The ProTime InRhythm System

A system for measurement of P — PT (INR)
manufactured by International Technidyne Corporation (ITC)

Report from the evaluation SKUP/2014/104

organised by SKUP at the request of Medic24 AS

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The report was written by SKUP, April 2014. For more details about SKUP, see attachment 1. Main author was Camilla Eide Jacobsen, SKUP in Norway.

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Attachment 6, 8 and 9 are included only in the copy to Medic24.

1. Summary

Background
The ProTime InRhythm™ System (InRhythm) is an in vitro diagnostic device for the quantitative measurement of Prothrombin Time / International Normalized Ratio (PT/INR) from capillary whole blood or fresh venous whole blood collected with no additives. The test system is intended for use by point of care healthcare professionals in the management of patients treated with oral vitamin K antagonist therapy.
The system is produced by International Technidyne Corporation (ITC), and has not been launched onto the Scandinavian market yet. The SKUP evaluation was carried out from January to March 2014 at the request of Medic24 in Norway.

The aim of the evaluation
- Estimation of the imprecision of InRhythm in a hospital laboratory (standardised and optimal conditions) and in primary health care centres
- comparing the InRhythm results achieved in a hospital laboratory and by two primary health care centres (intended users) with the results from an established hospital laboratory method for PT (INR)
- examination of the variation between three lots of test cuvettes
- evaluation of the user-friendliness of the InRhythm system and its user manual

Materials and methods
Capillary blood samples (third blood drop) from 102 patients on oral vitamin K antagonist treatment were measured on the InRhythm system at the hospital laboratory. Additionally, a total of 80 capillary samples (second blood drop) were tested at two primary health care centres (PHCCs). Three lots of test cuvettes were used. All results from the InRhythm were compared with the routine method of PT (INR) measurements at the hospital laboratory using citrated venous plasma samples (referred to as "the comparison method"). The quality goal for the imprecision was a repeatability CV of <5%. The quality goal for the accuracy was a deviation of ≤20% in the individual result from the comparison method result for 95% of the individual PT (INR) results.

Results
- For PT (INR) results <2,5 the repeatability CV was 3,4% in the hospital laboratory and 3,7 and 4,3% in the two PHCCs. For results ≥2,5 INR the CV was 4,9% (hospital), and 4,6 and 5,4% in PHCCs. In the therapeutic range 2,0 – 3,0 INR the CV was 4,1%.
- PT (INR) results <2,5 achieved on InRhythm in the hospital laboratory were on average 0,1 INR (-5,5%) lower than the results on the comparison method. No bias was observed with results <2,5 INR collected from the two PHCCs. For PT (INR) results ≥2,5 there was no bias observed.
- In the hospital laboratory 94% of the results with three lots of test cuvettes were within the limits for allowable deviation. For PHCCs the proportion of results within the limits was 89% (one lot of test cuvettes). Only small deviations between the three lots of test cuvettes appeared (visual inspection).
- The reproducibility CV achieved with the internal quality control solution *direct*CHECK Whole blood Control for InRythm was 18% in the hospital laboratory and 13% in the PHCCs.

- The percentage of technical errors was 0,8%. In addition it was recorded 2,5% errors related to too large blood drops.
- The users were satisfied with the user manual. The operation facilities were assessed as both satisfactory and intermediate. The time factors related to the InRhythm method were assessed as satisfactory and the quality control possibilities were assessed as unsatisfactory.

Conclusion

For PT (INR) results <2,5 the quality goal with a repeatability CV <5% was fulfilled for measurement performed at the hospital laboratory and most likely fulfilled for PHCCs. For PT (INR) results ≥2,5 the quality goal most likely was fulfilled for the hospital laboratory measurements and for the measurements at one of the PHCCs. For the other PHCC the quality goal most likely was not fulfilled. In the therapeutic range 2,0 – 3,0 the quality goal for repeatability was fulfilled (results from the hospital laboratory).

In the hospital laboratory InRhythm gave results 5,5% lower results than the comparison method for PT (INR) results <2,5. The quality goal for accuracy was neither fulfilled for the hospital laboratory nor for the PHCCs. The percentage of technical errors fulfilled the goal (≤2%).

The whole blood internal quality control material from the manufacturer was assessed as unsatisfactory. The control showed poor reproducibility, and should therefore not be used for analytical quality control.

The manual and time factors were assessed as satisfactory. The operations facilities of InRhythm were assessed partly as satisfactory and partly as intermediate due to the system's sensitivity for large drops of blood leading to the error message "Sample too large". Another comment mentioned was that the system must be placed stable when analysing samples. Overall the users found the InRhythm system fast and easy to handle.

Comments from Accriva Diagnostics (representing ITC and Accumetrics)

A letter with comments from Accriva Diagnostics is attached to the report.

2. Abbreviations and Acronyms

BLS	Biomedical Laboratory Scientist
CI	Confidence Interval
CV	Coefficient of Variation
DAK-E	Danish Quality Unit of General Practice
DEKS	Danish Institute of External Quality Assurance for Laboratories in Health Care
EQA	External Quality Assessment
Equalis	External quality assurance in laboratory medicine in Sweden
IRP	International Reference Preparation
ITC	International Technidyne Corporation
NKK	Norwegian EQA Program for Medical Biochemistry
Noklus	Norwegian Quality Improvement of Primary Care Laboratories
NS_EN ISO/IEC	Norsk Standard_Europeisk Norm International Organization for Standardization/International Electrotechnical Commission
PHCC	Primary health care centre
PT (INR)	Prothrombin Time International Normalized Ratio
RBT	Rabbit brain Thromboplastin
SD	Standard Deviation
SKUP	Scandinavian evaluation of laboratory equipment for primary health care
WHO	World Health Organization

3. Quality goals

3.1. Analytical quality

For the present, there are no generally recognised analytical quality goals for the determination of prothrombin time (PT), and no international (Gold) Standard for evaluation of Point of Care test instruments for prothrombin time measurements in primary health care.
The ISO 17593 standard [1] gives requirements for monitoring systems for self-testing of oral anticoagulant therapy. In SKUP's opinion, the quality goals for accuracy in the ISO 17593 standard (±30% for 90% of the results in the therapeutic range 2 – 4,5 INR(International Normalizes Ratio)) is too tolerant. Furthermore, there is no performance criterion for imprecision in the standard.

Setting quality goals based on biological variation is an acknowledged method [2,3].
It is recommended that analytical imprecision (repeatability, CV_a) 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 CV_{bw} 4% (intra-individual biological variation) and CV_{bb} 6,8% (inter-individual biological variation). According to Kjeldsen *et al.* [5], the "in-treatment within-subject biological variation" of PT (INR) is 10,1%. For systems used for monitoring, the analytical performance should aim at low imprecision compared to the within-subject 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 requirements to analytical quality for PT (INR) [6]: Bias ≤6% and imprecision ≤5% for instruments used in primary health care, and bias ≤3% and imprecision ≤3% for hospital instruments. There is no separate goal for the total error in the Danish specifications; however, estimated coefficient of variation in percent (CV%) for the matrix-effect is defined and an allowable deviation is given in the control system.

Based on the given data on biological variation for prothrombin time, and the fact that PT (INR) devices are designed for *monitoring* prothrombin time, SKUP recommends that these instruments should achieve a repeatability CV<5%. SKUP has not taken out a separate goal for bias, but a figure of 5% was used to calculate a quality goal for allowable deviation according to the model below.

In method evaluations and comparisons, one has to take the imprecision of the comparison method into account. SKUP allows an imprecision of the comparison method up to 3 CV%.
In addition, inter-laboratory-variation should be taken into the calculation of the allowable deviation, which SKUP has estimated to 3 CV%.

When comparing two prothrombin time methods, especially when the methods represent two different measuring principles, certain sample specific errors can be assumed. SKUP has chosen to include a variation of 5% in the error model for calculation of allowable deviation.

Allowable deviation = |±bias| + 1,65 x $\sqrt{CV^2_{testmethod} + CV^2_{comparisomethod} + CV^2_{betweenlab} + CV^2_{matrix}}$

= (5 + 1,65 x $\sqrt{25+9+9+25}$) = (5 + 13,6) ≈ ±19%

3.2. User-friendliness

The evaluation of user-friendliness is carried out by asking the evaluating person (end-users) to fill in a questionnaire divided into four sub-areas, see section 5.5.

3.3. Technical errors

SKUP recommends that the percentage of "tests wasted" caused by technical errors should not exceed 2%.

3.4. Principles for the assessments

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

3.4.1. Assessment of the analytical quality

The analytical results are assessed according to the quality goals set for the evaluation.

Precision

The decision whether the achieved CV fulfils the quality goal or not is made on a 5% significance level. The distinction between the ratings, and the assessment of precision according to the quality goal, are shown in table 1.

Table 1. The rating of precision

Distinction between the ratings	**Assessment according to the quality goal**
The CV is lower than the quality goal (statistically significant)	The quality goal is fulfilled
The CV is lower than the quality goal (not statistically significant)	Most likely the quality goal is fulfilled
The CV is higher than the quality goal (not statistically significant)	Most likely the quality goal is not fulfilled
The CV is higher than the quality goal (statistically significant)	The quality goal is not fulfilled

Trueness

The measured bias is given with a 95% confidence interval. The confidence interval is used for deciding if a difference between the two methods is statistically significant (two-tailed test, 5% significance level).

Accuracy

The accuracy is illustrated in a difference-plot with limits for the allowable deviation according to the quality goal. The fraction of results within the limits is counted.
The accuracy is assessed as either fulfilling the quality goal or not fulfilling the quality goal.

3.4.2. Assessment of three lots

Separate lot calculations are not performed. The results achieved with the three lots are included in the assessment of accuracy in the difference plots. If distinct differences between the lots appear, this will be pointed out and discussed.

3.4.3. Assessment of the user-friendliness

The user-friendliness is assessed according to the answers and comments given in the questionnaire (see section 5.5.). For each question, the user must choose between three given ratings, as for instance satisfactory, intermediate or unsatisfactory. The response from the users is reviewed and summed up. To achieve the overall rating ”satisfactory”, the tested equipment must reach the total rating of “satisfactory” in all four sub-areas of characteristics mentioned in section 5.5.

3.4.4. Assessment of the technical errors

The evaluating person registers the fraction of error codes and technical errors during the evaluation.

3.5. SKUP´s quality goals in this evaluation

As agreed upon when working on the protocol, the results from the evaluation of InRhythm are assessed against the following quality goals:

Repeatability CV_a (within-series imprecision).....….<5%

Allowable deviation
in the individual result from the comparison method result.....<±20%
Required percentage of individual results
within the allowable deviation*.....≥95%

Fraction of technical errors .....≤2%

User-friendliness, overall rating.....Satisfactory

*Not more than 1% of the results should deviate more than ±25%.

4. Materials and methods

4.1. Definition of the measurand

The Committee on Nomenclature, Properties and Units (C-NPU) describes clinical laboratory tests in a database [7]. In the NPU-database the specifications for the measurand in this evaluation are as shown in table 2.

Table 2. NPU-specifications

NPU code	Name of test according to NPU	Unit
NPU01685	P—Coagulation, tissue factor-induced; relative time(actual/normal; INR; IRP 67/40; proc.)	–
NPU21717	P—Coagulation, tissue factor-induced; rel.time(actual/norm; INR; IRP 67/40; II+V+VII+X)	–

IRP: International Reference Preparation

The analytical test according to NPU01685 refers to measurements performed with the Owren method. The test is mainly determined by the concentration of the Vitamin K dependent coagulation factors II, VII and X. The analytical test according to NPU21717 refers to measurements performed with the Quick method. The test is mainly determined by the concentration of the Vitamin K dependent coagulation factors, in addition to fibrinogen (factor I) and factor V.

Even if the tests according to NPU01685 and NPU21717 are not measuring exactly the same plasma components, the test results are used as if they did. In this report, the comparison method is an Owren method while the evaluated method InRhythm is a Quick method. The term "PT (INR)" will be used for the measurand in this report. As the measurement result is a ratio of the actual coagulation time divided with the normal coagulation time, there is no unit.

4.2. The evaluated measurement system ProTime InRhythm

The text in this section is derived mainly from the producer's (International Technidyne Corporation, ITC) information material and additional information from ITC.

The ProTime InRhythm™ System measures whole blood prothrombin time using fibrin clot formation and detection. The test is performed with a single-use disposable cuvette inserted into the instrument. When performing a test, a drop of blood is applied to the sample port on the cuvette and the instrument draws a precise volume of the sample into the micro-channels of the cuvette. Within the micro-channels the sample is mixed with the dried reagents, and the sample/reagent mixture is then pumped back and forth until clotting occurs. Sample/reagent motion is monitored by pressure change as it moves in the test micro-channels. A result is displayed when a preset change in pressure occurs. The blood sample is obtained from finger prick whole blood or fresh venous whole blood collected with no additives. The test system is intended for professional use in the management of patients treated with oral vitamin K antagonist therapy.

The ProTime InRhythm PT test cuvette comprises a sample port, sample sizing zone, two PT channels for result verification, one control channel in the therapeutic range, and one waste channel for excess blood. The cuvette includes hydrophilic seal tape that promotes a capillary

draw for sample collection and sizing. The two PT channels are used for testing the patient sample in duplicate and the control channel is used for simultaneous testing of an onboard quality control. The PT channels contain a small amount of dry PT reagent deposited along the bottom of the channel for patient testing. The InRhythm PT cuvettes contain proprietary preparation of commercially available sensitive recombinant thromboplastin with ISI close to 1.0, phospholipids, heparin neutralising agent and formulation buffer. Each lot is calibrated following WHO recommendations. The assigned MNPT and ISI are coded in the barcode of the cuvettes for each lot. The cuvette barcode also contains the lot code, and the expiration date. When the undiluted blood sample is applied, the dry PT reagent activates the coagulation cascade leading to fibrin formation. Clot formation is detected when a preset change in pressure occurs. The system uses sounds and icons to prompt the user at each procedural step.
The data management capabilities of the instrument include entry of patient and/or operator identification and designation of Quality Control levels, and identification of date and time of test results. Printing of results can be performed with an external ProTime InRhythm printer. The first, second or third drop of blood from the capillary prick can be used for sample application on the InRhythm system.

For technical data about the InRhythm system, see table 3. For more information about the InRhythm system, name of the manufacturer and the suppliers in the Scandinavian countries, see attachment 2 and 3. For product information, see attachment 4.

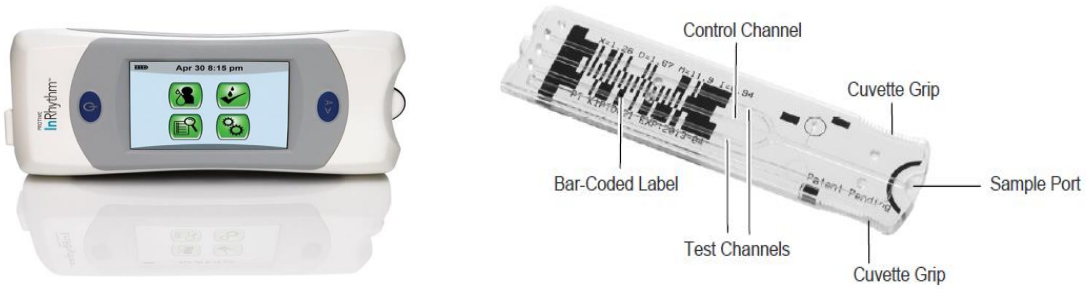

Figure 1. The ProTime InRhythm System

Table 3. Technical data from the manufacturer

Technical data for ProTime InRhythm	
Sample material	Capillary or fresh venous whole blood
Sample volume	13 µL
Measuring time	<1 minute (depending on INR level)
Measuring range	0,9 – 9,0 INR
Haematocrit range	25% – 55%
Storage capacity	1200 results
Electrical power supply	Rechargeable lithium ion battery

4.2.1. Control possibilities with ProTime InRhythm

Electronic self-checks: The InRhythm instrument performs self-checks as it is turned on (i.e. power on self-test) and during operation; the system verifies that timing, electrical, and mechanical functions are performing properly. No calibration or additional verification steps are required to start operate the instrument.

Onboard quality control: The test cuvette includes a control channel which is simultaneously analysed each time a test is performed. The channel contains human coagulation factors and buffer designed to verify proper sample collection and test procedure (operator performance, and to ensure assay reliability and function (reagent performance).

Two PT Channels (Δ or delta check): Each InRhythm PT test cuvette contains two patient test channels; testing of patient samples is therefore performed in duplicate. If the difference between the duplicate test results (Δ) does not agree within a specified limit, the test result is invalid and an error message is displayed and stored.

Internal analytical quality controls: ITC produces a liquid whole blood quality control for the InRythm System, called *direct*CHECK Whole Blood Control for InRythm, Level 1 and 2.

External analytical quality controls: Only the ITC whole blood *direct*CHECK controls can be used with the InRhythm system.

4.3. The selected comparison method

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

4.3.1. The selected comparison method in this evaluation

The selected comparison method in this evaluation of InRhythm is the routine method for PT (INR) at the Department of Medical Biochemistry at St. Olavs Hospital in Trondheim, Norway, hereafter called "the comparison method". The method is accredited after NS_EN ISO/IEC 17025 (Norsk Standard_Europeisk Norm International Organization for Standardization /International Electrotechnical Commission, 2005).

Instrument:	STA-R Evolution, STAGO (two identical instruments were used)	
Reagent:	STA-SPA+, Diagnostica STAGO	
Principle:	Owren's method, rabbit brain thromboplastin and adsorbed bovine plasma	
Traceability:	World Health Organization's (WHO's) manual tilt tube technique and the reference thromboplastin WHO IRP 67/40, through Rabbit brain Thromboplastin (RBT/90) [8-10]	
Calibrators:	Three point's calibration with Equalis (External quality assurance in laboratory medicine in Sweden) INR-calibrators from Equalis AB	
Reference range	0,9 – 1,2 INR	
Therapeutic range	*venous indication*	2,0 – 3,0 INR
	arterial indication	2,5 – 3,5 INR

4.3.2. Verification of the analytical quality of the comparison method

Precision

The repeatability of the comparison method was estimated from duplicate measurements of venous citrate samples from patients in stable (≥4 weeks) vitamin K antagonist treatment. The comparison method is accredited and the requested analytical CV is 2,4% at a PT (INR) level of approximately 3,0.

Trueness

- INR calibrators from Equalis were analysed on the comparison method (both instruments) as anonymous samples at different occasions during the evaluation period. The calibrator material is a pool of citrated anti-coagulated freeze-dried plasma of human origin (Swedish donors). The certified values are traceable to an internationally agreed reference measurement procedure (WHO's manual tilt tube technique) and the reference thromboplastin WHO IRP 67/40, through RBT/90 [8-10]. The procedures used to assign values are described in several publications and documents [11,12].

- INR calibrators from the Danish Institute for External Quality Assurance for Hospital Laboratories (DEKS) were used to get a link to the Danish PT (INR) level. The calibration materials from DEKS are freshly frozen pooled citrate-plasmas which serve as national reference plasmas in Denmark. The DEKS calibration is a three point's calibration with a

normal, therapeutic and high INR-value. The assigned values come from three Nordic expert laboratories. The calibrators were analysed on the comparison method (both instruments) at the start of, during and at the end of the evaluation.

Internal quality control
Internal quality control material from STAGO, STA-Scandinorm PT (INR) with value 1,05 INR and STA-Scandipath PT (INR) with value 2,81 INR, were analysed daily on both instruments in the evaluation period.

External quality control
The Department of Medical Biochemistry at St. Olavs Hospital participates in the external analytical assessment program for PT (INR) from NKK (the Norwegian External Quality Assessment (EQA) Program for Medical Biochemistry) / Labquality. Four times a year they receive a control material at two concentration levels of PT (INR). The controls have consensus values based on results from 69 participants using INR calibrators from Equalis.

4.4. The evaluation

4.4.1. Planning of the evaluation

Background for the evaluation
The InRhythm system was launched into a selected European market in 2013, but has not been launched into the Scandinavian market yet.

Inquiry about an evaluation
The Nordic sales and product manager Helena Olkkonen-Ure from Medic24 applied to SKUP in May 2013 for an evaluation of InRhythm.

Protocol, arrangements and contract
In November 2013, the protocol for the evaluation was approved, and Medic24 and SKUP signed a contract for the evaluation. The Department of Medical Biochemistry at St. Olavs Hospital in Trondheim agreed to do the practical work with the evaluation under standardised and optimal conditions. At the same time two primary health care centres (PHCCs) from Sør-Trøndelag County agreed to represent the end-users in this evaluation.

Preparations, training program and practical work
Biomedical laboratory scientist (BLS) Camilla Eide Jacobsen from SKUP started the preparations for the evaluation in August 2013. BLSs Hilde Hegseth and Per Hepsø were responsible for the evaluation at St. Olavs Hospital. Advisory BLS Guri A. Gulstad and Karina Hill Bjerkestrand, Noklus (Norwegian Quality Improvement of primary Care laboratories), agreed to administrate the practical work with the evaluation in PHCCs. The equipment for the evaluation was received in January 2014. Shortly after, two representatives from ITC together with Helena Olkkonen-Ure from Medic24 demonstrated the InRhythm system. Afterwards Camilla went through the evaluation procedure. The Advisory BLSs co-operated in the training of the two PHCCs. The practical work was carried out during two weeks at the PHCCs and nine weeks at St. Olavs Hospital, ending in March 2014.

4.4.2. Evaluation sites and persons involved

Department of Medical Biochemistry, St. Olavs Hospital, has 103 employees of which approximately 83 are BLSs.
PHCC: Hallset Legesenter has five physicians, three health secretaries, one medical secretary and one nurse.
Persaunet Legesenter has three physicians, three health secretaries and one BLS.
Both PHCCs use venous blood samples in their routine method for measurements of PT (INR).

An overview of the persons responsible for the various parts of the evaluation is given in table 4.

Table 4. Persons responsible for various parts of the evaluation

Name	Title	Place	Responsibility
Helena Olkkonen-Ure	Nordic Sales and Product Manager	Medic24 AS	Ordered the evaluation
Savino de Serio	International Sales Manager	ITC, Italy	Training and demonstration
Ariane von Forstner	International Sales Manager	ITC, Switzerland	Training and demonstration
Camilla Eide Jacobsen	BLS Master of Science	SKUP/Noklus	Responsible for the evaluation and statistical calculations, author of the report
Guri A. Gulstad Karina Hill Bjerkestrand	Advisory BLSs	Noklus	Guiding and supporting the PHCC
Hilde Hegseth Mari M. Skårvold Hanne Slupphaug Marlen Beistad Gjøril Hegglund	BLSs	Dept. of Medical Biochemistry, St. Olavs Hospital	Practical work with the evaluation of InRhythm
Mona Kristiansen	Health secretary		
Kari Bratberg	BLS	Dept. of Medical Biochemistry, St. Olavs Hospital	Responsible for the practical work with the comparison method
Inger Haugrønning Hege Elin Skogan Lillian Ottem Dahl	Health secretaries	PHCC Hallset	Practical work with the evaluation of InRhythm
Åse Jekthammer	Medical secretary		
Torgrunn Moholdt	Nurse		
Kirsten Halvorsen	BLS	PHCC Persaunet	Practical work with the evaluation of InRhythm
Tonje Wold Margrete Kviseth Gulbrandsen Siv Furunes	Health secretaries		

4.4.3. The evaluation model

The SKUP evaluation

SKUP evaluations for quantitative methods are based upon the fundamental guidelines in the book *"Utprøving av analyseinstrumenter"* [13]. The evaluation consists of two parallel parts. One part of the evaluation is carried out under standardised and optimal conditions by laboratory educated personnel in a hospital laboratory. This part documents the quality of the system under conditions as favourable as possible for achieving good analytical quality. The other part of the evaluation is carried out among the end-users in different PHCCs. This part documents the quality of the system under real-life conditions.

The aim of the evaluation

The evaluation of the InRhythm system comprises the following studies:

- An estimation of the repeatability of the InRhythm achieved with approximately 100 capillary whole blood samples, performed by BLSs in a hospital environment

- An estimation of the repeatability of the InRhythm achieved with approximately 80 capillary whole blood samples, performed in two PHCCs
- An assessment of the accuracy of InRhythm by comparing the results from the InRhythm (capillary whole blood samples analysed at St. Olavs Hospital and PHCCs) with the results from the comparison method (3,2% sodium citrated plasma samples)
- An assessment of the variation between three lots of the InRhythm test cuvettes
- An evaluation of the user-friendliness of the InRhythm system

4.4.4. The evaluation procedure under standardised and optimal conditions

Internal analytical quality control
The InRhythm instrument at the laboratory at St. Olavs Hospital was checked with the manufacturer's *direct*CHECK Whole Blood Control for InRhythm level 2 every evaluation day.

Recruitment of patients
Patients who participated in this study were those who presented at the outpatient clinic for routine (PT) INR monitoring. Blood samples were collected at the laboratory from patients who have been stable on vitamin K antagonist treatment for a minimum of 4 weeks. Participation was voluntarily and verbal consent was considered sufficient based on national regulations.

Blood sampling, handling of specimens and measurements
All samples for measurements on InRhythm were capillary samples. The samples were measured in duplicate using two skin-pricks from two separate fingers. In this evaluation the third drop of capillary blood was used for testing with the InRhythm system as the first and second drops were used for testing with the local point of care devices. If the InRhythm instrument showed an error code while analysing a sample, a new measurement was made in most cases. Three lots of InRhythm test cuvettes were used in the evaluation.

Samples for the comparison method were obtained from venous puncture and collected into vacutainer tubes with 3,2% sodium citrate. The citrate samples were taken immediately before testing of the capillary samples on the InRhythm. The tubes were inverted 8–10 times to ensure through mixing of the blood with the sodium citrate and then underwent centrifugation for 10 minutes at 2200g within two hours from sampling. Citrated fresh plasma was used for duplicate measurements of PT (INR) on the comparison method STA-R Evolution using the same instrument; either instrument 1 or instrument 2.

Recording of results
All results were registered in a form provided by SKUP and signed by the evaluators. All error codes were recorded.

The precision of InRhythm
Repeatability was calculated from the results of approximately 100 capillary samples measured in duplicate on the InRhythm. Formula 1 in attachment 5 was used for the calculation. The results are divided into two INR levels, and the CV is given with a 90% confidence interval.

Comparison of InRhythm versus STA-R Evolution
The comparison of InRhythm versus STA-R Evolution was carried out with results from approximately 100 capillary samples measured on InRhythm in duplicate and the results from

approximately 100 duplicate measurements of citrated plasma samples on the same STA-R Evolution using either instrument 1 or instrument 2.

Evaluation of user-friendliness
After the practical work was completed, the BLSs operators at St. Olavs Hospital evaluated the user-friendliness of the InRhythm by means of completing a questionnaire composed by SKUP, see section 5.5.

4.4.5. Evaluation procedure among the end-users in primary health care

Internal analytical quality control
The InRhythm instruments at PHCC1 and PHCC2 were checked with the manufacturer's quality control *direct*CHECK Whole Blood Control for InRythm, Level 2 every evaluation day.

Recruitment of patients
Patients who participated in this study were those who presented at the PHCC for routine (PT) INR monitoring. Blood samples were collected at the laboratory from patients who have been stable on vitamin K antagonist treatment for a minimum of 4 weeks. Participation was voluntarily and verbal consent was considered sufficient based on national regulations.

Blood sampling, handling of specimens and measurements
All samples for measurements on the InRhythm were collected from finger sticks using an Accu-Chek Safe-T-Pro Plus lancet with depth setting 2,3mm. The samples were measured in duplicate using two skin pricks from two separate fingers. The second drop of blood was used. If the InRhythm instrument showed an error code while analysing a sample, a new measurement was made in most cases. One lot of InRhythm test cuvettes was used in the evaluation.

Samples for the comparison method were obtained from venous puncture and collected into vacutainer tubes with 3,2% sodium citrate. The citrate venous samples were taken immediately before the testing of capillary samples on InRhythm. The sample tubes were transported to the Department of Medical Biochemistry for duplicate measurement of PT (INR) on the comparison method STA-R Evolution instrument 1 or instrument 2. Collection and transportation of the tubes with the citrated venous samples were performed according to normal routine procedures at the PHCCs.

Recording of results
All results were registered in a form provided by SKUP and signed by the evaluators. All error codes were recorded.

The precision of InRhythm
Repeatability was calculated from the results of approximately 80 capillary samples measured in duplicate on InRhythm. Formula 1 in attachment 5 was used for the calculation. The results are divided into two INR levels, and the CV is given with a 90% confidence interval.

Comparison of InRhythm versus STA-R Evolution
The comparison of InRhythm versus STA-R Evolution was carried out with results from approximately 80 capillary samples measured on InRhythm in duplicate and the results from approximately 80 duplicate measurements of citrate plasma samples on STA-R Evolution instrument 1 or 2.

Evaluation of user-friendliness

After the practical work was completed, the operators at PHCC1and PHCC2 evaluated the user-friendliness of InRhythm by means of completing a questionnaire composed by SKUP, see section 5.5.

5. Results and discussion

Statistical expressions and calculations used by SKUP are shown in attachment 5.

5.1. Number of samples

In the hospital evaluation a total of 102 samples for PT (INR) were collected. The 102 patients had capillary samples analysed on the InRhythm, 94 of the samples were analysed in duplicate. Measurements of 101 venous citrate samples were made on the comparison method STA-R Evolution (one sample was missing). 99 out of these 101 citrate samples were analysed in duplicate. The range of PT (INR) results was 0,9 – 4,4, and only seven of the PT (INR) results were >3,5. To be able to compare the statistical calculations from the hospital evaluation and the PHCC directly, the results from the hospital evaluation were divided in two PT (INR) levels instead of three as suggested in the protocol. In addition the repeatability is calculated for PT (INR) results in the therapeutic range 2,0 – 3,0.

In the primary health care evaluation PHCC1 and PHCC2 recruited 40 patients each. A total of 80 patients had their capillary samples analysed in duplicate on the InRhythm. Measurements of 80 venous citrate samples were made with the comparison method STA-R Evolution at St. Olavs Hospital. 78 out of these 80 citrate samples were analysed in duplicate. The results were divided in two PT (INR) levels.

5.1.1. Excluded and missing results

Hospital laboratory

- ID 87: no results from the comparison method (reason not explained). The results from this patient are therefore not part of the calculation of trueness or the assessment of accuracy, but they were included in the calculation of repeatability of InRhythm.
- ID 89, capillary samples on InRhythm: comments from the user about difficulties regarding sampling. The results were removed from all calculations.
- Eight patients had only one measurement on InRhythm. These results were removed before calculation of repeatability and trueness, but were included in the assessment of accuracy.
- ID 67: classified as an outlier according to Burnetts's model in the calculation of repeatability of InRhythm. The results were removed before calculation of trueness, but were included in the assessment of accuracy (the first of the duplicate measurements).
- ID 55 and 65: only single measurements with venous citrate samples on the comparison method. The results were removed before calculation of the comparison method's repeatability. The single measurements are used alone in the calculation of trueness and in the assessment of accuracy for these two patients.
- ID 92: classified as an outlier according to Burnetts's model in the calculation of trueness, but the results were included in the assessment of accuracy (the first of the duplicate measurements).

Primary health care centres

- ID 225 at PHCC2: comments from the user about difficulties regarding capillary sampling. The results were removed from all calculations.
- ID 196 at PHCC1and ID 223 at PHCC2: classified as outliers according to Burnett's model in the calculation of trueness, but were included in the assessment of accuracy (the first of the duplicate measurements).

– ID 186 and 191 at PHCC1: only single measurements with venous citrate samples on the comparison method. The single measurements are used alone in the calculation of trueness and in the assessment of accuracy.

5.1.2. Failed measurements

In the hospital laboratory the error message "Sample too large" (the sample size is too large to obtain a result) was registered on InRhythm eight times. The error messages "Cuvette insertion fault" and "Sampling fault" (the sample was not seen or was added too early) were both registered once.

In primary health care the error messages "Sample too large", "Barcode fault" (the cuvette barcode is invalid. Repeat the test using a new cuvette) and "Sampling fault" were all registered once.

In addition comments as "it takes a long time to fill the cuvette with blood" were registered six times but did not seem to have any influence on the measuring results.

The error message "Sample too large" can be generated as a result of adding excess capillary blood after the icon of "Stop adding sample" is displayed. The error message "Barcode fault" and "Sampling fault" can be due to technical error.

The fraction of technical errors was estimated to: (3/364) x 100 = 0,8%
In addition it was recorded 9/364 ~ 2,5% errors related to too large blood drops ("Sample too large").

Conclusion
The quality goal for fraction of technical errors ≤2% was fulfilled for InRhythm. In total 3,3% of the samples had to be repeated.

5.2. Analytical quality of the selected comparison method

5.2.1. Quality control

Internal quality control

In daily operation of the comparison method, the analytical quality of PT (INR) is monitored with the internal quality control material from STAGO; Scandinorm (target 1,05 INR) and Scandipath (target 2,81 INR). All control results from the evaluation period were within the limits the laboratory has set for the controls (data not shown).

External quality control

Results achieved in dispatches of external quality control material from NKK in August 2013, December 2013 and February 2014, shows that the comparison method STA-R Evolution at St. Olavs Hospital is in agreement with the other hospital laboratories (n=69) using INR calibrators from Equalis (data not shown).

5.2.2. The precision of the comparison method

To achieve a measure for the repeatability of the comparison method, the venous citrate sample collected of each patient was analysed in duplicate. The formula used for the calculation of repeatability (formula 1) is shown in attachment 5. The results have been checked to meet the imposed condition for using the formula (data not shown).

Repeatability

The repeatability CV of the comparison method with a 90% confidence interval (CI) is shown in table 5. Approximately 80% of the venous samples are analysed at STA-R Evolution instrument 2. The results from the two STA-R instruments are combined. The results are sorted and divided into two PT (INR) levels according to the first measurement on STA-R Evolution. Raw data is shown in attachment 6.

Table 5. Repeatability STA-R Evolution, venous citrate samples. PT (INR) results achieved by a BLS

PT (INR) level STA-R Evolution instrument 1 and 2	n	Excluded results	Mean value (interval) PT (INR)	CV (90% CI) %
<2,5	50	0	2,0 (0,9 – 2,4)	1,5 (1,5 – 2,0)
≥2,5	49	0	3,0 (2,5 – 4,3)	1,4 (1,3 – 1,7)

An account of the number of samples, and excluded and missing results, is given in section 5.1.

Discussion

The repeatability CV for the comparison method was approximately 1,5%.

5.2.3. The trueness of the comparison method

To demonstrate the trueness of the comparison method, the calibrators and the control from Equalis were analysed as anonymous samples at two different occasions; in the middle and at the end of the evaluation period. The calibrators from DEKS were analysed at three different occasions; in the beginning, in the middle and at the end of the evaluation period. The calibrating systems from Equalis and DEKS are different with respect to the production of the materials as

well as to the way the PT-values are set. The results achieved with the Equalis calibrators and control are shown in table 6. The results achieved with DEKS calibrators are shown in table 7.

Table 6. Equalis INR calibrators and control measured on the comparison method

Material	Certified value PT (INR) (uncertainty)	Date	n	Mean value PT (INR) instrument 1	Mean value PT (INR) instrument 2
Equalis INR calibrator Low	**1,06** (0,98 – 1,14)	28.01.14	5	1,10	1,10
		27.02.14	5	1,10	1,10
Equalis INR calibrator High	**2,73** (2,15 – 3,31)	28.01.14	5	2,76	2,72
		27.02.14	5	2,86	2,70
Equalis INR control	**2,37** (1,92 – 2,82)	28.01.14	5	2,36	2,38
		27.02.14	5	2,46	2,32

Table 7. DEKS INR calibrators measured on the comparison method

Material	Assigned value PT (INR) (uncertainty)	Date	n	Mean value PT (INR) instrument 1	Mean value PT (INR) instrument 2
DEKS INR calibrator Normal	**0,96** (0,93 – 0,99)	14.01.14	5	1,00	1,00
		04.02.14	5	1,00	1,00
		27.02.14	5	1,00	1,00
DEKS INR calibrator Therapeutic	**2,26** (2,19 – 2,33)	14.01.14	5	2,20	2,24
		04.02.14	5	2,20	2,20
		27.02.14	5	2,30	2,20
DEKS INR calibrator High	**3,74** (3,59 – 3,89)	14.01.14	5	3,80	3,72
		04.02.14	5	3,80	3,82
		27.02.14	5	3,94	3,64

Discussion

Table 6 shows that the results from the comparison method agree well with the Equalis calibrator low and high PT-value, and with the Equalis control. The achieved results are within the given uncertainty limits.

Table 7 shows that the results from the comparison method also agree well with the DEKS calibrators. Indeed the DEKS INR calibrator High analysed at instrument 1 the 27.02.14 was just above the upper uncertainty limit. Only four samples from the evaluation were analysed on instrument 1 around this date.

5.3. Analytical quality of InRhythm in a hospital laboratory

5.3.1. Internal quality control

The InRhythm instrument used by the BLS was checked with the manufacturer's control solution *direct*CHECK Whole Blood Control for InRhythm Level 2 each evaluation day. Seven of 24 control results were outside the upper control range limit of 3,9 INR. According to the insert from the manufacturer there may be several reasons for this: the inner glass ampoule was not adequately crushed, reconstituted control was not thoroughly mixed or vial cap was removed prior to inverting, allowing diluent to leak from vial. The reproducibility CV achieved with the control solution was approximately 18% (n=24) for all three lots of test cuvettes. Raw data is shown in attachment 7.

Comments

Due to considerably large imprecision, the internal quality control material from the manufacturer is not useable for revealing failing analytical quality. The system cannot use external liquid control material because these control materials are plasma-based. For further comments about the usefulness of the control material, see table D in section 5.5.1.

5.3.2. Comparison of the 1st and 2nd measurement

Two capillary samples were taken from each patient for PT (INR) measurements on InRhythm. For the calculation of repeatability, all results have been checked to meet the imposed condition for using formula 1 in attachment 5. There were no systematic differences pointed out between the paired measurements (data not shown).

5.3.3. The precision of InRhythm

Repeatability achieved under standardised and optimal conditions in a hospital laboratory

The repeatability obtained at the hospital laboratory with capillary blood samples is shown in table 8. The results are sorted and divided into two PT (INR) levels according to the first measurement on InRhythm. Three lots of test cuvettes were used. Raw data is shown in attachment 8.

Table 8. Repeatability InRhythm, capillary samples. PT (INR) results achieved by a BLS

PT (INR) level InRhythm	n	Excluded results	Mean value (interval) PT (INR)	CV (90% CI) %
<2,5	51	1*	1,9 (0,9 – 2,4)	3,4 (3,2 – 4,2)
≥2,5	42	0	3,0 (2,5 – 4,4)	4,9 (4,0 – 6,1)

The given numbers of results (n) are counted before the exclusion of results. Mean and CV are calculated after the exclusion of results. An account of the number of samples, and excluded and missing results, is given in section 5.1.
*One statistical outlier (ID 67) according to Burnett's model.

Discussion

The repeatability CV obtained under standardised and optimal conditions in a hospital laboratory was 3,4% for PT (INR) level <2,5, and the quality goal (<5%) was fulfilled. For PT (INR) level ≥2,5 the repeatability CV was 4,9% and the upper CI value was >5%. Most likely the quality goal was fulfilled. In the therapeutic range 2,0 – 3,0 INR the CV was 4,1% (CI 3,6 – 4,8%, n=52) and the quality goal was fulfilled (data not shown).

5.3.4. The trueness of InRhythm

The mean deviation of InRhythm results from the comparison method results (bias) was calculated from the results achieved by the BLS at the hospital laboratory. The results are sorted and divided into two PT (INR) levels according to the mean results on the comparison method. The bias of InRhythm in the hospital laboratory is shown in table 9.

Table 9. Bias, InRhythm. Results achieved by a BLS

PT (INR) level Comparison method	n	Excluded results	Comparison method, mean PT (INR)	InRhythm, mean PT (INR)	Bias (95% CI) PT (INR)	Bias, %
<2,5	44	1*	1,9	1,8	-0,11 ((-0,15) – (-0,06))	-5,5
≥2,5	47	0	3,0	2,9	-0,09 ((-0,19) – (+0,01))	-2,9

The given numbers of results (n) are counted before the exclusion of results. Mean and bias are calculated after the exclusion of results. An account of the number of samples, and excluded and missing results, is given in section 5.1.
* One statistical outlier (ID 92) according to Burnett's model.

Discussion

For PT (INR) level <2,5 a small, but statistically significant, bias was shown. InRhythm gave results 5,5% lower than the comparison method with an average mean bias of -0,1 INR. For PT (INR) level ≥2,5 no significant bias was pointed out and InRhythm showed results in agreement with the comparison method.

5.3.5. The accuracy of InRhythm

To evaluate the accuracy of PT (INR) results on InRhythm in the hospital laboratory, the agreement between InRhythm and the comparison method on STA-R Evolution is illustrated in an accuracy plot. The plot shows the deviation of single measurement results on InRhythm from the comparison method, and gives a picture of both random and systematic deviation, reflecting the total measuring error on InRhythm. The accuracy is demonstrated for the first measurement of the paired results, only.

The accuracy of the PT (INR) results on InRhythm is shown in figure 2. The three lots of test cuvettes are illustrated with different symbols in the plot. The limits for the tolerated deviation according to the quality goal (±20%), are shown with stippled lines.

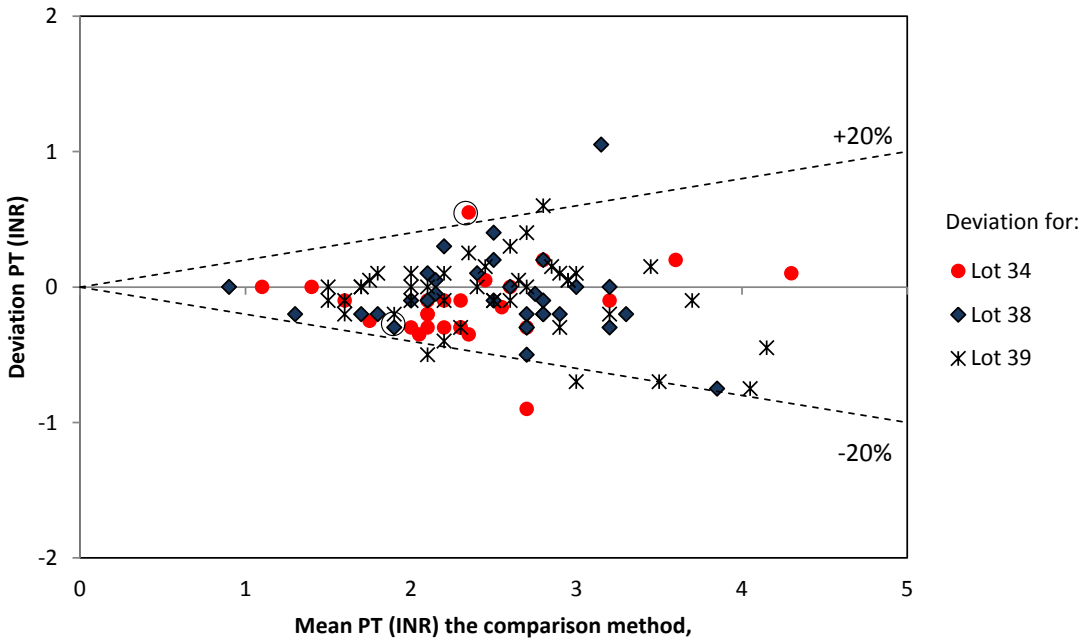

Figure 2. Accuracy. PT (INR) on InRhythm (three lots of test cuvettes) in a hospital laboratory. The x-axis represents the result of the comparison method on STA-R Evolution. The y-axis shows the difference between the first measurement on InRhythm and the result of the comparison method. The three lots of test cuvettes are illustrated with different symbols. Stippled lines represent the allowable deviation limits of ±20%, calculated by SKUP. ID 67 and 92, statistical outliers from the calculation of repeatability and trueness respectively, are illustrated with a circle around the symbol. Number of results (n) = 100. An account of the number of samples, and excluded and missing results, is given in section 5.1.

Discussion

In figure 2 six of 100 results obtained by the BLS were outside the allowable deviation limits of ±20%, two of these results (2%) deviate >±25%. The share of results within the limits was 94%, which means that the quality goal for accuracy was nearly fulfilled. There is no comments registered regarding the two results with deviation >±25%. These two results from InRhythm were reproducible, as shown with the duplicate measurements. 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 (blood applied directly onto the dry reagent strip). 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. Information on the medical history and demographic of the two patients may also provide more explanations on the observed discrepancy.

5.3.6. Bias with three lots of PT (INR) test cuvettes

In figure 2 only small deviations between the three lots of test cuvettes appear. Lot 34 tends to give slightly lower PT (INR) results than the comparison method. Lot 39 tends to give slightly higher PT (INR) results than the comparison method. Separate lot calculations are not performed.

5.4. Analytical quality of InRhythm in primary health care

5.4.1. Internal quality control

The InRhythm instruments used by PHCC1 and PHCC2 were checked with the manufacturer's control solution *direct*CHECK Whole Blood Control for InRhythm Level 2 each evaluation day. One control result was outside the control range (information about control results outside the given range is given in 5.3.1). The reproducibility CV achieved with the control solution was 13,5% (n=17). For comments about the usefulness of the control material, see table D in section 5.5.1. Raw data is shown in attachment 7.

5.4.2. Comparison of the 1st and 2nd measurement

Two capillary samples were taken of each patient for measurements on InRhythm. For the calculation of repeatability, all results have been checked to meet the imposed condition for using formula 1 in attachment 5. There were no systematic differences pointed out between the paired measurements (data not shown).

5.4.3. The precision of InRhythm

Repeatability achieved at two primary health care centres

The repeatability obtained at the two primary health care centres with capillary blood samples is shown in table 10. The results are sorted and divided into two PT (INR) levels according to the first measurement on InRhythm. One lot of test cuvettes was used (lot 39). Raw data is shown in attachment 9.

Table 10. Repeatability InRhythm, capillary samples. PT (INR) results achieved by the primary health care centres

InRhythm	PT (INR) level	n	Excluded results	Mean value (interval) PT (INR)	CV (90% CI) %
PHCC1	<2,5	19	0	2,0 (1,2 – 2,4)	3,7 (2,9 – 5,4)
	≥2,5	21	0	2,9 (2,5 – 4,0)	5,4 (4,5 – 7,3)
PHCC2	<2,5	21	0	2,1 (1,4 – 2,4)	4,3 (3,4 – 5,8)
	≥2,5	18	0	3,0 (2,5 – 4,2)	4,6 (3,7 – 6,3)

An account of the number of samples, and excluded and missing results, is given in section 5.1.

Discussion

For PT (INR) level <2,5 the repeatability CV at the two primary health care centres was between 3,7 and 4,3%. The upper CI values were >5%. Most likely the quality goal was fulfilled.
For PT (INR) level >2,5 the repeatability CV at the two primary health care centres was between 4,6 and 5,4%. For PHCC1 the CV was higher than the quality goal, but not statistically significant higher. Most likely the quality goal was not fulfilled. For PHCC2 the upper CI value was >5%. Most likely the quality goal was fulfilled.

5.4.4. The trueness of InRhythm in primary health care

The mean deviation of InRhythm results from the comparison method results (bias) was calculated from the results achieved by the two primary health care centres. The results are sorted and divided into two PT (INR) levels according to the mean results on the comparison method. The bias of the InRhythm results in PHCC is shown in table 11.

Table 11. Bias, InRhythm. Results achieved by the primary health care centres

InRhythm	PT (INR) level Comparison method	n	Excluded results	Comparison method, mean PT (INR)	InRhythm, mean PT (INR)	Bias (95% CI) PT (INR)
PHCC1	<2,5	22	1*	2,1	2,2	+0,08 ((-0,06) – (+0,22))
	≥2,5	18	0	2,9	2,8	-0,03 ((-0,15) – (+0,08))
PHCC2	<2,5	21	1**	2,0	2,1	+0,04 ((-0,03) – (+0,11))
	≥2,5	18	0	2,9	3,0	+0,07 ((-0,10) – (+0,23))

The given numbers of results (n) are counted before the exclusion of results. Mean and bias are calculated after the exclusion of results. An account of the number of samples, and excluded and missing results, is given in section 5.1.
*One statistical outlier (ID 196) according to Burnett's model.
** One statistical outlier (ID 223) according to Burnett's model.

Discussion

The PT (INR) measurements on InRhythm were in agreement with the comparison method.

5.4.5. The accuracy of InRhythm in primary health care

To evaluate the accuracy of PT (INR) results on InRhythm in primary health care, the agreement between InRhythm and the comparison method on STA-R Evolution is illustrated in an accuracy plot. The plot shows the deviation of single measurement results on InRhythm from the comparison method, and gives a picture of both random and systematic deviation, reflecting the total measuring error on InRhythm. The accuracy is demonstrated for the first measurement of the paired results, only.

The accuracy of the PT (INR) on InRhythm is shown in figure 3. The two primary health care centres are illustrated with different symbols in the plot. The limits for the tolerated deviation according to the quality goal (±20%), are shown with stippled lines.

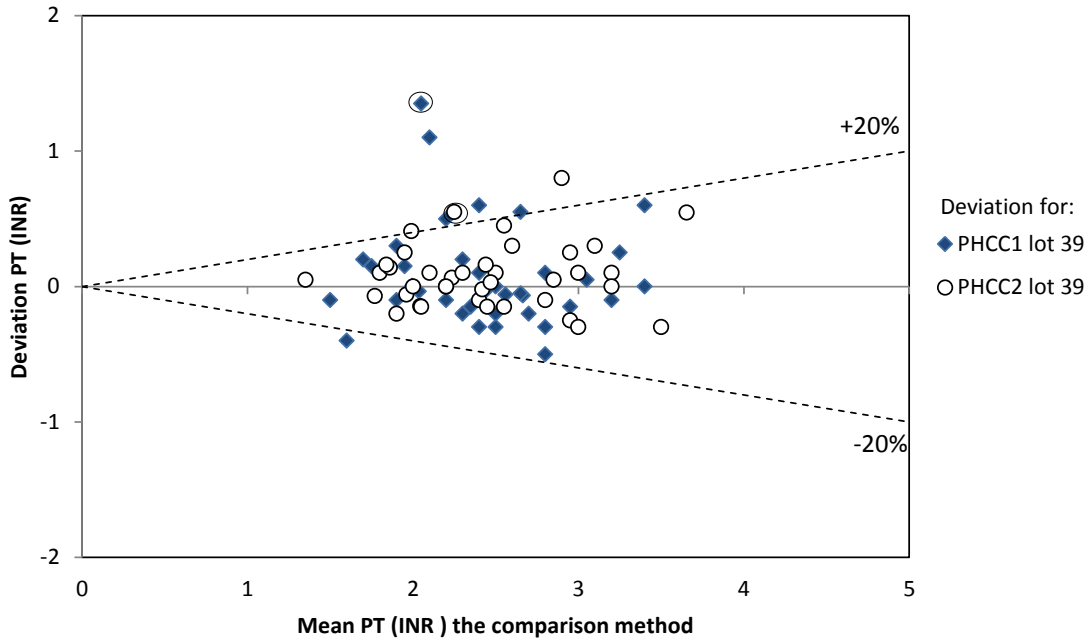

Figure 3. Accuracy. PT (INR) on InRhythm (one lot of test cuvettes; lot 39) in two primary health care centres. The x-axis represents the result of the comparison method on STA-R Evolution. The y-axis shows the difference between the first measurement on InRhythm and the result of the comparison method. The InRhythm system used at PHCC1 is represented with the symbol ◆ and at PHCC2 with ○**.** Stippled lines represent the allowable deviation limits of ±20%, calculated by SKUP. ID 196 at PHCC1 and ID 223 at PHCC2, statistical outliers from the calculation of trueness, are illustrated with a circle around the symbols. Number of results (n) = 79. An account of the number of samples, and excluded and missing results, is given in section 5.1.

Discussion

In figure 3, nine of 79 results obtained in PHCC were outside the allowable deviation limits of ±20%. The share of results within the limits was 89%, which means that the quality goal for accuracy was not fulfilled.

Three out of 79 results (3,8%) from PHCC deviated more than 25% from the comparison method. One of the three deviating results was already proved as an outlier and excluded in the calculation of trueness (table 11). These three results from InRhythm were reproducible, as shown with the duplicate measurements. Differences of this character are discussed in section 5.3.5.

5.5. Evaluation of user-friendliness

5.5.1. Questionnaire to the evaluators

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

At the end of the evaluation period, each user fills in a questionnaire about the user-friendliness of the instrument. The questionnaire is divided into four sub-areas:

- Rating of the information in the manual / insert / quick guide (table A)
- Rating of the operation facilities. Is the system easy to handle? (table B)
- Rating of time factors for the preparation and the measurement (table C)
- Rating of performing internal and external quality control (table D)

The end-users fill in table A and B. SKUP fills in table C and D, and in addition topics marked with grey colour in table A and B.

In the tables the first column shows what is up for consideration. The second column in table A and B shows the rating by the individual users at the evaluation sites. The last three columns show the rating options. The overall ratings from all the evaluating sites are marked in coloured and bold text. The last row in each table summarises the total rating in the table. The total rating is an overall assessment by SKUP of the described property, and not necessarily the arithmetic mean of the rating in the rows. Consequently, a single poor rating can justify an overall poor rating, if this property seriously influences on the user-friendliness of the system.

Unsatisfactory and intermediate ratings will be marked with an asterisk and explained below the tables. The intermediate category covers neutral ratings assessed as neither good nor bad.

Comment

In this evaluation, the user-friendliness was assessed at three evaluation sites; two primary health care centres and one hospital laboratory in the rating order PHCC2, PHCC1 and hospital laboratory.

Table A. Rating of the information in the manual

Topic	Rating	Assessment	Assessment	Assessment
General impression	**S, S, I**[1]	**Satisfactory**	**Intermediate**	Unsatisfactory
Table of contents	**S, S, S**	**Satisfactory**	Intermediate	Unsatisfactory
Preparations / Pre-analytic procedure	**S, S, S**	**Satisfactory**	Intermediate	Unsatisfactory
Specimen collection	**S, S, S**	**Satisfactory**	Intermediate	Unsatisfactory
Measurement procedure	**S, S, S**	**Satisfactory**	Intermediate	Unsatisfactory
Reading of result	**S, S, S**	**Satisfactory**	Intermediate	Unsatisfactory
Description of the sources of error	**S, -, S**[2]	**Satisfactory**	Intermediate	Unsatisfactory
Help for troubleshooting	**S, -, S**	**Satisfactory**	Intermediate	Unsatisfactory
Readability / Clarity of presentation	**S, S, S**	**Satisfactory**	Intermediate	Unsatisfactory
Keyword index	**S**	**Satisfactory**	Intermediate	Unsatisfactory
Measurement principle	**U**[3]	Satisfactory	Intermediate	**Unsatisfactory**
Available insert in Danish, Norwegian, Swedish	**S**	**Satisfactory**	Intermediate	Unsatisfactory
Total rating by SKUP		**Satisfactory**		

[1]The manual is of big size and comprehensive.
[2]We would like to have a "quick guide" with descriptions of error messages.
[3] There is no section in the manual explaining the measurement principle of the InRhythm system.

Table B. Rating of operation facilities

Topic	Rating	Assessment	Assessment	Assessment
To prepare the test / instrument	**S, S, S**	**Satisfactory**	Intermediate	Unsatisfactory
To prepare the sample	**S, S, -**	**Satisfactory**	Intermediate	Unsatisfactory
Application of specimen	**I, S, I[1]**	**Satisfactory**	**Intermediate**	Unsatisfactory
Specimen volume	**I, S, I[2]**	**Satisfactory**	**Intermediate**	Unsatisfactory
Number of procedure step	**S, S, S**	**Satisfactory**	Intermediate	Unsatisfactory
Instrument / test design	**I, I[3], I[3]**	Satisfactory	**Intermediate**	Unsatisfactory
Reading of the test result	**E, E, E**	**Easy**	Intermediate	Difficult
Sources of errors	**S, S, S**	**Satisfactory**	Intermediate	Unsatisfactory
Cleaning / Maintenance	**-, -, S**	**Satisfactory**	Intermediate	Unsatisfactory
Hygiene, when using the test	**I[4], S, S**	**Satisfactory**	**Intermediate**	Unsatisfactory
Size and weight of package	**S, -, I[5]**	**Satisfactory**	**Intermediate**	Unsatisfactory
Storage conditions for tests, unopened package	**S**	**+15 to +30°C**	+2 to +8°C	–20°C
Storage conditions for tests, opened package	**S**	**+15 to +30°C**	+2 to +8°C	–20°C
Environmental aspects: waste handling	**S**	**No precautions**	Sorted waste	Special precautions
Intended users	**S**	**Health care personnel or patients**	Laboratory experience	Biomedical laboratory scientists
Total rating by SKUP		**Satisfactory**	**Intermediate**	

[1]Several times we got the error message “Sample too large”. The instrument must be placed stable at a table when measuring samples. InRhythm cannot be moved to the finger, the finger has to be moved to the instrument.
[2]The instrument needs a “good” drop of blood; on the other hand the drop of blood must not be too big to avoid the error message “Sample too large”.
[3]The instrument is a little bit too big. The individually pouched test cuvettes are difficult to open. Unpractical that the system must be placed stable (on a table) when analysing samples.

[4]It is possible to spill blood when a used test cuvette is removed from the instrument.
[5]The instrument is a little bit too big.

Positive comments:

- The InRhythm system is fast and easy to handle
- The test cuvettes can be stored at room temperature
- The test cuvettes has a good design and size

Negative comments:
We have observed differences in PT (INR) results for the same patient depending on whether we use a large drop of blood or squeeze the finger during sampling.

Table C. Rating of time factors (filled in by SKUP)

Topic	Assessment	Assessment	Assessment
Required training time	**<2 hours**	2 to 8 hours	>8 hours
Durations of preparations / Pre-analytical time	**<6 min.**	6 to 10 min.	>10 min
Duration of analysis	**<10 min.**	10 to 20 min.	>20 min
Stability of test, unopened package	**>5 months**	3 to 5 months	<3 months
Stability of test, opened package[1]	>30 days	14 to30 days	<14 days
Stability of quality control material, unopened	**>5 months**[2]	3 to 5 months	<3 months
Stability of quality control material, opened[3]	>6 days or disposable	2 to 6 days	≤1 day
Total rating by SKUP	**Satisfactory**		

[1]Not rated. Once the test cuvette is taken out of the individually foil pouch, it has to be used within eight hours.
[2]The stability is >5 months if the control material is stored at +2 to +8°C. Stored at room temperature the stability is up to four weeks.
[3]Not rated. Reconstituted control material must be used immediately, as clotting will occur.

Table D. Rating of quality control (filled in by SKUP)

Topic	Assessment	Assessment	Assessment
Reading of the internal quality control*	**Satisfactory**	Intermediate	Unsatisfactory
Usefulness of the internal quality control	Satisfactory	Intermediate	**Unsatisfactory**[1]
External quality control	Satisfactory	Intermediate	**Unsatisfactory**[2]
Total rating by SKUP			**Unsatisfactory**

**direct*CHECK Whole Blood Control for InRhythm

[1]The imprecision (CV) achieved with the internal quality control material was considerably larger than the CV achieved with genuine sample material. The control material is therefore not usable for revealing failing analytical quality of the system.
[2]Only the whole blood control materials from ITC can be used with the InRhythm system (no plasma-based control material is recommended).

Negative comments:

- The control material is useless (comment from one PHCC)
- It is difficult to crush the inner glass ampoule
- The analysing of the control material was no good. The results were outside the range given from the manufacturer several times (comments from the BLS at the hospital laboratory)

The control material must be refrigerated (+2 to +8°C) to be stable until the marked expiration date. Stored at room temperature the stability is up to 4 weeks.

5.5.2. Assessment of the user-friendliness

Assessment of the information in the manual (table A)
The information in the manual is assessed as satisfactory. There was a comment regarding the size of the manual (A4-format) and that the manual was too comprehensive. The measurement principle is not explained in the manual.

Assessment of the operation facilities (table B)
The operation facilities are assessed as both satisfactory and intermediate. The error message "Sample too large" has been achieved several times in the PHCCs as well as in the hospital laboratory. The system seems to be sensitive for large drops of blood.
A disadvantage with the system is that the instrument must be placed stable when analysing a sample. One has to move the finger to the instrument and not opposite. Some evaluators thought that the instrument was a little bit too big, but overall they found the InRhythm system fast and easy to handle.

Assessment of time factors (table C)
The time factors are assessed as satisfactory. It is an advantage that the test cuvettes can be stored at room temperature for four weeks.

Assessment of quality control possibilities (table D)
The quality control possibilities are assessed as unsatisfactory. Due to considerably large imprecision, the internal quality control material from the manufacturer is not useable for revealing failing analytical quality. The system cannot use external liquid control material because these control materials are plasma-based.

6. References

1. ISO/FDIS 17593 2007; Clinical laboratory testing and in vitro medical devices – Requirements for in vitro monitoring systems for self-testing of oral anticoagulant therapy.

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3. Fraser C.G. & Hyltoft Petersen P. Quality goals in external quality assessment are best based on biology. Scand J Clin Lab Invest 1993; **53** suppl 212. Chapter I. Quality planning.

4. Ricos C. *et al.* Current databases on biological variation: pros, cons and progress. Scand J Clin Lab Invest 1999; **66** (4): 337 – 349.

5. Kjeldsen J., Lassen J.F., Hyloft Petersen P. & Brandslund I. Biological variation of international normalized ratio for prothrombin times, and consequences in monitoring oral anticoagulant therapy: computer simulation of serial measurements with goalsetting for analytical quality. Clin Chem 1997; **43**(11): 2175 – 2182.

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9. Van den Besselaar A.M. & Houdijk W.P. Use of lyophilized calibrant plasmas for simplified international normalized ratio determination with a human tissue factor thromboplastin reagent derived from cultured human cells. Clin Chem 2003; **49** (12): 2006 – 2011.

10. WHO. Expert committee on biological standardization - Requirements for thromboplastins and plasma used to control oral anticoagulant therapy. World Health Organization, Geneva Techical Report Series 889, 48th Report 1999.

11. Hillarp A. *et al*. Local INR calibration of the Owren type prothrombin assay greatly improves the intra- and interlaboratory variation. Thromb Haemost 2004; **91**: 3300 – 3307.

12. Arbetsbeskrivning A093, ver 1.0, 2005. Rutiner för åsättande av INR-värden till kalibratorer och kontrollmaterial för bestämning av protrombinkomplex enligt Owren. Equalis, Uppsala.

13. Christensen N.G., Monsen G. & Sandberg S. Utprøving av analyseinstrumenter. 1997: Alma Mater Forlag.

The organisation of SKUP

Scandinavian evaluation of laboratory equipment for primary health care, *SKUP*, is a co-operative commitment of Noklus[1] in Norway, DAK-E[2] in 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 purpose of SKUP is to improve the quality of near patient testing in Scandinavia by providing objective and supplier-independent information on analytical quality and user-friendliness of laboratory equipment. This information is generated by organising SKUP *evaluations*.

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

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

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

[2] SKUP in Denmark is placed in Nordsjællands Hospital. SKUP in Denmark reports to DAK-E (Danish Quality Unit of General Practice), an organisation that is supported by KIF (Foundation for Quality and Informatics) and Faglig udvalg (Professional Committee), which both are supported by DR (The Danish Regions) and PLO (The Organisation of General Practitioners in Denmark).

[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).

Facts about ProTime InRhythm

Parts of this form are filled in by ITC

Table 1. Basic facts

Name of the measurement system:	ProTime InRhythm
Dimensions and weight:	Width: 9,7cm Depth: 18,8 cm Height: 5,3cm Weight: 0,45kg
Components of the measurement system:	ProTime InRhythm Instrument and Test Cuvette
Measurand:	PT/INR
Sample material:	Whole blood
Sample volume:	13 µL
Measuring principle:	Clot formation
Traceability:	WHO standard IRP 67/40
Calibration:	Laboratory reference instrumentation
Measuring range:	0,9 – 9,0 INR
Linearity:	See measuring range
Measurement duration:	Depends on INR (i.e. INR 2 <1 minute)
Operating conditions:	12 – 32° C
Electrical power supply:	Yes
Recommended regular maintenance:	No
Package contents:	ProTime Instrument, AC/DC power, User Manual, Quick Reference Guide
Necessary equipment not included in the package:	ProTime InRhythm Test Cuvette

Table 2. Post analytical traceability

Is input of patient identification possible?	Yes
Is input of operator identification possible?	Yes
Can the instrument be connected to a bar-code reader?	No (integrated Barcode scanner)
Can the instrument be connected to a printer?	Yes
What can be printed?	Results
Can the instrument be connected to a PC?	Yes (POCT-1A compliant output)

Can the instrument communicate with LIS (Laboratory Information System)? If yes, is the communication bidirectional?	No
What is the storage capacity of the instrument and what is stored in the instrument?	1200 results
Is it possible to trace/search for measurement results?	Yes

Table 3. Facts about the reagent/test strips/test cassettes

Name of the reagent/test strips/test cassettes:	ProTime InRhythm Test Cuvette
Stability in unopened sealed vial:	9 months (ongoing stability; targeting 18 months)
Stability in opened vial:	24 hours less or equal to 50% relative humidity
Package contents:	50 cuvettes/box

Table 4. Quality control

Electronic self check:	Yes
Recommended control materials and volume:	Yes
Stability in unopened sealed vial:	12 months
Stability in opened vial:	N/A
Package contents:	10 vials/box

Information about manufacturer, retailers and marketing

Table 1. Marketing information

Manufacturer:	ITC
Retailers in Scandinavia:	Denmark: Vingmed Danmark A/S, Husby Alle 19, 2630 Taastrup Norway: Medic24 AS, Hagebyvegen 40, 3734 Skien Sweden: Medic24 AB, c/o Medical Log Point AB, Trankärrsgata 15, 425 37 Hisings Kärra
In which countries is the system marketed:	Globally ☐ Scandinavia☐ Europe X
Date for start of marketing the system in Scandinavia:	
Date for CE-marking:	April 16, 2013
In which Scandinavian languages is the manual available:	Swedish, Finnish, Norwegian, Danish

Product information, ProTime InRhythm

InRhythm serial numbers

Instrument PT60260311	Serial number	Used by
ProTime InRhythm	100333	St. Olavs Hospital
ProTime InRhythm	100652	PHCC1
ProTime InRhythm	100365	PHCC2
ProTime InRhythm	100329	extra

ProTime InRhythm PT Test cuvette

PT Test cuvette	Lot number	Expiry date	Used by
Test cuvette lot	K3PTD034	2014-05	St. Olavs Hospital
Test cuvette lot	K3PTD038	2014-07	St. Olavs Hospital
Test cuvette lot	K3PTD039	2014-07	St. Olavs Hospital, PHCC1, PHCC2

Other equipment used in the evaluation

Other equipment	Lot number	Expiry date	Used by
Vacuette 3,2% Sodium citrate tube	A131007X A131216J	2014-10 2014-12	St. Olavs Hospital
	A131000L	2014-10	PHCC1
	A130906Q	2014-09	PHCC2
ProTime InRhythm *direct*CHECK whole blood control level 2	H3DRA002	2014-08	St.Olavs, PHCC1, PHCC2
Skin Cleansing Swab	884810	2016-03	PHCC1, PHCC2
Accu-Chek Safe-T-Pro Plus lancet	X205012	2017-10	St. Olavs Hospital
	X266006	2017-10	PHCC1, PHCC2

Statistical expressions and calculations

This chapter with standardised text deals with the statistical expressions and calculations used by SKUP. The statistical calculations will change according to the type of evaluation. The descriptions in this document are valid for evaluations of quantitative methods with results on the ratio scale.

Statistical terms and expressions

The definitions in this section come from the ISO/IEC Guide 99; International Vocabulary of Metrology, VIM [a].

Precision

Definition: Precision is the closeness of agreement between measured quantity values obtained by replicate measurements on the same or similar objects under stated specified conditions.

Precision is measured as *imprecision*. Precision is descriptive in general terms (good, poor e.g.), whereas the 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. CV is usually reported in percent.

To be able to interpret an assessment of precision, the precision conditions must be defined.
Repeatability is the precision of consecutive measurements of the same component carried out under identical measuring conditions (within the measuring series).
Reproducibility is the precision of discontinuous measurements of the same component carried out under changing measuring conditions over time.

Trueness

Definition: Trueness is the closeness of agreement between the average of an infinite number of replicate measured quantity values and a reference quantity value.

Trueness is inversely related to systematic measurement error. Trueness is measured as *bias*. Trueness is descriptive in general terms (good, poor e.g.), whereas the bias is reported in the same unit as the analytical result or in percent.

Accuracy

Definition: Accuracy is the closeness of agreement between a measured quantity value and the true quantity value of a measurand.

Accuracy is not a quantity and cannot be expressed numerically. A measurement is said to be more accurate when it offers a smaller measurement error. Accuracy can be illustrated in a difference-plot. Accuracy is descriptive in general terms (good, poor e.g.).

a. ISO/IEC Guide 99:2007, International vocabulary of metrology – Basic and general concepts and associated terms, VIM, 3rd edition, JCGM 200:2008.

Statistical calculations

Statistical outliers

The criterion promoted by Burnett [b] is used for the detection of outliers. The model takes into consideration the number of observations together with the statistical significance level for the test. The significance level is set to 5%. The segregation of outliers is made with repeated truncations, and all results are checked. Where the results are classified according to different concentration levels, the outlier-testing is carried out at each level separately. Statistical outliers are excluded from the calculations.

Calculation of imprecision

The precision of the field method is assessed by use of paired measurements of genuine patient sample material. The results are divided into three concentration levels, and the estimate of imprecision is calculated for each level separately, using the following formula [c,d]:

$$SD = \sqrt{\frac{\sum d^2}{2n}}$$

d = difference between two paired measurements
n = number of differences

(formula 1)

This formula is used when the standard deviation can be assumed reasonable constant across the concentration interval. If the coefficient of variation is more constant across the concentration interval, the following formula is preferred:

$$CV = \sqrt{\frac{\sum (d/m)^2}{2n}}$$

m = mean of paired measurements

(formula 2)

The two formulas are based on the differences between paired measurements. The calculated standard deviation or CV is still a measure of the imprecision of single values. The imposed condition for using the formulas is that there is no systematic difference between the 1st and the 2nd measurement of the pairs. The CV is given with a 90% confidence interval.

Calculation of bias

The mean deviation (bias) at different concentration levels is calculated based on results achieved under 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 of the duplicate results on the field method. The mean difference is shown with a 95% confidence interval.

Assessment of accuracy

The agreement between the field method and the comparison method is illustrated in a difference-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 the field method and the mean value of the duplicate results on the comparison method. The number of results within the quality goal limits is counted and assessed.

b. Burnett RW. Accurate estimation of standard deviations for quantitative methods used in clinical chemistry. Clinical Chemistry 1975; **21** (13): 1935 – 1938.
c. Saunders E. Tietz textbook of clinical chemistry and molecular diagnostics, 2006. Chapter 14, Linnet K., Boyd J. Selection and analytical evaluation of methods – with statistical techniques. Elsevier Saunders ISBN 0-7216-0189-8.
d. Fraser C.G. Biological variation: From principles to practice, 2006. Chapter 1, The Nature of Biological Variation. AACC Press ISBN 1-890883-49-2.

Raw data PT (INR), internal quality control, ProTime InRhythm

ProTime InRhythm *directCHECK* control level 2
Lot no. H3DRA002
Expiry date 2014-08
PT (INR) Control range **2,2 – 3,9**

Results from the hospital laboratory, standardised and optimal conditions

Date	Result QC InRhythm
20.jan	3,8
21.jan	3,5
22.jan	3,2
23.jan	3,5
24.jan	3,4
27.jan	3,9
28.jan	3,5
29.jan	3,5
30.jan	3,9
03.feb	4,5
03.feb	2,9
06.feb	2,5
07.feb	3,9
11.feb	6,9
12.feb	3,5
14.feb	3,6
17.feb	4,5
18.feb	3,4
20.feb	4,2
24.feb	4,6
25.feb	4,0
28.feb	5,3
12.mar	2,6
13.mar	2,8

Results from primary health care centres

Date	Result QC InRhythm	PHCC
13.jan	3,1	PHCC1
14.jan	2,9	PHCC1
15.jan	2,7	PHCC1
16.jan	2,8	PHCC1
20.jan	2,5	PHCC1
21.jan	2,8	PHCC1
22.jan	3,3	PHCC1
23.jan	2,8	PHCC1
28.jan	2,8	PHCC1
10.jan	4,4	PHCC2
13.jan	3,8	PHCC2
14.jan	2,4	PHCC2
15.jan	3,6	PHCC2
16.jan	3,4	PHCC2
20.jan	2,8	PHCC2
22.jan	2,9	PHCC2
21.jan	2,6	PHCC2
23.jan	2,5	PHCC2

SKUP-info

ProTime InRhythm system for måling av PT-INR
Produsent: International Technidyne Corporation (ITC)
Norsk forhandler: Medic24
Sammendrag fra en utprøving i regi av SKUP

Konklusjon
InRhythm viste en upresishet (CV) mellom 3,4 og 4,3 % for INR-resultater <2,5 og en CV mellom 4,6 og 5,4 % for INR-resultater >2,5. Totalt 94 % av resultatene oppnådd under optimale betingelser var innenfor grensen for tillatt avvik (± 20 %) i forhold til resultat på rutinemetoden. Hos brukerne på to legekontor var 89 % av resultatene innenfor grensen for tillatt avvik. Kvalitetsmålet for nøyaktighet ble dermed ikke oppfylt.
Brukerne syntes InRhythm var rask og enkel å bruke. Brukervennligheten ble oppsummert som tilfredsstillende og middels tilfredsstillende.

ProTime InRhythm er et instrument for måling av PT-INR, beregnet for bruk av helsepersonell. Instrumentet benytter testkyvetter til engangsbruk. Prøvematerialet er kapillærblod eller friskt venøst fullblod. Prøvevolum er 13 µL. Analysetid er mindre enn ett minutt, avhengig av INR-nivå. InRhythm kan lagre 1200 resultater. Måleområdet er 0,9 – 9,0 INR.

Utprøvingen ble utført under optimale betingelser i et sykehuslaboratorium og hos brukerne på to legekontor. Det ble tatt blodprøver av 102 personer på sykehuset og til sammen 80 personer på de to legekontorene. Tre lot av testkyvetter ble benyttet. Resultatene fra InRhythm (kapillærblod) ble sammenlignet med resultatene fra rutinemetoden for måling av PT-INR på sykehuset (plasma). Kvalitetsmål, presisjon: CV ≤ 5 %. Kvalitetsmål, nøyaktighet: mer enn 95 % av resultatene på InRhythm må avvike mindre enn 20 % fra en anerkjent metode for måling av PT-INR.

Resultater. For resultat under 2,5 INR viste analysen en upresishet (CV) på 3,4 % når målingene ble utført under optimale betingelser på sykehuslaboratoriet, og en upresishet på 3,7 og 4,3 % når målingene ble utført av brukerne på de to legekontorene. For resultat ≥2,5 INR var CV 4,9 % når målingene ble utført på sykehuslaboratoriet, og 4,6 og 5,4 % når målingene ble utført på de to legekontorene. I terapeutisk område (2,0 – 3,0 INR) var CV 4,1 % på sykehuslaboratoriet.
Totalt var 94 % av resultatene oppnådd under optimale betingelser med tre lot av testkuvetter innenfor grensen for tillatt avvik. Hos brukerne på de to legekontorene var 89 % av resultatene (en lot) innenfor grensen.
Andel tekniske feil var 0,8 %. Det ble rapportert 2,5 % feil relatert til for stor bloddråpe. En intern fullblodskontroll fra produsenten viste dårlig presisjon.

Brukervennlighet. Brukerne syntes InRhythm var rask og enkel å bruke. De var fornøyde med brukermanualen. Brukervennligheten til instrumentet ble oppsummert som tilfredsstillende og middels tilfredsstillende. En årsak til vurderingen middels tilfredsstillende, var systemets sensitivitet for store bloddråper. For stor bloddråpe gir feilmelding.

Tilleggsinformasjon. Fullstendig rapport fra utprøvingen av InRhythm, SKUP/2014/104, finnes på SKUPs nettside www.skup.nu. Opplysninger om pris fås ved å kontakte leverandør. Laboratoriekonsulentene i Noklus kan gi råd om analysering av PT-INR på legekontor. De kan også orientere om det som finnes av alternative metoder/utstyr.

List of previous SKUP evaluations

Summaries and complete reports from the evaluations are found at www.skup.nu. In addition, SKUP reports are published at www.skup.dk, where they are rated according to the national Danish quality demands for near patient instruments used in primary health care. SKUP summaries are translated into Italian by Centre for Metrological Traceability in Laboratory Medicine (CIRME), and published at http://users.unimi.it/cirme. SKUP as an organisation has no responsibility for publications of SKUP results on these two web-sites.

The 30 latest SKUP evaluations

Evaluation no.	Component	Instrument/testkit	Producer
SKUP/2014/104	PT (INR)	ProTime InRhythm	ITC International Technidyne Corporation
SKUP/2014/105	Glucose[1]	Accu-Chek Aviva	Roche Diagnostics
SKUP/2013/87	Glucose[1]	Wella Calla Light	Med Trust Handelsges.m.b.H.
SKUP/2013/100	Glucose[1]	Mylife Unio	Bionime Corporation
SKUP/2013/97	NT-proBNP	Cobas h 232 POC system	Roche Diagnostics GmbH
SKUP/2013/92	CRP	Eurolyser smart 700/340	Eurolyser Diagnostica GmbH
SKUP/2013/99*	Glucose	Accu-Chek Mobile	Roche Diagnostics
SKUP/2013/98*	Glucose	Accu-Chek Aviva	Roche Diagnostics
SKUP/2013/85	Glucose, β-Ketone	Nova StatStrip	Nova Biomedical Corporation, USA
SKUP/2013/96	Hemoglobin	DiaSpect Hemoglobin T	DiaSpect Medical GmbH
SKUP/2013/68	Allergens	ImmunoCap Rapid	Phadia AB Marknadsbolag Sverige
SKUP/2012/95	Glucose[1]	Mendor Discreet	Mendor Oy
SKUP/2012/94	Glucose[1]	Contour XT	Bayer Healthcare
SKUP/2012/91	HbA1c	Quo-Test A1c	Quoient Diagnostics Ltd
SKUP/2011/93*	Glucose	Accu-Chek Performa	Roche Diagnostics
SKUP/2011/90	CRP	*i*-Chroma	BodiTech Med. Inc.
SKUP/2011/84*	PT-INR	Simple Simon PT and MixxoCap	Zafena AB
SKUP/2011/86	Glucose[1]	OneTouch Verio	LifeScan, Johnson & Johnson
SKUP/2011/77	CRP	*Confidential*	
SKUP/2011/70*	CRP	smartCRP system	Eurolyser Diagnostica GmbH
SKUP/2010/83*	Glucose	*Confidential*	
SKUP/2010/78	HbA1c	In2it	Bio-Rad
SKUP/2010/80	PT (INR)	INRatio2	Alere Inc.
SKUP/2010/89*	Glucose	FreeStyle Lite	Abbott Laboratories
SKUP/2010/88*	HbA1c	*Confidential*	
SKUP/2010/82*	Glucose, protein, blood, leukocytes, nitrite	Medi-Test URYXXON Stick 10 urine test strip and URYXXON Relax urine analyser	Macherey-Nagel GmBH & Co. KG
SKUP/2010/81*	Glucose	mylife PURA	Bionime Corporation
SKUP/2010/67	Allergens	*Confidential*	
SKUP/2010/79*	Glucose, protein, blood, leukocytes, nitrite	CombiScreen 5SYS Plus urine test strip and CombiScan 100 urine analyser	Analyticon Biotechnologies AG
SKUP/2010/73	Leukocytes	HemoCue WBC	HemoCue AB

*A report code followed by an asterisk indicates that the evaluation is not complete according to SKUP guidelines, since the part performed by the intended users was not included in the protocol, or the evaluation is a follow-up of a previous evaluation, or the evaluation is a special request from the supplier.

[1] Including a user-evaluation among diabetes patients

Accriva
diagnostics
Representing ITC and Accumetrics

SKUP Norway
Noklus
Boks 6165
NO-5892 Bergen

September 26, 2014

Dear Ladies and Gentlemen,

Thank you for your evaluation report on the ProTime InRhythm whole blood PT/INR monitoring system (InRhythm). Accriva Diagnostics (Representing ITC and Accumetrics) would like to thank the SKUP team for conducting this study.

We feel the low negative bias (average 0.1 INR, -5.5% at INR ≤2.5) observed with the hospital laboratory is clinically insignificant and has no impact on patient safety. We are not sure why this bias occurred. Of note, it is well documented that different laboratories generate different INR results with the same patient samples; the same principle applies at the point-of-care (e.g. Jacobson AK. Warfarin Monitoring: of Point of Care Testing Limitations and Interpretations of Prothrombin Time. *J Thromb Thrombolysis* 2008; 25, 10-11).

The percentage of technical errors did successfully fulfill the SKUP goal, and we would like to confirm that the operator can always bring the device to the patient's finger for collecting the blood sample.

It is well known that plasma based controls yield tighter reproducibility CV results, however these results are only relevant if the PT (INR) monitor measures plasma samples from patients, similar to plasma based laboratory systems. Point-of-care systems for PT (INR) monitoring utilize whole blood patient samples and the InRhythm system utilizes a whole blood control to best represent the actual point of care testing process.

Overall, we are pleased with the majority of the results of this study, as it is clear that the InRhythm system is safe and reliable for managing patients on oral VKA therapy, when used by health care professionals.

Best regards,
Accriva Diagnostics

Kenneth D. Baker, M.D.

Soumaya El Rouby, Ph.D.

MPIN006 0914