test strips) under standardised and optimal measuring conditions. The glucose concentration range in the samples was 2,0 – 21,1 mmol/L. The hematocrit range was 31 – 48 %.

The effect of hematocrit is shown in figure 4. The x-axis in the plot shows the hematocrit value in percentage and the y-axis shows the difference in glucose concentration between FreeStyle Lite and the comparison method (FreeStyle Lite – the comparison method) in mmol/L. The trend-line is shown in the figure.

The raw data is shown in attachment 9.

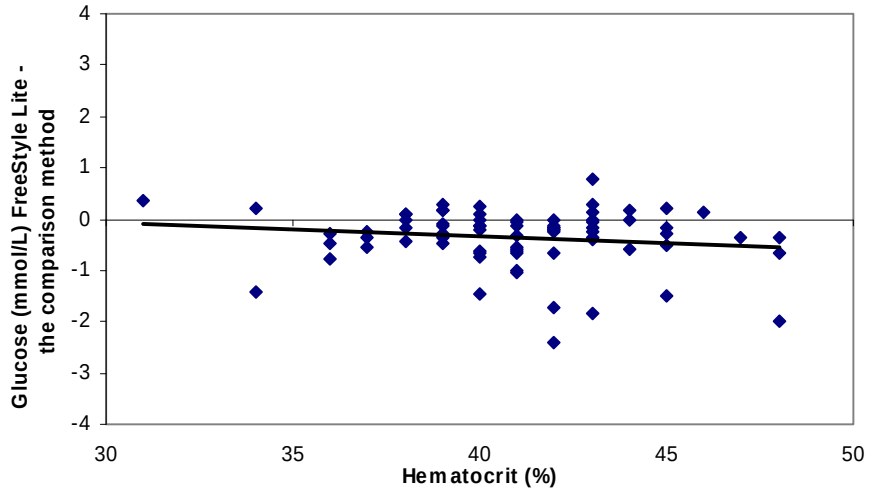

Figure 4. The effect of hematocrit at glucose measurements on FreeStyle Lite measured under standardised and optimal conditions. The x-axis shows the hematocrit value in %. The y-axis shows the difference in glucose concentration between FreeStyle Lite and the comparison method (FreeStyle Lite – the comparison method) in mmol/L, n= 76

Discussion
Glucose measurements on FreeStyle Lite did not seem to be affected by hematocrit in this study. Hematocrit outside the range 31 – 48 % has not been tested.

5.5. Practical points of view

The most important response regarding user-friendliness comes from the users themselves. The end-users often emphasize other aspects than those pointed out by more extensively trained laboratory personnel.

Questionnaires

Each diabetes patient filled in a questionnaire about the user-friendliness and a questionnaire about the user guide of FreeStyle Lite when they attended the final consultation (n = 80). The biomedical laboratory scientists were available for clarifying questions, and there was room for free comments.

The questionnaires about the user-friendliness and about the user guide are attached to the report (in Norwegian), see attachment 10 and 11.

5.5.1. Evaluation of the user-friendliness of FreeStyle Lite

The questionnaire about the user-friendliness was made up of nine questions concerning FreeStyle Lite. Table 15 summarizes six questions where the diabetes patients were asked to rank the answers on a scale from 1 to 6, where 1 is difficult and 6 is simple. The mean score is 5,6, 4,7 and 5,8 on the questions about inserting a strip into the meter, filling the strip with blood and removing the strip from the meter, respectively. This indicates that the diabetes patients seemed satisfied with the insertion and removing of the strip, but that some of them thought it was a bit difficult to fill the strip with blood. The mean score is 5,6 on the question about reading the figures in the display. The diabetes patients also seemed satisfied with operating the meter, all in all. The mean score is 5,1. Regarding FreeStyle lancet pen the mean score is 5,4, which indicates that most of the diabetes patients were satisfied with the lancet pen too.

Table 15. FreeStyle Lite - Questions about the meter

Questions about FreeStyle Lite		Mean	Range	Not answered (% of total)	Total number
How will you rank the following questions on a scale from 1 to 6, where 1 is difficult and 6 is simple	To insert a strip into the meter	5,6	1 - 6	0	80
	To fill the strip with blood	4,7	1 - 6	0	80
	To remove the strip from the meter	5,8	2 - 6	0	80
	To read the figures in the display	5,6	1 - 6	0	80
	All in all, to operate the meter	5,1	1 - 6	0	80
	To operate FreeStyle lancet pen	5,4	1 - 6	11	80

The diabetes patients were asked if they had any positive and/or negative comments about FreeStyle Lite.

Positive comments
72 diabetes patients reported one or more advantages with FreeStyle Lite. The most often reported advantages are distinctly grouped as follows:

1. Small and convenient meter (42)
2. The meter has short measuring time (32)
3. Easy to use (22)
4. The meter/strip needs a small blood sample volume (9)
5. Display light and test strip light (6)
6. No coding (5)

Negative comments
38 diabetes patients reported one or more disadvantages with FreeStyle Lite. The most often reported disadvantages are distinctly grouped as follows:

1. Different problems with the test strips (for instance the test strips are not singly packed or in a disc, difficult to get out of the box, difficult to insert the test strips, the test strips are too large, the blood has to be filled from the side of the strip) (16)
2. Difficult to fill the test strip with blood (9)
3. The lancet pen (5)
4. The meter is too small (4)
5. Too small figures in the display, too small letters (4)
6. The carrying case (4)

Table 16 shows the answers to the last question about FreeStyle Lite. 8 % of the diabetes patients answered that they had technical problems with the meter during the testing period. One of the diabetes patients wrote that the meter sometimes didn't work. Two of the diabetes patients got a new meter because the first meter didn't work/stopped working. Written comments from the others indicate that their problems were not technical ones after all.

Table 16. FreeStyle Lite – Questions about the meter

Question about FreeStyle Lite	Yes (%)	No (%)	Not answered (%)	Total number
Did you have any technical problems with the meter during the testing period?	8	91	1	80

5.5.2. Evaluation of the FreeStyle Lite user guide

In the questionnaire about the user guide each diabetes patient was first asked whether he/she had used the guide. If the answer was no, they were to ignore the rest of the questionnaire.

Table 17 shows that 90 % of the diabetes patients had used the guide. Only one of the diabetes patients that had used the guide answered that he/she was not satisfied with the description of how to perform a blood glucose measurement with the meter, but he/she didn't write what was missing. Seven of the diabetes patients thought the guide had essential shortcomings. They meant that the use of the lancet pen and the setting of the operating options of the device should have been better described. Most of the diabetes patients were satisfied with the user guide.

Table 17. FreeStyle Lite – Questions about the user guide

Questions about the user guide	Yes (%)	No (%)	Not answered (%)	Number
Have you been reading in the user guide?	90	9	1	80
If yes, did you read the entire user guide?	67	25	8	73
And/or did you consult the user guide when needed?	62	11	27	73
Are you satisfied with the description of how to perform a blood glucose measurement with the meter?	97	1	1	73
Do you think the user guide has essential shortcomings?	10	84	7	73
All in all, are you satisfied with the user guide?	86	8	5	73

5.5.3. The biomedical laboratory scientist's evaluation

The biomedical laboratory scientists thought FreeStyle Lite was easy to use. They thought it was an advantage that the meter has short measuring time and that the meter/strip needs a small blood sample volume. They did not report any disadvantages with FreeStyle Lite. The biomedical laboratory scientists were quite satisfied with the user guide. They commented that some of the diabetes patients had asked for an instruction guide for the lancet pen.

6. References

1. Stöckl D, Baadenhuijsen H, Fraser CG, Libeer JC, Petersen PH, Ricos C, ”Desirable Routine Analytical Goals for Quantities Assayed in serum”. Eur J Clin Biochem 1995; **33** (3): 157 – 169.
2. American Diabetes Association. Self-monitoring of blood glucose. Diabetes Care 1996; **19** (suppl 1): 62 – 66.
3. Skeie S, Thue G, Sandberg S, “Patient-derived Quality Specifications for Instruments Used in Self-Monitoring of Blood Glucose”. Clinical Chemistry 2001; **47** (1): 67 – 73.
4. In vitro diagnostic test systems - Requirements for blood-glucose monitoring systems for self- testing in managing diabetes mellitus, ed. ISO. 2003.
5. Kristensen, G.B., et al., Standardized evaluation of instruments for self-monitoring of blood glucose by patients and a technologist. Clin Chem, 2004. **50**(6): p. 1068-71.
6. www.skup.nu: Reports and summaries from evaluations under the direction of SKUP.
7. National Institute of Standards and Technology, Certificate of Analysis, Standard Reference Material® 965a, Glucose in Frozen Human Serum
8. Thienpont, L.M., et al., Determination of reference method values by isotope dilution-gas chromatography/mass spectrometry: a five years' experience of two European Reference Laboratories. Eur J Clin Chem Clin Biochem, 1996. **34**(10): p. 853-60.
9. Christensen, N.G, Monsen G, Sandberg S, Utprøving av analyseinstrumenter. 1997: Alma Mater Forlag.
10. Skeie, S., et al., Instruments for self-monitoring of blood glucose: comparisons of testing quality achieved by patients and a technician. Clin Chem, 2002. **48**(7): p. 994-1003.
11. Quality specifications for glucose test strips reimbursement from NAV http://www.uib.no/isf/noklus/diabetes/kravspes.pdf.
12. Burnett RW, “Accurate Estimation of Standard Deviations for Quantitative Methods Used in Clinical Chemistry”. Clinical Chemistry 1975; **21** (13): 1935 – 1938.
13. Saunders, E. Tietz textbook of clinical chemistry and molecular diagnostics. 2006. Chapter 14, Linnet, K., Boyd, J. “Selection and analytical evaluation of methods – with statistical techniques”, ISBN 0-7216-0189-8.
14. Fraser, C.G. Biological variation: From principles to practice. 2006. Chapter 1 “The Nature of Biological Variation”. AACC Press. ISBN 1-890883-49-2.

Attachments

1. Serial numbers, FreeStyle Lite blood glucose meters used by the diabetes patients
2. Information letter to the diabetes patients (in Norwegian)
3. Raw data glucose, internal quality control (Autonorm), the comparison method
4. Raw data glucose, FreeStyle Lite results under standardised and optimal conditions
5. Raw data glucose, FreeStyle Lite results, the diabetes patients' measurements at NOKLUS
6. Raw data glucose, FreeStyle Lite results, the diabetes patients' measurements at home
7. Raw data glucose, internal quality control, FreeStyle Lite
8. Raw data glucose, results from the comparison method
9. Raw data hematocrit
10. Questionnaire, user-friendliness (in Norwegian)
11. Questionnaire, user guide (in Norwegian)
12. "SKUP-info". Summary for primary health care (in Norwegian)
13. List of evaluations organised by SKUP

Attachments with raw data are included only in the report to Abbott Norge AS.