CoaguChek® XS

A system for measurement of prothrombin time [P—PT (INR)] manufactured by Roche Diagnostics

Report from an evaluation
under standardised and optimal conditions in a hospital laboratory
and in primary heath care
organised by SKUP

SKUP/2007/55

The organisation of SKUP

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

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

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

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

Each evaluation is presented in a *SKUP report* to which a unique *report code* is assigned. The code is composed of the acronym SKUP, the year and a serial number. A report code, followed by an asterisk (*), indicates a special evaluation not complete according to the guidelines, e.g., the part performed by the intended users was not included in the protocol. If suppliers use the SKUP name in marketing, they have to refer to www.skup.nu and to the report code in question. For this purpose the company can use a logotype available from SKUP containing the report code.
SKUP reports are published at www.skup.nu 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 see attachment 8.

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

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

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

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1. Summary

Background
The new Coaguhek® XS System is designed for use in patient self testing of prothrombin time
(PT). It will be the successor of the current CoaguChek® S System. The detection principle is
based on an amperometric measurement of the thrombin activity initiated by starting the
coagulation cascade using a human recombinant thromboplastin. CoaguChek XS is based on the
Quick method, while the methods used in Scandinavian hospitals are based on the Owren method.
The sample material is capillary whole blood and the sample volume is 10 µL. The PT result is
ready within one minute and displayed in INR. Measuring range for PT (INR) is from 0,8 to 8,0.

The aim of the evaluation
The aim of the evaluation of CoaguChek XS was to
   - Get a measure of the analytical quality achieved under standardised and optimal
     conditions by experienced laboratory trained people in a hospital laboratory
   - Get a measure of the analytical quality achieved by the users in primary health care
   - Evaluate the user-friendliness

Materials and methods
Samples from 72 outpatients on long-term oral anticoagulation therapy were collected in the
outpatient clinic at the hospital laboratory. Of these patients, 24 also contributed with a second
sample at a second occasion, giving a total of 96 samples. For CoaguChek XS, the samples were
capillary samples in duplicate, and for the comparison method venous citrate samples were
collected. At the primary care centre, samples from 40 patients were collected.
The designated comparison method was a PT method with SPA reagent on a STA Compact
instrument, both from Stago, calibrated with calibrators from EQUALIS.
The analytical quality goal of SKUP for PT is: Repeatability (CV) <5 % and a total error <±20 %.

Results
The precision of CoaguChek XS is good. The repeatability CV is approximately 3 % under
standardised and optimal conditions in a hospital laboratory as well as in a primary health care
centre. The quality goal for the repeatability is attained. No systematic difference between the
measurements on CoaguChek XS and the comparison method is pointed out. The main
impression of the accuracy of CoaguChek XS is good. Four results clearly deviate from the rest,
with high results on CoaguChek XS relative to the comparison method. The four deviating results
are the reason why CoaguChek XS does not fulfil the quality goal for the total error set by SKUP.
The deviating results are not a result of a trend or a general systematic deviation. The deviating
results are reproducible and can most probably be explained by matrix effects in the samples from
the individual patients. If these results are disregarded, the quality goal is fulfilled.
The users in this evaluation find CoaguChek XS easy to use and are pleased with the device.

Conclusion
The analytical quality of CoaguChek XS is good and so is the user-friendliness. CoaguChek XS
seems well suited for use in the primary health care.

Comments from the manufacturer
For comments and additional information from Roche, please see attachment 6 and 7.

2. Analytical quality goals

To qualify for an overall good assessment in a SKUP evaluation, the measuring system must show satisfactory analytical quality as well as and satisfactory user-friendliness.

At present, there are no generally recognised analytical quality goals for the determination of prothrombin time, and no international (Gold) Standard for evaluation of Point of Care test instruments for the prothrombin time measurement in primary health care.
The new ISO-standard for anticoagulant therapy self-testing [1] is still under development. According to SKUP, the coming ISO-standard has too tolerant quality goals. In our opinion, the submitted claim for minimum acceptable system accuracy (total error) of ± 30 % for 90 % of the results is too tolerant. Unfortunately, there is no performance criterion for imprecision in the standard. In the international consultative round and following voting over the draft standard, Sweden and Norway commented on the draft standard and then voted no to the final suggestion.

Setting quality goals on the basis of biological variation is an acknowledged method [2, 3].
It is recommended that analytical imprecision should be less than, or equal to, half the intra-individual biological variation. Ricos et al. [4] state the biological variation for prothrombin time as 4 % (CV_{bw}) and 6,8 % (CV_{bb}). According to Kjeldsen, Lassen et al. [5], the "in-treatment within-subject biological variation" of PT (INR) is 10,1 % CV. For systems used for monitoring, the analytical performance should aim at low imprecision compared with the within-subject biological variation ($CV_a \leq 1/2\ CV_{bw}$) [6].

CV_a The analytical imprecision expressed as coefficient of variation in percent (CV %). This imprecision is called repeatability in the result part of this report.
CV_{bw} The biological variation within healthy individuals, also called the intra-individual biological variation
CV_{bb} The biological variation between healthy individuals, also called the inter-individual biological variation

In principle, quality goals based on biological variation do not take into account clinical requirements.

A committee appointed by the National Ministry of Health in Denmark has specified the demands to analytical quality for PT (INR) [7]:
Bias ≤±6 % and reproducibility (CV) ≤5 % for instruments used in primary health care, and bias ≤±3 % and reproducibility (CV) ≤3 % for hospital instruments. There is no separate goal for the total error in the Danish specifications.

Based on the given data on biological variation for prothrombin time, and the fact that anticoagulant devices are designed for *monitoring* prothrombin time, SKUP recommends that these instruments should achieve a repeatability (CV) below 5 %. SKUP has not taken out a separate goal for the bias, but sets out on the other hand a quality goal for the total measuring error. The term total-error is used for the combined effects of imprecision and bias. An acceptable bias can be calculated as 1/16 of the therapeutic interval for the prothrombin time, while a minimum goal can be calculated as 1/8 of the therapeutic interval. This gives an acceptable bias at approximately ±2,5 % at the PT (INR) level 2,5. Accordingly, the bias should not exceed ±5 % at the same PT-level. SKUP has used a bias of ±5 % in the calculation of the total error.

In method evaluation and method comparisons, one has to take the imprecision of the comparison method into account. SKUP allows an imprecision of the comparison method up to 3 %. In addition various comparison methods are not likely to give exactly the same INR-results. The differences should be regarded as an inter-laboratory variation and should be taken into the calculation of the total error as imprecision. SKUP has estimated the contribution of the inter-laboratory variation (CV) to the total error to 3 %.

When comparing two different prothrombin time methods, either both methods use Owren-based reagents, or especially when one of the methods is a "Quick-method", there is often a certain "interference" or matrix-effect which will manifest itself. When comparing INR-results from a Quick-method and an Owren-method, this effect is a result of real method differences. It can be discussed whether one should incorporate this effect in the total error quality goal it self or not. As an alternative, one can accept more results outside the quality-limits when it comes to the final evaluation. SKUP has chosen to put the probable matrix effect in to the calculation. Under given conditions the real matrix effect can be calculated. SKUP has set the contribution of matrix effect at the same magnitude as the imprecision (5 %).

The quality goal of SKUP for the total error (TE) was calculated as follows:

$$TE = \text{bias } 5\,\% + 1{,}65 \text{ x } \sqrt{CV^2_{testmethod} + CV^2_{comparisonmethod} + CV^2_{betweenlab} + CV^2_{matrix}}$$

$$= 5\,\% + 1{,}65 \text{ x } \sqrt{25 + 9 + 9 + 25} = 5 + 13{,}6 \approx 19\,\%$$

> The analytical quality goals of SKUP for PT (INR) are
>
> > *Repeatability, CV$_a$: <5 %*
> > *Total error: <±20 %*

It is accepted that up to 5 % of the results can deviate more than ±20 %. Only 1 % of the results should deviate more than ±25 %. The results achieved with CoaguChek XS will be discussed and evaluated in proportion to these quality goals.

3. Materials and methods

3.1. The prothrombin time test [P—PT (INR]

The Scientific Division of IFCC (International Federation of Clinical Chemistry and Laboratory Medicine) together with IUPAC (International Union of Pure and Applied Chemistry) cooperate in the committee "Nomenclature, Properties and Units (C-NPU)". The committee has defined most diagnostic tests in the NPU database. The prothrombin time test [P—PT (INR)] is internationally performed according to two different method principles, namely the Owren method and the Quick method. The Scandinavian hospital laboratories use wet chemistry analysis procedures based on the Owren method. In other parts of the world the PT method according to Quick is dominating. The main difference between Owren and Quick methods is the extent of sample dilution and the sensitivity towards Factor V and fibrinogen. The final plasma dilution in the Owren method is 1:21, whereas the authentic Quick method has a sample dilution of 1:3. The Owren method gives a measure of the activity in plasma of the vitamin-K dependent coagulation factors II, VII and X, whereas the Quick method is sensitive for Factor II, V, VII and X and fibrinogen (Factor I).
The NPU data base defines the prothrombin time test [P—PT (INR)] according to Owren and Quick as follows:

Method	Formal full name of test	NPU code
Owren	P—Coagulation, tissue factor-induced; relative time (actual/normal; INR; IRP 67/40; procedure)	NPU01685
Quick	P—Coagulation, tissue factor-induced; relative time (actual/normal; INR; IRP 67/40; II+V+VII+X)	NPU21717

3.2. The CoaguChek XS device

3.2.1. *Description of CoaguChek XS*

CoaguChek XS is a new and small meter designed to be a real hand-held meter. It weighs 175g (with batteries) and fits the size of the palm. The blood sample is capillary whole blood and the sample size is 10 μL. The capillary sample can be taken using the CoaguChek Softclix lancing device. The sample application point is outside the meter, and the test strip has both top and side dosing. The measuring range for PT (INR) is 0,8 – 8,0. The memory can store 100 results. The test strips can be stored in room temperature with 18 months stability. The method is heparin insensitive.

CoaguChek XS presents a new electrochemical detection method for the clotting time. The test strip contains reagent in dried form. The reactive components of the thromboplastin reagent are human recombinant Tissue Factor (hrTF), phospholipides and a peptide substrate, Electrocyme TH, which can be used for the determination of serine proteases like thrombin. The reagent is more sensitive than reagents used by Roche before, with an ISI-value of 1,0. When a sample is applied, the Tissue Factor activates the coagulation cascade leading to the formation of thrombin. The enzyme thrombin cleaves Electrocyme TH into a residual peptide and electrochemically active phenylenediamine, thereby generating an electrical signal, which is registered.

The prothrombin measurement at CoaguChek XS is a modified version of the Quick method. The method is sensitive for Factor II, V, VII, X and fibrinogen (Factor I). The blood is mixed undiluted with the dried reagent in the test strip.

The CoaguChek XS test strips are calibrated against WHO standards, implying a manual tilt tube reference method using international Reference Preparations rTF/95 and CRM 149S. In this calibration the ISI for a master lot for CoaguChek XS was determined. The master lot will be used when the ISI of further lots are going to be determined.

The *On-Board Integrated system* (OBIS) shall secure that a result is displayed only if several quality checks are passed. The meter "self check" ensures reliability of meter hard- and software. The "failsafe" features shall ensure proper sample application and sufficient blood volume and that the test is being performed properly. The *Onboard Single-channel Strip control* (OS2C system) checks reagent integrity of each test strip. The system refuses strips which are exposed too long to high temperature, humidity or light. The OS2C system works with the patient's whole blood sample. Liquid controls are not planned for this system, as Roche wants to enforce the OBIS principle. The liquid controls intended for *CoaguChek XS Plus* will still be examined in this evaluation.

CoaguChek XS and CoaguChek XS Plus
Additional information from Roche, please see attachment 7.

3.2.2. *Product information, CoaguChek XS*

CoaguChek XS is manufactured by:
Roche Diagnostics GmbH
D-68298 Mannheim
Germany
Internet: www.coaguchek.com, www.roche-diagnostics.com

Suppliers of CoaguChek XS in the Scandinavian countries:

Denmark:
Roche a/s   Phone: +45 3639 9999
Industriholmen 59   Fax: +45 3639 9900
DK-2650 Hvidovre

Norway:
Roche Diagnostics Norge AS   Phone: +47 23 37 33 00
Postboks 6610 Etterstad   Fax: +47 23 37 33 99
0607 Oslo   e-mail: liv_janne.oevrebust@roche.com

Sweden:
Roche Diagnostica Scandinavia AB   Phone: + 46 08-404 88 00

Box 147   Fax: + 46 08-404 88 75
161 26 Bromma   e-mail: roche.kundsupport@roche.com
CoaguChek XS instruments
Lot number 05603061, Serial number UP 00022630 (used in the hospital evaluation)
Lot number 05603061, Serial number UP 00022597 (used in primary health care)
Lot number 05603061, Serial number UP 00022591 (reserve)

CoaguChek XS test strips
Lot number 20148132, with preliminary expiry date 06-2006, was used for the first 59 patients.
The short shelf life was an extra-precaution during the development of the product. The expiry
date is later extended with 6 – 12 months.
Lot number 20148537, with expiry date 01-2007, was used from patient number 60 and further
on, including most of the patients in the group that participated twice.

CoaguChek XS Plus control
Lot number 20151701, expiry date 11-2006

3.2.3. *Technical data*
Technical data from the producer is shown in table 1

Table 1. Technical data from the manufacturer.

TECHNICAL DATA FOR COAGUCHEK XS	
Working temperature	$+18 — +32^{o}$ C
Sample	Capillary whole blood
Blood sample size	10 μL
Units	INR
Measuring time	Within one minute
Measuring range	PT (INR) 0,8 — 8,0
International sensitivity index, ISI	1,0
Thromboplastin	Recombinant Tissue factor
Memory	100 results
Power supply	4 x AAA batteries (no external power supply)
Operating time with battery	Approximately 60 tests
Meter size	Hand-held, 138 x 78 x 27 mm
LCD Size	47 x 47 mm
Weight	175 g (with batteries)

3.3. The designated comparison method

3.3.1. *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.

3.3.2. *Description of the designated comparison method in this evaluation*
The automated laboratory instrument STA Compact® (Diagnostica Stago, France) using the SPA-reagent (Diagnostica Stago, France) was assigned to be the comparison method in this evaluation. This method is the routine method for the determination of PT (INR) in the laboratory at Haraldsplass Diaconal Hospital (HDS), and the laboratory leader and the staff agreed to take the responsibility for the practical work connected with the evaluation.
The SPA reagent is a combined rabbit brain thromboplastin. The final dilution of the citrate plasma is 1:21. The method is sensitive for decreased activity of Factor II, VII and X. The method is calibrated with two calibrators from EQUALIS (External Quality Assurance in Laboratory Medicine in Sweden). The calibrators are traceable to the reference thromboplastin RBT/90 from WHO. The comparison method is an Owren method, and is the most used method in Norwegian hospital laboratories for measurement of PT (INR). Setting Thrombotest aside, all hospital methods in Norway are calibrated with EQUALIS INR calibrators.

3.3.3. *Procedures in the laboratory at HDS*
Fresh SPA reagent is made every morning. Possible reagent leftovers from the night are discarded. When the instrument needs calibration, freshly made reagent is kept at room temperature for four hours in advance, according to the guidelines. The daily internal quality control is performed with Scandinorm and Scandipath from Stago. To monitor the stability of the SPA reagent during the day, and the stability of the INR level over time, a human plasma pool produced in the laboratory at HDS is continuously analysed day and night. The pool is made of freshly frozen citrate plasma with a PT (INR) value at approximately 3. An aliquot of the control is thawed every morning and is placed in the STA Compact instrument for the next 24 hours. The control results slightly changes through the day, giving a poorer CV than with freshly thawed controls, or if only results achieved at the same time of each day are compared. The plasma pool results are primarily used to reveal any systematic shift in PT-level over time.
During the evaluation period, two lots of reagent were used. The system was calibrated in April, before the evaluation had started, and recalibrated 17.08.2006 when the reagent lot was changed.

3.3.4. *Product information, the comparison method*
Instrument
STA Compact® from Diagnostica Stago, France. Serial no. 6120561.

Reagent
STA-SPA 50 reagent from Diagnostica Stago, France, for the determination of the combined Factors II-VII-X on STA Compact instruments.
Lot no. 50281 was used from the evaluation started in May until 17.08.2006. This lot of reagent was calibrated at the instrument 04.04.2006 with calibrators from EQUALIS.
Lot no. 51751, with expiry date 2007-06, was used from 17.08.2006 and throughout the rest of the evaluation period. This lot of reagent was calibrated 17.08.2006.

Calibrators
EQUALIS calibration kit for P—PT (INR) according to Owren.
Calibrator Low, lot no. 13, expiry date 2006-11. Certified value, PT (INR): 1,096 ±0,093 (95 % CI).
Calibrator High, lot no. 14, expiry date 2006-11. Certified value, PT (INR): 3,63 ±0,45 (95 % CI).
Control, lot no. 15, expiry date 2006-11. Certified value, PT (INR): 2,95 ±0,34 (95 % CI).

Internal quality control
Scandinorm
Producer: Diagnostica Stago, France. Lot no. 50187 was used from the start of the evaluation until11.08.2006. Expiry date 2007-01. Stated PT (INR) value from producer: 1,00. Internal PT (INR) target value at the laboratory at HDS: 0,98 ± 0,078.
Lot no. 52501 was used from 11.08.2006 and throughout the rest of the evaluation period. Stated PT (INR) value from producer: 0,95. Preliminary internal PT (INR) target value in at the laboratory at HDS: 0,93 ± 0,074. From 03.10.2006 the internal PT (INR) target value was adjusted to 0,967.

Scandipath
Producer: Stago, France. Lot no. 50811 was used from the start of the evaluation until 05.09.2006. Expiry date 2007-03. Stated PT (INR) value from producer: 2,85. Internal PT (INR) target value at the laboratory at HDS: 2,55 ±0,204.
Lot no. 60103 was used from 05.09.2006 and throughout the rest of the evaluation period. Expiry date: 2008-01. Stated PT (INR) value from producer: 3,05. Preliminary internal PT (INR) target value at the laboratory at HDS: 2,75 ±0,220. From 03.10.06 the internal PT (INR) target value was adjusted to 2,852 ±0,228.

Patient control/Stability control
The stability control is a patient plasma pool, freshly frozen after sampling.
Lot no. 1/2006 was used from May until 09.07.2006. PT (INR) = 3,59 ±0,359.
Lot no. 2/2006 was used from 09.07.2006 until 05.10.2006. PT (INR) = 3,00 ±0,300.
Lot no. 3/2006 was used from 05.10.2006. PT (INR) = 3,12 ±0,312.

Coagulation sodium citrate tubes
Vacuette, evacuated 2 mL 3,2 % (0,105 mol/L) Sodium Citrate tubes from Greiner.

3.3.5. *The analytical quality of the comparison method*
The analytical quality of the comparison method is demonstrated by means of the patient samples in the evaluation, together with different control and calibrating materials.
Repeatability is shown by means of 96 patient samples. Each patient sample in the evaluation was analyzed in duplicate.
Daily internal quality control is performed with Scandinorm and Scandipath from Diagnostica Stago. Scandinorm is freeze-dried, citrated normal human plasma. Scandipath is freeze-dried, citrated abnormal human plasma. The laboratory at HDS sets up their own target values for the two controls. As well as monitoring the daily analytical quality, the results achieved over time with the two control materials can give a picture of the reproducibility of the method.

To monitor the stability of the reagent during the day, and the stability of the PT level over time, a human plasma pool produced at the laboratory at HDS is continuously analysed day and night. The pool is made of freshly frozen plasma and has a PT (INR) value at approximately 3.
There is no Gold Standard and a real true value for PT (INR). The PT values will depend both on the choice of reagent, the calibrators and the instrument. The comparison method at the laboratory at HDS is the most commonly used PT (INR) system in Norway, with SPA-reagent at a Stago-instrument, calibrated with calibrators from EQUALIS. The following materials have been analyzed to verify the PT (INR) level of the comparison method ("trueness"):

INR calibrators from EQUALIS
The calibration kit from EQUALIS concists of two PT (INR) calibrators and one control. The three materials are manufactured by MediRox AB. Each material is a pool of citrated anti-coagulated freeze-dried plasma of human origin (Swedish donors), supplied in a siliconized glass bottle sealed with a rubber stopper and an outer plastic screw cap. The certified values are traceable to an internationally agreed reference measurement procedure (WHO's manual tilt tube technique) and the reference thromboplastin WHO RBT/90 [8,9]. The procedures used to assign values are described in several publications and documents [10,11,12].

INR calibrators from DEKS, the Danish Institute for External Quality Assurance for Hospital Laboratories
The calibration materials from DEKS are freshly frozen pooled citrate-plasmas which serve as national reference plasmas. The assigned value of the so called ISI calibrator is the mean value obtained by testing with manual tilt tube technique against international reference preparations of thromboplastins; BCT/099 (human plain), OBT/79 (bovine combined), RBT/79 (rabbit plain) and CRM 149R (rabbit plain). The value of later calibrators is compared with the previous calibrator. The normal calibrator was assigned with a "consensus" PT (INR) value of 1,00. Today, the ISI calibrator has been replaced by two frozen pools of plasmas, one at the therapeutic level with PT (INR) = 2 – 3 and one at a higher level with PT (INR) about 4.

INR Controls produced at NOKLUS
NOKLUS produces control materials at regular intervals for the Norwegian external quality assessment scheme. The materials are freshly frozen pooled citrate plasma from Norwegian donors. The NOKLUS controls "White" and "Blue" were available for SKUP in this evaluation. Control batch white 20904 has been used in eight different surveys and control batch blue 20805 has been used in three surveys. The INR-value of the controls used by NOKLUS in the surveys is the overall method-mean achieved in the external quality assessment scheme. In addition, method-mean values are calculated separately according to different types of reagent in use. More than 40 laboratories participate in the "SPA-group", and 20 hospital laboratories form the part using Nycotest PT reagent.

3.4. Planning of the evaluation

3.4.1. *Background for the evaluation*
CoaguChek XS (XS for eXtra Small) is a new and small meter designed to be a real hand-held meter. The blood sample is capillary whole blood and the sample size is 10 µL. The sample application point is outside the meter, and the test strip has both top and side dosing. CoaguChek XS presents a new electrochemical detection method for the clotting time. The test strip contains reagent in dried form. The thromboplastin is human recombinant Tissue Factor. The reagent is more sensitive than reagents used earlier by Roche, with an ISI-value of 1,0.
Roche is launching the new instrument into the Scandinavian market and wanted to demonstrate the analytical quality and user friendliness of the device in a SKUP evaluation.

3.4.2. *Arrangements about the evaluation*
Liv-Janne Øvrebust from Roche Diagnostics Norway turned to SKUP in January 2006 and asked for a SKUP evaluation of CoaguCek XS. Roche and SKUP made an informal agreement about the evaluation shortly after, and a preliminary protocol for the evaluation was sent to Roche at the end of February. The protocol was agreed upon after some minor adjustments. The evaluation was planned and prepared in detail and the practical training with CoaguChek XS was done in March. The equipment necessary for the evaluation was received at NOKLUS Centre in April. The contract for the evaluation was set up and signed in May, and the first patients enrolled in the study at the same time.

3.4.3. *Evaluation sites and persons involved*
According to the SKUP model for evaluations of laboratory equipment for primary care, an evaluation should be made under standardised and optimal conditions in a hospital laboratory by experienced laboratory-educated people, and under real-life conditions in the hands of the intended users at primary care centres. Generally, at least two primary care centres participate in the evaluation.
According to Roche, their basic aim was to get a comparison of the INR level of the new instrument with a "typical" Norwegian hospital PT (INR) level. An evaluation in primary health care was therefore not of current interest. Under pressure from SKUP, yet it was decided to include one primary care centre in the evaluation.
The evaluation of CoaguChek XS was performed at the laboratory of Haraldsplass Diaconal Hospital in Bergen and at the primary care centre Legekontoret i Løbergsalleen. At Løbergsalleen, two doctors and to health secretaries work. In their small laboratory they have an ordinary CoaguChek as their routine PT (INR) device. Both health secretaries participated in the evaluation work with CoaguChek XS. A survey of the persons responsible for the various parts of the evaluation is given in table 2 on the next page.

Table 2. Persons responsible for various parts of the evaluation

Stein Binder	Biomedical laboratory scientist. laboratory consultant, NOKLUS Vest	Evaluation instructor for the personnel at Legekontoret i Løbergsalleen
Grete Monsen	Biomedical laboratory scientist, Project manager, SKUP	Responsible for the evaluation. Author of this report
Marte Hammersland Eli Vik Skare Kjersti Østrem	Biomedical laboratory scientists	Operators of the evaluation of CoaguChek XS in the laboratory at HDS
Anne Elisabeth Solsvik	Biomedical laboratory scientist, Quality manager in the laboratory, HDS	Responsible for the evaluation in the laboratory at HDS
Solveig Heimark	Secretary in the laboratory, HDS	Coordinator of the patient consultations and the sampling in the laboratory at HDS
Liv-Janne Øvrebust	Product Manager, Point of care Roche Diagnostics Norway	Ordered the evaluation
Anette Fossen Halgjerd Boge	Health secretaries at Legekontoret i Løbergsalleen	Carried out the measurements on CoaguChek XS in primary health care

To make contact with SKUP in Norway:

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Box 6165   E-mail: grete.monsen@noklus.no
N-5892 Bergen   Internet: www.skup.nu

3.4.4. *Recruitment of patients*
The SKUP evaluation model describes an evaluation involving a total of 100 patient samples. The plan was to enrol 100 outpatients attending laboratory PT monitoring, and ensure that all of them were on long-term, stabilized oral anticoagulant treatment (OAT). It soon became clear, however, that these patients, in a much larger extent than only a few years ago, were not attending the hospital outpatient clinics any more, but get their PT monitored at the primary care centres by their general practitioner (GP). Unfortunately, the recruitment of patients did not progress as fast as hoped for. In addition, the summer holiday period lay ahead for laboratory staff, patients and coordinators. Under these circumstances, a letter was sent to some GPs having an agreement to collaborate with the laboratory at HDS asking for help to recruit some of their OAT patients. At the same time, an advertisement was composed for the daily press. In the newspaper announcement the patients in the primary health care were asked to volunteer for the evaluation study. Samples from 15 hospitalized patients were also collected and included at that time, to add to the total number of samples. The results from the hospitalized patients were rejected later on, and are not part of the final data set.

The letter did not pay off, but approximately 25 extra patients were recruited as a result of the advertisement in the daily press. The intensive recruiting efforts resulted in a total of 72 patients. 24 of these patients showed up twice in the hospital outpatient clinic during the evaluation period, and were allowed to participate for a second time. The 24 results from the second consultation are included in the calculations of the imprecision, but are excluded with regard to the calculation of accuracy and trueness, to avoid the potential risk of an influence in double dose of matrix effects of single patients.

3.5. Evaluation procedure

3.5.1. *Training*
Liv-Janne Øvrebust from Roche Diagnostics in Norway came to NOKLUS Centre in March to demonstrate CoaguChek XS for SKUP and to train the evaluators. Present at the demonstration and the training were Grete Monsen and Una Sølvik from NOKLUS Centre, Anne Elisabeth Solsvik, the quality leader of the laboratory at HDS, and Eli Vik Skare and Kjersti Østreim, two biomedical laboratory scientists designated to do the practical work with the evaluation. The training of the staff at the primary care centre, Legekontoret i Løbergsalleen, was done the same day. Laboratory consultant Stein Binder, NOKLUS Vest, participated in the training at the primary care centre, and instructed the staff about the details in the evaluation.

3.5.2. *Evaluation procedure in the hospital laboratory (standardised and optimal conditions)*
The evaluation in the hospital laboratory was done by the biomedical laboratory scientists/laboratory educated personnel who had previously received thorough training. The evaluation was done in exact accordance with the protocol and user manual. All possible disturbances of, and interferences with, the measurements were tried kept at a minimum. The evaluation under standardised and optimal conditions documents the quality of the system under as good conditions as possible.

3.5.3. *Sampling and sample-handling*
The patients who enrolled in the evaluation were on long-term, stabilized oral anticoagulant treatment. The collection of the samples was made in the outpatient clinic at the laboratory at HDS. For the comparison method, venous blood was drawn in an evacuated tube (3,2 % sodium citrate). The sampling as well as further treatment of the samples for the comparison method followed the internal routines of the laboratory in detail. Continuously after the sampling, and always within two hours, the samples for the comparison method were centrifuged for 15 minutes at 2500 g. Plasma was separated and placed in the instrument directly. The samples were included among the routine PT-analysis at the laboratory. Unlike the routine samples, the samples for the evaluation were measured in duplicate, simply by ordering a rerun for these series. As a rule, the PT-results from the comparison method were available within two hours after the sampling had taken place.
Two capillary samples were taken from each patient for measurement on CoaguChek XS. The first drop of blood from a fingertip was applied within 15 seconds on the test strip already inserted in the device. After the first measurement a new fingertip was pricked and the measurement was repeated with a new drop of blood.

3.5.4. *Evaluation procedure in primary health care*
Samples from 40 patients in treatment with vitamin-K antagonists attending the primary care centre for routine monitoring of their PT (INR) were collected for the evaluation study. The PT routine device at the centre was CoaguChek. In addition to the routine measurement, two capillary samples were taken from each patient for measurement on CoaguChek XS. According to the protocol and the agreements made with Roche, venous samples for transport to the hospital and the comparison method were not collected.

4. Statistical expressions and calculations

4.1. Statistical terms and expressions

4.1.1. *Precision*

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

4.1.2. *Accuracy*

Accuracy is the closeness of agreement between the result of one measurement and the true value. Inaccuracy is a measure of the deviation of a single measurements 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 in a difference-plot 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, acceptable and poor e.g.), whereas bias is the estimate, reported in the same unit as the analytical result or in %. The bias at different PT (INR) levels will be summarised in tables.

4.2. Statistical calculations

4.2.1. *Number of samples*
72 outpatients participated in the evaluation. 24 of these patients showed up twice in the hospital outpatient clinic during the evaluation period and donated a second sample at this occasion. As an outset, this gives a total number of 96 samples. For three of the patients the sampling of one of the two capillary samples was not successful, resulting in only one counting result for these three. This gives the following number of results for the different statistical calculations, before possible outliers are excluded:
93 duplicate results for the calculation of imprecision of CoaguChek XS.
70 duplicate results + 2 single results on CoaguChek XS and 72 corresponding duplicate results on the comparison method for the calculation of trueness/bias.
All 96 results are shown in the figure showing accuracy/total error, but the 24 results from the second consultation are marked with a differentiating symbol and are not included in the counting for the quality goal.
For details about the recruitment of an adequate number of patients, see section 3.4.4.
A summary of missing and excluded results is found in section 4.2.3.

4.2.2. *Statistical outliers*
All the results are checked for outliers according to Burnett [13], 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 PT (INR) levels, the outlier-testing is done at each level separately. Statistical outliers are excluded from the calculations. Possible outliers will be commented on under each table.

4.2.3. *Missing or excluded results*
Besides the statistical outliers, some results are missing or excluded for other reasons.

Imprecision of CoaguChek XS
ID no. 59, the first consultation: the second capillary sample for CoaguChek XS failed
ID no. 76, the first consultation: the second capillary sample for CoaguChek XS failed
ID no. 24, the second consultation: the second capillary sample for CoaguChek XS failed
Because the imprecision is based on duplicate samples of each patient, these three results are not included in the calculation of the imprecision of CoaguChek XS.

Trueness of CoaguChek XS
ID no. 67 is excluded in the first truncation
ID no. 25 and ID no. 46 are excluded in a second truncation.

4.2.4. *Calculations of imprecision based on duplicate results*
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 the two parallel measurements of every duplicate, the calculated standard deviation is still a measure of the imprecision of single values, and completely comparable with the more generally used calculation based on repeated measurements of only one sample. The assumption for using this formula is that no systematic difference between the 1st and the 2nd measurement of the duplicate is acceptable. Table no. 3 shows that there is no systematic difference in the PT (INR) value between the 1st and the 2nd measurements at CoaguChek XS in this evaluation.

Table 3. Comparison of the 1st and the 2nd measurement on CoaguChek XS. T-test for paired values.

	PT (INR) Level	Mean 1st measurement PT (INR)	Mean 2nd measurement PT (INR)	Mean difference 2nd – 1st measurement PT (INR)	95 % CI for the mean difference PT (INR)	n
CoaguChek XS	< 2	1,625	1,650	0,025	-0,18 — +0,23	12
	2 – 3,5	2,590	2,584	0,006	- 0,14 — +0,15	69
	> 3,5	4,025	4,042	0,017	-0,43 — +0,46	12

4.2.5. *Calculation of trueness*
To measure the trueness of the results on CoaguChek XS, the average bias at three levels of PT (INR) is calculated based on the results obtained under standardised and optimal measuring conditions. A paired t-test is used with the mean values of the duplicate results on the comparison method and the mean values on CoaguChek XS. The mean difference is shown with a 95 % confidential interval.

4.2.6. *Calculation of accuracy*
To evaluate the accuracy of the results on CoaguChek XS, the agreement between CoaguChek XS and the comparison method is illustrated in a difference plot. In the plot the x-axis represents the mean value of the duplicate results on the comparison method. The y-axis shows the difference between the first measurement on CoaguChek XS with two lots of test strips and the mean value of the duplicate results at the comparison method.

5. Results and discussion

5.1. Analytical quality of the designated comparison method

5.1.1. *The precision of the comparison method*
The repeatability of the comparison method is demonstrated by means of the patient samples in the evaluation. Each of the 96 samples was analysed in duplicate. The results are divided in three groups according to the PT (INR) level, and the calculation of the repeatability is made for each level separately. There are only four samples with PT (INR) >3,5 at the comparison method. To be able to differentiate between the repeatability at the therapeutic level and a higher INR level, the cut off value between the two levels is set at PT (INR) = 3,0.
The reproducibility is demonstrated by means of the internal controls Scandinorm and Scandipath.

Internal quality control with Scandinorm and Scandipath
Scandinorm and Scandipath were always analysed on the comparison method together with the samples from the evaluation. In addition, the two internal control materials were analysed by routine in the laboratory several times during the day, giving a considerably number of control results. Only the results connected to the evaluation are included in the calculations of the reproducibility.

The reproducibility of the comparison method can also be calculated from the results of the patient control produced at the laboratory for monitoring the stability of the method. As discussed in section 3.3.3, the variation with the patient control covers more than the actually method reproducibility, and gives a higher CV than with freshly thawed materials.

The repeatability of the comparison method is shown in Table 4 on the next page.
The raw data is shown in attachment 1.

Internal quality control results and reproducibility with Scandinorm and Scandipath and reproducibility are shown in Table 5.
Raw data is shown in attachment 2.

The reproducibility of the comparison method with the patient control is shown in Table 6.

Table 4. Repeatability with patient samples, the comparison method.

PT (INR) Level	PT (INR) average (range)	CV % (95 % C.I.)	n	Outliers
< 2,0	1,7 (1,1 — 2,0)	1,2 (0,9 — 1,9)	17	0
2,0 – 3,0	2,5 (2,0 — 3,0)	1,5 (1,3 — 1,8)	63	0
> 3,0	3,4 (3,0 — 4,6)	1,4 (1,0 — 2,1)	16	0

Table 5. Reproducibility with freeze dried control materials, the comparison method.

Control	PT (INR) target value from producer	Period	PT (INR) achieved value	CV % (95 % C.I.)	n
Scandinorm	1,00	09.05.06 — 10.08.06	0,97	1,6 (1,3 — 1,9)	64
	0,95	21.08.06 — 15.11.06	0,96	2,5 (2,1 — 3,1)	53
Scandipath	2,85	09.05.06 — 21.08.06	2,53	2,7 (2,3 — 3,2)	75
	3,05	21.08.06 —15.11.06	2,81	4,4 (3,7 — 5,4)	53

Table 6. Reproducibility with patient plasma controls, the comparison method.

Period	Lot no.	PT (INR) internal target value	CV % (95 % C.I.)	n	Outliers
May - July	1/2006	3,59 ±0,359	4,2 (4,0 — 4,6)	390	0
August - October	2/2006	3,00 ±0,300	4,2 (3,8 — 4,6)	225	0
October - November	3/2006	3,12 ±0,312	4,6 (4,2 — 4,9)	311	0

Discussion

The precision of the comparison method is good. The repeatability CV is between 1,0 and 1,5 %. With freeze dried control materials the reproducibility CV is between 2 and 4 %. All internal control results were within the stated limits for the controls.

The CV achieved with the patient control is approximately 4,5 %. The CV achieved with the patient control would be considerably lower if the control was freshly thawed each time, but this is not the purpose of this control (see section 3.3.3).

5.1.2. *The trueness of the comparison method*

To demonstrate the trueness of the comparison method, the calibrators from EQUALIS were analysed as anonymous samples at three different occasions in the evaluation period. The Danish calibrators from DEKS and NOKLUS control materials have also been analysed.
The results achieved with EQUALIS calibrators are shown in Table 7.
The results with DEKS calibrators and the control materials from NOKLUS are shown in table 8.

Table 7. EQUALIS calibrators measured on the comparison method.

Material	PT (INR) Certified value	Date	PT (INR) Comparison method, average value	n
EQUALIS INR calibrator Low	1,096 ±0,093	22.05.06	1,07	3
		08.09.06	1,10	3
		07.11.06	1,08	2
EQUALIS INR calibrator High	3,63 ±0,45	22.05.06	3,46	3
		08.09.06	3,45	3
		07.11.06	3,28	2
EQUALIS INR control	2,95 ±0,34	22.05.06	2,81	3
		08.09.06	2,87	3
		07.11.06	2,72	2

Table 8. DEKS calibrators and NOKLUS Control materials on the comparison method.

Material	PT (INR) assigned value	Date	PT (INR) comparison method, average value	n
DEKS INR calibrator Normal	0,96 ±0,026	19.05.06	0,96	3
		08.09.06	1,01	1
		07.11.06	0,95	2
DEKS INR calibrator Therapeutic	2,30 ±0,09	19.05.06	2,16	3
		08.09.06	2,23	2
		07.11.06	2,06	2
DEKS INR calibrator High	3,92 ±0,22	19.05.06	3,49	3
		08.09.06	3,45	2
		07.11.06	3,24	2
NOKLUS control White*	2,0** 2,1***	08.09.06	1,88	2
		07.11.06	1,80	2
NOKLUS control Blue*	3,0** 3,2***	08.09.06	2,80	2
		07.11.06	2,67	2

* The PT (INR) values of the NOKLUS controls "White" and "Blue" result from the NOKLUS external quality assessment scheme.
** Overall mean for the hospital laboratories using SPA-reagent and PT (INR) instrument from Stago. More than 40 laboratories participate in this group and the group represents the majority of the Norwegian hospital laboratories.
*** Overall mean for the 20 hospital laboratories using Nycotest PT reagent on Thrombolyzer or Thrombotrack.

Discussion

Table 7 shows that the comparison method agrees well with the EQUALIS calibrator with certified PT (INR) value at approximately 1,0. It is clear, however, that the comparison method has a small negative bias compared to the EQUALIS calibrator with the high PT value [PT-(INR) = 3,6]. The achieved values are still within the uncertainty limits of the calibrator. The negative bias also appears in the therapeutic range, as shown with the EQUALIS Control, but is not as distinguished as for the higher PT values.

The results in Table 8 achieved with the NOKLUS Control materials confirm the small negative bias of the comparison method. The significant differences between the "SPA/Stago group" and the "NycoTest PT group" have been shown repeatedly during the last years in Norway. If this evaluation had been performed with Nycotest PT reagent, the results on the comparison method most probably would have been slightly higher. Still this would not influence the conclusions in this report.

Table 8 also shows that the negative bias of the comparison method tends to get more distinct when compared to the Danish DEKS Calibrators. The calibrating systems from EQUALIS and DEKS are quite different, with respect to the production of the materials as well as the way the calibrators get the certified PT-values. For high PT-values, the discrepancy between the two calibrating systems has been shown before by others. EQUALIS, as well as the Expert Group for coagulation appointed by EQUALIS are looking deeper into this matter.

Due to the present bias of the comparison method, it was decided that all results from the comparison method should be adjusted to meet with the target values for the two EQUALIS calibrators and the EQUALIS control. The adjustment was done by means of the following regression equation ($R^2 = 1,0$):

$$y = 1,0866x - 0,0864$$

Further on in this report, whenever CoaguChek XS results are compared with the comparison method (trueness and accuracy), the results from the comparison method have already been adjusted according to this equation.

5.2. Analytical quality of CoaguChek XS in use at a hospital laboratory

5.2.1. *The precision of CoaguChek XS (standardised and optimal conditions)*

The repeatability of the CoaguChek XS is demonstrated by means of 93 patient samples analysed in duplicate. The results are divided in three groups according to the PT (INR) level, and the calculation of the repeatability is made for each level separately.

The repeatability is shown in table 9.
The raw data is shown in attachment 3.

Table 9. Repeatability, CoaguChek XS. Results achieved under standardised and optimal test conditions

PT (INR) Level	PT (INR) average (range)	CV % (95 % C.I.)	n	Outliers
< 2,0	1,6 (1,1 – 1,9)	2,8 (2,0 – 4,7)	12	0
2,0 – 3,5	2,6 (2,0 – 3,5)	3,7 (3,2 – 4,4)	69	0
> 3,5	4,0 (3,6 – 5,4)	1,8 (1,2 – 3,0)	12	0

Discussion

The precision of the PT (INR) measurements on CoaguChek XS is good. The CV is approximately 3 % and the quality goal of SKUP is attained.

5.2.2. *Internal quality control on CoaguChek XS*

There are no liquid controls planned for CoaguChek XS. The *Onboard Single-channel Strip control* (OS2C system) checks reagent integrity of each test strip and refuses strips which are exposed too long to high temperature, humidity or light. For CoaguChek XS Plus, on the other hand, a control is designed. To get an expression of how the *CoaguChek XS Plus Control* will function on CoaguChek XS, the liquid control has been tested in this evaluation.

The results with CoaguChek XS Plus Control on CoaguChek XS are shown in table 10.
Raw data is shown in attachment 4.

Table 10. Reproducibility with CoaguChek XS Plus Control on CoaguChek XS

CoaguChek XS Plus Control Given value, PT (INR)	PT (INR) average (range)	CV % (95 % C.I.)	n
-	2,2 (2,1 – 2,3)	3,4 (2,7 – 4,5)	32

Discussion

CoaguChek XS Plus Control gives reproducible INR results on CoaguChek XS.

5.2.3. *The trueness of CoaguChek XS (standardised and optimal conditions)*
The trueness of CoaguChek XS is calculated from 72 (69 after exclusion of outliers) results
achieved by three biomedical laboratory scientists in a hospital laboratory. The reduction from 96
to 72 results is because 24 of the patients donated samples at two occasions, of which the latter
was excluded. The exclusion is to prevent the bias from being influenced by a double dose of a
possible individual matrix effects. Inclusion of the 24 results only influences the estimate
marginally. Two lots of test strips were used.

The bias of CoaguChek XS relative to the comparison method is shown in Table 11.
The raw data with CoaguCehk XS is shown in attachment 3.

Table 11. Bias. Mean difference between CoaguCheck XS and the comparison method, based on the mean of each
duplicate on both methods. Results achieved under standardised and optimal conditions. N = 72

PT (INR) Level	CoaguChek XS mean PT (INR)	Mean deviation from the comparison method, INR (95 % CI)	n	Outliers
< 2,0	1,67	0,01 (-0,10 - +0,13)	9	0
2,0 – 3,5	2,61	-0,06 (-0,11 - +0,08)	54	3*
> 3,5	4,17	0,007 (-0,74 - +0,75)	6	0

* ID no. 67 is excluded in the first truncation and ID no. 25 and no. 46 are excluded in a second truncation.

Discussion
No bias between CoaguChek XS and the comparison method is pointed out.

5.2.4. *The accuracy of CoaguChek XS under standardised and optimal conditions*
To evaluate the accuracy of the results on CoaguChek XS, the agreement between CoaguChek XS
and the comparison method is illustrated in a difference plot. The plot shows the deviation of
single results on CoaguChek XS from the true value. The plot gives a picture of both random and
systematic deviation and reflects the total measuring error.
The total error is demonstrated only for the first measurements of all the paired results. The results
with the second samples of the 24 patients who donated samples at two occasions are also shown
in the figure, but in a differentiating symbol. Possible patient matrix effects are thus not allowed
to influence the results in double doses.
The limits in the plot are based on the quality goals discussed in chapter 2 in this report.
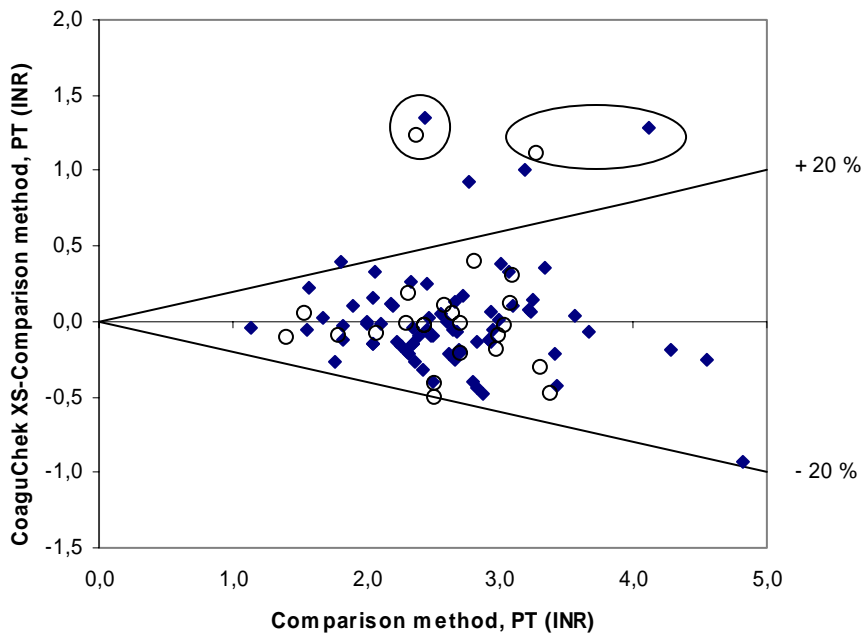
The accuracy of CoaguChek XS is shown in Figure 1.

Figure 1. The accuracy of CoaguChek XS. The filled diamonds are the first 72 results in the evaluation. The open circles are results from a second consultation for 24 of the same patients. Four of the obvious "outliers" (two pair of results) are from the same two patients, and these results are encircled.

Discussion

The main impression of the accuracy of CoaguChek XS is good. No systematic difference between the measurements on CoaguChek XS and the comparison comes forward. This assessment is valid for the results from the total group of patient, including the patients that participated twice in the evaluation.

Six results clearly deviate from the rest. The six deviating results are obvious outliers. In fact, three of the four deviating results of the 72 original results were already proved as outliers and excluded in the calculation of bias (table no. 11). But the six results are not ordinary, accidental outliers. The deviation in fact, is reproducible, as shown by good agreement between the duplicate measurements of each sample. In addition, two of the outliers were confirmed later on in the evaluation and these deviations are thereby reproducible also over time (encircled in the figure). The two remaining outlier-results have not been measured on a second occasion.

Differences of this character are most probably due to individual matrix effects caused by method differences. The sensitivity of the Quick- and Owren-method for various coagulation factors is different. The differences in the reagents are additionally amplified due to different dilution of the samples. The Owren method has a 1:21 dilution of the samples whereas the blood is undiluted in the modified Quick method applied on e.g. CoaguChek XS. Greater or lesser degree of sample-dilution could be an important contributor to systematic PT-discrepancies in individual patients. One should always be aware of the possibility for such deviating results when comparing Quick- and Owren-based methods. After the evaluation was finished, it became clear that one of the outlier results is from a patient who suffers from Lupus. Lupus is known to give different effect on the different PT methods. The four (of 72) clearly deviating results are the reason why CoaguChek XS not fulfils the quality goal set by SKUP. The four results are not results of a trend, and if disregarded, the quality goal is fulfilled.

5.3. Analytical quality in primary health care

5.3.1. *The precision of CoaguChek XS*
The repeatability of the CoaguChek XS in one primary health care centre is demonstrated by means of 40 patient samples analysed in duplicate. The results are divided in two groups according to the PT (INR) level, and the calculation of the repeatability is made for the two PT (INR) levels separately.

The repeatability is shown in table 12.
Raw data is shown in attachment 5.

Table 12. Repeatability, CoaguChek XS. Results achieved in a laboratory in primary health care

PT (INR) Level	PT (INR) average (range)	CV % (95 % C.I.)	n	Outliers
< 2,5 INR	1,6 (1,1 – 1,9)	3,7 (2,8 – 5,4)	19	0
> 2,5 INR	2,6 (2,0 – 3,5)	2,4 (1,8 – 3,4)	21	0

Discussion
The precision at CoaguChek XS as shown by the users at one laboratory in primary health care is good.

5.3.2. *The agreement between CoaguChek XS and CoaguChek*
The results achieved with CoaguChek XS at the primary care centre were compared with the results with their routine method, an ordinary CoaguChek. A t-test for paired values showed no significant difference between the two methods (calculations not shown).

Raw data is shown in attachment 5.

5.4. Evaluation of user-friendliness
The most important response regarding user-friendliness of any laboratory equipment intended for the users in primary health care comes from the users themselves. The end-users often emphasize other aspects than those pointed out by more extensively trained laboratory personnel.

5.4.1. *Evaluation of user-friendliness by laboratory educated personnel in a hospital laboratory*
No technical problems occurred during the evaluation period. The battery had to be changed once. After replacing the battery, all options on the instrument must be set from the beginning.
The three biomedical laboratory scientists who were responsible for the practical work with CoaguChek XS in the outpatient clinic at the hospital laboratory sum up their experiences with CoaguChek XS as follows:

- The device is easy to use
- The result is displayed within one minute
- Training is required to gain proper technique for applying a sufficient drop of capillary blood to the test strip without spilling
- The measurement is performed with the first blood drop after the fingertip is pricked. If an error message occurs during the measurement, the patient has to be pricked again
- Setting the instrument options takes some time and feels inconvenient with the patient sitting next to you

5.4.2. *Evaluation of user-friendliness by the users in primary health care*
The primary health care centre filled in a questionnaire about the user-friendliness and the user manual of CoaguChek XS. The questionnaire summarises six questions where the answers should be ranked on a scale from 1 to 4, where 1 was poor and 4 was very good. Overall, the primary health care centre was very satisfied with CoaguChek XS and the user manual. Only one instrument "technical proble" occurred during the test period. This was an error 6, which is a measuring error. Changing the test-strip solved the problem.

Comments
The primary health care centre reported several advantages with CoaguChek XS. The advantages reported were as follows:
– Easy to fill the test-strip with blood
– No need for a pipette to transfer the blood from the finger to the test-strip
– Easy to work hygienically with the instrument
– The instrument has a short measuring time
– Handheld, removable instrument
– The small size of the instrument

One disadvantage with CoaguChek XS was reported:
– The button for resetting (SET-button) was not ideally centred. It was easy to touch this button by accident, especially for left-handed persons

6. References

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Attachments

Attachment 1. Raw data, STA Compact, results from patient samples

Attachment 2. Raw data, STA Compact, results from internal quality controls

Attachment 3. Raw data, CoaguChek XS, results from patient samples at the hospital laboratory

Attachment 4. Raw data, CoaguChek XS Plus Control results

Attachment 5. Raw data, CoaguChek XS, results from the primary heath care centre

     Raw data, CoaguChek routine results

Attachment 6. Comments from Roche

Attachment 7. Additional information from Roche, CoaguChek XS and CoaguChek XS Plus

Attachment 8. Evaluations under the direction of SKUP

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