ACCU-CHEK® Compact Plus

A meter designed for glucose self-measurement manufactured by Roche Diagnostics

Report from an evaluation organised by

SKUP

The evaluation was ordered by Roche Diagnostics Norge AS

SKUP/2005/43

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

Summary

Background
Accu-Chek Compact Plus is a meter designed for glucose self-measurements by diabetics. The meter is produced by Roche and is supplied in Scandinavia by Roche Diagnostics. Accu-Chek Compact Plus was launched onto the Norwegian market in May 2005.

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 Compact Plus is done under the direction of SKUP during the spring of 2005.

The aim of the evaluation
The aim of the evaluation of Accu-Chek Compact Plus is to

- reflect the analytical quality under standardised and optimal conditions (performed by biomedical laboratory scientists)
- reflect the analytical quality by the users (80 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 Compact Plus regarding user-friendliness
- evaluate the Accu-Chek Compact Plus user-manual

Materials and methods
80 diabetics took part in the evaluation. 40 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 Compact Plus before they did a finger prick and performed two measurements on the meter. The biomedical laboratory scientists also took capillary samples of the diabetics and measured twice at Accu-Chek Compact Plus. In addition, two capillary samples were taken to a designated comparison method. The post group received the Accu-Chek Compact Plus 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 Compact Plus.

Results

- Accu-Chek Compact Plus shows acceptable precision. The CV is approximately 3 % under standardised and optimal measuring conditions and between 3 and 6 % when the measurements are performed by diabetics.
- The agreement with a designated comparison method is good. Quality goals set in ISO 15197 are achieved under standardised and optimal measuring conditions, and at the final consultation even the quality goals set by ADA are achieved. When handled by the diabetics, Accu-Chek Compact Plus also shows accurate results. 100 % of these results are within the "adjusted ISO-goal" and 99 % are also within the quality goals set in ISO 15197.
- One of the three lots of test strips that were used showed significantly lower values than the comparison method. In spite of this deviation, the results attain the quality goal.
- Glucose measurements at Accu-Chek Compact Plus seem to be affected by the hematocrit values of the samples in higher degree than described in the package insert. Glucose values are over-estimated when the hematocrit is below 35 %. With hematocrit values over approximately 45 % the glucose values are under-estimated.
- The diabetics summarise the Accu-Chek Compact Plus device as easy to use. As a whole they were pleased with the device. The diabetics that had used the user manual were satisfied with the manual.

Conclusion

Glucose measurements on Accu-Chek Compact Plus 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-goal. One of the three lots of test strips that were used showed significantly lower values than the comparison method, but the results are still within the ISO-goal. The glucose results in this evaluation are affected by hematocrit in a higher degree than described in the package insert. In spite of the hematocrit effect, the glucose results still fulfil the quality goal set by ISO. The users find the Accu-Chek Compact Plus 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.

1. The organisation of SKUP

Scandinavian evaluation of laboratory equipment for primary health care, SKUP, is a cooperative venture by Norway, Sweden and Denmark. SKUP was established in the autumn of 1997 at the initiative of professionals and health authorities in the three countries. SKUP is led by a Scandinavian expert group. The secretariat is located at NOKLUS Centre in Bergen, Norway.

The goal of SKUP is to produce objective and independent information concerning the quality and user-friendliness of laboratory equipment for physicians' offices outside the hospital. This information is generated by organizing SKUP's own evaluation program.

The SKUP evaluation is standardised according to SKUP's general evaluation guidelines. The evaluation follows a protocol based on these guidelines, but the protocol is always adjusted to the actual evaluation in cooperation with the supplier. The SKUP evaluation consists of two comparable parts. One part of the evaluation is done under standardised and optimal measuring conditions and the other part is performed by the users the equipment is produced for. Primarily, SKUP evaluates equipment intended for the primary health care, but SKUP can also offer evaluations of equipment for self monitoring blood glucose (SMBG). The evaluations of SMBG are conducted under standardised and optimal conditions and among diabetics.

SKUP personnel are financed with funds from their respective countries, while the actual testing is funded by the equipment suppliers. For suppliers SKUP offers an opportunity to have their equipment subjected to standardised testing all over Scandinavia. For consumers it means easy access to objective information on equipment, and health care authorities will be able to gain an overview of the equipment (and its quality) available on the market at any given time.

SKUP distributes information about evaluated equipment to physicians' offices, laboratory medical councils, laboratory advisors and health political authorities. The evaluation reports are presented at www.skup.nu.

A unique evaluation code number is assigned to every SKUP evaluation report. The code is composed of the name SKUP, and the year and number of the evaluation. This applies for all evaluations following the complete SKUP standard evaluation procedure. Pre marketing evaluations, evaluations without the user's contribution, supplementary evaluations and special evaluations on request from the producer/supplier are in addition marked with a star in connection to the evaluation number. If the company makes use of SKUP's name in the marketing of an instrument, they have to refer to www.skup.nu and the actual evaluation number at the same time. If required, the company can get access to a SKUP logo where this information is an integral part.

2. Planning of the evaluation

Mette Engebretsen from Roche Diagnostics, Norway, applied to SKUP in the autumn of 2004 for an evaluation of the glucose meter Accu-Chek Compact Plus. In October 2004 SKUP gave a written offer, and April 1st 2005 a preliminary suggestion regarding how to organise the evaluation was sent. The protocol for the evaluation of Accu-Chek Compact Plus was accepted April 11th 2005. A contract was set up between Roche and SKUP in June 2005. The Laboratory at Haraldsplass Diaconal Hospital accepted to carry out the analytical part of the evaluation dealing with the samples for the comparison method.

The Accu-Chek Compact Plus system is produced and supplied by Roche Diagnostics. The system was launched onto the Norwegian market in May 2005. SKUP carried out a user-evaluation of Accu-Chek Compact Plus blood glucose meter system during the spring of 2005. Further on in the report Accu-Chek Compact Plus will be referred to as Compact Plus.

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 two biomedical laboratory scientists (see chapter 4.1.1.)
- An examination of analytical quality among approximately 80 diabetics
- An examination of agreement between Compact Plus and a designated comparison method
- A comparison of analytical quality among diabetics with and without 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 Compact Plus
- An evaluation of the user-manual of Compact Plus

The blood sampling of the diabetics and the measurements on Compact Plus under standardised and optimal conditions, were done by Ingunn Barli and Tone C. Hovelsen, biomedical laboratory scientists, SKUP/NOKLUS Central Norway, Levanger Hospital. 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.

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. Compact Plus 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 Compact Plus 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 requirement should apply for measurements by the diabetics. Previous investigations under the direction of the NOKLUS-project ”Diabetes-Self-measurements” [5,7], and results from evaluations under the direction of SKUP, have showed that few of the self-monitoring glucose meters that were tested met the ISO-requirements. The results by the diabetics therefore have to be discussed towards a *modified* goal suggested by NOKLUS, with a total error of 25 %. This modified goal has wide, and not ideal, limits. The modified requirements for diabetics will be tightened up over time as the meters improve due to technological development.

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 and are expressed by means of the standard deviation (SD) or coefficient of variation (CV). Precision is descriptive in general terms (good, poor), whereas imprecision is an estimate, reported in the same unit as the analytical result (SD) or in % (CV). 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. Compact Plus

Compact Plus is a blood glucose monitoring system based on reflectometrical 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 is calibrated to report plasma glucose values. Compact Plus uses drums with 17 test strips, and the meter is automatically calibrated when inserting a new drum. An electronic check is performed automatically and a test strip is pushed forward when the meter is turned on with a button. The system requires a blood volume of 1.5 µL and provides a result within 5 seconds. The test principle of Compact Plus is as follows: Glucose oxidoreductase splits glucose. The coenzyme in the reaction is pyrroloquinolone quinone (PQQ). An indicator changes from yellow to blue by means of a mediator and a redox-process. The blue colour is read reflectometrically.

The meter has the capacity of storing 300 results in memory. Accu-Chek Softclix Plus lancet pen is fastened to the Compact Plus meter. The lancet pen can be used either when fastened to the meter or it can be taken off the meter. The meter information can be downloaded to a computer through the meter's data port by means of Accu-Chek Infrared Cable. Compact Plus have a sound mood for weak-sighted. Technical data from the manufacturer is shown in table 1.

Table 1. Technical data from the manufacturer.

TECHNICAL DATA FOR ACCU-CHEK COMPACT PLUS	
Ambient temperature	10 – 40 °C
Sample volume	1,5 µL
Measuring time	Up to 5 seconds
Measuring range	0,6 – 33,3 mmol/L
Hematokrit	25 – 65 %
Memory	300 tests
Power supply	2 batteries (AAA, LR 03, AM4 or micro) or 2 rechargeable NiMH batteries (type AAA)
Operating time	Approximately 1000 tests
Dimension	W= 113 mm, H= 49 mm, D= 30 mm (without the lancing device) W= 115 mm, H= 56 mm, D= 30 mm (included the lancing device)
Weight	App. 130 g (included batteries, the test drum and the lancing device)

4.2.1. Product information, Compact Plus

Compact Plus blood glucose meter system
Manufactured by: Roche Diagnostics GmbH

Suppliers of Compact Plus in 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

82 Compact Plus blood glucose meters were used in this evaluation.
Serial no. GP00543293(called meter A) and serial no. GP00541935(called meter B) were used by the biomedical laboratory scientist under the standardised and optimal conditions.
Attachment 1 gives serial numbers for the 80 meters that were used by the diabetics.

Accu-Chek Compact teststrips:

Lot-no. 20631042	Expiry 2006-04
Lot-no. 20631142	Expiry 2006-04
Lot-no. 20629943	Expiry 2006-03

Accu-Chek Compact Autocontrol:

Lot-no. 22390421	Expiry 2006-07

4.3. Designated comparison method

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

Verifying of trueness
The results from 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 [8]. 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 (lithium heparin) and urine 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 based on the method by Slein, utilising hexokinase and glucose-6-phosphate dehydrogenase enzymes. The method is implemented on the Advia 1650 Chemistry System from Bayer, with reagents and calibrators from Bayer. The Advia 1650 Chemistry System Glucose Hexokinase II method is a two-component reagent. Sample is added to Reagent 1, which contains buffer, ATP and NAD. Absorbance readings of the sample in Reagent 1 are used to correct for interfering substances in the sample. Reagent 2 is added, which initiates the conversion of glucose and the development of an absorbance at 340 nm. The difference between the absorbance in Reagent 1 and Reagent 2 is proportional to the glucose concentration. The measuring principle in the Advia 1650 is as follows: Glucose is phosphorylated by ATP in the presence of hexokinase. The glucose-6-phosphate that forms is oxidised in the presence of glucose-6-phosphate dehydrogenate causing the reduction of NAD to NADH. The absorbance of NADH is measured as an endpoint reaction at 340 nm.

Internal quality assurance of the Advia 1650 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 for this evaluation. The controls were measured as the first and the last samples in all the series. The results are summarised in table 5.

4.3.1. Product information, comparison method

Designated comparison method Advia 1650
Manufactured by: Bayer AS
Serial no. CA 175524-196

Reagents
Bayer Glucose Hexokinase method II (B01-4597-01)
Lot-no. 0581X

Calibrator
Chemistry Cal Bayer
Lot-no. 179747 Expiry 2005-10 Reference value = 13.5 mmol/L

Internal control
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 control
(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

Tubes used for sampling for the designated comparison method
Microvette CB 300 LH (litium-heparin) manufactured by Sarstedt AS
Lot-no. 4074301 Expiry 2007-11
Lot-no. 4075101 Expiry 2007-12

Centrifuge used for samples for the designated comparison method:
Eppendorf Centrifuge 5415D, manufactured by Eppendorf AG Hamburg
Serial no. 0057100

4.4. Evaluation procedure

4.4.1. Model for the evaluation

The practical work with the evaluation was carried out during 8 weeks from May to June 2005 (from week number 19 to week number 26) at Levanger Hospital in Central Norway. The practical work was done by Ingunn Barli and Tone C. Hovelsen. They are biomedical laboratory scientists.

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 best possible conditions. The other part of the evaluation was done by diabetics. In order to determine the analytical quality of Compact Plus by the users, 80 diabetics tested their blood glucose using Compact Plus. The diabetics were divided into two groups (random distribution). 40 diabetics were called in and received personal training in how to use the blood glucose meter, here called the "training group". 40 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.

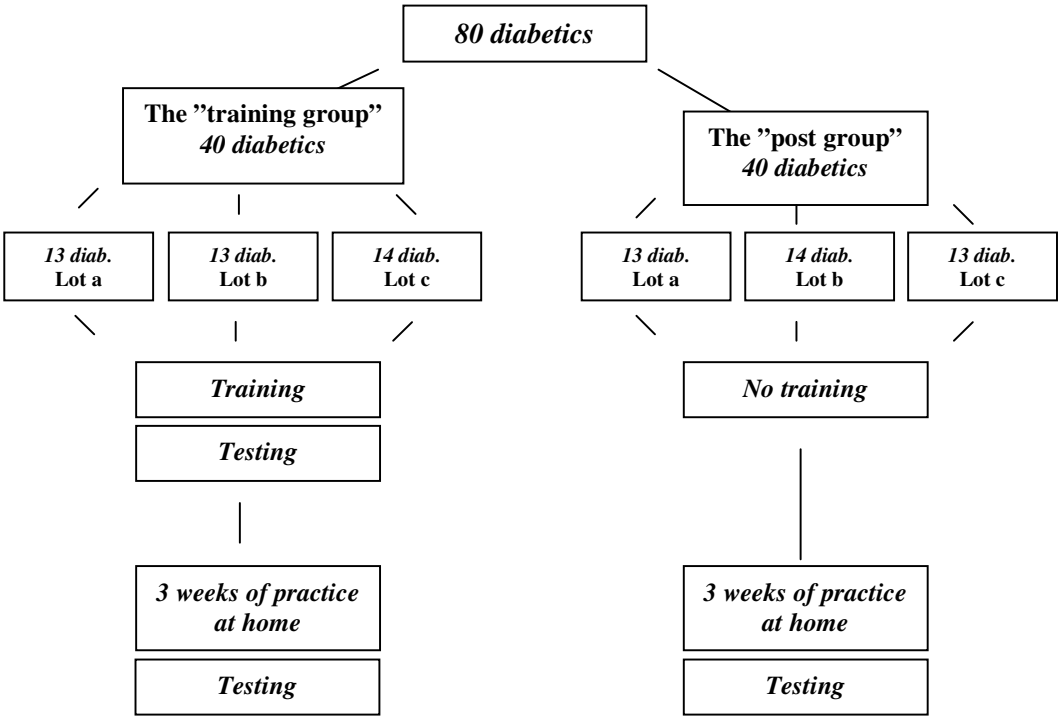

Figure 1. Model for the evaluation

All the diabetics could not participate in the user evaluation during the same weeks. The biomedical laboratory scientists had capacity to receive approximately 25-30 diabetics a week. Therefore the start-up was spread out over 3 weeks, and the final consultation consequently spread out correspondingly.

4.4.2. Recruiting of the diabetics

The Compact Plus glucose meter was tested in use by 80 diabetics. The evaluation started with 85 diabetics of whom 5 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 Compact Plus as their own device. Characteristics of the diabetics in the group are shown in table 2.

Table 2. Characteristics of diabetics included (n=80).

		Diabetics
Total		80
Sex	Men	48
	Women	32
Age (years), median and range		55 (18 – 74)
Diabetes	Type 1	24
	Type 2	54
	Don't know	2
Treatment	Insulin	28
	Insulin and tablets	12
	Tablets	29
	Tablet and diet	4
	Diet	6
	Unspecified	1
Frequency of SMBG	Less than weekly	3
	1 – 3 per week	20
	4 – 6 per week	6
	7 – 10 per week	15
	> 10 per week	31
	Doesn't measure	0
	Unspecified	5

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/Accutrend (model not specified) (4), Accu-Chek Sensor/Comfort/Accutrend Sensor (13), Ascensia (model not specified) (2), Ascensia Breeze/Dex/Dex 2 (12), Ascensia Contour (7), Glucometer Elite/Elite XL (7), FreeStyle/FreeStyle Mini (12), MediSence Precision (model not specified) (9), MediSence Precision Xtra/ Xceed (4), OneTouch GlucoTouch (1) , OneTouch Ultra (4), doesn't do SMBG (3) and unspecified (2).

4.4.3. The training group at the first consultation

The 40 diabetics selected to participate in a training programme were called in two and two at the time. They received the Compact Plus device along with test strips, lancet pen, lancets, user manual, and an instruction letter with explanations regarding what to do with the Compact Plus 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. Ingunn Barli and Tone C. Hovelsen were in charge of the training of the diabetics, after having been trained themselves by a representative from Roche.

Training programme
The training programme covered a simple demonstration of how to use Compact Plus 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 40 diabetics made duplicate blood glucose tests on Compact Plus. These results were registered for the evaluation. Afterwards they brought the Compact Plus 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 40 diabetics in the "post group" received the Compact Plus device by post, along with test strips, lancet pen, lancets, user manual and an instruction letter with explanations regarding what to do with the Compact Plus 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 two duplicate tests were done. The results of these tests were registered.

4.4.5. Use of Compact Plus by the diabetics at home

The diabetics used Compact Plus 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 Compact Plus 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 Compact Plus. 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 on Compact Plus 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 on Compact Plus in the evaluation. To document correct functioning on the Compact Plus-meters used by the diabetics during the test period, the biomedical laboratory scientist in charge of the practical work controlled the meters 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 80 diabetics were called for, one by one, to a consultation. Each diabetic brought their assigned Compact Plus meter and the remaining test strips to this consultation. They made duplicate blood glucose tests on Compact Plus. These results were registered for the evaluation. Finally, a venous sample for hematocrit was taken.

The questionnaires
After all the blood samples were collected and the measurements on Compact Plus were done, the diabetics filled out two questionnaires. The first questionnaire was about the user-friendliness of the Compact Plus 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 Compact Plus or return it to the project.

4.4.7. Evaluation under standardised and optimal conditions

The biomedical laboratory scientists used two Compact Plus blood glucose meters for the evaluation (meter "A" and meter "B"). Meter "A" was used for one lot of test strips for all measurements on all the diabetics. 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 standard and optimal conditions.

Accu-Chek Compact Plus		Lot 20631042 (n)	Lot 20631142 (n)	Lot 20629943 (n)
Meter A	1st consultation	40 x 2		
	2nd consultation	80 x 2		
Meter B	1st consultation	28 x 2	12 x 2	
	2nd consultation		38 x 2	42 x 2
Total		148 x 2	50 x 2	42 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 on 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 diabetic's 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 procedure, 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 Compact Plus 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 Compact Plus. In the package insert hematocrit from 25 – 65 % is 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 for Advia 1650. The samples were frozen directly as the plasma was separated and the plasma was stored at minus 80 °C. The samples were gathered and sent frozen in a quantity of about 80 samples at a time. The samples were transported under cold storage (minus 18 °C to minus 24 °C) to NOKLUS Centre in Bergen where they were kept at minus 80 °C until the analysis took place.

Analysing the samples for the comparison method
The samples were analysed with Advia 1650. Recommended minimum volume for analysis of glucose on Advia 1650 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 Compact Plus 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 scientists evaluated the user-friendliness of Compact Plus and the user-manual. 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 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 40 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 Compact Plus at home for three weeks.
3. Results from 40 diabetics in the "post group" who had not participated in the training programme, but who had practised using Compact Plus at home for three weeks.
4. Results from 120 measurements under standardised and optimal conditions
5. Results from 120 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

80 diabetics completed the evaluation. The 40 diabetics in the "training group" met at two consultations and the 40 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
120 x 2 (duplicates) x 4 (meter A, meter B, diabetic's meter, comparison method) = 960 samples.

5.2. Statistical outliers

All results are checked for outliers according to Burnett [9], 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 438, ID 514, ID 516, ID 542 and ID 556 at the final consultation had a difference > 10 % between the paired results on the comparison method. The difference was confirmed by a re-run. As a consequence of this, these results are excluded when Compact Plus is compared with the comparison method (accuracy and trueness). The results are included in the calculations regarding the imprecision at Compact Plus because each set of duplicate measurements on Compact Plus is completed in less then a minute. ID 438, ID 514, ID 516, ID 542 and ID 556 are also excluded from calculation regarding the effect of hematocrit for the same reason.
- ID 466's assigned meter had a malfunction at the final consultation and no results could be obtained.
- ID 467 had only one measurement at meter A and meter B at the first consultation, and ID 439 had only one measurement at meter B at the final consultation. Because the repeatability is calculated based on paired results, ID 467 and ID 439 have to be omitted from the calculation of repeatability under standardised and optimal conditions. In the calculation of trueness these single results are looked upon as the estimate of the true value, and are included in the calculation.
- In the calculation of repeatability based on the diabetics' measurements at home some measurements had to be excluded. ID 429 had no duplicate measurements. ID 498 had only one duplicate measurement. ID 502 had four duplicate measurements, but with the result HI on both measurements one day. ID 522 had only one duplicate measurement. This means that 15 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

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 on Compact Plus in this evaluation (see comments below).

Table 4. No systematic differences between 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	P	n
Compact Plus	Meter A	< 7	5,1	5,1	0,04	0,307	18
		7 – 10	8,5	8,5	-0,01	0,826	43
		> 10	13,2	13,3	0,16	0,006	52
	Meter B	< 7	5,1	5,2	0,14	0,015	19
		7 – 10	8,3	8,4	0,08	0,095	41
		> 10	13,1	13,1	-0,01	0,912	51

Comments
The difference in glucose concentration between the first and the second measurement of the paired results is neglect able. Four of the six differences are not significant. At the glucose concentration level >10 mmol/L at meter A and at the glucose concentration level < 7 mmol/L 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 on Compact Plus, 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 Compact Plus meter A.

5.6. Calculation of accuracy

To evaluate the accuracy of the results at Compact Plus, the agreement between Compact Plus 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 Compact Plus 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 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 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	5,2	52	0	0,6 (0,5-0,7)
Autonorm 2	15,0 ± 1,05	15,1	52	0	0,6 (0,5-0,8)

Discussion
The precision of the comparison method is good. The repeatability is approximately 0,5 CV% (see table 6 and 7) and the reproducibility is less than 1 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 on 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	14.06.05	**1,918** (1,898 - 1,938)	1,98	5	0,6 (0,4 - 1,1)	+3,3
	04.07.05		1,97	6		+2,8
	Total		**1,98**	**11**		**+3,0**
Level 2	14.06.05	**4,357** (4,309 - 4,405)	4,43	5	0,5 (0,4 - 0,9)	+1,7
	06.07.05		4,46	6		+2,4
	Total		**4,45**	**11**		**+2,1**
Level 3	15.06.05	**6,777** (6,704 - 6,850)	6,94	5	0,3 (0,2 - 0,5)	+2,3
	06.07.05		6,97	6		+2,8
	Total		**6,95**	**11**		**+2,6**
Level 4	15.06.05	**16,24** (16,05 - 16,43)	16,44	5	0,4 (0,3 - 0,7)	+1,2
	11.07.05		16,48	6		+1,5
	Total		**16,46**	**11**		**+1,4**

Table 6 reveals that glucose results at Advia 1650 are approximately 2 % higher than the target values from NIST. Even though the obtained results are only just outside the given uncertainty limits for the Reference Material, it was decided that all results from Advia should be adjusted according to the findings presented in the table above. The adjustment was done by means of the following regression equation ($R^2 = 1,0$):

$y = 0,9892x – 0,0555$

From now on in this report, whenever any result from Advia is presented, the result has already been adjusted according to this equation.

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 [8].
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 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	10.06.05	3,20	3,15	7		0,4 (0,3-0,6)	-1,5
	16.06.05		3,15	6			-1,4
	28.06.05		3,15	6			-1,6
	Total		**3,15**	**19**	**0**		**-1,5**
NOKLUS 2	10.06.05	7,78	7,78	7		0,3 (0,2-0,4)	-0,3
	17.06.05		7,72	6			-0,8
	29.06.05		7,72	6			-0,8
	Total		**7,73**	**19**	**0**		**-0,6**

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). In this evaluation, deviations > 10 % were regarded as not acceptable and such results were excluded without further discussion. This applies for ID 438, ID 514, ID 516, ID 542 and ID 556. For further explanation, see chapter 5.3. One sample with a low glucose concentration (below 4,2 mmol/L) had a difference just over the limit at 0,22 mmol/L, but is still included in the calculations. 16 of 120 paired results at the comparison method gave deviations between 4 and 10 %. For 15 of these 16 samples the deviation was less than 6 %. The sample with difference between 6 and 10 % concern normal glucose concentration, where a deviation expressed in percent more easily exceeds the limitations. 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 16 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 Compact Plus

6.2.1. Precision of Compact Plus

The Compact Plus 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.

The 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 6.

Table 8. Compact Plus – Repeatability (results with patient samples) measured under standard and optimal conditions.

Compact Plus	Glucose level (mmol/L)	Mean value glucose (mmol/L)	n	Outliers	CV % (95 % CI)
Meter A	< 7	4,7	21	0	2,8 (2,1 – 4,0)
Meter B	< 7	4,9	23	0	3,6 (2,8 – 5,1)
Meter A	7 – 10	8,4	44	0	2,9 (2,4 – 3,7)
Meter B	7 – 10	8,4	41	1	2,4 (2,0 – 3,1)
Meter A	> 10	13,3	53	1	2,3 (1,9 – 2,8)
Meter B	> 10	13,1	52	1	2,7 (2,3 – 3,3)

- ID 467 at the first consultation had only one measurement at meter A and meter B, and is excluded
- ID 439 at the final consultation had only one measurement at meter B and is excluded
- 1 outlier at meter A, glucose level > 10 mmol/L
- 1 outlier at meter B, glucose level 7 – 10 mmol/
- 1 outlier at meter B, glucose level > 10 mmol/L

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 control 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 7.
Raw data from the diabetics' measurements at home is shown in attachment 8.

Table 9. Compact Plus – Repeatability (results with patient samples) measured by the "training group" and the "post group".

Compact Plus	Consultation	Glucose level (mmol/L)	Mean value glucose (mmol/L)	n	Outliers	CV % (95 % CI)
At NOKLUS	1st training	< 7	4,6	5	0	2,7 (1,6 – 7,7)
	2nd training	< 7	4,0	7	0	7,1 (4,6 – 15,7)
	Post group	< 7	5,8	8	1*	5,5 (3,7 – 11,3)
At home		< 7	5,5	120	7	5,0 (4,5 – 5,7)
At NOKLUS	1st training	7 – 10	8,5	14	0	4,7 (3,4 – 7,5)
	2nd training	7 – 10	8,0	12	0	2,9 (2,1 – 5,0)
	Post group	7 – 10	8,5	9	0	2,9 (1,9 – 5,5)
At home		7 – 10	8,5	137	9	4,3 (3,8 – 4,8)
At NOKLUS	1st training	> 10	13,1	21	0	2,9 (2,2 – 4,2)
	2nd training	> 10	12,4	21	0	3,3 (2,5 – 4,8)
	Post group	> 10	14,5	21	0	5,5 (4,2 – 7,9)
At home		> 10	12,8	111	1	5,4 (4,8 – 6,2)

- ID 466 is missing because the assigned meter had a malfunction
- 15 home measurements are missing and 17 outliers among the home measurements are excluded

* One result excluded after visual inspection

Comments

The CV at glucose level < 7 mmol/L in the training group at the second consultation is 7,1 %. Only seven results belong in this group, and consequently the CV confidence interval is wide. The relative weak CV achievement at the low glucose concentration level is mainly affected by a single result. This refers to a very low glucose concentration with duplicate measurements at 2,4 and 3,1 mmol/L. The difference between the two measurements is still not big enough to be regarded as an outlier, and the result is not excluded. The actual CV is 5,6 % without this result.

Reproducibility with Internal Quality Control

The results for reproducibility are obtained with the Accu-Chek Compact Autocontrol. The measurements are carried out on meter A and B during the whole evaluation period and at all the meters in use by the diabetics. All the control measurements are done by the biomedical laboratory scientist. The control measurements on the diabetics' meters were done with the test strips that were distributed to each diabetic. The control solution was kept at NOKLUS during the evaluation period.

The reproducibility of Compact Plus at meter A and B is shown in table 10.
The reproducibility at all the meters of the diabetics is shown in table 11.
Raw data is shown in attachment 5.

Table 10. Compact Plus – Reproducibility (results with Accu-Chek Compact Autocontrol) measured by the biomedical laboratory scientist on meter A and on meter B.

Compact Plus	Lot of strips	Target value (mmol/L)	Mean value glucose (mmol/L)	n	Outliers	CV % (95 % CI)
Meter A	20631042	8,5 – 11,5	10,4	26	0	4,5 (3,5 – 6,2)
Meter B	20631042	8,5 – 11,5	10,5	7	0	2,3 (1,5 – 5,1)
	20631142	8,6 – 11,6	10,3	11	0	2,6 (1,8 – 4,5)
	20629943	9,0 – 12,2	10,7	8	0	3,3 (2,2 – 6,7)

Table 11. Compact Plus – Reproducibility (results with Accu-Chek Compact Autocontrol) measured by the biomedical laboratory scientist on the diabetics' meters.

Compact Plus	Lot of strips	Target value (mmol/L)	Mean value glucose (mmol/L)	n	Outliers	CV % (95 % CI)
1st consultation*						
The diabetics' meters	20631042	8,5 – 11,5	10,6	13	0	4,2 (3,0 – 6,9)
	20631142	8,6 – 11,6	10,5	12	0	1,4 (1,0 – 2,3)
	20629943	9,0 – 12,2	11,0	13	0	2,4 (1,7 – 4,0)
2nd consultation**						
The diabetics' meters	20631042	8,5 – 11,5	10,8	25	0	2,6 (2,1 – 3,7)
	20631142	8,6 – 11,6	10,5	27	0	3,2 (2,5 – 4,3)
	20629943	9,0 – 12,2	11,1	26	0	2,8 (2,2 – 3,9)

* ID 496 and ID 503 are missing QC-result
**ID 428 and ID 466 are missing QC-result. ID 466's meter had a malfunction.

Discussion
The precision at Compact Plus is acceptable. The repeatability obtained under standardised and optimal conditions is approximately 3 %. The repeatability obtained at NOKLUS by the diabetics is acceptable with a CV between 3 and 6 % when the measurements are performed by the diabetics. The CV at glucose level < 7 mmol/L in the training group at the second consultation is 7,1 %. As mentioned in the comments on page 28, this relative weak CV is due to one single 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 Compact Plus was good when measured with an internal control solution. The CV was approximately 3 %. At the diabetics' meters the reproducibility are good both at the first consultation and the second consultation. The CV was from 1,4 – 4,2 %.

6.2.2. Trueness

The trueness of Compact Plus is calculated from the results done by the biomedical laboratory scientist at the final consultation (the "training group" and the "post group") and is shown in table 12.

Table 12. Mean difference between Compact Plus 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	5,4	5,3	8,4	8,2	13,4	13,2
Mean deviation from the comparison method, mmol/L (95 % CI)	-0,1 (-0,2 – 0,0)		-0,2 (-0,3 – 0,0)		-0,2 (-0,4 – 0,0)	
n	13		24		38	
Outliers	0		0		0	
p-value	0,044		0,011		0,048	

- ID 438, ID 514, ID 516, ID 542 and ID 556 had a difference > 10 % between the paired results at the comparison method and are excluded.

Discussion

The trueness of Compact Plus is good. Table 12 shows that there is a small, but significant bias between Compact Plus and Advia. Compact Plus gives glucose values 0,1 – 0,2 mmol/L lower than the comparison method. This bias has no importance and the results still fulfil the quality goal set by ISO.

6.2.3. Accuracy

To evaluate the accuracy of the results at Compact Plus, the agreement between Compact Plus and the comparison method is illustrated in two difference plots. The difference plots give a picture of both random and systematic deviation and reflect the total measuring error at Compact Plus. 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 a previous chapter of 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, Compact Plus meter B, under standardised and optimal measuring conditions, with the first measurements at the final consultation is shown in figure 2 (two lots of test strips).
The accuracy, Compact Plus, as measured by the diabetics with the first measurement at the final consultation is shown in figure 3 (three lots of test strips).
The accuracy is summarised in table 13 and discussed afterwards.

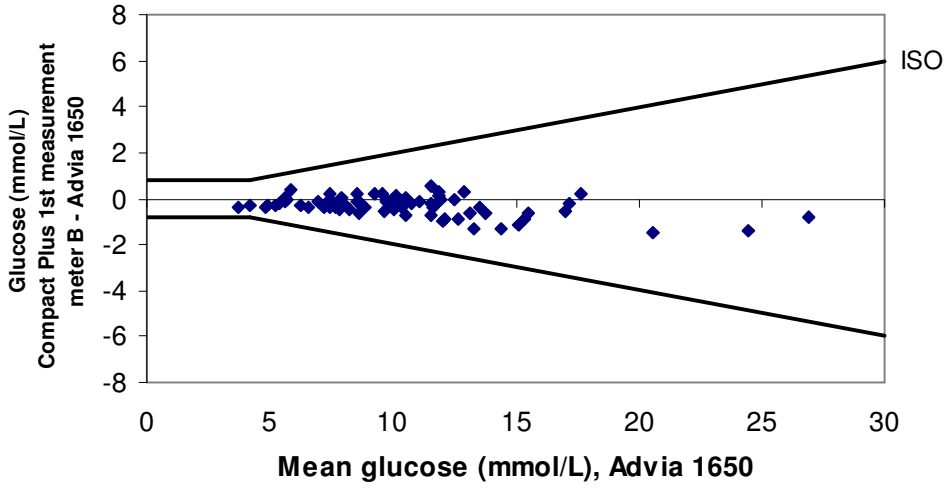

Figure 2. Accuracy. Compact Plus meter B (two lots of test strips) under standardised and optimal measuring conditions at the final consultation. The x-axis represents the mean value of the duplicate results at the comparison method. The y-axis shows the difference between the first measurement at Compact Plus and the mean value of the duplicate results at the comparison method. n = 75.

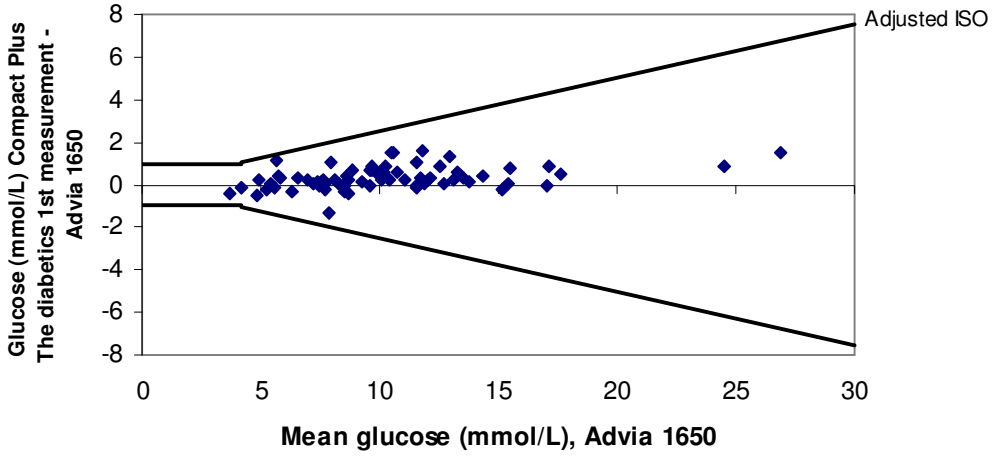

Figure 3. Accuracy. The diabetics' self-measurements at the final consultation. Two lots of test strips.
The x-axis represents the mean value of the duplicate results at the comparison method. The y-axis shows the difference between the first measurement at Compact Plus and the mean value of the duplicate results at the comparison method. n = 75.

Table 13. Total error of Compact Plus results compared to the comparison method. Percentage Compact Plus 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 consentrations ≤ 4,2)	**< "adjusted ISO"** < ± 25 % (and < ± 1,0 mmol/L at consentrations ≤ 4,2)	
Biomedical laboratory scientist	1st	A 1st measurement	40	93	97,5		
		B 1st measurement	40	93	100		
Biomedical laboratory scientist	2nd	A 1st measurement	75	95	100		
		B 1st measurement	75	99	100		2
Diabetics at NOKLUS	1st	1st measurement	40	90	100	100	
	2nd	1st measurement	74	88	99	100	3

- ID 438, ID 514, ID 516, ID 542 and ID 556 had a difference > 10 % between the paired results at the comparison method at the final consultation and are excluded.
- ID 466 had no measurements at the final consultation because the assigned meter had a malfunction

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. The first measurements at the final consultation are also within the ADA-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. 99 % of the results are within the ISO-goal and 100 % are within the "adjusted ISO-goal".

Conclusion

The Compact Plus 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 on meter A were performed with one lot of test strips. The measurements on meter B were performed with three different lot numbers of test strips, on 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 Compact Plus 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 20631042**	**The comparison method**	**Meter B Lot 20631142**	**The comparison method**	**Meter B Lot 20629943**
Mean glucose, mmol/L	9,6	9,6	9,7	9,7	10,5	10,1
Mean deviation from the comparison method, mmol/L (95 % CI)	0,0 (-0,1 – 0,1)		-0,1 (-0,2 – 0,0)		-0,4 (-0,5 – (-0,3))	
n	28		33		40	
Outliers	0		2*		0	
p-value	0,956		0,086		<<0,05	

- ID 438, ID 514, ID 516, ID 542 and ID 556 had a difference > 10 % between the paired results at the comparison method at the final consultation and are excluded.
- ID 439 and ID 467 had only one result at Compact Plus. In the calculation these results represent the best estimation of the sample and are not excluded.

* The 2 outliers are excluded one by one by two truncations.

Discussion

A significant difference between lot 20631042 and 20631142 and the comparison method was not determined here. Lot 20629943 gives significantly lower values than the comparison method, but the results are still within the ISO-limits.

7. Effect of hematocrit

The package insert of Accu-Chek Compact test strips states that the glucose concentrations are not affected by hematocrit values between 25 – 65 %. To measure the effect of hematocrit at Compact Plus, a venous sample was taken of the diabetics (voluntary) at the second consultation. All the diabetics were willing to have a sample for hematocrit taken.

The measurements on Compact Plus are performed under standardised and optimal measuring conditions. The glucose concentration range in the samples was from 3,7 to 26,9 mmol/L. The hematocrit range was 34 – 52%.

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 Compact Plus and the comparison method (Compact Plus – 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.

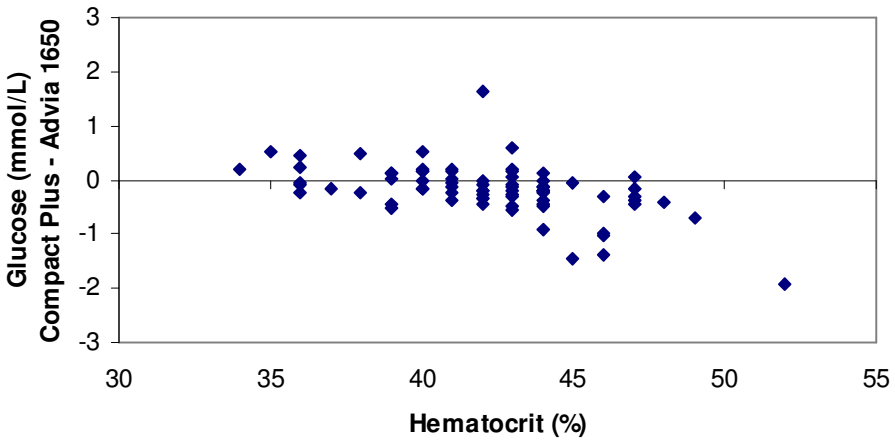

Figure 4. The effect of hematocrit at glucose measurements (in mmol/L) at Compact Plus under standardised and optimal conditions. The x-axis shows the hematocrit value in %. The y-axis shows the difference in glucose concentration between Compact Plus and the comparison method in mmol/L. n= 75

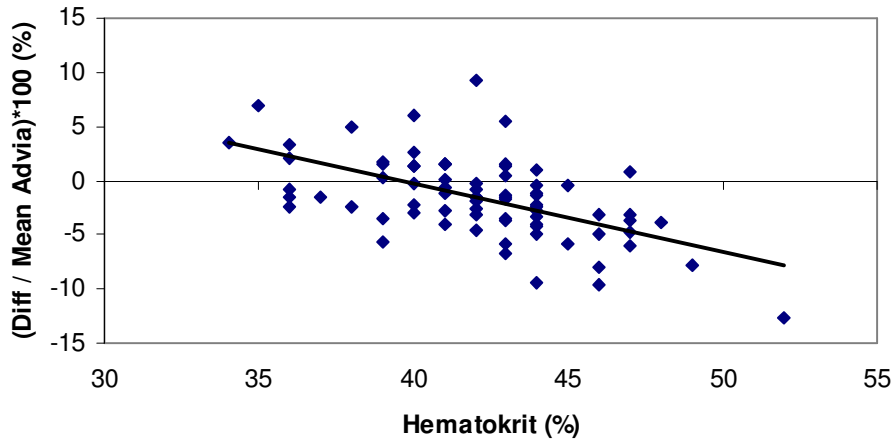

Figure 5. The effect of hematocrit at glucose measurements on Compact Plus under standardised and optimal conditions. The x-axis shows the hematocrit value in %. The y-axis shows the difference in glucose concentration between Compact Plus and the comparison method (Compact Plus – the comparison method)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

- ID 438, ID 514, ID 516, ID 542 and ID 556 had a difference > 10 % between the paired results on the comparison method and are excluded.

Discussion

Glucose measurements on Compact Plus are affected by the hematocrit values of the samples. The trend-line in figure 5 shows that glucose values at Compact Plus are over-estimated when the hematocrit is below 35 %. With hematocrit values over approximately 45 % the glucose values are under-estimated. In spite of the hematocrit effect, the glucose results still fulfil the quality goal set by ISO.

8. Practical points of view

Questionnaires

Each diabetic filled out a questionnaire about the user-friendliness and a questionnaire about the user manual of Compact Plus when they attended the final consultation (n = 80). Some diabetics needed assistance in filling out the questionnaires.

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

8.1. Evaluation of user-friendliness of Compact Plus

The questionnaire about the user-friendliness had nine questions concerning Compact Plus and one question concerning the Accu-Chek Softclix Plus lancet pen. In addition, each diabetic should give the name of the blood glucose meter he/she uses ordinarily on the same questionnaire.
Table 15 summarizes seven 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 5,7, 5,6 and 5,8 on the questions about inserting or changing a test strip drum, filling the strip with blood and removing the strip from the meter, respectively. This indicates that the diabetics seemed satisfied with the use of the test strips and the test strip drums. The mean is 6,0 and 5,9 on the questions about reading the figures in the display and recognizing the meters' sound signal. The diabetics also seemed satisfied with operating the meter, all in all. The mean is 5,4. Regarding Accu-Chek Softclix Plus lancet pen the mean is 5,2, which indicates that the diabetics were satisfied with the lancet pen, too. The answers to these questions are summarized in table 15 and 16.

Table 15. Compact Plus - Questions about the meter and about Accu-Chek Softclix Plus lancet pen

Questions about Compact Plus and about Accu-Chek Softclix Plus lancet pen		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 insert or change a test strip drum	5,7	3 - 6	0	80
	2. To fill the strip with blood	5,6	2 - 6	0	80
	3. To read the figures in the display	6,0	5 - 6	0	80
	4. To remove the test strip from the meter	5,8	4 - 6	0	80
	5. To recognize the meters' sound signal	5,9	4 - 6	0	80
	6. All in all, to operate the meter	5,4	2 - 6	0	80
	7. To operate Accu-Chek Softclix Plus lancet pen	5,2	1 - 6	14	80

Table 16 shows the answers to the last question about Compact Plus. 14 % of the diabetics answered that they had technical problems with the meter during the testing period. Written comments indicate that these problems were not technical ones.

Table 16. Compact Plus – Questions about the meter.

Question about Compact Plus	Yes (%)	No (%)	Not answered (%)	Total number
Did you have any technical problems with the meter during the testing period?	14	84	3	80

Positive comments
68 diabetics reported one or more advantages with Compact Plus. The most often reported advantages are distinctly grouped as follows:

1. "total package concept" (23)
2. easy to use (18)
3. drums with test strips (25)
4. the meter has short measuring time (20)
5. the meter/strip needs little blood sample volume (4)
6. to read the figures in the display/good display (5)
7. good lancet pen (7)

Negative comments
39 diabetics reported one or more disadvantages with Compact Plus. The most often reported disadvantages are distinctly grouped as follows:

1. the meter is too big (24)
2. the meter makes too much noise
   (both too loud signal and too much noise during measurements) (8)
3. the values varies (3)
4. disadvantages with the lancet pen (4)

8.2. Evaluation of the user manual for Compact Plus

On the questionnaire about the user manual each diabetic first was 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 90 % of the diabetics had used the user manual, i.e. 72 of the 80 diabetics that participated in the study. 91 % 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. 88 % of the diabetics were quite satisfied with the user manual. Three of the diabetics meant the user manual was too long and complicated, and one thought it was too many possible reasons for each error (e.g. E5).

Table 17. Compact Plus – Questions about the user manual.

Questions about the user manual	Yes (%)	No (%)	Not answered (%)	Number
Have you been reading in the user manual?	90	6	4	80
If yes, did you read the entire user manual?	32	53	15	75
And/or did you consult the user manual when needed?	71	7	23	75
1. Are you satisfied with the description of how to perform a blood glucose measurement with this meter?	91	3	7	75
2. Do you think the user manual has essential shortcomings?	1	88	11	75
3. All in all, are you satisfied with the user manual?	88	3	9	75

The biomedical laboratory scientists thought Compact Plus was easy to use and that it was an advantage with drums with test strips. They agreed with the diabetics that it was much noise from the meter especially during measurements and movement of the drum and they thought that the absorbance of blood at the test strips could have been better.

9. References

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10. Attachments

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

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