Accuracy of the CoaguChek XS for point-of-care international normalized ratio (INR) measurement in children requiring warfarin

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Summary
Point-of-care INR (POC INR) meters can provide a safe and effective method for monitoring oral vitamin K antagonists (VKAs) in children. Stollery Children’s Hospital has a large POC INR meter loan program for children requiring oral VKAs. Our protocol requires that POC INR results be compared to the standard laboratory INR for each child on several consecutive tests to ensure accuracy of CoaguChek XS® (Roche Diagnostics, Basel Switzerland) meter. It was the objective of the study to determine the accuracy of the CoaguChek XS by comparing whole blood INR results from the CoaguChek XS to plasma INR results from the standard laboratory in children.

Keywords
Point-of-care, international normalized ratio, warfarin, home monitoring, child

Introduction
Increasing numbers of children are requiring thromboprophylaxis using vitamin K antagonist (VKA) oral anticoagulant therapy which must be regularly monitored to avoid both thrombotic and bleeding complications and ensure safety and efficacy (1–5). The gold standard method for monitoring VKA therapy is the prothrombin time (PT) testing of plasma collected via venipuncture which is expressed as an international normalised. Monitoring VKA in children is difficult as they usually have complex underlying health problems, are on multiple medications, have inconsistent nutritional intake, and are often difficult to venesect (5, 6). A further challenge is that many children with underlying cardiac conditions require long-term thromboprophylaxis.

The point-of-care (POC) international normalised ratio (INR) monitor requires a minimal blood sample volume, produces an INR result within 1 minute (min), enables timely drug dosage adjustment, and prompt attention to critical values. The POC INR monitor test can be performed at the patients’ convenience and eliminates the need for the patient to visit the laboratory. This convenience facilitates more frequent INR testing; a requirement for children when illness is present or when there is a change in diet or medication (1, 5, 7, 8). For these reasons the use of the POC INR monitor is used for INR measurement in children as it an option for improving oral VKA monitoring in children (8–16).

To date, there are 10 publications (11–15, 17–19) evaluating the use of POC INR meters in children (Table 1). The CoaguChek® (Roche Diagnostics, Basel Switzerland) monitor has been used in children with success. The CoaguChek monitor was investigated in nine studies. Publications were either retrospective (12) or prospective cohort studies (11–15, 17–21). Subject numbers per study ranged from 14 (14) to 60 children (19). Study duration ranged from a single INR test performed in each subject...
Eight of the study protocols were created with a strong clinical focus, providing an approach to monitoring anticoagulation therapy safely and effectively in children both in hospital and at home. Two of the papers report on self-management (or management by parents) of warfarin therapy, where the key outcomes are the time spent in the therapeutic range (TTR) and the incidence of adverse events (11, 12). The measure for evaluating the reliability of INR results generated at home was inconsistent between

Table 1: Summary of paediatric studies and outcome data for children using POC INR monitors on oral anticoagulation therapy.

<table>
<thead>
<tr>
<th>Author</th>
<th>Study goal</th>
<th>Educational initiatives</th>
<th>Linear regression analysis</th>
<th>TTR achieved (POC, Lab)</th>
<th>Diff. between INRs</th>
<th>Frequency of adverse events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hill et al. 2007</td>
<td>To assess the validity of CoaguChek S</td>
<td>Not discussed</td>
<td>Interclass correlation coefficient .75</td>
<td>64%</td>
<td>Compared mean difference of home meter INR diff = 0.055 units</td>
<td>No haemorrhagic or bleeding events</td>
</tr>
<tr>
<td>Newall et al. 2006</td>
<td>To assess CoaguChek S performance and determine the influence of education on accuracy</td>
<td>Standardized education program based on PRE-CEDE model</td>
<td>Lins correlation r² = 0.949</td>
<td>64%</td>
<td>Compared mean difference of home meter INR diff = 0.055 units</td>
<td>No haemorrhagic or bleeding events</td>
</tr>
<tr>
<td>Ignjatovic et al. 2004</td>
<td>To assess accuracy of reliability of CoaguChek and Thrombotest INR meters</td>
<td>Not discussed</td>
<td>CoaguChek r = 0.885</td>
<td>64%</td>
<td>Compared mean difference of home meter INR diff = 0.055 units</td>
<td>No haemorrhagic or bleeding events</td>
</tr>
<tr>
<td>Mahonen et al. 2004</td>
<td>To evaluate the feasibility of home monitoring in the paediatric population.</td>
<td>Yes, didactic plus written materials provided</td>
<td>Not presented</td>
<td>69%</td>
<td>70% varied by &lt; 0.5 units , mean variation 0.3 units</td>
<td>No haemorrhagic or bleeding events</td>
</tr>
<tr>
<td>Christensen et al. 2003</td>
<td>To assess the time within TTR and incidence of clinical complications in a self-management group, and compare this data with previous publications</td>
<td>Not discussed</td>
<td>Not presented</td>
<td>65%, No comparison</td>
<td>Not presented</td>
<td>No major bleed, No thrombotic events</td>
</tr>
<tr>
<td>Nowatzke et al. 2003</td>
<td>To compare INR measurements on four point-of-care monitors in children.</td>
<td>Not discussed</td>
<td>Not presented</td>
<td>70%</td>
<td>70% varied by &lt; 0.5 units , mean variation 0.3 units</td>
<td>No haemorrhagic or bleeding events</td>
</tr>
<tr>
<td>Christensen et al. 2001</td>
<td>To assess the quality of self management of oral anticoagulant therapy in children with congenital heart disease.</td>
<td>Yes</td>
<td>Not presented</td>
<td>76%, No comparison</td>
<td>Not presented</td>
<td>No haemorrhagic or thrombotic events</td>
</tr>
<tr>
<td>Marzinotto et al. 2000</td>
<td>To prospectively evaluate a whole blood PT monitor in children requiring OAT. Phase 1 Clinic study Phase 2 Home study</td>
<td>Yes</td>
<td>Clinic POC: r² = 0.96</td>
<td>Not presented</td>
<td>71% of paired INR tests had a difference of &lt; 0.5 INR units</td>
<td>No major bleed, No thrombotic event</td>
</tr>
<tr>
<td>Andrew et al. 1996</td>
<td>To assess the accuracy of home monitor results compared to standard laboratory results, for patients requiring OAT.</td>
<td>r² = 0.81 to 0.93</td>
<td>67.9% POC 67.2% Lab</td>
<td>Not presented</td>
<td>90% of all INRs between 2.0–3.5 within 0.8 INR units of agreement</td>
<td>One major bleed, One thrombotic event</td>
</tr>
<tr>
<td>Massicotte et al. 1995</td>
<td>To prospectively evaluate a whole blood PT monitor in consecutive children requiring warfarin therapy.</td>
<td>Yes</td>
<td>r² = 0.93</td>
<td>Not presented</td>
<td>90% of all INRs between 2.0–3.5 within 0.8 INR units of agreement</td>
<td>One major bleed, One thrombotic event</td>
</tr>
</tbody>
</table>
publications, and no paper identified a pre-requisite level of agreement that would be considered an acceptable variant between home and laboratory INR tests. Within four studies, patient/parent education programs around POC INR testing were discussed where study participants underwent a practical training program designed and provided by the anticoagulation nurse (11–13, 19).

Primary outcomes included comparison of the INR reported between the POC monitor and a venous sample (11–13, 15, 19–21), or time in therapeutic range (TTR) (11). The use of POC devices in paediatric home INR monitoring programs has produced variable outcomes with respect to correlation between home- and hospital-based INR results. However, an acceptable level of agreement can be obtained between INRs measured at home and those measured in a laboratory ($r^2 = 0.87$) (19). Nonetheless the results were not as reliable as those obtained by trained personnel within a tertiary paediatric centre ($r^2 = 0.92$) (12). Therefore, education programs delivered in preparation for home INR monitoring in the paediatric population may impact upon accuracy of results generated by home INR programs (Table 1).

The CoaguChek XS® POC INR system measures the INR using 10 µl of whole blood obtained by finger prick which is easily applied to a test strip. The monitor has an embedded quality control (on-board single channel strip control) which tests the integrity of each single test strip while the test strip is being used for patient blood testing. Two levels of performance are evaluated. Firstly, the amount of Resazurin in the test area of each individual test strip is quantified which corresponds with the quantity of all components in the formulation used for clot detection. Secondly, the strips integrated quality control function quantifies the amount of by-product Resorufin which assess for incorrectly handled / stored test strips. The calibration concept of the new CoaguChek XS system is in agreement with the "WHO guidelines for thromboplastins and plasmas used to control anticoagulant therapy" (22). The manufacturer uses a master lot of test strips which is directly calibrated by comparison to international reference preparations (IRP), and represents the manufacturer’s working standard. Further calibration in routine manufacturing of test strips is performed versus this master lot using whole blood samples from patients on oral anticoagulation and from normal donors. The mean international sensitivity index (ISI) for the CoaguChek XS prothrombin time test is 1.01 (23). The monitor uses an amperometric (electrochemical) method to monitor blood clotting induced by thromboplastin within the test strip to determine the PT. The PT is then converted to an INR using the ISI previously determined and encoded on the chip for each lot of test strips. This meter has been evaluated in adults with favourable results (24, 25). Regardless of the relative ease of use and minimal invasiveness of the POC monitor, the successful development and implementation of a home POC INR monitoring program requires demonstration that the results provided by the monitor are both accurate and precise.

Objective
The objective of this study was to determine the accuracy and precision of the INR determination of the CoaguChek XS meter as compared to the gold standard method of venous collection with laboratory analysis using blood obtained from a cohort of children requiring anticoagulation with warfarin. We hypothesized that the CoaguChek XS meter would provide accurate INR measurements in children and perform as well as previous CoaguChek models, and therefore would be suitable for use in children requiring warfarin.

Methods
The Paediatric Anticoagulation Program at the Stollery Children’s Hospital, a large quaternary care institution in Edmonton, Alberta, Canada, cares for all children with or at risk for thrombosis who require thromboprophylaxis. This program has a large POC INR meter program. Children requiring warfarin therapy are loaned a CoaguChek XS meter for a period of up to one year. The KIDCLOT-POC® is a standardized education program completed by patients and their caregivers before independent use of the POC INR meter (26). The educational program is designed to ensure all potential POC INR meter users demonstrate accurate testing technique preceding independent meter use. Two initial POC meter-laboratory comparisons are required for each patient within the first week of patient meter use to ensure accuracy of meter results to a measured laboratory INR.

Determination of precision
To meet accreditation standards precision measurements are required on all new POC devices prior to their clinical implementation. The usual assessment of precision requires the repeated analysis of a stabilized material for the analyte(s) of interest (27). As no stabilized material is available for PT-INR testing by the CoaguChek XS, 10 separate blood drops were obtained from three different adult volunteers over 5 min and tested on 10 different CoaguChek XS systems using one reagent strip lot. One volunteer was receiving oral anticoagulation for valve thromboprophylaxis, another volunteer self-dosed with 8 mg warfarin for two days before the assessment of precision, the last volunteer was not anticoagulated. Up to three different capillary fingerstick punctures were required per volunteer to obtain the 10 blood drops. The standard deviations of the three sets of replicate PT-INR measurements were then calculated. The standard deviation of the 10 measurements provides a measure of between instrument and within day variation which should exceed the within instrument / between day variation which is usually evaluated in imprecision studies.

Determination of accuracy
The CoaguChek XS method for INR measurement was compared with the gold standard laboratory method for INR measurement. The INR is not a true value but is calculated using the patient PT value in seconds (sec) divided by the geometric mean of the reference PT range (for the respective reagent/analyser combination), taken to the power of the ISI. The use of the INR value is an attempt to account for different analyzers and thromboplastin reagents used in PT testing. Comparison INR samples were collected using venipuncture and sent to the central pathology laboratory at the University of Alberta Hospital in Edmonton, Alberta, Canada for testing. The laboratory method...
consisted of phlebotomists drawing venous samples of blood into 1.8 ml sodium citrate tubes. Following centrifugation (1,700 x g, 10 min) plasma samples were then analysed in a centralized laboratory using RecombiPlastTin® (Haemoliance®, Instrumentation Laboratory). Accuracy of meter results was determined within the first week of patient meter use. A laboratory INR test was performed and within one hour an INR was performed using whole non-citrated blood on the CoaguChek XS INR meter on two occasions. Comparison one (t₁) was performed by a health care professional using a non-citrated venous sample and comparison two (t₂) was performed using a fingerstick with CoaguChek XS application performed by the patient/parent trained in meter use. Laboratory INR uses citrated blood while the POC meter uses whole non-citrated blood which is standard clinical practice. A priori, a pre-determined ≤15% difference between laboratory INR and meter INR determinations was operationally defined to be acceptable as any difference less than or equal to 15% which would not alter clinical management for patients in our practice, and in addition would be consistent with published criteria for clinical relevance (28–32).

**Clinically relevant agreement**

Clinically relevant agreement was defined based on whether or not the difference between the dual INR measurements would be likely to result in different clinical management (warfarin dosing). In the early 1990s, Anderson et al. developed a model to define clinical relevance related to INR results and warfarin dose adjustments (34). Two types of agreement are described. Firstly, expanded agreement is defined as when:
1. both the paired INR measurements are within the therapeutic range, or
2. both are above the therapeutic range, or
3. both are below the therapeutic range, or
4. when one is within the therapeutic range and the pair is within 0.5 units.

Paired INRs falling within these measures would not result in a change in the warfarin dose, and therefore these two values are considered in agreement. Secondly, narrow agreement is as described with expanded agreement but its narrowest parameter for agreement is that the paired INRs fall within with 0.4 units.

All INR POC meters underwent a standardized pre-established protocol (Fig. 1). Initially, the meters were sent to Clinical Engineering Department, tagged for inventory and entered into a database for tracking health device alerts. Once completed, the meters were sent to the Point of Care Laboratory within the University of Alberta Hospital which requires a short acceptance evaluation for each new POC INR meter before clinical usage. This included a minimum of four (range 4–15) CoaguChek XS meter/laboratory comparisons performed on adults within the Point of Care Department. For comparison, the results from both the CoaguChek XS meter and clinical laboratory were plotted against each other and regression of the line of best fit returned a slope of approaching unity, intersection with the origin and an $r^2 = 0.96$ (equation for the line of best fit $y = 0.92x + 0.047$ [34]). Once the initial performance evaluation was completed in the Point of Care Laboratory, the meters were returned to the Paediatric Anticoagulation Program for use in the loan program.

**Study design**

The target population consisted of all children <18 years of age requiring more than three months of warfarin therapy within Stollery Children’s Hospital. These children/families were approached to participate in the study.

The POC meter loan program requires families to participate in a standardized educational program (KIDCLOT©) regarding warfarin therapy and POC INR meter use. Practical elements included a hands-on approach to POC INR meter use and testing technique, as well as laboratory INR comparison of the POC INR on a minimum of two patient blood samples during the instruction period and yearly thereafter.

The study was reviewed and approved by the University of Alberta ethics committee and informed consent was obtained from all children and/or their guardians.

All children and families approached for participation in the study consented.
Statistical analysis/ accuracy assessment

Bland-Altman’s (35) 95% limits of agreement were calculated as the mean difference between the INR pairs ± 1.96 times the standard deviation of the difference. The mean of the paired measurements were plotted against the difference. Bland-Altman’s limits of agreement were calculated separately for the first (t1) and second calibration (t2) of the meters. The % deviation of the POC INR relative to the laboratory INR are presented as the median with 99% confidence interval (CI) (based on 1,000 bootstrap replications).

Results

Precision was initially measured prior to implementation of the CoaguChek XS meter within our institution. The volunteers’ mean INR, standard deviation, and coefficients of variation were: 1.04 (standard deviation [SD] = 0.52, coefficient of variation [CV] = 5.0%), 1.39 (0.057, 4.1%) and 3.02 (0.063, 2.1%) for the warfarin naive, the two-dose warfarin and the chronically warfarin maintained volunteers, respectively.

The study sample population consisted of 62 consecutive children aged 18 months to 17 years (Table 2), who were referred to the Paediatric Anticoagulation Program at the Stollery Children’s Hospital between September 2006 and October 2007. Patient age was evenly distributed across age groups (Table 1). All patients required warfarin, and their indication for therapy is reported in Table 2. Fifty-eight of 62 patients had two or more paired POC / laboratory INR measurements. Both expanded and narrow agreements according to Anderson et al. (33) were 100% at t1 and 98% at t2, respectively.

The average difference between the CoaguChek XS INR and laboratory INR and Bland-Altman’s 95% limits of agreement at the two calibration timepoints were 0.11 (-0.20; 0.42) and 0.13 (-0.22; 0.48), respectively. The corresponding Bland-Altman plots are shown in Figure 2.

The average difference between the CoaguChek XS INR and the laboratory INR in the current study was 0.1, i.e. the CoaguChek XS INR was on average 0.1 INR units lower than the laboratory INR and Bland-Altman’s 95% limits of agreement at the two calibration timepoints were 0.11 (-0.20; 0.42) and 0.13 (-0.22; 0.48), respectively. The corresponding Bland-Altman plots are shown in Figure 2.

The median deviation of the POC INR relative to the laboratory INR was 5.6% (99%CI 2.0; 9.1) and 5.7% (99%CI 2.4; 9.1) at the two calibration timepoints, respectively.

Discussion

The objective of this study was to determine the accuracy and precision of INR determination of the CoaguChek XS meter compared to the gold standard method of venous blood collection with laboratory INR in a cohort of children. Accuracy was determined by comparison of measured INRs on the CoaguChek XS compared to the gold standard laboratory INR and a measure of accuracy is estimated using the Bland-Altman plots.

The precision of the instrument, a measure that was determined from the repeated analysis of volunteers’ blood, are of the same magnitude as those obtained by routine laboratory coagulation analysers when running stabilized controls over several weeks (within analyser and day-to-day variability). However, once the manufacturer of the CoaguChek XS, Roche, makes a stabilized PT-INR control material for quality control purposes, the within analyser and day-to-day variability, of the CoaguChek XS will be at least equivalent, but more likely, smaller than that observed in our study.

Accuracy determination relies on the assumption that the laboratory INR value is the true INR value. However, INR is a calculated value with a number of assumptions, the most important being that the ISI of the thromboplastin in the laboratory is accurate. There are two studies, n=17 adults with 59 paired INR comparisons (25) and Brauns’s study (24), evaluating the accuracy of CoaguChek XS INR determination in adults which demonstrated good CoaguChek XS / laboratory correlation by Passing Bablock method (r=0.91) (36). However, to date, no study has evaluated use of the CoaguChek XS meter in infants and children, and this study provides the first evaluation the CoaguChek XS meter in children.

The numerous challenges associated with warfarin management in children include developmental haemostasis, complex underlying health problems (Table 2), multiple medications, inconsistent nutritional intake, difficult venous access, needle phobias (5, 6), and concomitant viral illnesses. The POC INR test can be performed when indicated at the patients’ convenience overcoming many of these challenges. Of critical importance is the rapid, accurate INR result that enables timely drug dosage adjustment and prompt attention to critical values. Response time to correct out-of-range values and/or maintain patients in the therapeutic range may play a critical role in reducing the incidence of thrombotic and haemorrhagic complications and contribute to an improved clinical condition for the patient, with economic benefits to the health care system (37).

The results of this study validate the CoaguChek XS meter to be accurate and precise for use in children prescribed warfarin therapy.

The average difference between the CoaguChek XS INR and the laboratory INR in the current study was 0.1, i.e. the Coagu-

Table 2: Age groups and indications for anticoagulation in 59 patients receiving warfarin. DVT, deep venous thrombosis.

<table>
<thead>
<tr>
<th>Age group</th>
<th>DVT</th>
<th>机械心瓣膜</th>
<th>Kawaski’s disease with giant aneurysms</th>
<th>Dilated cardiomyopathy</th>
<th>DVT</th>
</tr>
</thead>
<tbody>
<tr>
<td>18 months – 4 years</td>
<td>20</td>
<td>11</td>
<td>3</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>5 years – 10 years</td>
<td>21</td>
<td>11</td>
<td>3</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>11 years – 17 years</td>
<td>18</td>
<td>11</td>
<td>3</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

The table shows the age groups and indications for anticoagulation in 59 patients receiving warfarin, categorized by DVT, mechanical aortic valve, Kawasaki’s disease with giant aneurysms, dilated cardiomyopathy, and DVT.
CoaguChek XS INR was on average 0.1 INR units lower than the laboratory INR with 95% of differences falling within the range of –0.2 to 0.4 INR units (t1) and –0.2 to 0.5 INR units (t2), respectively. At both calibration time points, 91% of INR pairs fell within 0.3 units of each other, providing further evidence of strong agreement between the two methods. Agreement between INR pairs appears to be somewhat reduced for laboratory INRs > 4.0 (Fig. 2). However, the number of INRs in that range was too small to draw any conclusions.

While Bland-Altman’s 95% limits of agreement are important for the assessment of the accuracy of a method, they ultimately fail to provide what is important clinically: namely, how often differences between the POC and laboratory INR will result in differing warfarin management decisions. Both expanded and narrow agreements were 100% at t1 and 98% and t2, respectively. This means that virtually all POC INRs in this study would likely not have resulted in a different clinical management decision (warfarin dose) (28–32). However, none of these clinical agreement rules were ever validated against actual clinical management decisions.

Ensuring POC users have learned and demonstrated accurate testing technique may positively influence CoaguChek XS-laboratory INR result concordance. Marzinotto et al. demonstrated inconsistencies in the level of agreement between POC INR results generated at home compared with those performed in a hospital setting by trained health care professionals (19). This may reflect lack of proficiency in performing the POC INR test by users (14). In this study, the CoaguChek XS meter users were pa...
tients and their families who participated in the KIDCLOT-POC educational program to ensure their proficiency in POC INR testing.

All 62 patients described the meter easy to use, preferred POC INR testing over standard laboratory testing, and continued to use the CoaguChek XS meter. In this study, one patient discontinued meter use due to financial limitations related to the cost of the test strips. In addition, there was an approximate 1% failure rate in the CoaguChek meters purchased for patient use by the Paediatric Thrombosis Program. One meter measured INR values grossly different from the laboratory INR (> 0.5 units) necessitating the return of this meter to the manufacturer for replacement. This demonstrates the importance of validation of each POC INR meter prior to use. Repeat validations every 6–12 months ought to be considered to ensure continued accuracy of meter INR determinations.

Conclusions
INR values generated by CoaguChek XS meters showed acceptable agreement with our hospital laboratory INR. The differences between paired INRs were not sufficient to change clinical management decisions. This CoaguChek XS meter appraisal demonstrates accuracy and reproducibility of meter performance (multiple meters, multiple operators and multiple tests). Scheduled evaluation of user proficiency in meter testing technique and regular laboratory comparisons at onset of use and every 6–12 months to ensure continued accuracy of meter results are recommended (38).

References