ACCU-CHEK® Sensor

ACCU-CHEK® Sensor Comfort Glucose

Meter and test strips designed for glucose self-measurement manufactured by Roche Diagnostics

Report from an evaluation organised by

SKUP

The evaluation was ordered by Roche Diagnostics, Norway

SKUP in Norway, NOKLUS, Division of General Practice, University of Bergen, 5009 Bergen, www.SKUP.nu

SKUP/2006/48

Summary

Background
The Accu-Chek Sensor meter and the Accu-Chek Sensor Comfort Glucose test strips are designed for glucose self-measurements by diabetics. The meter and the test strips are produced by Roche and are supplied in Scandinavia by Roche Diagnostics. The system was launched onto the Norwegian market in 1998.

In order to give reimbursement for the test strips, The National Social Insurance Office (*Rikstrygdeverket*) in Norway instructs the companies to carry out an evaluation that includes a user-evaluation among diabetics. The evaluation of Accu-Chek Sensor/Accu-Chek Sensor Comfort Glucose is done under the direction of SKUP from October to December 2005. Further on in the report Accu-Chek Sensor/Accu-Chek Sensor Comfort Glucose will be referred to as Accu-Chek Sensor.

The aim of the evaluation
The aim of the evaluation of Accu-Chek Sensor is to

- reflect the analytical quality under standardised and optimal conditions (performed by a biomedical laboratory scientist)
- reflect the analytical quality by the users (77 diabetics)
- compare the analytical quality among diabetics with and without training
- compare the analytical quality among diabetics before and after three weeks of practise
- check the variation between three lots of test strips
- examine if hematocrit interferes with the measurements
- evaluate Accu-Chek Sensor regarding user-friendliness
- evaluate the Accu-Chek Sensor user-manual

Materials and methods
77 diabetics took part in the evaluation. 39 participants had two consultations (the "training group") and the rest had one consultation (the "post group"). At the first consultation the diabetics in the "training group" were given a standardised instruction about the Accu-Chek Sensor before they did a finger prick and performed two measurements at the meter. The biomedical laboratory scientist also took capillary samples of the diabetics and measured twice at Accu-Chek Sensor. In addition, two capillary samples were taken to a designated comparison method. The "post group" received the Accu-Chek Sensor by post and no training was given. Both groups of diabetics carried out a practice period of 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 finally answered questionnaires about the user-friendliness and the user-manual of Accu-Chek Sensor.

Results

- Accu-Chek Sensor shows acceptable precision. The CV is approximately 3 % under standardised and optimal measuring conditions and between 2 and 6 % when the measurements are performed by diabetics.

- The trueness of Accu-Chek Sensor is good. Accu-Chek Sensor gives glucose values from 0,1 – 0,3 mmol/L higher than the comparison method. This bias has no importance and the results still fulfil the quality goal set by ISO.
- The agreement with a designated comparison method is good. Quality goals set in ISO 15197 are achieved under standardised and optimal measuring conditions. When handled by the diabetics, Accu-Chek Sensor also shows accurate results. These results are within the "adjusted ISO-goal" and also within the quality goals set in ISO 15197.
- Two of the three lots of test strips that were used showed significantly higher values than the comparison method. The bias is small, and the results still attain the quality goal.
- Glucose measurements at Accu-Chek Sensor do not seem to be affected by hematocrit values between 35 – 50 %. Hematocrit outside this range has not been tested.
- The diabetics summarise the Accu-Chek Sensor device as easy to use. Most of them were pleased with the device. The diabetics that had used the user manual were satisfied with the manual.

Conclusion

Glucose measurements at Accu-Chek Sensor have acceptable precision. The results obtained under standardised and optimal measuring conditions are within the quality goals set in the ISO-guide 15197. The measurements performed by the diabetics are also within the ISO-goals. Two of the three lots of test strips that were used showed significantly higher values than the comparison method. The bias is small, and the results still attain the quality goal. The glucose results are not affected by hematocrit. The users find the Accu-Chek Sensor device easy to use and they are quite satisfied with the device.

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Attachments with raw data are included only in the copy to Roche Diagnostics.

1. The organisation of SKUP

Scandinavian evaluation of laboratory equipment for primary health care, *SKUP*, is a co-operative commitment of NOKLUS[1] in Norway, the "Afdeling KKA"[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 Centre in Bergen, Norway.

The goal of SKUP is to produce reliable, objective and independent information about the 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 of blood glucose. As long as 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 in return, receives 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 representative. SKUP signs *contracts* both with the requesting company and with the evaluating laboratories. A *complete evaluation* requires both one part performed by experienced laboratory personnel 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 a supplier uses 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 from SKUP containing the report code. SKUP reports are published at www.skup.nu and summaries are distributed to physicians' offices, councils for laboratory medicine, laboratory instructors and healthcare authorities. For a detailed list of previous SKUP evaluations, please look in the attachments of this report.

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[1] NOKLUS (Norwegian Quality Improvement of Primary Care Laboratories) is an organisation attached to "Seksjon for Allmennmedisin" (Section for General Medicine) at the University of Bergen.

[2] "The SKUP-division in Denmark" is an organisation created through an agreement between the national "Fagligt Udvalg vedrørende Almen Praksis" (Professional Committee for General Practice) and the "Afdeling KKA" (Department for Clinical Chemistry) at the University Hospital in Odense. "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 owned by "Sveriges Kommuner och Landsting" (Swedish Association of Local Authorities and Regions), "Svenska Läkarsällskapet" (Swedish Society of Medicine) and IBL (Swedish Institute of Biomedical Laboratory Science).

2. Planning of the evaluation

Mette Engebretsen from Roche Diagnostics, Norway, applied to SKUP in the autumn of 2004 for evaluations of the glucose meters Accu-Chek Compact Plus, Accu-Chek Aviva and Accu-Chek Sensor. An agreement was made to go through with the evaluations of Accu-Chek Compact Plus and Accu-Chek Aviva during spring of 2005 and the evaluation of Accu-Chek Sensor during the autumn of 2005. A contract was set up between Roche and SKUP in June 2005. September 19th a preliminary suggestion regarding how to organise the evaluation of Accu-Chek Sensor was sent to Roche. The protocol for the evaluation was accepted October 6th 2005. The Laboratory at Haraldsplass Diaconal Hospital (HDH) accepted to carry out the analytical part of the evaluation dealing with the samples for the comparison method.

The Accu-Chek Sensor system is produced and supplied by Roche Diagnostics. The system was launched onto the Norwegian market in 1998. SKUP carried out the user-evaluation of Accu-Chek Sensor blood glucose meter system from October to December 2005.

SKUP evaluations are made according to guidelines in the book "*Evaluation of analytical instruments. A guide particularly designed for evaluations of instruments in primary health care*" (Christensen, Monsen et al. 1997) [1]. 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 diabetics, based on the model by the NOKLUS-project "*Diabetes-Self-measurements*" [2].

The evaluation comprises the following studies:

- An examination of analytical quality under standardised and optimal conditions done by a biomedical laboratory scientist
- An examination of analytical quality among approximately 80 diabetics
- An examination of agreement between Accu-Chek Sensor and a designated comparison method
- A comparison of analytical quality among diabetics with and without a training programme
- A comparison of analytical quality among diabetics before and after three weeks of practise
- An examination of variation between three lots of test strips
- An examination to see if hematocrit interferes with the measurements
- An evaluation of user-friendliness of Accu-Chek Sensor
- An evaluation of the user-manual of Accu-Chek Sensor

The blood sampling of the diabetics and the measurements at Accu-Chek Sensor under standardised and optimal conditions, were done by Lise Walberg, biomedical laboratory scientist and laboratory consultant, SKUP/NOKLUS. Two biomedical laboratory scientists, Wenche Eilifsen Hauge and Kjersti Østrem, were given the responsibility for the practical work with the comparison method at the Laboratory at HDH. The statistical calculations and the report writing are done by Marianne Risa, SKUP/NOKLUS Centre in Bergen.

3. 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. Accu-Chek Sensor 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 [3]. According to the American Diabetes Association (ADA) the imprecision of new glucose devices must be less than 5 % [4]. Other authors also recommend an imprecision of 5 % or less [5].

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 Accu-Chek Sensor is found in ISO 15197, *In vitro diagnostic test systems – Requirements for blood glucose monitoring systems for self-testing in managing diabetes mellitus* [6]. The ISO-guide is an international protocol for evaluating meters designed for glucose monitoring systems.

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 by trained laboratory staff. Ideally, the same quality requirements should apply for measurements by the diabetics. Previous investigations under the direction of the NOKLUS-project “Diabetes-Self-measurements” in 1997 [5,7] showed that few of the self-monitoring glucose meters that were tested at the time met the ISO-requirements. Subsequent SKUP-evaluations confirmed these findings. As a consequence, the results by the diabetics 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 diabetics over time, as the meters hopefully improved due to technological development. More recent evaluations performed by SKUP [8] clearly show that the quality goals set by ISO 15197 now can be achieved also by the diabetics. But for the time being, the quality demands adjusted to the diabetics’ self-measurements, still apply.

Quality demands, adjusted to the diabetics 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.

4. Materials and methods

4.1. Statistical terms and expressions

4.1.1. Precision

The common 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 the precisely defined terms *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 as “good”, “acceptable” and “poor”, 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 a single measurements deviation from a 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. Accu-Chek Sensor

Accu-Chek Sensor is a blood glucose monitoring system based on biosensor technology. The system consists of a meter and dry reagent test strips designed for capillary blood glucose testing by people with diabetes or by health care professionals. The test strips used in this evaluation are calibrated to report plasma glucose values. The meter is turned on by insertion of an Accu-Chek Sensor Comfort test strip. The system requires calibration by the user (snap-in code chip). The user has to make sure that the code number displayed by the meter when the meter is activated matches the code number printed on the test strip box. The test principle of Accu-Chek Sensor is as follows: Glucose dehydrogenase converts glucose to gluconolactone. The coenzyme in the reaction is pyrroloquinolone quinone (PQQ). A current is produced by means of an electron-transporter (ferro/ferricyanid) and a redox-process. The current produced is in proportion to the glucose concentration.

The test strips are packed in a plastic bottle with flip-top closure and desiccant. The system requires a blood volume of 4 µL. The blood is drawn into the test strip and a yellow window at the test strip must be completely filled with blood. If the window is not completely filled, more blood can be applied within 15 seconds. The result is provided within 26 seconds. The meter has the capacity of storing 480 results in the memory. When analysing an Accu-Chek Sensor Comfort Control Solution, the meter has to be told it is a control. Accu-Chek Softclix adjustable lancet pen is used to form a drop of blood on the fingertip. The meter information can be downloaded to a computer. Technical data from the manufacturer is shown in table 1.

Table 1. Technical data from the manufacturer.

TECHNICAL DATA FOR ACCU-CHEK SENSOR	
Ambient temperature	14 – 40 °C
Sample volume	4 µL
Measuring time	26 seconds
Measuring range	0,6 – 33,3 mmol/L
Hematocrit	20 – 65 % for glucose concentrations < 11,1 mmol/L 20 – 55 % for glucose concentrations > 11,1 mmol/L
Memory	480 tests
Power supply	1×3V lithium battery supply (DL or CR2032)
Operating time	Approximately 1000 tests
Dimension	W= 84 mm, H= 56 mm, D= 20 mm
Weight	57 g

4.2.1. Product information, Accu-Chek Sensor

Accu-Chek Sensor blood glucose meter system
Manufactured by: Roche Diagnostics GmbH

Suppliers of Accu-Chek Sensor in the Scandinavian countries:

Sweden:	Norway:	Denmark:
Roche Diagnostics	Roche Diagnostics Norge AS	Roche a/s
Karlsbodav.30	Brynsengfaret 6B	Industriholmen 59
Box 147	PB 6610 Etterstad	2650 Hvidovre
161 26 Bromma	N-0607 Oslo	
Sweden	Norway	Denmark
Phone: +46 08-404 88 00	Phone: +47 23 37 33 00	Phone: +45 36 39 99 99
www.accuchek.roche.se	www.accu-chek.no	www.accuchek.roche.dk

79 Accu-Chek Sensor blood glucose meters were used in this evaluation.
Serial no. 8525538154 (called meter A) and serial no. 8525525786 (called meter B) were used by the biomedical laboratory scientist under the standardised and optimal conditions.
Attachment 1 gives serial numbers for the 77 meters that were used by the diabetics.

Accu-Chek Sensor Comfort Test Strips:

Lot-no. 548679	Expiry 2006-08
Lot-no. 548755	Expiry 2006-09
Lot-no. 548713	Expiry 2006-08

Accu-Chek Sensor Comfort Control 1:

Lot-no. 43010	Expiry 2006-10-27

4.3. 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 results from self-monitoring blood glucose devices (SMBG-devices) must be compared with a recognized comparison method. 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 with four levels of glucose concentrations 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 at a Reference laboratory in Belgium; Laboratory for Analytical Chemistry, University of Gent, Belgium [9]. The results are summarized in chapter 6.1.2.

The designated comparison method in this evaluation
In this evaluation, the routine method for quantitative determination of glucose in human serum, plasma (e.g. lithium heparin), urine and cerebrospinal fluid (CSF) at the Laboratory at Haraldsplass Diaconal Hospital 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 at Architect *ci*8200 System from Abbott Laboratories, with reagents and calibrators from Abbott Laboratories. The measuring principle in the Architect *ci*8200 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 NADP to NADPH. The NADPH produced absorbs light at 340 nm and can be detected spectrophotometrically as an increased absorbance.

Internal quality assurance of the Architect ci8200 comparison method during the evaluation period
The Autonorm Human Liquid Control Solutions at two levels from Sero AS were part of all the measuring series in this evaluation. The controls were measured in duplicate as the first and the last samples in all the series. The results are summarised in table 5.

4.3.1. Product information, the comparison method

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

Reagents
Glucose Reagent Kit, List No. 7D66
Lot-no. 32024HW00 Expiry 2006-06-23

Calibrator
Multiconstituent Calibrator. List No. 1E65
Lot-no. 19906M200 Expiry 2006-02-28 Reference value, cal 1 = 5,55 mmol/L
Reference value, cal 2 = 24,31 mmol/L

Internal controls
Seronorm Autonorm Human Liquid 1 and 2, Sero AS
Liquid 1: Value = 5,2 ± 0,36 mmol/L Lot-no. NO3588 Expiry 2006-01
Liquid 2: Value = 15,0 ± 1,05 mmol/L Lot-no. MI4298 Expiry 2006-07

NOKLUS controls
(ID-GCMS method; reference value from Laboratory for Analytical Chemistry, University of Gent, Belgium)
Level 1: Value = 3,20 ± 0,010 mmol/L
Level 2: Value = 7,78 ± 0,026 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
Accu-Chek Softclix Pro: Lot-no. WIP 011
Accu-Chek Softclix Pro lancets: Lot-no. WIP 45 G 3 Expiry 2008-12-31
Accu-Chek Softclix Pro lancets: Lot-no. WIR 27 H 4 Expiry 2009-12-31

Tubes used for sampling for the designated comparison method
Microvette CB 300 LH (lithium-heparin) manufactured by Sarstedt AS
Lot-no. 5070201 Expiry 2008-01

Centrifuge used for samples for the designated comparison method
Heraeus Biofuge Pico Serial no. 291323

4.4. Evaluation procedure

4.4.1. Model for the evaluation

The practical work with the evaluation was carried out during 10 weeks from October to December 2005 (from week number 42 to week number 51) at Innlandet Hospital, Gjøvik, in Norway. The practical work was done by Lise Walberg. She is a biomedical laboratory scientist.

The evaluation consisted of two parallel evaluations. One part of the evaluation was done by the biomedical laboratory scientist under standardised and optimal conditions. This part of the evaluation is done by laboratory educated personnel, completely according to the protocol and user manual after having received thoroughly training. All possibilities for disturbance of, and interference with, the measurements will be 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 diabetics. In order to determine the analytical quality of Accu-Chek Sensor by the users, 77 diabetics tested their blood glucose using Accu-Chek Sensor. The diabetics were divided into two groups (random distribution). 39 diabetics were called in and received personal training in how to use the blood glucose meter, here called the "training group". 38 diabetics received the blood glucose meter and instructions by post, here called the "post group".
The reason for dividing the diabetics into a "training group" and a "post group" is that this reflects the actual market situation regarding training when diabetics acquire blood glucose meters [2]. The model for the evaluation is shown in figure 1.

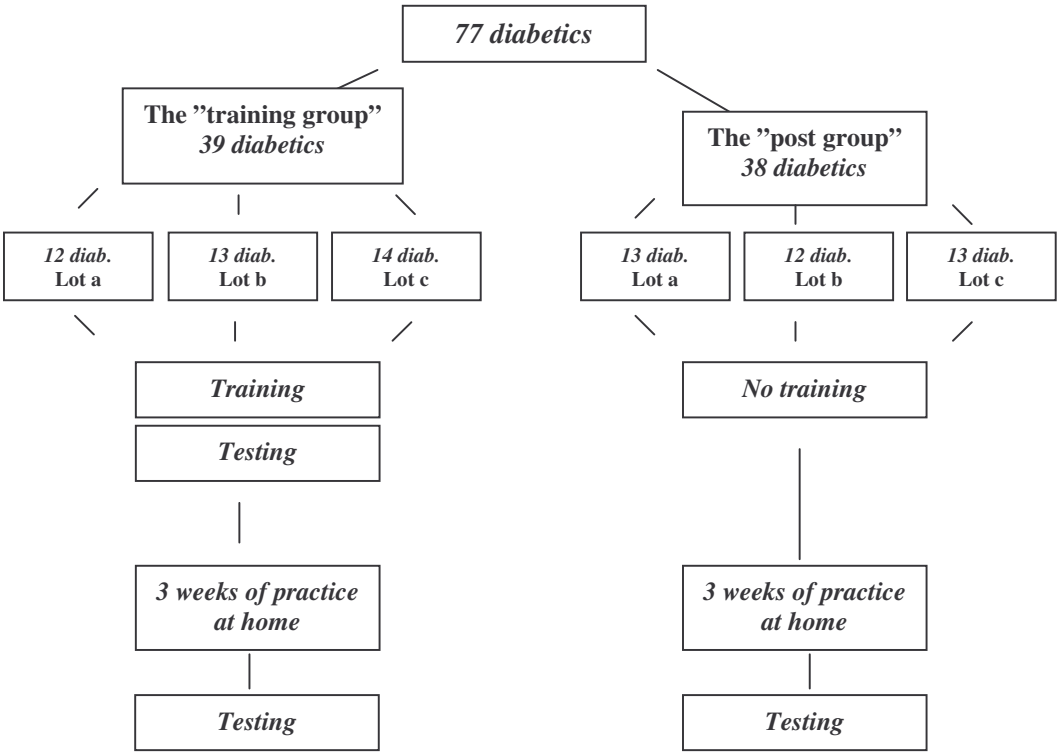

Figure 1. Model for the evaluation

All the diabetics could not participate in the user evaluation during the same weeks. The biomedical laboratory scientist had capacity to receive approximately 20 diabetics a week. The start-up was spread out over 4 weeks, and the final consultation consequently spread out correspondingly.

4.4.2. Recruiting of the diabetics

The Accu-Chek Sensor glucose meter was tested in use by 77 diabetics. The evaluation started with 85 diabetics of whom 8 did not have the opportunity to participate after all or didn't show up. The diabetics were recruited through advertisement in the daily press and by mail inquiry sent to members of the local branch of the Norwegian Diabetes Association. The group of diabetics was representative for diabetics who carry out self-monitoring of blood glucose (SMBG). The group included diabetics from across a range of self-monitoring frequencies, i.e. diabetics who performed self-monitoring often (one or more times a day) and those who performed self-monitoring less frequently (once a week). None of the diabetics used Accu-Chek Sensor as their own device, but one of the diabetics had used Accu-Chek Sensor earlier. Characteristics of the diabetics in the group are shown in table 2.

Table 2. Characteristics of diabetics included (n=77).

		Diabetics
Total		77
Sex	Men	41
	Women	36
Age (years), median and range		54 (19 – 75)
Diabetes	Type 1	28
	Type 2	42
	Don't know	7
Treatment	Insulin	38
	Insulin and tablets	8
	Tablets	22
	Diet	8
	Unspecified	1
Frequency of SMBG	Less than weekly	2
	1 -3 per week	12
	4 – 6 per week	10
	7 – 10 per week	17
	> 10 per week	32
	Doesn't measure	2
	Unspecified	2

Some of the diabetics used more than one SMBG-device at home, but only one device is registered here. The SMBG-devices that the diabetics used regularly were:
Accu-Chek Aviva (1), Accu-Chek Compact/Compact Plus (16), Ascensia Breeze/Dex/Dex 2 (6), Ascensia Contour (8), Ascensia Elite (3), Euroflash (1), FreeStyle/FreeStyle Mini (6), MediSence Precision QID (1), MediSence Precision Xtra/Xceed (7), OneTouch Basic (1), OneTouch GlucoTouch (4), OneTouch Ultra/Ultra Smart (22).

4.4.3. The "training group" at the first consultation

The 39 diabetics selected to participate in a training programme were called in two and two at the time. They received the Accu-Chek Sensor device along with test strips, lancet pen, lancets, user manual, and an instruction letter with explanations regarding what to do with the Accu-Chek Sensor 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. Lise Walberg was in charge of the training of the diabetics, after having been trained herself by a representative from Roche.

Training programme
The training programme covered a simple demonstration of how to use Accu-Chek Sensor with an explanation of the display and error messages, insertion of the test strips, blood sampling and drawing of 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 diabetics received the same instruction.

Blood sampling
After having been trained, the 39 diabetics made duplicate blood glucose tests at Accu-Chek Sensor. These results were registered for the evaluation. The biomedical laboratory scientist collected samples for the evaluation under standardised and optimal conditions (see chapter 4.4.7.). Afterwards the diabetics brought the Accu-Chek Sensor blood glucose meter home to use the meter over a three-week period. After this period, they attended a final consultation and made two new duplicate blood glucose tests, which were registered.

4.4.4. The "post group"

The 38 diabetics in the "post group" received the Accu-Chek Sensor device by post, along with test strips, lancet pen, lancets, user manual and an instruction letter with explanations regarding what to do with the Accu-Chek Sensor 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 consultation where they made duplicate blood glucose tests at Accu-Chek Sensor. The results of these tests were registered. In addition, the biomedical laboratory scientist collected samples for the evaluation under standardised and optimal conditions.

4.4.5. Use of Accu-Chek Sensor by the diabetics at home

The diabetics used Accu-Chek Sensor 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 manual at once when they receive the meter. As the diabetics should evaluate the user manual at the final consultation, it would be unfortunate if the practice period at home was too long. During the practice period the diabetics used Accu-Chek Sensor 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 diabetics familiarised themselves with the new device during the first two weeks. Each diabetic used approximately 25 test strips to measure his/her blood glucose with Accu-Chek Sensor. They could choose when to do the measurements themselves. Fasting was not necessary. If more convenient to them, they could perform the measurement at the same time as they measured their blood glucose with their own meter.

The third week

During the third week the diabetics performed five measurements in duplicate at Accu-Chek Sensor on 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 diabetics are not familiar with control solutions for self-measurements. Therefore they were not instructed to use control solution at Accu-Chek Sensor in the evaluation. To document correct functioning of the Accu-Chek Sensor-meters used by the diabetics during the test period, the biomedical laboratory scientist in charge of the practical work checked the meters with the control solution when the diabetics were called for the consultations.

4.4.6. The final consultation

Blood sampling

After the three week practice period at home, the 77 diabetics were called for, one by one, to a consultation. Each diabetic brought their assigned Accu-Chek Sensor meter and the remaining test strips to this consultation. They made duplicate blood glucose tests at Accu-Chek Sensor. 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.

The questionnaires

After all the blood samples were collected and the measurements at Accu-Chek Sensor were done, the diabetics filled in two questionnaires. The first questionnaire was about the user-friendliness of Accu-Chek Sensor device, the second about the user-manual. The questionnaires (in Norwegian) are attached to the report. After the evaluation, the diabetics could choose whether to keep Accu-Chek Sensor or return it to the project.

4.4.7. Evaluation under standardised and optimal conditions

The biomedical laboratory scientists used two Accu-Chek Sensor blood glucose meters for the evaluation (meter A and meter B). Meter A was used for one lot of test strips for all the measurements. Meter B was used for the same three lots as distributed among the diabetics. In this way, the variation between the three lots, or more precisely, the agreement of the three lots to the comparison method, can be assessed. The number of samples for each lot of 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.

Accu-Chek Sensor		Lot 548679 (n)	Lot 548755 (n)	Lot 548713 (n)
Meter A	1st consultation	39 x 2		
	2nd consultation	77 x 2		
Meter B	1st consultation	4 x 2	21 x 2	14 x 2
	2nd consultation	18 x 2	28 x 2	31 x 2
Total		138 x 2	49 x 2	45 x 2

Blood sampling

Meter A and meter B were checked by means of the manufacturer's control solution every day they were used.

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

1. The biomedical laboratory scientist took a sample for the comparison method
2. The diabetic took duplicate samples for their assigned meter
3. The biomedical laboratory scientist took samples and analysed at meter A, B, A, and B
4. The biomedical scientist took a new sample for the comparison method
5. The biomedical laboratory scientist measured internal quality control at the diabetics' meter

The duration of the sampling should not exceed 10 minutes.

The order of meter A and B was changed between each diabetic, 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 diabetic 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 glucose meter test.

At the final consultation, i.e. after the period with use of Accu-Chek Sensor at home, a venous sample for hematocrit determination was taken. Hematocrit may influence blood glucose readings, especially in meters designed for self-monitoring. This also applies to Accu-Chek Sensor. In the package insert hematocrit from 20 – 65 % for glucose concentrations < 11,1 mmol/L and hematocrit from 20 – 55 % for glucose concentrations > 11,1 mmol/L are recommended.

Handling of the samples for the comparison method
The samples for the comparison method were capillary taken using a Microvette Li-heparin tube from Sarstedt. The samples were centrifuged immediately for three minutes at 13 000 g, and plasma was separated into sample vials. The samples were frozen directly as the plasma was separated and the plasma was stored at minus 80 °C. The samples were transported under cold storage (minus 18 °C to minus 24 °C) to NOKLUS Centre where they were kept at minus 80 °C until the analysis took place.

Analysing the samples for the comparison method
The samples were analysed at Architect. Recommended minimum volume for analysis of glucose at Architect in this evaluation was 120 µL plasma. The samples were thawed at NOKLUS Centre just before they were analysed. The first and the second sample for the comparison method, taken at the start and at the end of each blood sampling, reflect the stability of the glucose concentration during the sampling time. When the paired measurements give agreeable glucose concentrations at the comparison method, the mean of the two results is 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 Accu-Chek Sensor results were excluded for accuracy and trueness calculations. Differences between 4 and 10 % are discussed and included in the calculations (see chapter 6.1.3.). 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.

The questionnaires
The biomedical laboratory scientist evaluated the user-friendliness of Accu-Chek Sensor and the user-manual. The biomedical laboratory scientist provided a description in the form of key words and looked for any defects and deficiencies or whether there was anything in the system that did not function optimally.

4.4.8. Evaluation of analytical quality

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

1. Results from 39 diabetics in the "training group" who had participated in the training programme, but not practised using the blood glucose meter at home.
2. Results from the same diabetics after they had practised using Accu-Chek Sensor at home for three weeks.
3. Results from 38 diabetics in the "post group" who had not participated in the training programme, but who had practised using Accu-Chek Sensor at home for three weeks.
4. Results from 116 measurements under standardised and optimal conditions
5. Results from 116 measurements from the comparison method.

The results from the group with and without training were compared (group 2 and 3) and the results from the group with and without practise at home (group 1 and 2) were also compared. All the diabetic measurements were evaluated against the results achieved under standardised and optimal conditions. User-friendliness and user-manual were evaluated by means of questionnaires.

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

5. Statistical calculations

5.1. Number of samples

77 diabetics completed the evaluation. The 39 diabetics in the "training group" met at two consultations and the 38 diabetics in the "post group" met at one consultation. Blood samples were taken at each consultation. This means that the total number of samples is
116 x 2 (duplicates) x 4 (meter A, meter B, diabetic's meter, comparison method) = 928 samples.

5.2. Statistical outliers

All results are checked for outliers according to Burnett [10], with repeated truncations. 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. 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 all calculations. Possible outliers will be commented on under each table.

5.3. Missing or excluded results

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

- ID 313 and ID 383 had no hematocrit result and are missing from calculation regarding the effect of hematocrit.
- In the calculation of repeatability based on the diabetics' measurements at home some measurements are missing. ID 354, ID 368, ID 377, ID 393 and ID 413 had only four duplicate measurements. ID 379 and ID 388 had only one duplicate measurement. ID 364 had not done home measurements. This means that 18 results are missing from this calculation.

5.4. Calculations of imprecision based on duplicate results

Two capillary samples were taken of each diabetic to meter A, meter B, the diabetic's meter and to the comparison method at each consultation. The imprecision was calculated by use of paired measurements, 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 two and two paired measurements, the SD 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 there must be no systematic difference between the 1st and the 2nd measurement. Table 4 shows that there is no systematic difference in glucose

concentration between the paired measurements at Accu-Chek Sensor in this evaluation (see comments below table 4).

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
Accu-Chek Sensor	Meter A	< 7	5,3	5,4	0,09	0,02 – 0,16	43
		7 – 10	8,4	8,4	0,01	-0,12 – 0,14	31
		> 10	13,6	13,6	0,04	-0,14 – 0,22	42
	Meter B	< 7	5,3	5,4	0,13	0,06 – 0,20	44
		7 – 10	8,4	8,3	-0,06	-0,21 – 0,09	29
		> 10	13,5	13,5	0,03	-0,14 – 0,20	43

Comments
The difference in glucose concentration between the first and the second measurement of the paired results is negligible. Four of the six differences are not significant. At the glucose concentration level < 7 mmol/L at meter A and at meter B there is a small and statistical significant difference, but the difference is of no importance here.

5.5. Calculation of trueness

To measure the trueness of the measurements at Accu-Chek Sensor, 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 at the comparison method and the mean result at Accu-Chek Sensor meter A.

5.6. Calculation of accuracy

To evaluate the accuracy of the results at Accu-Chek Sensor, the agreement between Accu-Chek Sensor and the comparison method is illustrated in difference plots. In the plots the x-axis represents the mean value of the duplicate results at the comparison method. The y-axis shows the difference between the first measurement at Accu-Chek Sensor meter B with three lots and the mean value of the duplicate results at the comparison method.

6. Results and discussion

6.1. Precision and trueness of the designated comparison method

6.1.1. 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 diabetic samples 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 with a time gap between the first and the second sample for each diabetic. 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 sampling, and not the precision of the method (see 6.1.3). To get a good estimate of the repeatability of the comparison method in this evaluation, the results from the documentation of the trueness were used. Both the NIST-standards and the NOKLUS controls are genuine patient materials with no additives, and the standards and 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 repeatability is calculated as a combined CV %.

The reproducibility of the comparison method is shown in table 5. The results are obtained with the internal control solution at two levels of glucose concentrations. The controls were analysed in duplicate in the beginning and at the end of each series of samples, giving a total number of more than 100 results. In table 5 only the first result in each series is included. All of the results were inside the limits of the target values for the controls. The results are shown in attachment 3.

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

Control Solution	Target value glucose (mmol/L)	Mean value glucose (mmol/L)	n	Outliers	CV % (95 % CI)
Autonorm 1	5,2 ± 0,36	5,0	46	0	1,5 (1,2 – 1,9)
Autonorm 2	15,0 ± 1,05	14,7	46	0	1,3 (1,1 – 1,6)

Discussion

The precision of the comparison method is good. The repeatability is approximately 1,0 CV% (see table 6 and 7) and the reproducibility is approximately 1,5 CV%.

6.1.2. 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 at several occasions during the evaluation period. SRM 965a consists of ampoules with human serum with certified concentrations and uncertainties for glucose at four concentrations. The SRM 965a materials cover a glucose concentration range from 1,9 to 16,2 mmol/L.

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 at the comparison method during the evaluation period.

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	30.11.05	**1,918** (1,898 - 1,938)	1,9	5	0,0 *	0
	05.01.06		1,9	5		0
	25.01.06		1,9	5		0
	Total		**1,9**	**15**		**0**
Level 2	30.11.05	**4,357** (4,309 - 4,405)	4,38	5	0,8 (0,6 – 1,3)	0,5
	05.01.06		4,38	5		0,5
	25.01.06		4,40	5		1,0
	Total		**4,39**	**15**		**0,7**
Level 3	30.11.05	**6,777** (6,704 - 6,850)	6,82	5	0,5 (0,4 – 0,9)	0,6
	06.01.06		6,78	5		0,0
	25.01.06		6,80	5		0,3
	Total		**6,80**	**15**		**0,3**
Level 4	30.11.05	**16,24** (16,05 - 16,43)	16,24	5	0,5 (0,4 – 0,8)	0,0
	06.01.06		16,34	5		0,6
	25.01.06		16,26	5		0,1
	Total		**16,28**	**15**		**0,2**

* The comparison method gives values with only one decimal. All the measurements at level 1 gave the result 1,9 mmol/L, and thereby the CV at this level is 0,0 %.

To verify the trueness of the comparison method, 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 at a Reference laboratory in Belgium; Laboratory for Analytical Chemistry, University of Gent, Belgium [9].
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 at the comparison method during the test period.

Control solution	Date	Target value from Reference lab. in Belgium (mmol/L)	Mean value glucose (mmol/L)	n	Outliers	Combined CV% (95% CI)	% deviation from target value
NOKLUS 1	14.12.05	3,20	3,20	6		1,2 (0,9 – 2,1)	0,0
	11.01.06		3,15	6			-1,6
	Total		**3,18**	**12**	**0**		**-0,8**
NOKLUS 2	14.12.05	7,78	7,73	6		0,8 (0,5 – 1,3)	-0,6
	11.01.06		7,80	6			+0,3
	Total		**7,77**	**12**	**0**		**-0,2**

Discussion
The trueness of the comparison method is very satisfactory.

6.1.3. Stability of the glucose concentration during sampling

The first and the second sample for the comparison method, taken at the start and at the end of each blood sampling, reflect the stability of the glucose concentration during the sampling time (see chapter 4.4.7). Deviations > 10 % are regarded as not acceptable in an evaluation like this and such results are excluded without further discussion. In this evaluation no samples had a deviation > 10 %. Four samples with a low glucose concentration (below 5,5 mmol/L) had a difference just over the limit at 0,22 mmol/L, but are still included in the calculations. 14 of 116 paired results at the comparison method gave deviations between 4 and 10 %. For 10 of these 14 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 18 results. The percentage number of results that falls within the different quality limits is not dependent on keeping or excluding these results. In both cases, the final results in the evaluation fulfil the quality goals set by ISO.

6.2. Precision, trueness and accuracy of Accu-Chek Sensor

6.2.1. The precision of Accu-Chek Sensor

The Accu-Chek Sensor meters in the user evaluation were checked by the biomedical laboratory scientists with the manufacturer's control solution. All of the results were inside the limits of the control.

All results from the calculations 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 is shown in table 8. The table gives the results from the biomedical laboratory scientists' measurements at the first and the final consultation together. Raw data is shown in attachment 4.

Table 8. Accu-Chek Sensor – Repeatability (results with diabetic samples) measured under standard and optimal conditions.

Accu-Chek Sensor	Glucose level (mmol/L)	Mean value glucose (mmol/L)	n	Outliers	CV % (95 % CI)
Meter A	< 7	5,4	43	0	3,2 (2,6 – 4,1)
Meter B	< 7	5,3	44	0	3,4 (2,8 – 4,4)
Meter A	7 – 10	8,4	31	0	2,9 (2,3 – 3,9)
Meter B	7 – 10	8,4	29	0	3,3 (2,6 – 4,5)
Meter A	> 10	13,6	42	0	3,0 (2,5 – 3,8)
Meter B	> 10	13,5	43	0	2,9 (2,4 – 3,7)

Repeatability obtained by the diabetics

The repeatability obtained by the diabetics with capillary blood samples is shown in table 9. The table gives the results from the measurements at the first and second consultation for the "training group", the consultation for the "post group", together with the results they obtained at home. The results obtained at home of course have 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 diabetics did not quite understand "the recipe" on how to perform and report the five duplicate measurements they were supposed to carry out according to the written instruction they had received.

Raw data from the diabetics' measurements at NOKLUS is shown in attachment 5.
Raw data from the diabetics' measurements at home is shown in attachment 6.

Table 9. Accu-Chek Sensor – Repeatability (results with diabetic samples) measured by the "training group" and the "post group".

Accu-Chek Sensor	Consultation/diabetic group	Glucose level (mmol/L)	Mean value glucose (mmol/L)	n	Outliers	CV % (95 % CI)
At NOKLUS	1st/training group	< 7	5,1	15	0	4,0 (3,0 – 6,4)
	2nd/training group	< 7	5,1	18	0	2,7 (2,0 – 4,1)
	The "post group"	< 7	5,7	10	0	2,5 (1,7 – 4,6)
At home***		< 7	5,3	133	3	5,5 (4,9 – 6,3)
At NOKLUS	1st/training group	7 – 10	7,9	8	1*	2,8 (1,8 – 6,1)
	2nd/training group	7 – 10	8,3	8	0	4,3 (2,9 – 8,9)
	The "post group"	7 – 10	8,6	13	0	2,3 (1,7 – 3,8)
At home***		7 – 10	8,4	124	3	4,7 (4,2 – 5,4)
At NOKLUS	1st/training group	> 10	13,0	16	0	3,8 (2,8 – 5,8)
	2nd/training group	> 10	15,4	13	0	8,7 (6,3 – 14,4)**
	The "post group"	> 10	12,8	15	0	4,3 (3,2 – 6,8)
At home***		> 10	12,7	103	1	7,5 (6,7 – 8,8)

* One result excluded after visual inspection.

** In this group one result with duplicate measurements at 12,5 and 17,7 mmol/L has a considerable effect on the CV. The difference between the two measurements is still not large enough to be noticed as a statistical outlier, mainly because the number of results in the group is low. The result is not excluded, but appears as a non-typical result. The actual CV is 5,9 % without this result.

*** 18 home measurements are missing and 7 outliers among the home measurements are excluded.

Reproducibility with Internal Quality Control

The results for reproducibility are obtained with the Accu-Chek Sensor Comfort Control 1. The measurements are carried out at meter A and B during the whole evaluation period. The reproducibility of Accu-Chek Sensor at meter A and B is shown in table 10.

Internal Quality Control at the diabetics' meters

The control measurements at the diabetics' meters were done with the Accu-Chek Sensor Comfort Control 1. All the control measurements are done by the biomedical laboratory scientist with the test strips that were distributed to each diabetic. The control solution was kept at NOKLUS during the evaluation period. The imprecision at all the meters of the diabetics is shown in table 11.

Raw data for all measurements with the internal quality control is shown in attachment 7.

Table 10. Accu-Chek Sensor – Reproducibility (results with Accu-Chek Sensor Comfort Control 1) measured by the biomedical laboratory scientist at meter A and meter B.

Accu-Chek Sensor	Lot of strips	Target value (mmol/L)	Mean value glucose (mmol/L)	n	Outliers	CV % (95 % CI)
Meter A	548679	2,3 – 4,0	3,0	23	0	5,8 (4,5 – 8,2)
Meter B	548679	2,3 – 4,0	3,0	4	0	3,2 (1,8 – 11,8)
	548755	2,4 – 4,1	2,9	13	0	5,5 (3,9 – 9,1)
	548713	2,4 – 4,1	3,0	8	0	4,0 (2,6 – 8,1)

Table 11. Accu-Chek Sensor – Imprecision (results with Accu-Chek Sensor Comfort Control 1) measured by the biomedical laboratory scientist at the diabetics' meters.

Accu-Chek Sensor	Lot of strips	Target value (mmol/L)	Mean value glucose (mmol/L)	n	Outliers	CV % (95 % CI)
1st consultation						
The diabetics' meters	548679	2,3 – 4,0	3,1	12	0	4,6 (3,2 – 7,7)
	548755	2,4 – 4,1	2,8	13	0	5,1 (3,7 – 8,5)
	548713	2,4 – 4,1	3,0	14	0	4,9 (3,6 – 7,9)
2nd consultation						
The diabetics' meters	548679	2,3 – 4,0	3,2	25	0	5,1 (4,0 – 7,1)
	548755	2,4 – 4,1	3,0	25	0	5,9 (4,6 – 8,3)
	548713	2,4 – 4,1	3,1	27	0	7,6 (6,0 – 10,4)

Discussion

The precision at Accu-Chek Sensor is acceptable. The repeatability obtained under standardised and optimal conditions is approximately 3 %. The repeatability obtained at NOKLUS when the measurements are performed by the diabetics, is acceptable with a CV between 2 and 6 %. As mentioned below table 9, the relative weak CV at glucose level > 10 mmol/L in the "training group" at the final consultation is due to one single result. The CVs for the groups with and without training programme (the "training group" and the "post group") are not significantly different. The CVs for the groups with and without practise at home (1st and 2nd training) are not significantly different either. This indicates that Accu-Chek Sensor is a robust system, easy to use, and that training is not essential for a good result. The results at home show that the diabetics have been practising with the new system according to the instructions, but one should not make a point of the calculated CV values.

The reproducibility at Accu-Chek Sensor was acceptable when measured with an internal control solution. The CV was approximately 5 %.

6.2.2. The trueness of Accu-Chek Sensor

The trueness of Accu-Chek Sensor is calculated from the results achieved by the biomedical laboratory scientist at the final consultation (the "training group" and the "post group"). The calculations are based on measurements at meter A with lot-no. 548679 and are shown in table 12.

Raw data from the samples at the comparison method is shown in attachment 8.

Table 12. Mean difference between Accu-Chek Sensor and the comparison method, based on the mean of each duplicate at both methods. 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	5,5	5,6	8,7	8,9	13,8	14,1
Mean deviation from the comparison method, mmol/L (95 % CI)	0,14 (0,03 – 0,24)		0,22 (0,01 – 0,43)		0,30 (-0,02 – 0,61)	
n	30		23		24	
Outliers	0		0		0	

Discussion

The trueness of Accu-Chek Sensor is good. Table 12 shows that there is a small, but significant bias between Accu-Chek Sensor and Architect. Accu-Chek Sensor gives glucose values from 0,1 – 0,3 mmol/L higher than the comparison method. This bias has no importance and the results still fulfil the quality goal set by ISO.

6.2.3. The accuracy of Accu-Chek Sensor

To evaluate the accuracy of the results at Accu-Chek Sensor, the agreement between Accu-Chek Sensor and the comparison method is illustrated in two difference plots. The plots show the deviation of single measurement results at Accu-Chek Sensor from the true value, and give a picture of both random and systematic deviation and reflect the total measuring error at Accu-Chek Sensor. The total error is demonstrated for the first measurements of the paired results, only. At meter A only one lot of test strips were used. At meter B three different lots were used. The same three lots were randomly distributed between the diabetics.

The limits in the plots are based upon the quality goals discussed in chapter 3 in this report. Under standardised and optimal measuring conditions the ISO-goal at ± 20 % is used. For the diabetics' self-measurements the "adjusted ISO-goal" at ± 25 % is used.

The accuracy, Accu-Chek Sensor meter B, under standardised and optimal measuring conditions, with the first measurements at the final consultation is shown in figure 2.
The accuracy, Accu-Chek Sensor, as measured by the diabetics with the first measurement at the final consultation is shown in figure 3.
The accuracy is summarised in table 13 and discussed afterwards.

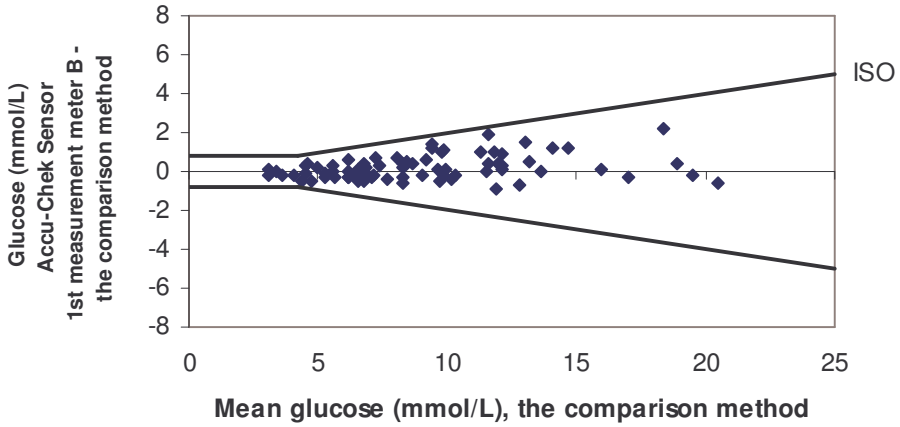

Figure 2. Accuracy. Accu-Chek Sensor meter B (three lots of test strips) under standardised and optimal measuring conditions at the final consultation. The x-axis represents the mean value of the duplicate results at the comparison method. The y-axis shows the difference between the first measurement at Accu-Chek Sensor and the mean value of the duplicate results at the comparison method, n = 77.

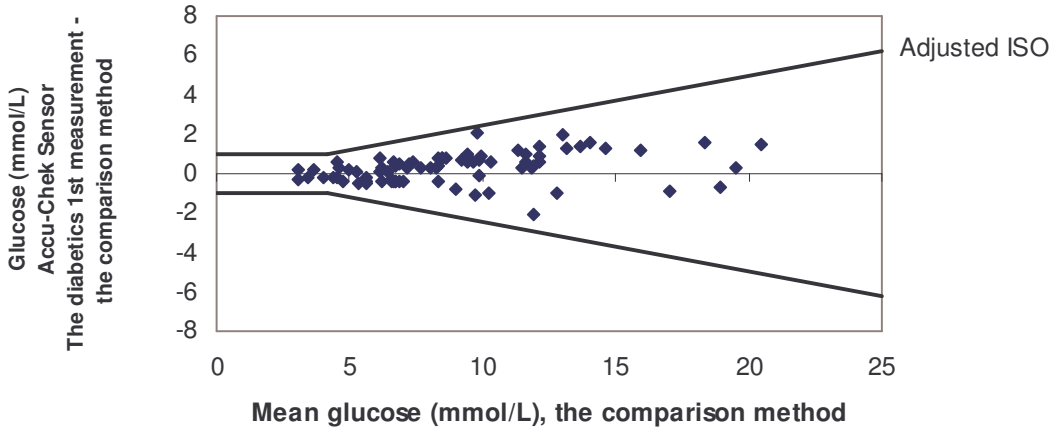

Figure 3. Accuracy. The diabetics' self-measurements at the final consultation. Three lots of test strips.
The x-axis represents the mean value of the duplicate results at the comparison method. The y-axis shows the difference between the first measurement at Accu-Chek Sensor and the mean value of the duplicate results at the comparison method, n = 77.

Table 13. Total error of Accu-Chek Sensor results compared to the comparison method. Percentage Accu-Chek Sensor results within the quality 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 scientist	1st	A 1st measurement	39	92	100		
		B 1st measurement	39	92	100		
Biomedical laboratory scientist	2nd	A 1st measurement	77	91	100		
		B 1st measurement	77	88	100		2
Diabetics at NOKLUS	1st	1st measurement	39	85	97	97	
	2nd	1st measurement	77	87	99	100	3

Discussion

Figure 2 shows that all the results obtained under standardised and optimal measuring conditions are within the ISO-limits. The summing up in table 13 shows that all the first measurements at the first and the final consultation are within the ISO-limits.

Figure 3 shows that all the diabetics' first self-measurements at the final consultation fulfil the "adjusted ISO-goal". The results also fulfil the ISO-goal, as shown in table 13. All the results are within the "adjusted ISO-goal" and 99 % are within the ISO-goal.

Assessment of accuracy

The Accu-Chek Sensor device fulfils the quality goals set in the ISO 15197 when used under standardised and optimal conditions. The quality goals are also met by the measurements of the diabetics.

6.3. Variation between three lots of test strips

All the measurements at meter A were performed with one lot of test strips. The measurements at meter B were performed with three different lots of test strips, in three different groups of diabetics. The three lots can not be compared with each other because the mean glucose concentrations in the three groups of diabetics are different. To measure the variation between the three lots, all the mean glucose results at Accu-Chek Sensor obtained under standardised and optimal conditions at 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 at meter B and the comparison method under standardised and optimal conditions at the final consultation.

	The comparison method	**Meter B Lot 548679**	**The comparison method**	**Meter B Lot 548755**	**The comparison method**	**Meter B Lot 548713**
Mean glucose, mmol/L	8,5	8,8	9,5	9,6	8,9	9,1
Mean deviation from the comparison method, mmol/L (95 % CI)	0,33 (0,03 – 0,62)		0,14 (-0,05 – 0,33)		0,24 (0,07 – 0,41)	
n	18		28		31	
Outliers	0		0		0	

Discussion
Lot 548755 gives glucose results in agreement with the comparison method. Lot 548679 and lot 548713 gives significantly higher values than the comparison method, but the results are still within the ISO-limits.

6.4. Effect of hematocrit

The package insert of Accu-Chek Sensor Comfort Glucose test strips states that glucose concentrations < 11,1 mmol/L are not affected by hematocrit values between 20 – 65 % and glucose concentrations > 11,1 mmol/L are not effected by hematocrit values between 20 – 55 %. To measure the effect of hematocrit at Accu-Chek Sensor, a venous sample was taken of the diabetics (voluntary) at the second consultation. Unfortunately there is no hematocrit result for two of the diabetics and they are therefore missing from this calculation.

The measurements at Accu-Chek Sensor are performed under standardised and optimal measuring conditions. The glucose concentration range in the samples was from 3,1 to 20,5 mmol/L. The hematocrit range was 35 – 50 %.

The effect of hematocrit is shown in figure 4 and figure 5. The x-axis in the plots shows the hematocrit value and the y-axis shows the difference in glucose concentration between Accu-Chek Sensor and the comparison method (Accu-Chek Sensor – the comparison method). In figure 4 the difference in glucose concentration is shown in mmol/L, and in figure 5 the difference is shown in %. Raw data is shown in attachment 9.

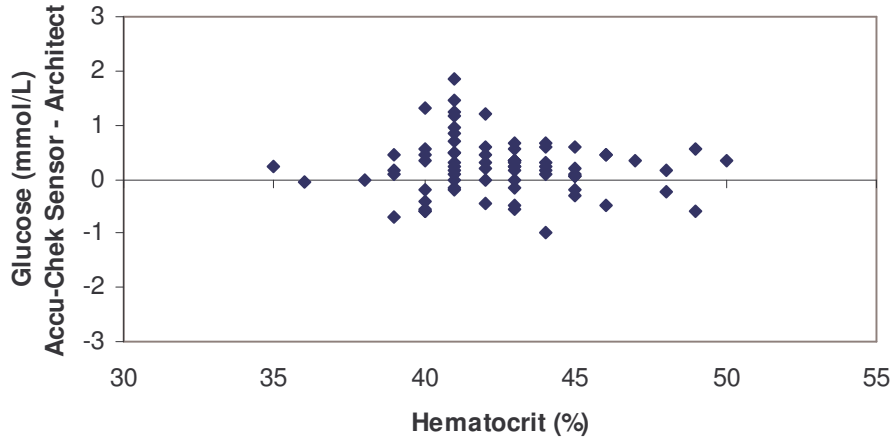

Figure 4. The effect of hematocrit at glucose measurements (in mmol/L) at Accu-Chek Sensor under standardised and optimal conditions. The x-axis shows the hematocrit value in %. The y-axis shows the difference in glucose concentration between Accu-Chek Sensor and the comparison method in mmol/L, n= 75

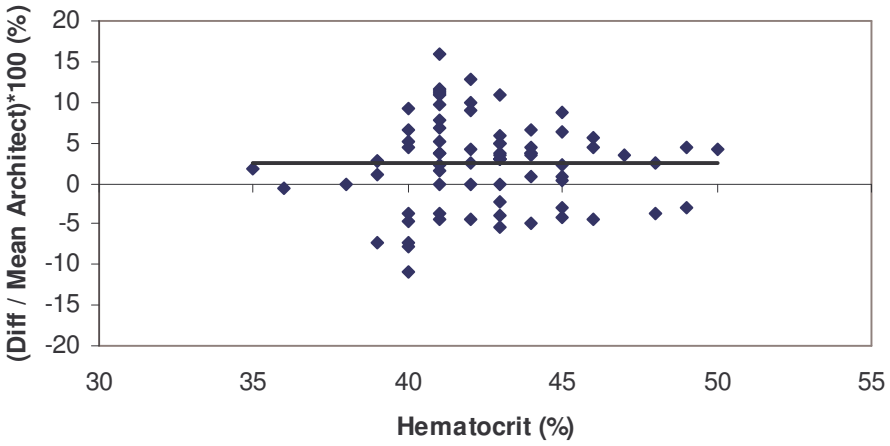

Figure 5. The effect of hematocrit at glucose measurements at Accu-Chek Sensor under standardised and optimal conditions. The x-axis shows the hematocrit value in %. The y-axis shows the difference in glucose concentration between Accu-Chek Senor and the comparison method (Accu-Chek Sensor – the comparison method) in %, n=75

- ID 313 and ID 383 have no hematocrit result and are excluded.

Discussion

The trend-line in figure 5 shows that the glucose measurements at Accu-Chek Sensor do not seem to be affected by hematocrit values between 35 – 50 %. Hematocrit values outside this range have not been tested.

7. Practical points of view

Questionnaires

Each diabetic filled in a questionnaire about the user-friendliness and a questionnaire about the user manual of Accu-Chek Sensor when they attended the final consultation (n = 77). Some diabetics needed assistance in filling in the questionnaires.

Questionnaire about the user-friendliness (in Norwegian), see attachment 10.
Questionnaire about the user manual (in Norwegian), see attachment 11.

7.1. Evaluation of user-friendliness of Accu-Chek Sensor

The questionnaire about the user-friendliness had nine questions concerning Accu-Chek Sensor. Table 15 summarizes six questions where the diabetics were asked to rank the answers on a scale from 1 to 6, where 1 is difficult and 6 is simple. The mean is 5,8 and 5,3 on the questions about inserting a strip into the meter and about filling the strip with blood, respectively. This indicates that the diabetics seemed satisfied with the use of the test strip. The diabetics also seemed satisfied with use of the meter. The mean is between 5,2 and 6,0 on the questions about coding the meter, reading the figures in the display, and operating the meter, all in all.

Table 15. Accu-Chek Sensor - Questions about the meter.

Questions about Accu-Chek Sensor		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:	1. To code the meter	5,6	3 – 6	0	77
	2. To insert a strip into the meter	5,8	3 – 6	0	77
	3. To fill the strip with blood	5,3	2 – 6	0	77
	4. To read the figures in the display	6,0	5 – 6	0	77
	5. To recognize the meters' sound signal	5,6	1 – 6	3	77
	6. All in all, to operate the meter	5,2	1 - 6	0	77

Table 16 shows the answers to the last question about Accu-Chek Sensor. 17 of the 77 diabetics answered that they had technical problems with the meter during the testing period. Written comments indicate that these problems were not technical ones but 14 of the 17 diabetics commented problems with the batteries.

Table 16. Accu-Chek Sensor – Questions about the meter.

Question about Accu-Chek Sensor	Yes (%)	No (%)	Not answered (%)	Total number
Did you have any technical problems with the meter during the testing period?	22	55	23	77

Positive comments
42 diabetics reported one or more advantages with Accu-Chek Sensor. The advantages reported are distinctly grouped as follows:

1. easy to use (18)
2. to read the figures in the display/good display (9)
3. the test strips were easy to use/large test strips (9)
4. the small size of the meter (6)
5. calculates average values (5)
6. practical carrying case (4)
7. easy to code the meter (3)
8. good lancet pen (3)
9. the meter has short measuring time (2)

Negative comments
41 diabetics reported one or more disadvantages with Accu-Chek Sensor. The most often reported disadvantages are distinctly grouped as follows:

1. the measuring time is too long (30)
2. the meter/strip needs large blood sample volume (10)
3. different comments about the strips (for instance too big, have to change every time) (6)

One of the diabetics commented that the meter ought not to give any answer if too little blood sample volume was applied.

7.2. Evaluation of the user manual for Accu-Chek Sensor

On the questionnaire about the user manual each diabetic was first asked whether he/she had used the manual. If not, they were to ignore the rest of the questions in the questionnaire.

Table 17 shows that 94 % of the diabetics had used the user manual, i.e. 72 of the 77 diabetics that participated in the study. 97 % answered they were satisfied with the description of how to perform a blood glucose measurement with this meter. One of the diabetics thought the manual had essential shortcomings, but the diabetic did not mentioned what was missing. 96 % of the diabetics were quite satisfied with the user manual

Table 17. Accu-Chek Sensor – Questions about the user manual.

Questions about the user manual	Yes (%)	No (%)	Not answered (%)	Number
Have you been reading in the user manual?	94	5	1	77
If yes, did you read the entire user manual?	48	45	7	73
And/or did you consult the user manual when needed?	64	14	22	73
1. Are you satisfied with the description of how to perform a blood glucose measurement with this meter?	97	1	1	73
2. Do you think the user manual has essential shortcomings?	1	90	8	73
3. All in all, are you satisfied with the user manual?	96	3	1	73

7.3. The biomedical laboratory scientists' evaluation

The biomedical laboratory scientist thought Accu-Chek Sensor was easy to use. Her positive comments was that the test strips were big and easy to use, it was an advantage that she could do a visual inspection to see if the strip was completely filled and she thought it was easy to code the meter. Her negative comments were that in proportion to newer meters the Accu-Chek Sensor needs a large blood sample volume and has a long measuring time. At the start of the evaluation she had to replace one of her meters because of problems with the power. Problems with the power also occurred for some of the diabetics. The biomedical laboratory scientist got phone calls from diabetics with this problem, she had to send new batteries to some of them and she had to either change batteries or put them in better place in many of the diabetics' meters before they could do any measurements with them. The biomedical laboratory scientist was satisfied with the user manual and also with the short version of the manual.

8. References

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9. Attachments

1. Serial numbers, Accu-Chek Sensor meters
2. Information letter to the diabetics (in Norwegian)
3. Raw data, internal quality control, Architect
4. Raw data, Accu-Chek Sensor results under standardised conditions, meter A and B
5. Raw data, Accu-Chek Sensor results, the diabetics measurements at NOKLUS
6. Raw data, Accu-Chek Sensor results, the diabetics measurements at home
7. Raw data, internal quality control, Accu-Chek Sensor
8. Raw data, Architect results, diabetics
9. Raw data, hematocrit
10. Questionnaire, user-friendliness (in Norwegian)
11. Questionnaire, user manual (in Norwegian)
12. SKUP evaluations

Attachments with raw data are included only in the report to Roche Diagnostics.