International Normalised Ratio Monitoring in Children: Comparing the accuracy of portable point-of-care monitors to standard of care laboratory monitoring at Red Cross War Memorial Children's Hospital

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Declaration

I, Ryan Moore, declare that the work on which this dissertation is based is my own original work (except where acknowledgement is indicated otherwise) and that no part of this work has been or will be submitted for another degree in this university or any other.

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Abstract

Background. There is an increasing trend in the use of long-term oral anticoagulation therapy in children. Monitoring the international normalised ratio (INR) is an integral part in management of these patients, but standard laboratory testing of the INR presents challenges in this age group. Point-of-care INR monitors such as the Mission® PT/INR monitor provide advantages in efficiency and accessibility but have not been evaluated for accuracy in the South African paediatric setting.

Objectives. This is a feasibility study with the aim to evaluate the accuracy of the Mission® PT/INR Monitor in comparison to standard laboratory INR measurement, in children presenting for INR testing.

Methods. We compared the accuracy of the Mission® PT/INR monitor to the Sysmex Cs-2100i laboratory analyser in 37 children aged between 1 year and 17 years, who presented for INR testing. The sample size was limited due to time constraints. 40 paired POC INR and laboratory INR values were obtained.

Results. The majority of participants in the study were outpatients (62%) and required INR testing as part of screening in non-cardiac disease (81%) - the majority had chronic liver disease, and a minority were on warfarin therapy (13.5%). The mean INR value on the Mission® PT/INR was 1.49 (standard deviation (SD) 0.73) and was comparable to the Sysmex Cs-2100i (mean INR value 1.39 with SD 0.69). The Bland-Altman difference plot revealed good agreement. Bias between the two methods was 0.13 (SD 0.23). In total, 92.5% of POC INR values were within 0.5 units of laboratory INR value.

Conclusion. The Mission® PT/INR point-of-care monitor has a clinically acceptable level of accuracy in children when compared with laboratory INR measurement, but larger studies are needed in the paediatric setting to evaluate patient safety and clinical outcomes. There is a need for implementing POC INR monitoring in outpatient settings but this practice will require robust assessment of infrastructure and quality control before application.

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Abbreviations

aPPT	Activated partial thromboplastin time
CCC	Concordance Correlation coefficient
CI	Confidence interval
INR	International normalised ratio
LMWH	Low molecular weight heparin
POC	Point-of-care
PT	Prothrombin time
PIHT	POC INR Home Testing
RT	reptilase time
RCWMCH	Red Cross War Memorial Children's Hospital
SD	Standard deviation
TT	Thrombin time
TTR	Time in therapeutic range
VKA	Vitamin K antagonist

CHAPTER 1:

INTRODUCTION AND LITERATURE REVIEW

INTRODUCTION

The twenty-first century has seen a rise in the use of anticoagulant medication for both primary prophylaxis and treatment of thromboembolism in children.[1,2] This trend is the result of advances in paediatric heart surgery and the use of life-saving therapies, including extracorporeal membrane oxygenation, prosthetic heart valves and central venous access devices. As a result, medical practitioners are increasingly required to become familiar with treatment strategies and the monitoring of oral anticoagulant therapy.[2] Of the oral anticoagulant agents available, Vitamin K antagonists (VKAs, such as warfarin) remain the most commonly used, with estimation of the International Normalised Ratio (INR) being a measure of treatment efficacy. However, therapeutic drug monitoring in children on warfarin, through regular phlebotomy and standard laboratory INR testing, presents unique challenges in the paediatric setting.[1] Fortunately, point-of-care (POC) INR measurement devices have been developed as a suitable alternative, and in adult populations have been shown to be accurate in comparison to standard laboratory INR testing and improve clinical management and patient-reported quality of life.[3,4] These devices have also been validated for use in children, but have not yet been evaluated in the South African paediatric setting.

This chapter will review:

1) Basics of coagulation testing in children with a focus on INR testing
2) Current trends in VKA therapy in children
3) Therapeutic monitoring in children on VKA therapy
4) Description and uses of POC INR monitoring in children
5) POC INR monitoring devices that have been researched for use in children
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My search strategy encompassed a literature search and was performed using these databases: MEDLINE, Google Scholar, Clinical Key, Clinical Evidence and Pubmed. The keywords that were used included: Point-of-care, International Normalised Ratio, INR, coagulation, testing, monitoring, validation, children, paediatrics. The search yielded 3 review articles, 2 guideline papers and 31 studies.

Coagulation testing in children

Blood coagulation tests are one of the most commonly requested in inpatient and outpatient paediatric patients. There are numerous tests available for testing the coagulation system in children, each of which have different indications and applications in clinical practice. These include tests of clotting time such as prothrombin time (PT), activated partial thromboplastin time (aPTT), thrombin time (TT) and reptilase time (RT) as well as various coagulation factor assays.[5,6] Indications for coagulation testing in paediatric clinical practice include the investigation of bleeding disorders, preoperative assessment of haemostasis, assessment of liver synthetic function and the monitoring of anticoagulation therapy for patients on VKAs and heparin therapy. [5,6]

Prothrombin Time testing and International Normalised Ratio

The PT assesses the extrinsic and common pathways of coagulation. It measures the time it takes for plasma to form a fibrin clot after exposure to tissue factor. After the addition of calcium to the citrated plasma solution, along with the tissue factor and phospholipid, the formation of the fibrin clot is detected by various means including visual, optical and electromechanical methods. The result is measured in seconds and is reported along with a control value and INR value. The normal range for the PT depends on the laboratory and instrument/ reagent combination - in most laboratories, the normal range is around eleven to thirteen seconds. [7,8]

The INR value is calculated as a ratio of the patient's PT to a control PT value, which is obtained using an international reference thromboplastin reagent. Therefore, as long as the thromboplastin reagent/ instrument system is calibrated correctly, the INR value for a particular blood sample will be similar in any laboratory using any thromboplastin reagent/ instrument system. This makes the INR test useful for VKA therapeutic monitoring as it allows comparison of the patient's plasma INR at different times and from different institutions. The INR in a healthy adult is between 0.9-1.1. [6,7] The PT/ INR values in particular have uses in the evaluation of suspected bleeding disorders, diagnosis of disseminated intravascular coagulation, monitoring of VKA therapy and the assessment of liver synthetic function.

Laboratory testing of coagulation is subject to numerous quality control measures to ensure accurate testing. Factors related to sample collection and handling that may affect accuracy and are related to [6]:

1) Suitability of the blood sample - plasma should be used for coagulation testing as clotting factors are removed with the serum preparation process;
2) Volume of blood used - the appropriate ratio of sodium citrate to whole blood is essential to avoid inaccurate results - a fixed ratio of 1-part citrate to 9 parts whole blood is required and therefore tubes should not be over- or underfilled;
3) Collection tube used - the light blue tube containing 3.2% sodium citrate is used as a standard for laboratory coagulation tests;
4) Mixing of blood and citrate - gentle inversion to ensure appropriate mixing of citrate solution with whole blood is required;
5) Elapsed time and temperature - timeous testing of the sample (to avoid degradation of coagulation factors), usually within 24 hours of phlebotomy is essential for accurate testing. Tubes are not to be frozen before testing.

Other sources of interference that may lead to inaccurate results include contamination with intravenous solutions and anticoagulants, or interference with coagulation times due to the presence of lipaemia, hyperbilirubinaemia, haemolysis or polycythaemia. Various drugs and pathological processes may lead to a prolonged PT/INR value (Table 1) [6].

Table 1. Causes of prolonged PT/INR in children

1) Vitamin K antagonists such as warfarin
2) Vitamin K deficiency - seen in malnutrition, prolonged broad-spectrum antibiotic use and pancreatic exocrine insufficiency
3) Acute and chronic liver disease
4) Disseminated intravascular coagulation
5) Deficiency of factors involved in the extrinsic pathway - may be inherited or acquired

6) Antiphospholipid antibodies

Warfarin therapy in children

VKAs, unfractionated and low molecular weight heparin are the anti-coagulant options most widely available for the prevention and treatment of venous and arterial thromboembolism, and each is associated with particular side effects. Data on the use of newer oral anticoagulants (e.g. direct thrombin inhibitors or Factor Xa inhibitors) in children are limited and are therefore less commonly used. Table 2 shows the most common indications for anticoagulant therapy in children.

Table 2. The most common Indications for anti-coagulant therapy in children

Cardiac	Non-cardiac
Prophylaxis after cardiac surgery - Fontan surgery, Blalock-Taussig Shunt	Primary Pulmonary Hypertension
Mechanical prosthetic valves	Acute arterial stroke
Kawasaki Disease with large aneurysms	Deep venous thrombosis
Dilated cardiomyopathy with severe left ventricular dysfunction	Anti-phospholipid syndrome
Ventricular assist devices	

There are limited randomized trials in children to guide the use of oral anticoagulant therapy, with the majority of recommendations being extrapolated from adult literature.[2] VKAs are the most commonly used oral anti-coagulants in the paediatric population, and in paediatric cardiac patients is most commonly indicated for prophylaxis after surgery for univentricular heart palliation (Fontan procedure), mechanical prosthetic valves, large aneurysms following Kawasaki Disease, dilated cardiomyopathy with severely impaired left ventricular function and primary pulmonary hypertension.[2,9] Warfarin and other VKAs (known as coumarins) result in prolongation of PT by inhibiting the enzyme Vitamin K epoxide reductase, which is responsible for converting Vitamin K epoxide (produced by the action of intestinal bacteria) to biologically active vitamin K. This in turn impairs the function of vitamin K-dependent clotting factors II (prothrombin), VII, IX and X (Figure 1).

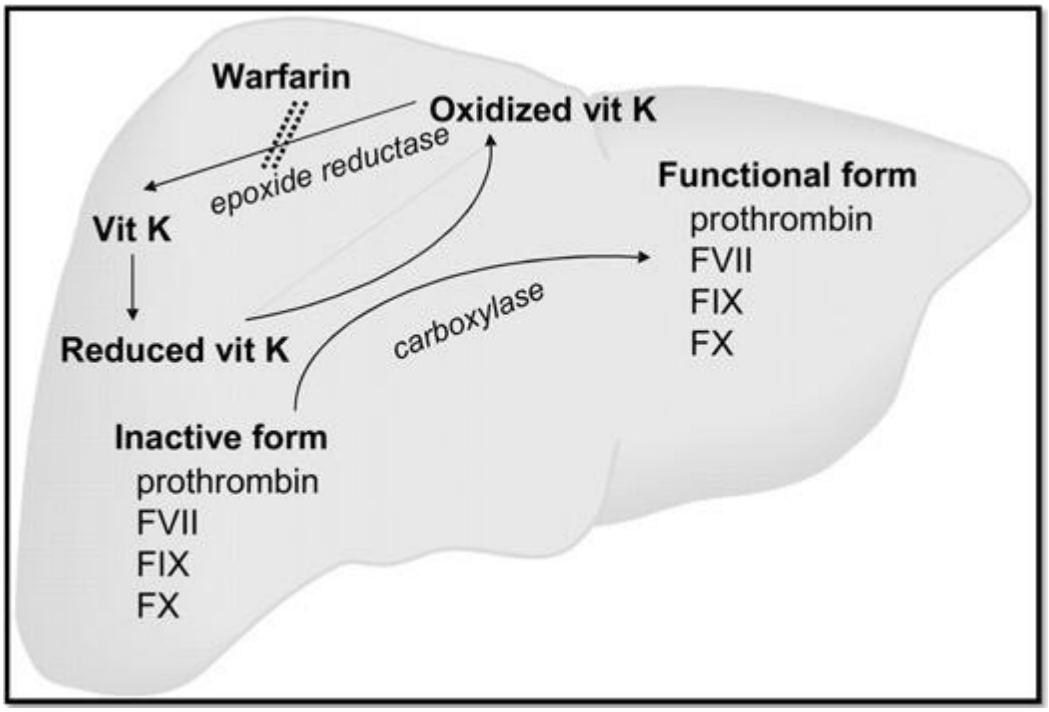

Figure 1. Mechanism of action of warfarin[10]

Although VKAs are the most widely studied oral anticoagulant, their use presents a number of limitations when used for long-term therapy in children. Adverse effects include bleeding (most common), skin necrosis, gangrene, osteoporosis, hair loss and tracheal calcification.[2] The need for frequent phlebotomy for INR monitoring in a population with inherently difficult vascular access adds cost and burden. Furthermore, warfarin has numerous pharmacologic interactions with disease states, drugs and diet which may interact to increase the risk of bleeding or reduce treatment efficacy.[7] For example, infants who are breastfed are more sensitive to warfarin compared to infants who are formula-fed due to the lower content of vitamin K in breastmilk. Contraindications to warfarin therapy include previous hypersensitivity reactions to warfarin, severe renal or liver impairment, severe hypertension, infective endocarditis, pericardial effusion, active ulceration and cerebral or dissecting aortic aneurysm.[11]

Low molecular weight heparin (LMWH), enoxaparin being the most widely studied, has several potential benefits in that it requires minimal monitoring, exhibits fewer drug interactions or dietary interference and has a reduced risk of osteoporosis and heparin-induced thrombocytopenia compared to other agents. The therapeutic ranges of optimised management have been derived from adult data, however and the rates of major bleeding are uncertain. [12,13]

Minor bleeding includes bruising, epistaxis, excessive bleeding from cuts, while major bleeding is defined as bleeding into a major organ or requiring blood transfusion. Various studies describe rates of haemorrhage between 0.2 - 12.2%.[13]

Therapeutic monitoring in children on Warfarin therapy

Warfarin has a narrow therapeutic index and is subject to numerous drug and food interactions. Maintaining a patient's INR within a designated therapeutic range is necessary to balance the risk of preventing thrombosis and embolization against the risk of bleeding and haemorrhage. A target INR in the range 2.0-3.0 is appropriate for most indications, including venous thromboembolism, atrial fibrillation and severe ventricular systolic dysfunction. In children, a therapeutic range of 2.0-3.0 is also recommended for aortic bileaflet mechanical valves.

Time in the therapeutic range (TTR) is used as a measure for the safety and efficacy of VKA therapy. This refers to the amount of time a patient's INR is within the designated target range.[12] This is crucial for minimising patient morbidity and mortality. Optimising the paediatric patient's clinical management provides additional challenges in that drug pharmacokinetics, illness as well as drug and food interactions, contribute to narrow therapeutic windows. The frequent non-availability of paediatric drug formulations further complicates monitoring and reduces predictability.[13]

Further challenges in therapeutic drug monitoring in children are posed by the regular requirement for phlebotomy so that standard laboratory-based investigations can be performed. This is compounded by inherently difficult venous access, in addition to relatively large volume of blood required to perform the test. Testing methodology is one of the variables that can lead to INR instability, with different testing methods using different methods for clot detection, different thromboplastin reagents and different sample types.[14]

Point-of-Care Diagnostics

Point-of-care (POC) INR testing refers to testing that can be performed using a device located near the patient as opposed to a central laboratory. A POC test is performed with a capillary sample placed on a strip, with a test result yielded in real time. This capillary sample is placed on the strip within 30 seconds to avoid interference with the INR value as a result of tissue-

factor release or activation of the clotting cascade.[15] Plasma or anti-coagulated whole blood should not be used. The monitor then uses an electrochemical method for clot detection, based on thrombin generation. Devices report the result as either a PT (in seconds) or as an INR.

POC INR testing has been shown to provide a safe and accurate alternative to standard laboratory INR testing in adults and allows for rapid generation of results with resultant improved patient care.[3,4] POC INR monitors have also been shown to be a reliable alternative to lab INR testing in children, and perform well when used in a hospital or clinic setting or when used by patients for self-testing at home.[7,16] There are however limitations to these studies as large patient numbers are required to assess the risk of complications and is not feasible in children.

POC INR Monitoring devices which have been tested in children

Validation studies have been performed on many of the available POC INR monitors in children and have been shown to perform equally well when used within hospital/ clinic settings or by patients for self-testing in their homes.[7]

The CoaguChek ® XS system (Roche Diagnostics) has been well studied in adult and paediatric patients on long-term oral anti-coagulant therapy. Moon et al compared 120 paired POC INR values to standard laboratory INR values in 42 children (under 16 years) with heart disease on anticoagulant therapy, in an outpatient setting. They found the difference in INR values between the two methods was consistently <0.5 with a mean difference between the two methods of 0.08 units. They concluded that the CoaguChek XS device is as accurate as the laboratory method, and faster and more convenient.[17]

Bauman et al also compared the CoaguChek XS device to laboratory INR values in a smaller cohort of adults and children who were warfarinised with ventricular assist devices. 6 children and 10 adults were enrolled with 73 paired INR comparisons taken for the children cohort. The study found the average difference between the two methods was -0.10 (with a Bland-Altman 95% limits of agreement -1.1;0.93). The Lin Concordance correlation coefficient (CCC) was 0.80 (95%CI 0.60;0.92). CCC is calculated as a product of a measure of accuracy (the bias

correlation factor) and a measure of precision (Pearson correlation coefficient). A CCC of 1 indicates perfect agreement.[3] They concluded that POC INR devices were moderately accurate in patients with VADs, but less accurate than in patients without VAD.[3]

Collela et al found that the CoaguChek XS POC device underestimated the INR results by only 0.08u ($p<0.0001$).[18] This evidence is supported by other studies that have found a non-significant variability between POC devices and laboratory tests when the target range is 2-3, further validating the suitability of POC devices for outpatient/ home-based care. The authors advised caution when INR values are greater than 3.5. In such cases a confirmatory laboratory-based INR should be performed. [19,20]

Lawrie et al however found that with the CoaguChek XS INRs between 4.5-8 were comparable to laboratory INRs.[21] In a study on adult patients, Vazquez et al found there was poor accuracy for POC INR values that were greater than 3, and suggested the application of a correction factor in these cases to improve accuracy.[22] Moiz et al found overall good accuracy with the CoaguCheck XS Pro, and found that the discrepancy in results in only 11 of the 200 INR samples led to differences in dosing decisions.[23]

In South Africa, a study by Benade et al compared the accuracy of the CoaguChek XS monitor with that of a standard laboratory analyser in 304 adult patients on standard warfarin therapy, who presented for routine INR testing. The study found the mean INR results between the two methods to be comparable with good agreement on Bland-Altman difference plot analysis as long as readings were in the target range (2.0 - 3.5). The difference between the two methods showed increased variability when the INR on the laboratory analyser was greater than 3.5.[4]

The CoaguChek S device has also been studied for home monitoring of oral anticoagulant therapy in children. Hill et al compared in 129 paired INR samples in children under 18 years of age, on long-term anti-coagulant therapy in an outpatient setting. They found the overall intraclass correlation coefficient between the CoaguChek S and standard laboratory method was 0.75 (95%CI 0.66-0.82) and that on average the POC INR device underestimated INRs by 0.11 (+/- 0.54 units), but that for lab INRs of 3.5 units or higher, the POC device overestimated the value by 0.49 (+/- 1.09 units). They concluded that the CoaguChek S is valid for in-home INR monitoring, but that POC INR values higher than 3.5 should be interpreted cautiously and rechecked.[19]

The INRatio2 PT/INR monitor (Alere Ltd) was previously recommended by the National Institute for Health Care Excellence for self-monitoring in children and adults on long-term anticoagulant therapy but in 2015 the device was withdrawn from the market as there were reported incidents of device malfunction and as well as reported INR results that were lower than expected.[24] The problem of under-reading by the INRatio PT/INR was raised when the results of the Re-LY trial were published in 2009. This was a multi-centre non-inferiority study comparing the safety and efficacy of warfarin to a novel anti-coagulant dabigatran in patients with non-valvular AF.[25] The study found that while both high- and low-dose dabigatran were associated with fewer strokes than warfarin therapy, it was noted that there was a lower than expected rate of INR control in the warfarin group (measured as time in therapeutic range, TTR), which could not be explained just by the fact that there was higher enrollment of Re-LY participants who had not been on long-term VKA therapy. Other important assessments of INR control were also not reported in the study, including local ISI calibration and external quality control of INRs. Since being removed from the market, no replacement device has as yet been released for the INRatio2 PT/INR monitor.

Other devices that are available on the international market include CoagMax (Microvisk) - no studies have as yet been published on this device; and microINR (iLine microsystems) with several published studies showing mixed results on the performance of the device. [26,27]

Clinical Settings in which POC INR Devices have been researched

Three different settings for POC INR monitoring and management in patients on long-term anticoagulant therapy have been utilized [28]:

1) POC INR testing within a health care facility where immediate results are obtained and instructions on dosage are given to patients [1];
2) POC INR testing at home with results phoned to a health facility or practitioner who provides instructions on drug dosing (i.e. self-testing);
3) POC INR testing at home with patients adjusting their own drug dosing based on a pre-determined dosing nomogram (i.e. self-management);

POC INR monitoring within the home (also known as POC INR Home Testing, PIHT) has been shown to be a feasible method of INR testing and is associated with non-inferior warfarin/ INR control compared with standard laboratory monitoring.[3] Methodological limitations in study designs make it difficult to measure true safety and efficacy in monitoring of oral anticoagulant therapy in children. As a result, TTR is commonly used as a surrogate measure for safety and efficacy of warfarin therapy.[3] Christensen et al provided a review of studies which evaluated POC INR Home Testing (PIHT) with self-testing and found that TTR compared favorably with laboratory monitoring (63-83% vs 50%).[29]

Patient self-management has been evaluated in numerous studies - in one randomized controlled trial (where patients were randomized to continue self-testing or self-management), TTR was similar in both groups (83%) with patients in the self-management group reporting higher health-related quality of life and satisfaction with therapy.[30]

While potential advantages of using POC INR testing in children on long-term anti-coagulant therapy include greater convenience to patients with resultant improvement in treatment compliance and more frequent monitoring, patients may experience increased anxiety about their disease and coagulation monitoring. Furthermore limitations to the use of POC devices include the cost of the device, the need for specialized training and strict adherence to quality standards outside of the clinical laboratory setting. [6,31]

POC devices are already in use for home-based self-management in Europe and Australia with patients describing higher quality of life and satisfaction with therapy. Bauman et al have described home-based management and self-testing programs where TTR was 83%.[3]

POC testing in the South African setting

POC INR testing is of particular value in resource-limited settings, where it can provide rapid real-time INR results, and can be used in the home-setting, thereby reducing cost and improving patient care. This is especially relevant in the South African setting where rural or remote locations require patients to travel great distances in order to have centralized INR testing done for therapeutic monitoring. Red Cross War Memorial Children's Hospital (RCWMCH) in Cape Town provides services to children on long-term warfarin, not only from the Cape Town Metropole but from across the Western Cape and neighbouring provinces.

Some of these patients travel from far with paid-for transport to have their INR tested at the central laboratory and to be evaluated by clinicians.

Devices have previously been validated in the South African setting in adults on long-term oral anticoagulant therapy and have been shown to be accurate and precise, although accuracy and precision tend to decrease with INR values above 4.5-5.0. As mentioned, the CoaguChek XS has been shown to be accurate for use in a tertiary hospital outpatient setting for adults on long-term warfarin therapy. It is suggested that the CoaguChek XS monitor be utilised in a clinic setting as a screening tool for patients on long-term oral anticoagulant therapy, but that a vigorous quality-control system would be needed.[4] The microINR POC INR monitor was evaluated in adults on warfarin therapy who presented for INR testing at a tertiary academic setting and was found to be accurate and precise.[32] The Coag-Sense INR system was evaluated in 202 adults on warfarin therapy and found to be adequate in terms of accuracy, although the test strip error rate was found to be high.[32]

No studies have as yet been published which evaluate the use of POC INR monitors in a paediatric setting in South Africa. Although the absolute number of paediatric patients on long-term warfarin therapy is far less than that of adults, the number of children on warfarin therapy is increasing. A study evaluating the validity of POC INR monitors in the South African paediatric setting would be relevant considering the large number of our paediatric patients who live in remote areas as well as the inherent difficulties with obtaining regular INR samples by phlebotomy in the paediatric group. A POC INR monitor validated for use in South African children would contribute to our knowledge of therapeutic monitoring which reduces the financial cost of travelling far distances for centralized INR laboratories (thereby reducing the cost to the lab as well), as well as the cost of missed school days and workdays. POC INR monitors would also allow more frequent testing in an age group in which warfarin has inherently variable pharmacokinetics.

Validation Methodology

Two main methodological differences exist in comparing the POC INR devices to lab INR measurements. One technique uses whole blood for testing with the POC INR monitor

(obtained while doing phlebotomy) while the other uses a capillary sample (obtained by fingerprick).

Clinically relevant agreement between INR pairs has previously been determined as[33]:

1) Both INR values are within the therapeutic range, or
2) Both values are above or below the therapeutic range, or
3) Only one value is within the therapeutic range, yet the pair are within 0.4 units of each other

The POC INR is collected according to standard technique (as prescribed by the manufacturer of the POC INR device) by a trained phlebotomist, using a single fingerprick (with a lancet) and collecting the capillary sample on a device-specific test strip. The POC INR result is obtained within 1 -2 minutes, depending on the device used. This is followed sequentially by collection of the standard laboratory INR sample as a venous blood sample drawn into a 3.2% citrate tube. The laboratory INR specimen is delivered to a central laboratory for analysis using standard operating procedures including quality control measures. [1,4] Ideally, the paired samples are collected within 1 hour of each other and the laboratory INR sample is delivered to the lab within 30 mins of collection. Some studies report collecting the POC INR result on the same day as the laboratory INR was collected.[3]

Bauman at al found that the CoaguChek XS INR measurements were accurate compared with laboratory INR measurements when venous whole blood was used on the POC device. Two separate pairs of readings were obtained from 62 children. Bland-Altman's 95% limits of agreement were 0.11 (-0.20; 0.42) and 0.13 (-0.22; 0.48) at the two time points, respectively.[34] The accuracy of the POC monitor using capillary blood was evaluated by Karon et al when they compared the accuracy of capillary whole blood INR on several different devices including the CoaguChek XS.[35] They found more than 90% of results on the CoaguChek XS were within 0.4 INR units of the reference laboratory method.

In reporting and comparison of POC INR and laboratory results, agreement between the results is evaluated using standard difference plots. The average and limit of agreement between the two methods is often demonstrated in the Bland-Altman difference plot, reported with 95% limits of agreement.[35] Some studies report the Lin’s concordance correlation coefficient

(CCC) to assess the agreement between the POC INR value and the laboratory INR value, as described above.

Mission® PT/INR monitor from Acon Labs

In this feasibility study, we used the Mission® PT/INR monitor from Acon laboratories (San Diego, USA) which was released for use in South Africa in 2016. The battery- or AC power-operated handheld device is marketed as suitable for use by medical professionals and for home testing.

It uses individually packaged, uniquely calibrated test strips which do not require refrigeration and have a shelf life of 2 years. The strips are impregnated with recombinant human thromboplastin with an international sensitivity index (ISI) of 1.0. Specific instructions are included on optimal conditions for obtaining the fingerprick sample to ensure an accurate result. After depositing a single drop of capillary blood on the test strip (or 15 microlitres of venous whole blood) it reports PT and INR results within 2 minutes and can report INR results between 0.7 and 7.0. Clot detection is by optical fluorescence. No result is displayed if internal quality control conditions are not met or if an inadequate volume of capillary blood is deposited on the strip.

Validation studies have been performed on adult patients in the Unites States. The Clinical Comparison report published by Acon Laboratories (San Diego, USA) in 2016, reported on the results of paired POC INR- laboratory INR values in 219 volunteer adult subjects (180 on long-term oral anticoagulant therapy) across four different clinical sites. The accuracy-performance component of the study found that the POC INR results met overall acceptance criteria for capillary blood samples at all four sites. The precision study found that acceptance criteria were met at only three of the sites.

The Mission® PT/INR device has been validated in a tertiary hospital outpatient adult setting in Johannesburg, South Africa. In a study by Louw et al, INR measurement was obtained by POC INR monitor and measured by standard laboratory analyser (STAGO STA-R Max laboratory analyser) in 329 adult patients on long-term warfarin therapy.[36] The study found the Mission PT/INR device to be accurate and showed for expanded and narrow clinical agreement across a range of INR values (1.2-6.0). A deviance between values greater than 4.5

was not demonstrated. The results obtained by the Mission PT/INR device were also shown to be reproducible. The authors recommended that POC INR devices be validated individually in the context that they are to be used and that clinical implementation will require guidelines to guide as to which results need repetition or formal laboratory testing.

Conclusion

POC INR monitors have been shown to be accurate in children in comparison to standard laboratory INR measurement within a narrow range of values, although outside of this range values are less predictable. However, there are no high-quality studies comparing the rate of complications in those using POC INR monitors to those monitored with laboratory INR measurement. This is owing mainly to methodological difficulties in study designs in children.

There have been no studies validating the accuracy of POC INR monitors in South African children, a group who in particular would benefit from this technology. A validated instrument for POC INR testing in the paediatric population would assist in reducing time and costs to both patient and hospital, as well as ensuring effective and acceptable health care. Based on the needs of a growing number of our patients at RCWMCH, we undertook a validation study of the Mission PT/INR monitor in children presenting for INR testing at our institution. This study aimed to determine the accuracy of the portable POC INR monitor in comparison to the current standard of care laboratory measurement of the INR value, in the unique setting of Red Cross War Memorial Children's Hospital (RCWMCH), a tertiary paediatric facility.

In addition, we described a number of other secondary variables, including patient demographics and disease profile, and compared logistical parameters such as time of sampling and time of result availability to help make inferences about costs incurred for patients, their families and the health system.

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CHAPTER 2:

PUBLICATION-READY MANUSCRIPT

(as per specifications for the South African Medical Journal - SAMJ)

International Normalised Ratio Monitoring in Children: Comparing the accuracy of portable point-of-care monitors to standard of care laboratory monitoring at Red Cross War Memorial Children's Hospital, South Africa - a feasibility study

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Background. There is an increasing trend in the use of long-term oral anticoagulation therapy in children. Monitoring the international normalised ratio (INR) is an integral part in management of these patients, but standard laboratory testing of the INR presents challenges in this age group. Point-of-care INR monitors such as the Mission® PT/INR monitor provide advantages in efficiency and accessibility but have not been evaluated for accuracy in the South African paediatric setting.
Objectives. This is a feasibility study with the aim to evaluate the accuracy of the Mission® PT/INR Monitor in comparison to standard laboratory INR measurement, in children presenting for INR testing.
Methods. We compared the accuracy of the Mission® PT/INR monitor to the Sysmex Cs-2100i laboratory analyser in 37 children aged between 1 year and 17 years, who presented for INR testing. The sample size was limited due to time constraints. 40 paired POC INR and laboratory INR values were obtained.
Results. The majority of participants in the study were outpatients (62%) and required INR testing as part of screening in non-cardiac disease (81%) - the majority had chronic liver disease, and a minority were on warfarin therapy (13.5%). The mean INR value on the Mission® PT/INR was 1.49 (standard deviation (SD) 0.73) and was comparable to the Sysmex Cs-2100i (mean INR value 1.39 with SD 0.69). The Bland-Altman difference plot revealed good agreement. Bias between the two methods was 0.13 (SD 0.23). In total, 92.5% of POC INR values were within 0.5 units of laboratory INR value.
Conclusion. The Mission® PT/INR point-of-care monitor has a clinically acceptable level of accuracy in children when compared with laboratory INR measurement, but larger studies are needed in the paediatric setting to evaluate patient safety and clinical outcomes. There is a need for implementing POC INR monitoring in outpatient settings but this practice will require robust assessment of infrastructure and quality control before application.

There are a growing number of children requiring long-term oral anticoagulant therapy, a trend which is largely the result of advances in paediatric heart surgery and the use of life-saving therapies, including extracorporeal membrane oxygenation,

prosthetic heart valves and central venous access devices. The most commonly used oral anticoagulant in children remains the Vitamin K antagonist, warfarin. [1,2] Table 1 shows common indications for long-term oral anticoagulant therapy in children.

Warfarin has a narrow therapeutic index and is sensitive to various interactions with disease states, drugs and foods. Furthermore, genetic polymorphisms in the clotting pathways also affect the metabolism of warfarin. As a result, children on long term warfarin therapy require regular monitoring of the International Normalised Ratio (INR) to ensure that it remains within a narrow therapeutic range. For most indications the target range is 2.0-3.0, while for children with mechanical heart valves the target range is 2.5-3.5.[3] Regular phlebotomy to allow for INR measurement at standard laboratory analysers poses a challenge in the paediatric population and is compounded by inherently difficult venous access, in addition to the relatively large volume of blood required to perform the test. The frequent non-availability of paediatric drug formulations further complicates monitoring and reduces the predictability of regular dosing.[4]

Point-of-care (POC) INR measurement devices have been developed as a suitable alternative to standard laboratory-based testing, and in adult populations have been shown to be accurate in comparison to standard laboratory INR testing and improve clinical management and patient-reported quality of life.[5,6] Further abroad, these devices have also been validated for use in and have been found to be accurate and reliable for "patient self-testing" at home, with telephonic guidance from a health provider, as well as for "patient self-management" according to a standardized dosing nomogram. POC devices are already in use for paediatric home-based self-management in Europe and Australia with patients describing higher quality of life and satisfaction with therapy.[6] Previously validated POC INR devices were shown to be accurate within a narrow range but showed greater deviations from laboratory INR values above 4.5.[7,8]

POC INR devices have as yet not been evaluated for use in the South African paediatric setting, where its advantages may be especially relevant as many patients live in rural or remote locations and are required to travel great distances in order to have centralized INR testing. The Red Cross War Memorial Children's Hospital (RCWMCH) in Cape Town, South Africa provides services to children on long-term warfarin therapy, not only from the Cape Town Metropole but from across the Western Cape and neighbouring provinces. Some of these patients travel from far with paid-for transport to have their INR tested at the central laboratory and to be evaluated by clinicians. The advantages of using POC INR testing in children include a smaller blood volume required for testing (15 microlitres obtained by finger-prick), smaller turnaround time for results, reduced need for taking time out of school or time off work, reduced cost of travelling and reduced cost to central laboratories for testing formal INRs.

Table 1. Common indications for oral anticoagulant therapy in children

Cardiac	Non-cardiac
Prophylaxis after cardiac surgery	Primary Pulmonary Hypertension
- Fontan surgery, Blalock-Taussig Shunt	Acute arterial stroke
Mechanical prosthetic valves	Deep venous thrombosis
Kawasaki Disease with large aneurysms	Anti-phospholipid syndrome
Dilated cardiomyopathy with severe left ventricular dysfunction	
Ventricular assist devices	

There a numerous POC devices available, and the Mission® PT/INR device (Acon Laboratories, San Diego, USA) has been evaluated in the South African adult outpatient setting.[9] This portable device was released in South Africa in 2016 and uses individually packaged, uniquely calibrated test strips which do not require refrigeration and have a shelf life of 2 years. Specific instructions are included on optimal conditions for obtaining the fingerprick sample to ensure accurate results.

The aim of this study was to evaluate the Mission® PT/INR POC INR testing device for accuracy in a South African tertiary paediatric setting at RCWMCH. In addition, we described secondary variables, including patient demographics and disease profile, and compared logistical parameters such as time of sampling and time of result availability to help make inferences about costs incurred for patients, their families and the health system.

This report was structured according to the guidelines in the STARD checklist (Standards for Reporting Diagnostic accuracy studies), and all aspects of those guidelines have been included herein.

Methods

Study design and participants

The study was performed as an observational descriptive study based at RCWMCH, a tertiary paediatric facility in Cape Town, South Africa. It served as a feasibility study to lay the groundwork for future data collection. Eligible participants included all children aged between 12 months and 18 years of age who presented at the facility for INR testing, regardless of the indication or diagnosis. In order to be eligible for enrolment, participants had to be accompanied by a consenting primary caregiver. Both inpatients and outpatients were eligible and blood samples were collected at different sites in the hospital including the National Health Laboratory Service (NHLS) phlebotomy area, inpatient wards and outpatient clinics. Very young children (under 12 months of age) and critically ill children (located in the Medical Emergencies Unit or Paediatric Intensive Care Unit) were excluded from enrolment. The primary care giver participants received a participant-information sheet in the language of their choice (English, Afrikaans or isiXhosa), and gave voluntary informed consent. Assent was obtained in addition from children aged 5 years or older. Children who refused assent were not included in the study - there was one such case (in a child older than 7 years of age).

The sample size of paired samples was calculated based on interclass correlation of 5% and confidence interval of less than 5% - this value was calculated as n=138 paired tests. Due to time constraints, only a limited sample number of paired samples were obtained. 37 eligible children were enrolled with 40 paired POC INR and standard laboratory INR measurements obtained. Repeat sampling on the same patient was allowed where repeat INR measurements were ordered by the managing clinician.

Ethics approval was obtained from the Human Research Ethics Committee (HREC) of the University of Cape Town (HREC reference no. 730/2018).

Study protocol

Blood samples for INR analysis were obtained consecutively by venepuncture (by a trained phlebotomist or by hospital medical staff) for collection in citrated tubes (1.8 ml BD Vacutainer from BD-Plymouth, PL6 7BP, UK - containing 0.2 mL 3.2% sodium citrate) for measurement on the Sysmex CS-2100i (Sysmex, Kobe, Japan) coagulation analyser in the laboratory and then by fingerprick (done by the investigator) for measurement on the Mission® PT/INR device. All venous blood INRs were processed at the laboratory within 5 hours of collection.

The venous INR samples were analysed on the Sysmex CS-2100i coagulation analyser using standard operating procedures including the performance of internal quality control material. This

analyser system uses Thromborel®S (Siemens Healthcare diagnostics, Tarrytown, USA) as a reagent and employs a photo-optic method of clot detection, with multiwavelength scanning to correct for samples affected by haemolysis, icterus or lipaemia which may interfere with the assay.

All Mission® PT/INR values were obtained by the investigator who had training in appropriate use of the device according to the manufacturer's guidelines. This device and associated supplies were provided by the regional Acon representative. Capillary blood (around 10 - 30 microlitres) was obtained by a fingerprick and applied to test strips and tested on the Mission® PT/INR device. The strips are impregnated with recombinant human thromboplastin with an international sensitivity index (ISI) of 1.0. After depositing a single drop of capillary blood on the test strip it reports PT and INR results within 2 minutes and can report INR results between 0.7 and 7.0. Clot detection is by optical fluorescence. No result is displayed if internal quality control conditions are not met or if an inadequate volume of capillary blood is deposited on the strip.

Main outcome measures and method comparison

Primary outcome values that were measured were the values of paired POC and laboratory INR values. The INR results obtained for the two methods were compared to establish accuracy of the POC INR device. Where participants were on warfarin therapy, their doses were adjusted (by the primary managing clinician) according to the standard laboratory INR result. We recorded the times of either sample collection, time of authorization and time of result availability, as well as the location of sample collection. Furthermore, we recorded secondary variables such as patient demographics and disease profile (as they related to the indication for INR sampling), and details of current anti-coagulation therapy.

Data management and statistical analysis

Participants were assigned a sequential study number and data were initially captured anonymously on hard copy and then transferred to an electronic database for storage and maintenance (RedCap® database). Results were then collated on a spreadsheet and graphically summarised using standard descriptive statistical techniques.

We expressed continuous data variables as mean ±SD, percentage or coefficient of variation, as appropriate. A Bland-Altman plot to assess the magnitude of agreement was obtained between the two methods. A p-value of 0.05 was considered significant. Statistical analyses were performed using Stata 15.1 (Statacorp®).

We used the Wilcoxon signed-rank test to compare paired INR values, and Spearman's rank correlation to correlate the results from the two methods. Finally, the accuracy of POC values was determined by comparison to the INR values from the laboratory method using linear regression analysis.

Results

Study Population

Thirty-seven patients were enrolled into the study, with forty paired POC INR and laboratory INR values. Therefore, three patients had a second INR taken during the course of the study. Table 2 shows the demographic profile of the study sample.

Two thirds of the study sample were males, with a spread across the age ranges, although the majority were older than 7 years of age and able to provide written assent for participation in the study. Most were outpatients at the time of testing.

Although the majority of participants hailed from the Cape Town Metropole, there were a significant number who resided outside of Cape Town and even from outside the province. Although the

sites of sample collection tended to be in an outpatient setting, not all samples were collected in the setting that reflected the hospital admission status of the participant.

Table 3 summarises the disease profile of the participants in the study sample. The minority of participants had their INRs tested for primary cardiac indications (19% vs 81%). Most of those were known cardiac patients, more than half having had cardiac surgery. Two participants were newly diagnosed with dilated cardiomyopathy (DCMO) and one participant with an unoperated complex cardiac lesion had INR testing as a screening measure prior to a cardiac catheterisation procedure.

Non-cardiac indications for INR testing predominated in the study sample. The vast majority of these patients had liver disease as the primary indication for INR testing, most of whom had chronic liver disease related to biliary atresia. Only one patient had underlying venous thromboembolism as the primary indication for INR testing. The remainder of the participants had INR testing as a screening measure - ten had INR testing to exclude a bleeding disorder (recurrent epistaxis, easy bruising, haematuria, family history of bleeding disorder, acute pancreatitis with DIC), two patients known with cystic fibrosis had INR testing as part of a screen for liver disease, one had routine INR screening pre-procedure, and one had INR testing after ingestion of a toxin with anti-coagulant properties.

The minority of participants had comorbidities that were not related to the primary indication for INR testing. There were no HIV positive patients and only one patient had confirmed pulmonary tuberculosis. The remaining participants had systemic disorders including endocrine abnormalities or immunologic diseases.

Table 2. Demographic profile of study sample

Total number of participants n=37 N (%)	N (%)
Gender	
Male	23 (62)
Female	14 (38)
Age (years, months)	
Youngest	1y 1m
Oldest	17y
Mean	8y
< 5 years	10 (27)
5 - 6 years	5 (13.5)
>7 years	22 (59.4)
Hospital admission status	
Inpatient	14 (38)
Outpatient	23 (62)
Primary Place of Residence	
Cape Town Metropole	26 (70)
Western Cape (other than Cape Town)	7 (19)
Not from Western Cape	4 (11)
Place of Sample Collection	
Outpatient clinic	4 (11)
Inpatient Wards	15 (40)
Ambulatory Medicine department	3 (8)
Laboratory phlebotomy department	15 (40)

Profile of anticoagulant therapy

Five patients (13.5%) were on anticoagulant therapy including four on warfarin therapy and a fifth on aspirin. The dosing schedules for the participants on warfarin varied. Four of these participants were on 2,5 milligrams doses, each at varying weekly frequencies - varying from 3 times per week to 7 times per week. One participant was on 2.0 milligrams of warfarin 7 times per week. Warfarin was dispensed as 5 mg tablets which patients were instructed (by the pharmacy team) to disperse in a measured volume of water and then to draw up and administer the correct dose.

Details of sample collection

All laboratory INR samples were received by the laboratory on the same day as sample

collection - the average time to receipt by the laboratory was 32 minutes with a minimum time to receipt 0 mins while the maximum time to receipt was 4 hours 8 mins (IQR: 8 - 46 minutes). For one sample there was no time of collection available. The average time to INR result authorisation after receipt by the laboratory was 1 hour and 33 minutes (minimum 26 minutes, maximum 2 hours 34 minutes). All POC INR samples were obtained within 5 hours of laboratory INR sampling. The average time delay between POC INR and laboratory INR sampling was 1 hour 13 mins (min 6 minutes, maximum 4 hours 33 minutes). There was no time of collection available for 1 laboratory sample. The average time to POC INR result on the Mission® PT/INR device was 55 seconds.

Table 3. Disease profile of study sample

Total number of participants n=37	N (%)
Primary indication for INR testing	
CARDIAC	7 (19)
Fontan/Glenn circulation	1 (2.7)
Dilated cardiomyopathy	2 (5.4)
Prosthetic Valve	3 (8.1)
Kawasaki Disease	0
Primary Pulmonary Hypertension	0
Other	1 (2.7)
Known cardiac patient?	5 (13.5)
NON-CARDIAC	30 (81)
Liver Disease	13 (35.1)
Renal Disease	2 (5.4)
Venous Thromboembolism	1 (2.7)
Arterial Thromboembolism	0
Other	14 (37.8)
Comorbid illnesses	6 (16.2)
HIV	0
TB	1 (2.7)
Renal	0
Liver disease	0
Malignancy	1 (2.7)
Haematological	0
Other	4 (10.8)

Method comparison analysis

Table 4 summarises the comparison of the Mission® PT/INR and laboratory INR results.

The mean INR values for the Mission® PT/INR and the laboratory method compared favourably with means of 1.49 (SD 0.73) and 1.39 (SD 0.69) respectively (Table 4) - this represents a slight overestimation of INR values by the Mission® PT/INR device. Non-parametric tests showed that this slight overestimation was statistically significant (p-value 0.0012). 92.5 % of INR readings INR results on the POC INR device were within 0.5 units of the laboratory value.

The limit of agreement between the two methods of INR measurement are represented in the Bland-Altman difference plot (Figure 1) - this revealed good agreement with mean difference of 0.13 (-0.33; 0.58). Only two values were outside the 95% limits of agreement.

Discussion

In this feasibility study we sought to compare the accuracy of the Mission® PT/INR device to standard laboratory INR measurement, as well as describe the characteristics of the population of children who require INR monitoring at RCWMCH. Although the study sample was small, comparison of the accuracy of the Mission® PT/INR to laboratory INR testing showed good agreement over a wide range of INR values. This is in keeping with previous studies on the device in adults.[9]

We found that the majority of the children who required INR testing required INR testing for screening purposes in non-cardiac related illness, as opposed to monitoring of oral anticoagulation therapy. This is not unexpected as the absolute number of children under the age of 18 on long term oral anticoagulation is much

lower than the number of adult patients. The indications were varied but patients with chronic liver disease made up the majority.

The majority of patients requiring INR testing were outpatients and a significant proportion of these were from outside the Cape Town metropole. These findings are testament to the possible role that POC INR testing could play in an outpatient setting. A validated POC INR device could be used in peripheral clinic settings with the assistance of a health professional (such as a nurse or community doctor) and therefore save much in the way of patient and health service burden and finances. Such an endeavor will require further validation of individual devices at these settings with adequate training of both health care provider and patient to ensure quality assurance. Training protocols and training programmes have been developed by consensus recommendation and are already employed in paediatric communities in Europe and Australia.[6]

A comparison of the turnaround times to results for the two methods demonstrated the benefit that a rapid, real time INR measurement device would have for patients. In our setting, many travel from outside the metropole and wait for hours in busy outpatient units and day wards for their INR result so that appropriate dosage adjustment to warfarin therapy can be made. This time-consuming exercise presents a cost to patients financially in terms of workhours lost, as well as time out of school, and is a burden to busy central laboratories. Delays in time to obtaining the laboratory INR result is further complicated by delays in sending collected specimens to the lab.

The sample size was too small to allow for a meaningful evaluation of device accuracy in the cohort of patients on oral anticoagulant therapy. Future evaluation of the accuracy of POC INR testing in the cardiac cohort of children will require a larger study sample and probably expansion of the study to other INR testing sites to ensure an adequate sample size for power analysis.

Table 4. Comparison of Mission PT/INR and laboratory

Parameter	Mission® PT/INR	Laboratory
All INR results, N (%)	40 (100.0)	40 (100.0)
Mean INR (SD)	1.49 (0.73)	1.39 (0.69)
Mean difference (SD)	0,13 (0,23)	
% within 0.5 units	92.5	
INR <1.0, n (%)	6 (15.0)	12 (30.0)
Mean INR (SD)	0,82 (0,10)	0,95 (0,05)
Mean difference (SD)	0,11 (0,19)	
INR 1.0-1.9, n (%)	27 (67.5)	22 (55.0)
Mean INR (SD)	1,29 (0,17)	1.20 (0,23)
Mean difference (SD)	0,12 (0,23)	
INR 2.0-2.9, n (%)	5 (12.5)	4 (10.0)
Mean INR (SD)	2.40 (0,26)	2.26 (0,19)
Mean difference (SD)	0,17 (0,21)	
INR 3.0-3.9, n (%)	1 (2.5)	1 (2.5)
Mean INR (SD)	3.80	3.17
Mean difference (SD)		
INR 4.0-4.9, n (%)	1 (2.5)	1 (2.5)
Mean INR (SD)	4.00	4.25
Mean difference (SD)		

The research was conducted as part of a master degree in medicine, and as such the sample size was subject to time limitations. Data were collected and analysed as a pilot study, with further data collection to be completed by the research team going forward. The small sample size limited our ability to demonstrate increased variability in the difference between methods at higher INR values, as has been reported in other devices.[7,8] We were not able to perform advanced statistical and linear regression calculations on the basis of our small sample size, and this analysis should be the subject of future studies which expand on the cohort size.

There were four instances of error messages produced by the device during

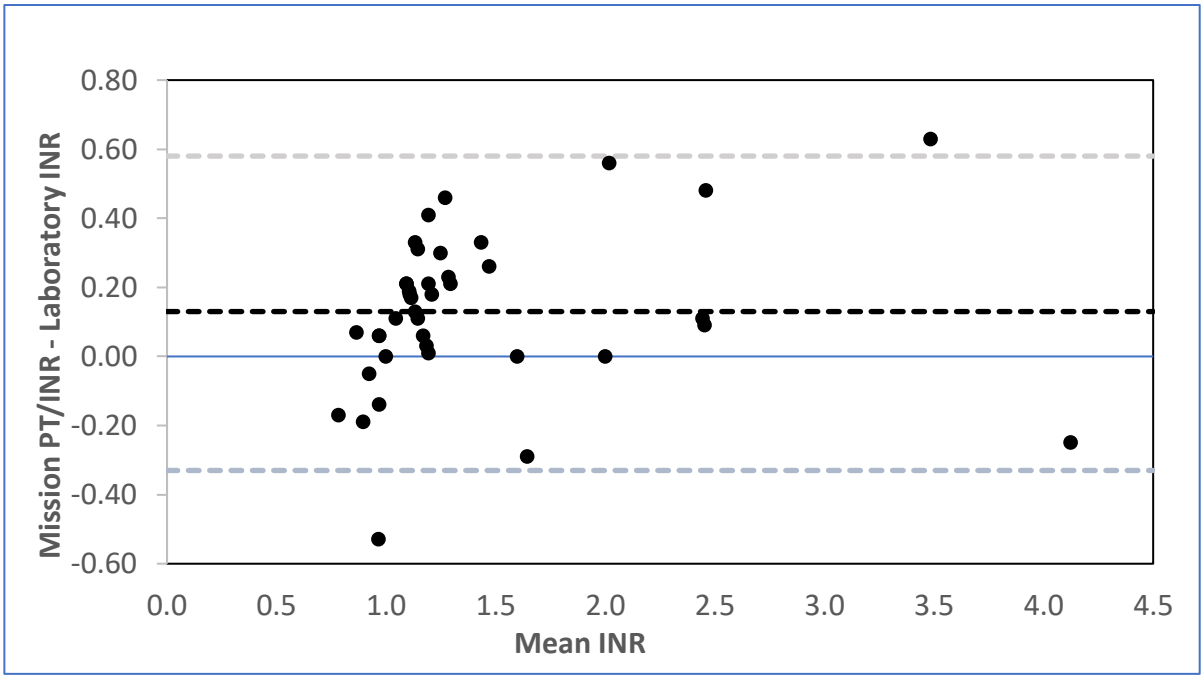

Figure 1. Bland-Altman analysis - 95% confidence intervals indicated (grey), bias (black). Markers show the difference between the two methods over the mean

fingerprick sampling. After discussion with the local distributor, these appeared to be related to the volume of blood sample collected or due to contamination of the blood sample (due to dirt on the subject's fingers). This occurrence highlighted the need for external quality control and support by the device manufacturers and distributors for future use of the Mission® PT/INR device.

This study is the first to evaluate the accuracy of POC INR devices in a paediatric population in South Africa. Although the study sample was small, it provided insight into the profile of children requiring INR testing a tertiary paediatric setting in South Africa. As such it has highlighted the need to extend this feasibility study further with collaborative data collection at multiple sites, either simultaneously or contiguously.

Conclusion

This feasibility study showed that the majority of patients at RCWMCH who required INR testing, did so for screening purposes in non-cardiac disease, with a minority of patients on long-term oral anticoagulation. The Mission® PT/INR has been shown to be accurate in a wide range of readings but follow-up research with a larger study sample is required to provide a power analysis of the accuracy of this device in a tertiary hospital paediatric setting. This study has laid the groundwork for such research.

Furthermore, this study has shown that this POC INR device may be implemented in an outpatient setting (including peripheral clinics) but that a detailed assessment of the infrastructure and capacity of such settings will be required to allow for appropriate and reliable quality control processes. Before implementation, staff will require training on optimal use and troubleshooting of the device, preferably according to a standard operating procedure, which should address how to proceed if INR readings fall outside of a prescribed range.

Acknowledgement. We thank the Paediatric Cardiac Research Unit at RCWMCH for providing stationery and printing facilities, as well as the laboratory and phlebotomy staff at NHLS for their assistance with identifying eligible participants.

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APPENDIX 1: RESEARCH PROTOCOL

International Normalised Ratio Monitoring in Children:

Comparing the accuracy of portable point-of-care monitors to standard of care laboratory monitoring at Red Cross War Memorial Children's Hospital

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This study will be conducted as a minor dissertation in the fulfilment of the degree Master of Medicine (Paediatrics) for Dr R Moore

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List of Abbreviations and Acronyms

INR:	International Normalised Ratio
PTT:	Partial Thromboplastin Time
POC:	Point of Care
RCWMCH:	Red Cross War Memorial Children's Hospital
SOC:	Standard of Care
TTR:	Time in therapeutic range
VKA:	Vitamin K antagonist

Background

The twenty-first century has seen an increase in the use of anticoagulant medication for both primary prophylaxis and treatment of thromboembolism in children. Advances in paediatric heart surgery and the use of life-saving therapies, including extracorporeal membrane oxygenation, prosthetic heart valves and central venous access devices have contributed to this trend. Medical practitioners are increasingly required to become familiar with treatment strategies and the monitoring of anticoagulant therapy.

There are limited randomized trials in children to guide the use of oral anticoagulant therapy, with the majority of recommendations being extrapolated from adult literature (Jain and Vaidyanathan 2010). Vitamin K antagonists (VKA, such as warfarin) are the most commonly used oral anti-coagulants in children. The most common indications for the use of these agents include prophylaxis after surgery for univentricular heart (Fontan procedure), mechanical prosthetic valves, large aneurysms following Kawasaki Disease, dilated cardiomyopathy with severely impaired left ventricular function and primary pulmonary hypertension (Jain and Vaidyanathan 2010).

Contraindications to warfarin therapy include hypersensitivity to warfarin, severe renal or liver impairment, severe hypertension, infective endocarditis, pericardial effusion, active ulceration and cerebral or dissecting aortic aneurysm (Vitale, De Feo et al. 1999).

VKAs, unfractionated and low molecular weight heparin are the anti-coagulant options most widely available, and each is associated with particular side effects. Data on the use of newer oral anticoagulants (e.g. direct thrombin inhibitors or Factor Xa inhibitors) in children are limited and are therefore less commonly used. VKAs remain the only oral agent available, with estimation of the International Normalised Ratio (INR) being a measure of treatment efficacy.

Maintaining a patient's INR within a designated therapeutic range is necessary to balance the risk of preventing thrombosis and embolization against the risk of bleeding and haemorrhage. Time in the therapeutic range (TTR) is used as a surrogate measure for the safety and efficacy of VKA therapy. This refers to the amount of time a patient's INR is within the designated target range (Jones, Newall et all 2011). This is crucial for minimising patient morbidity and mortality.

Low molecular weight heparin (LMWH), enoxaparin being the most widely studied, has several potential benefits in that it requires minimal monitoring, exhibits fewer drug interactions or dietary interference and has a reduced risk of osteoporosis and heparin-induced thrombocytopenia compared to other agents. The therapeutic ranges of optimised management have been derived from adult data, however and the rates of major bleeding are uncertain (Jones, Newall et al 2011; Monagle, Newall et al 2010). Major bleeding is defined as bleeding into a major organ or requiring blood transfusion. Various studies describe rates of haemorrhage between 0.2 - 12.2% (Monagle, Newall et al 2010).

Optimising the paediatric patient's clinical management provides additional challenges in that drug pharmacokinetics, illness as well as drug and food interactions, contribute to narrow therapeutic windows. The frequent non-availability of paediatric drug formulations further complicates monitoring and reduces predictability (Monagle, Newall et al 2010). Further challenges in therapeutic drug monitoring in children are posed by the regular requirement for phlebotomy so that standard laboratory-based investigations can be performed. This is compounded by inherently difficult venous access, in addition to relatively large volume of blood required to perform the test. Testing methodology is one of the variables that can lead to INR instability, with different testing methods using different methods for clot detection, different thromboplastin reagents and different sample types (Heneghan, Ward et al 2012).

Point-of-care (POC) coagulation measurement devices have been developed as a suitable alternative. A POC test is performed with a capillary sample placed on a strip, with a test result yielded in real time. This capillary sample is placed on the strip within 30 seconds to avoid potential interference with the INR value as a result of tissue-factor release or activation of the clotting cascade (Donaldson, Sullivan et al 2010). Plasma or anti-coagulated whole blood should not be used. POC devices provide rapid results using finger-prick capillary samples (therefore less painful), reduce anxiety for patients and parents, and encourage better patient adherence (Moon, Jeong et al 2010). POC devices are already in use for home-based self-management in Europe and Australia with patients describing higher quality of life and satisfaction with therapy (Bauman, Bruce et al 2013) Bauman et al have described home-based management and self-testing programs where TTR was 83% (Bauman, Bruce et al 2013).

Studies comparing the accuracy of POC devices to that of laboratory methods have been conducted. Collela et al found that the CoaguCheck XS (Roche Diagnostics) POC device underestimated the INR results by only 0.08u ($p<0.0001$) (Tomiyama 2012). This evidence is supported by other studies that have found a non-significant variability between POC devices and laboratory tests when the target range is 2-3, further validating the suitability of POC devices for outpatient/ home-based care. The authors advised caution when INR values are greater than 3.5. In such cases a confirmatory laboratory-based INR should be performed (Hill, Perreault et al 2007) (Kong, Lim 2008).

Lawrie et al however found that CoaguCheck XS INRs between 4.5 - 8 were comparable to laboratory INRs (Lawrie, Hills et al 2012). Furthermore, the CoaguCheck XS has been validated for use in 4-day old neonates and showed a Spearman correlation coefficient of 0.967 ($p<0.001$) (Ijima, Baba et al 2014). The use of POC devices has been extended to use in emergency units for adult patients with cerebrovascular disease to help guide treatment interventions (Nanduri, Tayal et al 2012) (Beynon, Erk et al 2015).

Purpose of the Study

There is a growing number of South African children requiring anticoagulation therapy. Current outpatient monitoring of oral anticoagulant therapy requires attendance at hospital outpatient clinics at regular intervals for standard laboratory-based INR testing.

For many of these patients this attendance is a distant and costly trip, and because of the inherent delay in treatment adjustments, these patients have to wait hours for test results. This results in parents frequently having to take a full day off from work and children missing an entire day of school. These factors often restrict monitoring to monthly intervals, limiting more frequent testing to ensure a greater TTR.

Meurer et al recommends that INR should initially be measured daily until stable and then gradually increasing intervals to weekly, biweekly and then monthly once therapeutic levels are achieved and are stable for at least eight weeks. The interval may need to be reduced in patients who are having difficulty in achieving therapeutic INR levels. In the South African setting such recommendations are difficult to follow for the abovementioned reasons. More frequent testing would be ideal to achieve consistent TTR.

A validated instrument for POC INR testing in the paediatric population would assist in reducing time and costs to both patient and hospital, as well as ensuring effective and acceptable health care (Gaw et al 2013). This study aims to validate a POC device against the laboratory-based gold standard in the unique setting of Red Cross War Memorial Children's Hospital (RCWMCH), a tertiary paediatric facility.

Research Question

Is the POC INR monitoring device system suitably accurate in comparison to standard of care (SOC) laboratory-based INR measurement for monitoring oral anticoagulation therapy in a paediatric population at a tertiary level paediatric hospital?

Aims and Objectives

Aims
This study aims to determine the accuracy of a portable POC INR monitoring device in comparison to the current SOC laboratory measurement method.

Objectives
1. To describe the accuracy of the INR POC monitoring device compared to the laboratory-based INR testing in the paediatric population.
2. To describe the time taken and costs incurred with the INR POC monitoring system compared to the laboratory testing method.

Methodology

Study site
The study will be conducted at Red Cross War Memorial Children's Hospital. RCWMCH is a tertiary-level hospital that serves as the referral hospital for the paediatric patient population of the Western Cape.

Study population
Children aged between 12 months and 18 years of age (≥12 months to <18 years) presenting to RCWMCH for INR testing will be approached for enrolment prior to INR testing.

Inclusion criteria

1. Patients ≥ 12 months to < 18 years of age
2. Participants will include those on oral anticoagulation for cardiac indications, as well as those on oral anticoagulation for other/ non-cardiac indications, regardless of primary managing service or diagnosis
3. Either admitted in hospital or attending the various outpatient clinics at RCWMCH.
4. Parent/ legal guardian willing and able to provide informed consent
5. Patient willing and able (appropriate for age) to assent to participation.

Exclusion criteria

1. Refusal/inability to consent/ assent
2. Age less than 12 months or 18 years of age or older
3. Critically ill children

Study Design

This study is a prospective observational study. All patients attending RCWMCH who require INR testing as per monitoring for oral anticoagulant therapy will be eligible for recruitment.

Recruitment and enrolment

Current treatment guidelines call for monthly INR testing in stable patients or more often if the INR value is <1.5 or >4. Research participants will be approached to join the study when they present for their laboratory-based INR testing at RCWMCH. This may occur in the hospital outpatient laboratory, in the various clinics within the hospital or in the inpatient setting. Typically, standard of care INR tests are performed by laboratory personnel using standard phlebotomy techniques to draw venous blood.

Laboratory personnel will be requested to contact the student investigator when standard of care INRs are to be performed. If patients/parents are willing to participate and provide informed consent (and assent of the child as appropriate), the student investigator will perform the finger prick and collect the sample to be tested with the POC INR device.

The POC sample will be collected within 15 mins of the collection of the venous blood sample. More than one sample may be used from the same patient. Clinical decisions will be based on the laboratory-based INR results.

Device Information

The Mission 1 PT/INR monitor manufactured by Acon will be used according to the manufacturer's guidelines (Appendix B). This device and associated supplies will be provided by the regional Acon representative.

Data Management and Statistical Analysis

Variables of Interest
Data that will be collected include:

- Date and Time of SOC INR sample collection
- Date and Time of POC INR sample collection
- Place/ venue of sample collection
- Gender of patient
- Date of birth of patient
- Place of Residence
- Last recorded weight and date weight taken
- Indication for INR monitoring
- Whether or not known CARDIAC patient (i.e. not first INR at RCWMCH)
- If not known to cardiac service, what is the diagnosis and what is the indication for INR monitoring? (text fields)
- Other chronic co-morbid illnesses
- Inpatient vs Outpatient status
- Type, dosage and duration of anticoagulants used in the last 30 days: dosing schedule
- NHLS laboratory INR value
- NHLS lab sample receipt time stamp
- NHLS lab sample result time stamp
- POC result value
- POC result date and time

Text field comments will include description of any adverse or unanticipated events that may impact data point values. Please refer to data collection form provided in appendices.

Sample Size Calculation

The sample size of paired samples was calculated based on interclass correlation of 5% and confidence interval of less than 5% - this value calculated as n=138 paired tests. We will express continuous data variables as mean ±SD, percentage or coefficient of variation, as appropriate.

Statistical Analysis Plan

We will use the Wilcoxon signed-rank test to compare paired INR values obtained using the POC INR and the laboratory method, and Spearman's rank correlation to correlate the results

from the two methods. Finally, the accuracy of POC values will be determined by comparison to the INR values from the laboratory method using linear regression analysis.

We will use a Bland-Altman plot to assess the magnitude of disagreement between the laboratory INRs and the INRs from the POC method. We will present values with 95% confidence intervals. A p-value of 0.05 will be considered significant. Statistical analysis will be performed using Stata 15.1 (Statacorp etc).

Description of Risks and Benefits

The Acon Mission 1 PT/INR monitor device is designed to use fresh capillary whole blood. The risks involved in the study are minimal and related to the finger-prick sample collection for the POC testing. The drop of blood must be a minimum of 15 microliters. Collection will cause minimal discomfort. The standard aseptic technique will be used. The additional amount of blood required for the POC testing is therefore minimal and is in line with WHO Blood for Research recommendations.

There will be no direct benefit to the children and families taking part in this study as standard laboratory-based results will be used for making clinical decisions. Patients and families will be informed of the POC test result. Whether the POC test result is abnormal or not, patients will be advised to wait for the laboratory result as per standard of care.

The potential benefit to the larger paediatric population would be the result of the recommendation to adopt the INR POC monitoring system – this system is hoped to reduce the amount of time and inconvenience required for children and their families who are undergoing INR testing and awaiting results-based treatment decisions.

Informed Consent Process

Approval for this study will be obtained from UCT Health Sciences Human Research Ethics Committee before any research activities commence. Informed consent will be obtained from a parent or legal guardian for participants younger than 18 years of age. Assent will be obtained from children between 7 and 17 years of age. Verbal assent will be obtained from children aged five to six years.

Patients and their families will be approached for participation while awaiting phlebotomy for the INR in the outpatient department laboratory waiting area. In the case of inpatients, participants and their families will be approached in the wards. The informed consent process will take place in the private examination rooms or at the patient's bedside.

Consent forms and patient information leaflets will be made available in English, isiXhosa and Afrikaans These consent and assent forms will have been approved by the Ethics Committee. The student investigator is fluent in English and Afrikaans. Hospital staff who are fluent in isiXhosa will be asked to translate and communicate the informed consent document to potential participants and their parents as necessary.

Reimbursement for Participation

There will be no reimbursement to participants or their families for participating in this study.

Privacy and Confidentiality

Signed consent, assent and data collection forms will be maintained in a locked office environment accessible only to the principal investigator and research support staff in the Children's Heart Disease Research Unit at RCWMCH.

The RedCap database system, supplied and supported by UCT, will be used to record and maintain the study data. Access to the system is secure and password protected. All enrolled participants will be assigned a study ID number by the RedCap software. A study ID number key will be maintained by the PI in a secure and confidential manner. This number will be used on the data collection form.

Patient birth date will be collected on the data collection form but will be converted to age at the time of collection for data export from RedCap for statistical analysis purposes, so that participant confidentiality will be protected.

Emergency care and insurance for research-related injuries

Patients are covered by the University of Cape Town no-fault insurance.

Budget

We will apply for Departmental MMed Funds to fund the study.

Estimated Project Budget - September 2018

Item	Cost	Quantity	Total
Printing - CRF, consent form/patient information leaflet and assent forms			R 1 500
Digital timer			R 250
Cotton and strapping tape for 138 patients			R 650
Consent/Assent translation services			R 1 500
Statistical Consultation and RedCAP database design			R 1 500
Misc Office supplies and sundries			R 600
Total			R 6 000

Distribution of findings

This research will be conducted as a minor dissertation in the fulfilment of the degree Master of Medicine (Paediatrics). The final manuscript should be suitable for publication in a peer-reviewed journal.

Information regarding the outcomes of the study will be shared with RCWMCH Department of Paediatrics, local secondary hospitals in the region (i.e. George Regional Hospital etc.) and with patients/ parents/ legal guardians whenever practical.

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APPENDIX 2: DATA CAPTURE FORM

Study ID _____

Hospital Record Number: _____

ELIGIBILITY

1. Does patient meet inclusion criteria?
   a. Yes
   b. No

Inclusion criteria

1. Age ≥ 12 months to < 18 years
2. Presents at RCWMCH for INR testing, regardless of indication or primary managing service
3. Inpatient or attending an outpatient clinic at RCWMCH
4. Parent/ legal guardian willing and able to provide informed consent
5. Patient willing and able (appropriate for age) to assent to participation

Exclusion criteria

6. Refusal/ inability to consent/ assent
7. Age less than 12 months or 18 years of age or older
8. Critically ill/ICU patient

INFORMED CONSENT/ ASSENT

1. Informed Consent given by parent/ legal guardian?
   a. Yes
   b. No

2. Assent given by child?
   a. Yes
   b. No
   c. Verbal (Ages 5 and 6 years)
   d. NA (Younger than 5 years)

DEMOGRAPHIC DATA

1. Gender
   - Male
   - Female

2. Date of Birth: _____
   (DD/MM/YYYY)

3. Date of Enrolment: _____
   (DD/MM/YYYY)

4. Age in months (auto-calculated): _____ (MMM)

5. Hospital admission status at time of INR testing
   - Inpatient
   - Outpatient
   - Other
     If other, please describe. _____ (FREE TEXT)

6. Primary Place of Residence:
   - Cape Town Metropole
   - Western Cape (other than Cape Town Metropole)
   - Not from Western Cape

7. Place of Sample Collection
   - Outpatient Clinic
   - Inpatient Ward
   - Ambulatory Medicine department
   - Laboratory phlebotomy department
   - Other
     Specify Other: _____ (FREE TEXT)

8. Last recorded weight in kilograms: _____ (XXX.X)

9. Date of last recorded weight: _____ (DD/MM/YYYY)

DISEASE PROFILE/ INDICATION FOR INR TESTING

Primary indication for INR testing

CARDIAC

- Fontan/Glenn
- DCMO
- Prosthetic Valves
- Kawasaki Disease
- Primary Pulmonary Hypertension
- Other cardiac indication, please describe _____

NON-CARDIAC

- Liver disease
- Renal Disease
- Venous Thromboembolism
- Arterial Thromboembolism
- Other non-cardiac indication, describe_____

If CARDIAC indication, is participant an established cardiac patient? (Not first INR at RCWMCH)

- Yes
- No
- Not Cardiac indication

If NON-CARDIAC indication, diagnosis? _____ Free Text

Concurrent illnesses that are not part of primary indication for INR testing:

- HIV
- TB
- Renal
- Liver
- Cancer/Malignancy
- Haematological
- Other, describe concurrent illness
  _____ (FREE TEXT)

DETAILS OF ANTICOAGULANT THERAPY

Has participant received anticoagulant therapy in last 30 days?

- Yes
- No
- Unsure

If answered YES to above, type of Anticoagulants used in last 30 days: - May choose more than one

- Warfarin
- Aspirin
- Heparin
- Clexane
- Other, describe. _____ (FREE TEXT)

If Warfarin, Start Date (DD/MM/YYYY) _____DATE

End Date (enter 00 if still on warfarin) (DD/MM/YYYY) _____DATE

Warfarin Dose at time of sample collection (XX.XX) (in milligrams) _____NUMBER

If Aspirin, Start Date (DD/MM/YYYY) _____DATE

End Date (enter 00 if still on aspirin) (DD/MM/YYYY) _____DATE

Aspirin Dose (XX.XX) (in milligrams daily) _____NUMBER

If Heparin, Start Date (DD/MM/YYYY) _____DATE

Heparin End Date (enter 00 if still on heparin) (DD/MM/YYYY) _____DATE

Heparin Dose (XX.XXX) (International units) _____NUMBER

If Clexane, Start Date (DD/MM/YYYY) _____DATE

Clexane End Date (enter 00 if still on clexane) (DD/MM/YYYY) _____DATE

Clexane Dose (XX.XXX) (in milligrams) _____NUMBER

Other coagulant, please describe _____ (FREE TEXT))

Other Coagulant Start Date (DD/MM/YYYY) _____DATE

Other Coagulant End Date (DD/MM/YYYY) _____DATE

Other Coagulant Dose (XX.XX) _____NUMBER

Specify units _____ (FREE TEXT))

Dosing Schedule

- Sunday
- Monday
- Tuesday

- Wednesday
- Thursday
- Friday
- Saturday

Weekly frequency/count (auto-calculated) _____NUMBER (X.XX)

DETAILS OF SOC/ LABORATORY INR TEST

Date of SOC INR Collection: _____ (DD/MM/YYYY)

Time of SOC INR Collection: _____ (HH:MM)

Date of SOC sample receipt (DD/MM/YYYY) _____DATE

Time of SOC sample receipt _____TIME (HH:MM)

Time of SOC result authorization _____TIME (HH:MM)

SOC/ Laboratory INR test result _____NUMBER (XX.XX)

DETAILS OF POC INR TEST

Date of POC INR Collection: _____ (DD/MM/YYYY)

Time of POC INR Collection: _____ (HH:MM)

Time of POC INR result available _____ (HH:MM)

POC INR test result _____NUMBER (XX.XX)

ADVERSE EVENTS

Adverse event?

- Yes
- No

AE Description _____ (FREE TEXT)

OTHER COMMENTS

Other comments _____ (FREE TEXT)

APPENDIX 3: Participant information, consent and assent forms (English, Afrikaans, isiXhosa)

PARENT/GUARDIAN INFORMATION LEAFLET AND CONSENT FORM

TITLE OF THE RESEARCH PROJECT:
International Normalised Ratio Monitoring in Children: Comparing the accuracy of portable point-of-care monitors to standard of care laboratory monitoring at Red Cross War Memorial Children's Hospital

RESEARCHERS NAME(S):
Doctor Ryan Moore
Professor Liesl Zuhlke
Professor Rik de Decker

ADDRESS:
Red Cross War Memorial Children's Hospital, Klipfontein Road, Rondebosch
UCT Human Research Ethics Committee - Floor E53, Room 46, Old Main Building, GSH, Observatory, 7925

CONTACT NUMBERS:
Doctor Ryan Moore – 082 867 0176
Professor Liesl Zuhlke – 076 844 4074
Professor Rik de Decker – 073 217 6351
UCT Human Research Ethics Committee – 021 650 3002

We wish to invite your child to take part in a research project – we cannot include your child in a research study without your permission ("consent"). Please take some time to read this information, which will explain the details of this project. Please ask the study staff or doctor any questions about any part of this project that you do not fully understand. It is very important that you fully and clearly understand what this research is about and how your child could be involved.

Your child's participation is **entirely voluntary,** and you are free to say no. If you say no, this will not affect your child negatively in any way whatsoever. You are also free to withdraw your child from the study at any point, even if you do agree to take par nowt.

This study has been approved by the Human Research Ethics Committee at the University of Cape Town and will be conducted according to the ethical guidelines and principles of the international **Declaration of Helsinki** (2013), **South African Guidelines for Good Clinical Practice** and **Ethics in Health Research: Principles, Processes and Structures** (2015).

What is this research study all about?
Sometimes doctors need to test how well a patient's blood clots. When people cut themselves they normally get a scab, which stops the bleeding. This is called "clotting" of blood. Sometimes blood doesn't clot normally, and this can cause heavy bleeding, so it is important to test whether blood clots normally or not. To do this we usually need to take

some blood by putting a needle into a vein in the arm, drawing some blood and then sending it to the laboratory ("lab") for clotting tests called the International Normalised Ratio or INR.

We want to see if we can do the same INR test without sending blood away to the lab, and by just using a small spot of blood taken by pricking a finger. We want to see if the fingerprick test is as good as the lab test. The fingerprick test is used in other countries already but it is not used much in South Africa.

We will ask other children who are also getting the lab test, and who agree to take part in the study, to do the same fingerprick test. We need about 138 children to agree to be in this study to get enough results to see if the fingerprick test works as well as the lab test.

Participating in this study should take less than five minutes of you and your child's time. The research part of being in this study is pricking your child's finger to obtain a drop of blood to test on the new device. Your child will still have your blood drawn from a vein in his/her arm whether or not you allow your child to be in this study.

If you allow your child to be in this study, we will prick your child's finger with a tiny needle called a lancet. He/she will feel a quick pinch. After the fingerprick we will put on some cottonwool to stop any bleeding. The spot of blood from the fingerprick will be tested in a machine to get a blood clotting result.

Why have we asked your child to participate?
We are asking if you will allow your child to take part in our study, because his/her doctor has ordered for blood to be taken for lab tests of clotting – the INR test. We will also ask other children who are having the same tests if they will take part in the study.

What will happen to your child if he/she takes part?
The research part of being in this study is pricking your child's finger to obtain a drop of blood to test on the new device. Your child will still have blood drawn from a vein in his/her arm whether or not you allow your child to be in this study.

Will your child benefit from taking part in this research?
There will be no direct benefit to you or your child for participating in this study. We will not use the results of the fingerprick test to make any decisions about your child's care or any changes to his/her medication dose. We are just looking to see if the results we get from the POC machine are the same as the results we get from the laboratory results.

The POC device provides INR results within seconds and if this test proves to be as reliable as the laboratory-based test - that usually takes about two hours to get results - children in the future may have to spend less time at the clinic or hospital to get their INR tested.

Are there in risks involved in your child taking part in this research?
The risks to your child for being involved in the study are small and are related to the finger-prick sample collection for the POC testing. The drop of blood must be a minimum of 15 microliters – a small dot.

The finger prick will cause a little pain that will last for a very short time (seconds). We will clean the prick spot and use some cottonwool to stop any bleeding.

If you do not agree for your child to take part, what alternatives do they have?
You don't have to agree to allow your child to be in this study. Participation is completely voluntary. You can say no. If you chose not to allow your child to participate, there will be no impact to the medical care your child receives today or in the future.

Who will have access to your child's medical records?
Only the researchers and their study team will know your child is in the study. Instead of using your child's name, we will use a code so other people can't know the information was about your child. We might present the results of the study at a conference or publish them in a journal, but we would never use your child's name when we do this.

What will happen in the unlikely event of some form injury occurring as a direct result of your taking part in this research study?
It is very unlikely that your child will experience physical harm if you allow him/her to be in this study. If something bad does happen, then your child will be looked after by one of the doctors on the study team.

Will you or your child be paid to take part in this study and are there any costs involved?
You will not be paid for allowing your child to take part in the study. There will also be no costs involved for you or your child, if you do allow him/her to take part.

Is there anything else that you should know or do?
If we ask you to allow your child to provide another sample at another time, we will ask for your permission and consent again.

You can contact the Health Research Ethics Committee at tel 021 650 3002 if you have any concerns or complaints about the ethical conduct of this study

You will receive a copy of this information and consent form for your own records.

Declaration by participant

By signing below, I …….. **agree for my child** ……to take part in a research study entitled "International Normalised Ratio Monitoring in Children: Comparing the accuracy of portable point-of-care monitors to standard of care laboratory monitoring at Red Cross War Memorial Children's Hospital".

I declare that:

- I have read or had read to me this information and consent form and it is written in a language with which I am fluent and comfortable.

- I have had a chance to ask questions and all my questions have been adequately answered.
- I understand that my child's participation in this study is **voluntary** and I have not been pressurised for my child to take part.
- I may choose for my child to leave the study at any time and will not be penalised or prejudiced in any way.
- My child may be asked to leave the study before it has finished, if the study doctor or researcher feels it is in his/her best interests, or if we do not follow the study plan, as agreed to.

Signed at (*place*) ..... on (*date*) ……..……..

…… **……**

Signature of participant Signature of witness

Declaration by investigator

I *(name)* …… declare that:

- I explained the information in this document to ……..
- I encouraged him/her to ask questions and took adequate time to answer them.
- I am satisfied that he/she adequately understands all aspects of the research, as discussed above
- I did/did not use a interpreter. (*If a interpreter is used then the interpreter must sign the declaration below.*

Signed at (*place*) ..... on (*date*) ……..……..

…… **……**

Signature of investigator Signature of witness

Declaration by interpreter

I *(name)* …… declare that:

- I assisted the investigator (*name*) ……. to explain the information in this document to (*name of participant*) …….. using the language medium of Afrikaans/Xhosa/other.

- We encouraged him/her to ask questions and took adequate time to answer them.
- I conveyed a factually correct version of what was related to me.
- I am satisfied that the participant fully understands the content of this informed consent document and has had all his/her question satisfactorily answered.

Signed at (*place*) ..... on (*date*) ……..……..

…… **……**

Signature of interpreter Signature of witness

PARTICIPANT INFORMATION LEAFLET AND ASSENT FORM
(7-17 years of age)

TITLE OF THE RESEARCH PROJECT:
International Normalised Ratio Monitoring in Children: Comparing the accuracy of portable point-of-care monitors to standard of care laboratory monitoring at Red Cross War Memorial Children's Hospital

Monitoring Blood Clotting in Children: Comparing a machine for finger-pricking to the laboratory method of checking blood clotting

RESEARCHERS NAME(S):
Doctor Ryan Moore
Professor Liesl Zuhlke
Professor Rik de Dekker

ADDRESS:
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CONTACT NUMBERS:
Doctor Ryan Moore – 082 867 0176
Professor Liesl Zuhlke – 076 844 4074
Professor Rik de Dekker – 073 217 6351
UCT Human Research Ethics Committee – 021 650 3002

What is RESEARCH?
Research is something we do to find out about the way things (and people) work. We use research projects or studies to help us find out more about disease or illness. Research also helps us to find better ways of helping children who are sick.

What is this research project all about?
When people cut themselves they normally get a scab, which stops the bleeding. This is called "clotting" of blood. Sometimes blood doesn't clot normally and this can cause children to bleed a lot, so it is important to test whether blood clots normally or not. To do this we usually need to take some blood from you by putting a needle into a vein in your arm, drawing some blood and sending it to the laboratory ("lab") for clotting tests called the INR.

We want to see if we can do the same INR test without sending blood away to the lab, and by just using a small spot of blood taken by pricking a finger. We want to see if the fingerprick test is as good as the lab test. The fingerprick test is used in other countries already but it is not used much in South Africa.

Why have I been invited to take part in this research project?
We are asking if you will take part in our study, because your doctor has ordered for your blood to be taken for lab tests of clotting. We will also ask other children who are having the same tests if they will take part in the study.

Who is doing the research?
I am a doctor who helps look after sick children. I work at Red Cross Children's Hospital here in Cape Town. My boss is Professor Liesl Zuhlke who is a doctor who looks after children with heart problems.

What will happen to me in this study?
Your doctor has asked for a lab INR test to see how your blood clots. This is important, and we need to do it even if you say "no" to this study. If you say "yes" to taking part in this study, we would like to also do a fingerprick test for blood clotting so we can compare the results.

To do this we will prick your finger with a tiny needle called a lancet. You will feel a quick pinch. After the fingerprick we will put on some cottonwool to stop any bleeding. The spot of blood from the fingerprick will be tested in a machine to get a blood clotting result.

We will ask other children who are also getting the lab test, and who agree to take part in the study, to do the same fingerprick test. We will put together all the test results at the end and see if the fingerprick method is as good as the lab method.

Can anything bad happen to me?
Nothing bad will happen to you if you say "yes", except for the small finger prick, which may be a bit sore (but it will be very quick). If at any time you feel scared or uncomfortable you can tell us and you don't need to carry on with the test.

Can anything good happen to me?
If you say "yes" to the fingerprick test, it won't really help you now, but if we can show that this test is as good as the normal lab test it will help other children in the future; because the fingerprick test is easier, quicker, and not as painful as normal blood tests.

Will anyone know I am in the study?
No-one apart from the researchers will know you are in the study. Instead of using your name, we will use a code so other people can't know the information was about you. We might present the results of the study or publish them in a journal (a medical magazine), but we won't use your name ever when we do this.

Who can I talk to about the study?
If you have any questions, you can speak to the researcher who is doing the fingerprick test or you can phone any of the numbers given above.

What if I say "no"?

You do not need to take part in this research project, even if your parent/guardian says that you may. If you change your mind about taking part at any time during the research, you can tell your parent/ guardian who can let the researchers know. You will not get into trouble and it will not affect the care that your doctor is giving you.

Do you understand this research study and are you willing to take part in it?

YES	NO

Has the researcher answered all your questions?

YES	NO

Do you understand that you can pull out of the study at any time?

YES	NO

_____ _____

Signature of Child Date

OUERLIKE/ VOOG INLIGTINGSBLAADJIE EN VERGUNNINGSVORM

TITEL VAN DIE NAVORSINGSPROJEK:
"International Normalised Ratio" monitering in kinders: vergelykbaarheid van draagbare monitors na laboratoriummonitering by Rooikruis Oorlogsgedenk Kinderhospitaal.

NAME VAN NAVORSERS:
Dokter Ryan Moore
Professor Liesl Zuhlke
Professor Rik de Decker

ADRES:
Rooikruis Oorlogsgedenk Kinderhospitaal, Klipfonteinpad, Rondebosch
Universiteit van Kaapstad, Komitee vir Menslike Navorskingsetiek - Vloer E53, Kamer 46, Old Main Building, GSH, Observatory, 7925

KONTAKNOMMERS:
Dokter Ryan Moore – 082 867 0176
Professor Liesl Zuhlke – 076 844 4074
Professor Rik de Decker – 073 217 6351
Universiteit van Kaapstad, Komitee vir Menslike Navorskingsetiek – 021 650 3002

Ons will u uitnooi om aan 'n navorsingsprojek deel te neem - ons kan nie u kind insluit by die navorsingsprojek sonder u toestemming nie. Lees gerus die blad deur, hierin word die besonderhede van hierdie projek verduidelik. Vra asseblief die navorsingpersoneel of -dokter enige vrae wat u ten opsigte van die projek mag hê. Dit is baie belangrik dat u duidelik verstaan waaroor hierdie navorsing gaan en hoe u kind betrokke sal wees.

U kind se deelname is heeltemal vrywillig, en u mag weier om u kind te laat deelneem. As u weier om u kind te laat deelneem, sal u kind nie op enige manier negatief beïnvloed word nie. U is ook vry om u kind te onttrek op enige tydstip, selfs al het u oorspronklik toestemming gegee.

Hierdie studie is goedgekeur deur die Komitee vir Menslike Navorskingsetiek by die Universiteit van Kaapstad, en sal volgens die etiese riglyne en beginsels van die **Internasionale Verklaring van Helsinki (2013), Suid-Afrikaanse Riglyne vir Goeie Etiese Praktyk** en **Gesondheidsnarvorsing: Beginsels, Prosesse en Strukture (2015).**

Waaroor gaan die navorsing?
Dokters moet soms toets hoe goed 'n patient se bloed kan stol. As 'n men hul self sny, kry hul gewoonlik 'n skurfte, wat die bloeding laat stop. Die proses word "stolling" genoem. Soms kan 'n mens se bloed nie mooi stol om 'n skurfte te maak nie, en dit kan swaar bloeding veroorsaak, so dit is belangrik om te toets of die mens blood normaalweg kan stol of nie. Om dit te doen moet ons gewoonlik bloed neem deur om 'n naald in die arm te sit, die bloed trek en dan dit na 'n laboratorium te stuur vir stollingstoetse - die toets noem ons "International Normalised Ratio" of "INR".

Ons wil kyk of ons dieselfde INR-toets kan doen sonder om dit na die laboratorium te stuur, en net deur ‘n vingerprik ‘n klein bloedvlek te neem. Ons wil sien of die vingerprik toets net so goed soos die laboratoriumtoets is. Die vingerpriktoets word al in ander lande gebruik, maar dit word selde in Suid-Afrika gebruik.

Ons sal ander kinders wat ook die laboratoriumtoets kry vra om deel te neem in die studie, so- dat hulle ook die vingerpriktoets kan kry. Ons het ongeveer 138 kinders noding om by die studie in te stem, sodat ons kan sien of die vingerpriktoets net so goed soos die laboratoriumtoets werk.

Dit sal minder as vyf minute neem om aan hierdie studie deel te neem. Die navorsing deel van die studie vereis net ‘n prik op u kind se vinger om ‘n druppel bloed te kry sodat ons ‘n toets kan doen op die nuwe toestel. Bloed sal steeds van u kind se aar moet geneem word, al gee u toestemming of nie.

As u toelaat dat u kind aan hierdie studie deelneem sal ons u kind se vinger met ‘n klein naaldjie steek - ons noem die naaldjie ‘n “lanset”. Hy/ sy sal ‘n kleine knypie voel. Na die stekie sal ons ‘n stukkie watte by die vinger sit om die bloeding te stop. Die druppeltjie bloed sal dan op ‘n masjien geplaas word om ‘n bloedstollings resultaat te kry.

Waarom het ons u gevra om u kind te laat deelneem?
Ons vra of u u kind sal toelaat om aan ons studie deel te neem, want sy/ haar dokter het beveel dat u kind ‘n laboratoriumtoets vir bloedstolling kry - dit is die INR toets. Ons sal ook ander kinders vra wat ook die bloedstollingstoets kry om deel te neem.

Wat sal met u kind gebeur as hy/ sy deelneem?
Die navorsing deel van hierdie studie is om u kind se vinger te steek om ‘n druppel bloed te kry om op die nuwe toestel te toets. Bloed sal steeds van u kind se aar moet geneem word, al gee u toestemming of nie.

Sal u kind daarby baat vind om aan hierdie navorsing deel te neem?
Nie u of u kind sal direk voordeel kry uit hierdie studie nie. Ons sal nie die resultaat van die vingerpriktoets gebruik om besluite te neem oor sy/haar versorging nie, of om enige veranderinge aan sy/ haar medikasie te maak nie. Ons wil net kyk of die resultate van die nuwe toestel ooreenstem met die resultate van die laboratoriumtoets.

Die masjientjie verskaf INR-resultate binne sekondes en as hierdie toets blyk om so betroubaar te wees as die laboratoriumtoets (wat gewoonlik twee ure neem om resultate te verskaf), is dit moontlik dat in die toekoms kinders minder tyd by die kliniek of hospitaal hoef te spandeer om hul INR te laat toets.

Is daar risiko’s as my kind deelneem in die navorsing?
Die risiko vir u kind as gevolg van die studie in klein en is verband aan vingerpriktoets. Die bloed druppeltjie is baie klein, en is minstens 15 mikroliter - ‘n klein kolletjie.

Die vingerprik sal ‘n bietjie pyn veroorsaak wat ‘n baie kort tydjie sal duur (sekondes). Ons sal die vinger skoon eerste skoonmaak en ons sal watte gebruik om die bloeding te stop.

As u nie saamstem dat u kind deelneem nie, watter alternatiewe het u dan?
U hoef nie saam te stem dat u kind deelneem aan die studie nie. Deelname is heeltemal vrywillig - u kan nee sê as u verkies om nie u kind te laat deelneem nie, daar sal geen invloed op die mediese sorg van u kind vandag of in die toekoms wees nie.

Wie het toegang tot die mediese rekords van u kind?
Slegs die navorsers en hul span sal weet dat u kind aan die studie deelneem. In plaas van u kind se naam te gebruik, gebruik ons ‘n kode sodat ander mense nie weet van u kind se inligting nie. Ons sal moontlik die resultate van die navorsing op ‘n konferensie aanbied of dit publiseer in ‘n mediese joernaal, maar ons sal nooit u kind se naam gebruik nie.

Wat sal gebeur in die onwaarskynlike geval dat u kind beseer is as gevolg van die navorsing?
Dit is onwaarskynlik dat u kind skade sal ly as u toelaat dat hy/sy aan die studie deelneem. As daar iets ergs gebeur sal u kind gesorg word deur een van die dokters in die navorsingspan.

Sal u kind betaal word om aan die studie deel te neem en is daar kostes daaraan verbonde?
U sal nie betaal word om toestemming te gee dat u kind deelneem nie. Daar is ook nie koste verbonde aan die studie as u wel toestemming gee nie.

Is daar iets anders wat u moet weet of doen?
As ons u vra om toe te laat dat ons op ‘n ander tydstip weer ‘n vingerprik doen op u kind sal ons weer vir u toestemming vra.

U kan die Komitee vir Gesondheidsnavorsingsetiek skakel by tel 0216503002 indien u enige vrae of klagtes het teenoor die etiese gedrag van die studie.

U sal ‘n afskrif van hierdie inligting en toerstemmingsvorm vir u eie rekords ontvang.

Verklaring deur deelnemer

Deur hieronder te teken, gee ek …….. **toestemming dat my kind** ……mag deelneem aan die studie benoemd “International Normalised Ratio” monitering in kinders: vergelykbaarheid van draagbare monitors na laboratoriummonitering by Rooikruis Oorlogsgedenk Kinderhospitaal.

Ek verklaar dat:

- Ek die inligting- en toestemmingsvorm gelees het, of dit was aan my gelees, en dat dit in ‘n taal geskryf waarmee ek vlot en gemaklik is.
- Ek ‘n kans gehad het om vrae te stel en dat al my vrae voldoende beantwoord is.
- Ek verstaan dat my kind se deelname **vrywillig** is en dat ek onder geen druk geplaas is om my toestemming te gee nie.
- Ek mag verkies dat my kind of enige tydstip die studie verlaat en hy/sy sal nie gepenaliseer word of op enige manier benadeel word nie.

- My kind mag gevra word om die studie te verlaat voordat dit afgehandel is, as die navorser voel dat dit in sy/ haar beste belang is, of as die studie proses nie gevolg word nie, soos ooreengekom.

Geteken by *(plek)* ..... op (*datum*) ……..……..

…… **……**

Handtekening van deelnemer Handtekening van getuie

Verklaring deur ondersoeker

Ek *(naam)* ……..…… verklaar dat:

- Ek die inligting in die dokument aan …….. verduidelik het.
- Ek hom/ haar aangemoedig het om vrae te stel en voldoende tyd geneem het om dit te beantwoord.
- Ek is tevrede dat hy/ sy all aspekte van die navorsing voldoende verstaan, soos hierbo bespreek.
- Ek het/ het nie 'n tolk gebruik nie *(as 'n told gebruik work moet die tolk die verklaring onderteken).*

Geteken by *(plek)* ..... op (*datum*) ……..……..

…… **……**

Handtekening van navorser Handtekening van getuie

Verklaring deur tolk

Ek *(naam)* ……..…… verklaar dat:

- Ek die navorser (naam) ……. gehelp het om die inligting in die dokument aan (*naam van deelnemer*) …….. te verduidelik deur middel van die taal Afrikaans/Xhosa/ander te gebruik.
- Ek hom/ haar aangemoedig het om vrae te stel en voldoende tyd geneem het om dit te beantwoord.
- EK het die feitlike korrekte weergawe van die inligting oorgegee.
- Ek is tevrede dat die deelnemer die inhoud van hierdie toestemmings dokument ten volle begryp en dat al hy/ sy vrae voldoende beantwoord is.

Geteken by *(plek)* ..... op (*datum*) ……..……..

……	**……**
Handtekening van navorser	Handtekening van getuie

DEELNEMER INLIGTINGSBLADJIE EN INSTEMMINGSVORM
(7-17 jaar oud)

TITEL VAN DIE NAVORSINGSPROJEK:
"International Normalised Ratio" monitering in kinders: vergelykbaarheid van draagbare monitors na laboratoriummonitering by Rooikruis Oorlogsgedenk Kinderhospitaal.

Monitering van bloedstolling in kinders: vergelyking van 'n masjien vir vingerprik met die laboratorium metode.

NAME VAN NAVORSERS:
Dokter Ryan Moore
Professor Liesl Zuhlke
Professor Rik de Decker

ADRES:
Rooikruis Oorlogsgedenk Kinderhospitaal, Klipfonteinpad, Rondebosch
Universiteit van Kaapstad, Komitee vir Menslike Navorskingsetiek - Vloer E53, Kamer 46, Old Main Building, GSH, Observatory, 7925

KONTAKNOMMERS:
Dokter Ryan Moore – 082 867 0176
Professor Liesl Zuhlke – 076 844 4074
Professor Rik de Decker – 073 217 6351
Universiteit van Kaapstad, Komitee vir Menslike Navorskingsetiek – 021 650 3002

Wat is navorsing?
Navorsing is iets wat ons doen om uit te vind oor die manier waarop dinge (en mense) werk. Ons gebruik navorsingsprojekte of studies om ons te help om meer uit te vind oor siektes. Navorsing help ons ook om beter maniere te vind om siek mense te help.

Waaroor gaan hierdie navorsingsprojek?
As mense hulself sny, kry hulle gewoonlik 'n skurfte, wat die bloeding laat stop. Dit is "bloedstolling" van bloed genoem. Soms stol die bloed nie normaal nie, en dit kan veroorsaak dat kinders baie bloei, daarom is dit belangrik om te toets of bloed normaalweg stol of nie. Om dit te doen, moet ons gewoonlik 'n bloedmonster neem deur om 'n naald in die arm te sit om bloed van 'n aar te neem. Ons stuur dan die bloed na die laboratorium vir 'n bloedstollingstoets wat ons 'n "INR" noem.

Ons wil kyk of ons dieselfde INR-toets kan doen sonder om bloed na die laboratorium te stuur, en net deur 'n klein druppeltjie bloed te neem deur middel van 'n vingerprik. Ons wil sien of die vingerpriktoets net so goed soos die laboratoriumtoets is. Die vingerprik toets word al reeds in ander lande gebruik, maar nie in Suid-Afrika nie.

Waarom is ek uitgenooi om aan hierdie navorsingsprojek deel te neem?

Ons vra of u aan ons studie sal deelneem, want u dokter het beveel dat u ‘n laboratoriumtoets vir bloedstolling kry - dit is die INR toets. Ons sal ook ander kinders vra wat ook die bloedstollingstoets kry om deel te neem.

Wie doen die navorsing?
Ek is ‘n dokter wat met siek kinders werk. Ek werk by die Rooikruis-kinderhospitaal hier in Kaapstad. My baas is professor Liesl Zuhlke, ‘n dokter wat omsien na kinders met hartprobleme.

Wat sal met my in die studie gebeur?
U dokter het gevra vir ‘n laboratorium INR-toets om te sien hoe jou bloed stol. Dit is belangrik, en ons moet dit, selfs al sê u “nee” vir hierdie studie. As u “ja” sêom deel te neem wil ons ook ‘n vingerprik toets vir bloedstolling neem sodat ons die resultate vir albei toetse kan vergelyk.

Om dit te doen, sal ons u vinger steek met ‘n klein naald wat ons ‘n “lanset” noem. U sal ‘n vinnige knypie voel. Na die vingerprik gebruik ons ‘n stukkie watte om bloeding te voorkom. Die bloed druppeltjie van die vingerprik sal in ‘n masjien getoets word om bloedstolling resultaat te kry.

Ons sal ander kinders wat ook die laboratoriumtoets kry vra om deel te neem, om dieselfde vingerprik toets te kry. Ons sal al die toetsresultate aan die einde opstel en kyk of die vingerprik metode net so goed soos die laboratorium metode is.

Kan iets sleg met my gebeur?
Niks sleg kan met jou gebeur as jy “ja” sê nie, behalwe vir ‘n klein vingerprik wat ‘n bietjie seer kan wees, maar baie vinnig sal wees. As u op enige tydstip bang of ongemaklik voel, kan u ons sê en dan hoef ons nie met die vingerprik toets voort te gaan nie.

Kan iets goeds met my gebeur?
As u “ja” sê vir die vingerprik toets, sal dit nie onmiddellik vir u baat vind nie, maar as die studie kan wys dat die vingerprik toets net so goed soos die laboratorium toets is, dan kan ons kinders in die toekoms help; omdat die vingerprik toets makliker, vinniger en minder pynlik is as die laboratorium toets.

Sal enigiemand weet dat ek aan die studie deelneem?
Niemand anders as die navorsers sal weet dat u aan die studie deelneem nie. In plaas van u naam te neem, sal ons ‘n kode gebruik sodat ander mense nie kan weet dat die inligting aan u behoort nie. Ons mag dalk die studie se resultate op ‘n mediese joernaal of tydskrif publiseer, maar ons sal nooit u naam gebruik nie.

Met wie mag ek oor die studie praat?
As u vrae het, kan u met die navorser wat die vingerprik toets doen praat, of u kan enige van die bogenoemde nommers skakel.

Wat as ek “nee” sê?
U hoef nie aan die navorsingsprojek deel te neem nie, al sê u ouer/ voog dat jy mag. As u later besluit om nie deel te neem nie, kan u vir u ouer/ voog sê, sodat hulle vir die navorser kan

vertel. Jy sal nie in die moeilikheid beland nie, en die sal nie die versorging wat u dokter aan u gee beïnvloed nie.

Verstaan u hierdie navorsing en is u bereid om daaraan deel te neem?

JA NEE

Het die navorser al u vrae beantwoord?

JA NEE

Verstaan u dat u enige tyd by die studie kan onttrek?

JA NEE

_____ _____

Handtekening van kind Datum

IPHEPHA LENKCAZELO LOMZALI/LOMNAKEKELI NEFOMU YEMVUME YOMTHATHI NXAXHEBA

UMXHOLO WEPROJEKTHI YOPHANDO:
Umlinganiselo Oqhelekileyo Wehlabathi Ohlolayo Ebantwaneni: Uthelekisa ukuchana kweepoyinti ezibanjwayo ezinyamekelayo nezihlolayo elabhorathri e-Red Cross War Memorial Children's Hospital

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Sithanda ukumema umntwana wakho ukuba athathe inxaxheba kwiprojekthi yophando – asikwazi ukuquka umntwana wakho kuphando lophononongo ngaphandle kwemvume yakho ("nikela imvume"). Nceda uziphe ixesha lokufunda le nkcazelo, eza kuchaza iinkcukacha zale projekthi. Nceda ubuze abasebenzi okanye ugqirha wophononongo nayiphi na imibuzo ephathelele nayiphi na inxalenye yale projekthi ongayiqondi ngokupheleleyo. Kubalulekile ukuba uqonde ngokupheleleyo nangokucacileyo oko kuqulethwe lolu phando kunye nendlela umntwana wakho anokubandakanyeka ngayo.

Ukuthatha inxaxheba komntwana wakho **kokokuzithandela ngokupheleleyo,** yaye ukhululekile ukuthi hayi. Ukuba uthi hayi, oku akuzokuchaphazela umntwana wakho kakubi nangayiphi na indlela. Ukhululekile ukurhoxisa umntwana wakho kolu phononongo nangaliphi na ixesha, kwanokuba uyavuma ukuthatha inxaxheba ngoku.

Olu phononongo luye lwagunyaziswa yiKomiti Yabantu Yophando Yokuziphatha kwiYunivesithi yaseKapa yaye luza kuqhutywa ngokuphathelele indlela yemiyalelo nemigaqo yokuziphatha yehlabathi **Yokwazisa ye-Helsinki** (2013), **Imiyalelo YoMzantsi Afrika yoQheliselo Lweyeza Elungileyo** kunye **Nokuziphatha Kuphando Lwempilo: Imigaqo, Iinkqubo kunye Nobume** (2015).

Lungantoni olu phononongo?
Maxa wambi, oogqirha kufuneka bavavanye indlela igazi lesigulane eliba lihlwili ngayo. Xa abantu bezisika ngokuqhelekileyo bafumana uqweqwe, nto leyo enqanda ukopha. Oku kubizwa ngokuba "lihlwili" legazi. Maxa wambi, ngokuqhelekileyo igazi alibi lihlwili, yaye

oku kusenokubangela ukopha kakhulu, kubalulekile ukuvavanya enoba igazi liba lihlwili ngendlela eqhelekileyo okanye akunjalo. Ukuze wenze oku, ngokuqhelekileyo kufuneka sithathe igazi elithile ngokufaka inaliti kumthambo wengalo, sitsale igazi size emva koko silithumele elebhorathri ("lebhu") livavanyelwe ukuba lihlwili nto leyo ebizwa ngokuba nguMlinganiselo Oqhelekileyo Wehlabathi okanye i-INR.

Sifuna ukubona enoba singenza uvavanyo olufanayo lwe-INR ngaphandle kokuthumela igazi elebhu, yaye nangokusebenzisa nje ichaphaza legazi elithathwe ngokuhlaba umnwe. Sifuna ukubona enoba uvavanyo lokuhlaba umnwe lulungile kusini na njengovavanyo lwaselebhu. Uvavanyo lokuhlala umnwe sithetha nje luyasetyenziswa kwamanye amazwe kodwa alukasetyenziswa kakhulu eMzantsi Afrika.

Siza kucela abanye abantwana abafumana uvavanyo olufanayo lwaselebhu, yaye abaye bavuma ukuthatha inxaxheba kuphononongo, ukuze benze uvavanyo olufanayo lokuhlaba umnwe. Sifuna malunga nabantwana abali-138 abaza kuvuma ukuba kolu phononongo ukuze sifumane iziphumo ezaneleyo ukuba uvavanyo lokuhlaba umnwe luyasebenza ngokunjalo nangovavanyo lwaselebhu.

Ukuthatha inxaxheba kolu phononongo kufanele kuthathe ngaphantsi kwemizuzu emihlanu yexesha lakho kunye nelomntwana wakho. Inxalenye yophando yokuba kolu phononongo kukuhlaba umnwe womntwana wakho ukuze sifumane icontsi legazi silivavanye kwidivayisi entsha. Umntwana wakho sekunjalo uza kuba negazi elitsalwe kumthambo wengalo yakhe enoba uyamvumela okanye akumvumeli umntwana wakho ukuba abe kolu phononongo.

Ukuba uyamvumela umntwana wakho ukuba abe kolu phononongo, siza kuhlaba umnwe womntwana wakho ngenaliti encinane ebizwa ngokuba yi-lancet. Uza kuva ukuhlatywa okukhawulezileyo. Ngemva kokuhlatywa emnweni siza kubeka i-cottonwool ukuze sinqande nakuphi na ukopha. Ichaphaza legazi elisemnweni liza kuvavanywa kumatshini ukuze sifumane imiphumo yokuba lihlwili.

Kutheni siye sacela umntwana wakho ukuba abe nenxaxheba?
Siyabuza enoba uza kuvumela umntwana wakho abe nenxaxheba kuphononongo lwethu, kuba ugqirha wakhe uye wayalela ukuba igazi lithathwe ukuze liyovavanyelwa ihlwili elebhu – uvavanyo lwe-INR. Kwakhona, siza kucela abanye abantwana abaye baba novavanyo olufanayo enova baza kuthatha inxaxheba kusini na kuphononongo.

Kuza kwenzeka ntoni kumntwana wakho ukuba uthatha inxaxheba?
Inxalenye yophando yokuba kolu phononongo kukuhlaba umnwe womntwana wakho ukuze sifumane ichaphaza legazi eliza kuvavanywa kwidivayisi entsha. Sekunjalo umntwana wakho uza kutsalwa igazi emthanjeni wengalo yakhe enoba uyamvumela okanye akumvumeli umntwana wakho ukuba abe kolu phononongo.

Ngaba umntwana wakho uza kuzuza ngokuthatha inxaxheba kolu phononongo?
Ayikho inzuzo engqalileyo oza kuyifumana okanye umntwana wakho ngokuthatha inxaxheba kolu phononongo. Asiyi kuzisebenzisa iziphumo zovavanyo zokuhlatywa komnwe ukuze senze naziphi na izigqibo ngokuphathelele ukunyamekelwa komntwana wakho okanye naluphi na utshintsho kwithamo leyeza lakhe. Sifuna ukubona enoba imiphumo esiyifumanayo kumatshini we-POC iyafana neziphumo esizifumana kwiziphumo zaselebhu.

Idivayisi ye-POC inikela iziphumo ze-INR ngemizuzwa nje yaye ukuba olu vavanyo lungqina ukuba lunokuthenjwa njengovavanyo olwenziwe elebhu – ngokuqhelekileyo oko kuthatha malunga neeyure ezimbini ukuze kufunyanwe iziphumo – abantwana kwixesha elizayo basenokuchitha ixesha elincinane ekliniki okanye esibhedlele ukuze bafumane uvavanyo lwabo lwe-INR.

Ngaba ikho imingcipheko ebandakanyekileyo kumntwana wakho ngokuthatha inxaxheba kolu phononongo?
Imingcipheko kumntwana wakho ngokuthatha inxaxheba kuphononongo incinane yaye inxulumene nesampulu yokuhlatywa komnwe eqokelelelwe uvavanyo lwe-POC. Icontsi legazi limele libe ubuncinane ne-15 le-microliters – ichaphaza elincinane.

Ukuhlatywa emnweni kuza kubangela intlungu encinane eza kuthatha ixesha elifutshane (imizuzwana). Siza kuyicoca indawo ekuhlatywe kuyo size sisebenzise i-cottonwool ukuze sinqande nakuphi na ukopha.

Ukuba awuvumi ukuba umntwana wakho athathe inxaxheba, yeyiphi enye into abanayo?
Akunyanzelekanga uvume ukuze umntwana wakho abe kolu phononongo. Ukuthatha inxaxheba kokokuzithandela ngokupheleleyo. Usenokuthi hayi. Ukuba ukhetha ukungamvumeli umntwana wakho ukuba abe nenxaxheba, oko akuyi kuchanaba ukunyamekelwa komntwana wakho kunyango alufumanayo namhlanje okanye kwixesha elizayo.

Ngubani oza kuhlola iingxelo zonyango zomntwana wakho?
Ngabaphandi neqela labo lophononongo kuphela abaza kwazi ukuba umntwana wakho ukuphononongo. Kunokuba sisebenzise igama lomntwana wakho, siza kusebenzisa ikhowudi ukuze abanye abantu bangazi inkcazelo ukuba ibingeyomntwna wakho. Sinenokubonisa iziphumo zophononongo kwingqungquthela okanye sizipapashe kwijenali, kodwa asisoze sisebenzise igama lomntwana wakho xa sisenza oku.

Kuza kwenzeka ntoni kwimeko apho ngandlela ithile kwenzeka ukulimala ngenxa yokuthatha inxalenye ngokungqalileyo kolu phando lophononongo?
Akunakwenzeka tu ukuba umntwana wakho onzakale emzimbeni ukuba uyamvumela abe kolu phononongo. Ukuba kwenzeka into embi, ngoko ke, umntwana wakho uya kunyamekelwa ngomnye wogqirha abakwiqela lophononongo.

Ngana wena okanye umntwana wakho niza kuhlawulwa ngokuthatha inxaxheba kolu phononongo yaye zikhona naziphi na iindleko ezibandakanyekileyo?
Awuyi kuhlawulwa ngokuvumela umntwana wakho ukuba athathe inxaxheba kuphononongo. Kwakhona, akuyi kubakho zindleko zibandakanyekileyo zakho okanye zomntwana wakho, ukuba uyamvumela ukuba athathe inxaxheba.

Ngaba ikho enye into ofanele uyazi okanye uyenze?
Ukuba siyakucela ukuba uvumele umntwana wakho ukuba anikele ngenye isampulu ngelinye ixesha, siza kucela imvume yakho yaye nephepha elinikela imvume kwakhona.

Unokuqhagamshela iKomiti Yophando Yokuziphatha Yempilo apha kule nombolo 021 650 3002 ukuba unazo naziphi na izinto ezikukhathazayo okanye izikhalazo ngokuphathelele indlela yokuziphatha yolu phononongo

Uza kufumana ikopi yale nkcazelo kunye nefomu enikela imvume ukuze uzigcinele yona kwiingxelo zakho.

Ukuvuma ngumthathi nxaxheba

Ngokutyobela ngezantsi, Mna …….. **ndiyavuma ukuba umntwana wam** ……ukuba athathe inxaxheba kuphando lophononongo olubizwa ngokuba "Umlinganiselo Oqhelekileyo Wehlabathi Ohlolayo Ebantwaneni: Uthelekisa ukuchana kweepoyinti ezibanjwayo ezinyamekelayo nezihlolayo elabhorathri e-Red Cross War Memorial Children's Hospital".

Ndiyavuma ukuba:

- Ndiye ndafunda okanye ndiyifundelwe le nkcazelo nefomu enikela imvume yaye ibhalwe ngolwimi endityibilika nendikhululeke ngalo.
- Ndiye ndaba nethuba lokubuza imibuzo yaye yonke imibuzo yam iye yaphendulwa ngokufanelekileyo.
- Ndiyaqonda ukuba umntwana wam ngokuthatha inxaxheba kolu phononongo **uyazithandela** yaye andikhange ndicinezelwe ukuba umntwana wam athathe inxaxheba.
- Ndisenokukhetha ukuba umntwana wam alushiye uphononongo nangaliphi na ixesha yaye andiyi kuhlawuliswa okanye ndicalulwe nangayiphi na indlela.
- Umntwana wam unokucelwa ukuba alushiye uphononongo ngaphambi kokuba luphele, ukuba ugqirha wophononongo okanye umphandi uvakalelwa ukuba kuza kulungelwa umntwana, okanye ukuba asilandeli izicwangciso zophononongo, njengoko bekuvunyiwe.

Ityobelwe apha (*indawo*) ..... nge (*umhla*) ……..

……	**……**
Utyobelo lomnthathi nxaxheba	Utyobelo lwengqina

Ukuvuma komphandi

Mna *(igama)* …… ndiyavuma ukuba:

- Ndiye ndayicacisa inkcazelo ekwelu xwebhu ku……..

- Ndiye ndamkhuthaza ukuba abuze imibuzo yaye ndiye ndazipha ixesha elaneleyo ukuze ndimphendule yona.
- Ndanelisekile kukuba eye waqonda ngokwaneleyo zonke iinkalo zophando, njengoko ziye zaxutyushwa ngasentla
- Ndisebenzise/andikhange ndisebenzise umguquleli. (*Ukuba kuye kwasetyenziswa umguquleli, ngoko ke, umguquleli kumele atyobele uvumo olusezantsi.*

Utyobelo apha (*indawo*) ..... nge (*umhla*) ……..……..

…… **……**

Utyobelo lomphandi Utyobelo lwengqina

Ukuvuma komguquleli

Mna *(igama)* ……..…… ndiyavuma ukuba:

- Ndiye ndanceda umphandi (*igama*) ……. Ukuze acacisele inkcazelo ekweli xwebhu (*igama lomthathi nxaxheba*) u…….. esebenzisa ulwimi lwe-Afrikansi/isiXhosa/nolunye.
- Siye samkhuthaza ukuba abuze imibuzo saza sazipha ixesha elaneleyo ukuze simphendule yona.
- Ndiye ndadlulisela ingxelo echanileyo yoko endiye ndakuxelelwa.
- Ndanelisekile kuba umthathi nxaxheba eye waqonda ngokupheleleyo okuqulethwe lolu xwebhu olwazisa ngokunikela imvume yaye uye waphendulelwa yonke imibuzo yakhe ngokwaneleyo.

Utyobelo apha (*indawo*) ..... nge (*umhla*) ……..……..

…… **……**

Utyobelo lomguquleli Utyobelo lwengqina

IPHEPHA LENKCAZELO LOMTHATHI NXAXHEBA NEFOMU ENIKELA IMVUME
(7-17 iminyaka ubudala)

UMXHOLO WEPROJEKTHI YOPHANDO:

Umlinganiselo Oqhelekileyo Wehlabathi Ohlolayo Ebantwaneni: Ukuthelekisa ukuchana kweepoyinti ezibanjwayo zokunyamekela ezihlolayo ukusa kwimilinganiselo yokunyamekela elabhorathri ehlolayo e-Red Cross War Memorial Children's Hospital

Ukuhlolisisa Ihlwili Kwigazi eBantwaneni: Ukuthelekisa umatshini nokuhlatywa ngokucofoza ukusa kwindlela yaselabhorathri yokujonga ukuba lihlwili

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Yintoni uPHANDO?
Uphando yinto esiyenzayo ukuze sifumanise ngendlela izinto (kunye namabantu) abasebenza ngayo. Sisebenzisa iiprojekthi zophando okanye izifundo ukuze zisincede sifumanise okungakumbi ngokuphathelele izifo okanye ukugula. Uphando lukwasinceda sifumane iindlela ezibhetele zokunceda abantwana abagulayo.

Lungantoni uphando lweprojekthi?
Xa abantu bezisika ngokuqhelekileyo bafumana uqweqwe, nto leyo enqanda ukopha. Oku kubizwa ngokuba "lihlwili" legazi. Maxa wambi, ngokuqhelekileyo igazi alibi lihlwili, yaye oku kunokubangela ukopha kakhulu ebantwaneni, ngoko kubalulekile ukuvavanya enoba igazi liba lihlwili ngendlela eqhelekileyo okanye akunjalo. Ukuze senze oku, ngokuqhelekileyo kufuneka sithathe igazi elithile kuwe ngokufaka inaliti kumthambo wengalo yakho, sitsale igazi size emva koko silithumele elebhorathri ("lebhu") livavanyelwe ukuba lihlwili nto leyo ebizwa ngokuba yi-INR.

Sifuna ukubona enoba sinokwenza okufanayo kuvavanyo lwe-INR ngaphandle kokuthumela igazi elebhu, yaye nokusebenzisa nje ichaphaza elincinane legazi ngokuhlaba umnwe. Sifuna ukubona enoba uvavanyo lokuhlaba umnwe lulunge

njengovavanyo lwaselebhu kusini na. Uvavanyo lokuhlaba umnwe lusetyenziswa kwamanye amazwe sithetha nje kodwa alusetyenziswa eMzantsi Afrika.

Kutheni ndiye ndamenywa ukuze ndithathe inxaxheba kule projekthi yophando?
Siyabuza enoba ungakwazi ukuthatha inxaxheba kuphononongo lwethu, kuba ugqirha wakho uye wayalela ukuba igazi lakho lisiwe elebhu ukuze livavanyelwe ihlwili. Kwakhona, siza kubuza abanye abantwana abafumana uvavanyo olufanayo enoba baza kuthatha inxaxheba kolu phononongo kusini na.

Ngubani owenza uphando?
Ndingugqirha onceda ekunyamekeleni abantwana abagulayo. Ndisebenza kwisiBhedlele Sabantwana se-Red Cross apha eKapa. Ibhosi yam nguProfesa Liesl Zuhlke ongugqirha onyamekela abantwana abaneengxaki zentliziyo.

Kuza kwenzeka ntoni kum kolu phononongo?
Ugqirha wakho uye wacela uvavanyo lwaselebhu lwe-INR ukuze abone enoba igazi lakho liba namahlwili. Oku kubalulekile, yaye kufuneka sikwenze kwanokuba uthi “hayi” kolu phononongo. Ukuba uthi “ewe” ukuthatha inxaxheba kolu phononongo, singathanda ukwenza uvavanyo lehlwili legazi ngokuhlaba emnweni ukuze sithelekise iziphumo.

Ukuze senze oku siza kuhlaba umnwe wakho ngenaliti encinane ebizwa ngokuba yi-lancet. Uza kuva ukuhlatywa okukhawulezileyo. Ngemva kokuhlatywa emnweni siza kubeka i-cottonwool ukuze sinqande nakuphi na ukopha. Ichaphaza legazi elisemnweni liza kuvavanywa kumatshini ukuze sifumane imiphumo yokuba lihlwili.

Siza kubuza abanye abantwana abakwafumana uvavanyo lwaselebhu, yaye abavumayo ukuthatha inxaxheba kuphononongo, ukuze nabo benze uvavanyo lokuhlaba umnwe olufanayo. Siza kubeka kunye zonke iziphumo zovavanyo ekugqibeleni size sibone enoba indlela yokuhlaba umnwe ilunge ngokufana nendlela yaselebhu.

Ngaba ikho into embi enokwenzeka kum?
Ayikho into embi eza kwenzeka kuwe ukuba uthi “ewe”, ngaphandle kokuhlatywa komnwe okuncinane, mhlawumbi esenokuba buhlungu kancinane (kodwa oku kuza kwenzeka ngokukhawuleza). Ukuba nangaliphi na ixesha uziva usoyika okanye awukhululekanga, unokusixelela yaye akuyomfuneko ukuqhubeka novavanyo.

Ngaba ikho into entle enokwenzeka kum?
Ukuba uthi “ewe” kuvavanyo lokuhlatywa emnweni, oko akuzokukunceda ngoku kodwa ukuba singabonisa ukuba olu vavanyo lulunge ngendlela efanayo kunovavanyo oluqhelekileyo lwaselebhu kuza kunceda abanye abantwana kwixesha elizayo; kuba uvavanyo lukuhlaba emnweneni lulula, luyakhawuleza, yaye alukho buhlungu kunovavanyo oluqhelekileyo lwegazi.

Ngaba ukho umntu oza kwazi ukuba ndikuphononongo?
Akekho umntu ngaphandle kwabaphandi oya kukwazi ukuba ukuphononongo. Kunokuba sisebenzise igama lakho, siza kusebenzisa ikhowudi ukuze abanye abantu bangayazi inkcazelo ukuba ibingawe. Sisenokubonisa iziphumo zophononongo okanye sizipapashe

kwijenali (imagazini yezonyango), kodwa asisoze sisebenzise igama lakho nanini na xa sisenza oku.

Ndinokuthetha nabani ngokuphathelele uphononongo?
Ukuba unayo nayiphi na imibuzo, unokuthetha nomphandi owenza uvavanyo lokuhlaba umnwe okanye unokufowunela naziphi na iinombolo ezinikelwe ngasentla.

Kuthekani ukuba ndithi "hayi"?
Akuyomfuneko ukuba ube yinxalenye kule projekthi yophando, kwanokuba umzali/umnakekeli wakho uthi ufanele wenjenjalo. Ukuba utshintsha ingqondo yakho ngokuphathelele ukuthatha inxaxheba nangaliphi na ixesha ebudeni bophando, unokuxelela umzali/ umnakekeli wakho onokwazisa abaphandi. Awuyi kuba sengxakini yaye oku akuyi kuchaphazela ukunyamekelwa kwakho ngugqirha wakho.

Ngaba uyaluqonda olu phando lophononongo yaye ukulungele ukuthatha inxaxheba kulo?

EWE	HAYI

Ngaba umphandi uye waphendula yonke imibuzo yakho?

EWE	HAYI

Ngaba uyaqonda ukuba unokuyeka kolu phononongo nangaliphi na ixesha?

EWE	HAYI

_____ _____
Utyobelo loMntwana Umhla

Mission®

PT/INR Test Strips

Package Insert

REF C132-4011 | English

INTENDED USE

Mission® PT/INR Test Strips are intended for use with the Mission® PT/INR Monitoring System to monitor blood clotting time in patients stabilized on Coumarin-type (e.g. warfarin) anticoagulation therapy. The Mission® PT/INR Test Strips use fresh capillary blood or fresh anticoagulant-free venous whole blood specimens. The results are reported in both Prothrombin Time and INR units. For in vitro diagnostic use only. The device is not intended to be used for screening purposes. For self testing and professional use.

SUMMARY

Oral anticoagulants are used to treat patients with atrial fibrillation, deep vein thrombosis (DVT), artifical heart valves, post myocardial infarctions and other cardiovascular disorders. These medications help to prevent blood clots, which can cause thromboembolic events such as stroke, recurrent myocardial infarction and pulmonary embolism. Warfarin, commonly known as Coumadin®[1] is frequently prescribed and acts by inhibiting the synthesis of vitamin K -dependent clotting factors.

Oral anticoagulant drug actions tend to be variable between different patients and are subject to change over time within a patient. Warfarin is a Narrow Therapeutic Index (NTI) drug which can be affected by factors such as drug interactions and dietary vitamin K.[2] As a result, periodic determination of INR is necessary for the individualized management of each patient's treatment. The INR system has become the standard quantitative measurement internationally because it corrects for variations among different instruments and reagents.

PRINCIPLE

The Mission® PT/INR Test Strips, when used as directed with the Mission® PT/INR Meter, will accurately and reliably measure Prothrombin Time (PT) and International Normalized Ratio (INR) values in fresh capillary blood from a fingerstick or fresh anticoagulant-free venous whole blood specimens. After inserting the test strip in the meter, the blood specimen is applied to the Specimen Application Area marked on the test strip. The meter detects the application of the specimen on the strip and initiates test timing. The membrane of the strip contains the reagents necessary to begin the coagulation reaction. The time from the initial specimen detection to the fluorescent signal response is used to calculate the reported blood Prothrombin Time and INR value.

COMPOSITION

Each test strip contains the following reagents: recombinant tissue factor, calcium and buffer. Each test strip individual foil pouch contains a drying agent.

PRECAUTIONS

- All blood specimens and containers, capillary transfer tubes, lancets and materials that have come in contact with blood specimen should be handled as if capable of transmitting infectious diseases and discarded in a biohazardous waste container. Follow your facility's biohazard control guidelines.
- For in vitro use only. Do not take internally.
- Check the code chip before running a PT test. Make sure to use the code chip that is included with the box of strips in use. Insert the code chip into the code chip slot. The code chip slot is located on the right side of the meter.
- Do not add additional test specimen material after the initial specimen volume has been applied to the test strip.
- The specimen should cover the entire specimen well. A new test should be run if an insufficient specimen is applied.
- Do not apply strong repetitive pressure to the finger to get excessive blood specimen.
- It is not required to wipe away the first drop of blood. However the drop must be applied within 15 seconds of the finger stick.
- Do not use strips beyond the expiration date printed on the foil pouch of each strip.
- Venous whole blood collection must be done with an anticoagulant-free syringe.
- Current health status may affect test results and may cause unexpected or inaccurate results. Health factors need to be taken into consideration when interpreting results and decisions of medical relevance are not to be taken without consulting a physician. Changes to treatment should only be made after professional consultation.

STORAGE AND HANDLING

- Test strips should be stored in the original foil pouches and box.
- Test strips may be stored at or below room temperature, 2 °C to 30 °C (36 °F to 86 °F). The strips may be refrigerated.
- If test strips are stored in the refrigerator, they must return to room temperature by sitting in a room temperature atmosphere in their own foil packaging for at least 15 minutes prior to use.
- The test strip should be used immediately upon removal from the foil pouch.
- Do not use the test strips beyond the expiration date printed on the foil pouch.

SPECIMEN COLLECTION AND PREPARATION

- Acceptable specimens include fresh capillary (fingerstick) or arm venous whole blood.
- Fresh capillary or fresh venous whole blood specimens must be tested immediately after collection.
- The minimum specimen volume is one hanging drop of capillary whole blood or 15µL of fresh venous whole blood.

MATERIALS

Materials Provided:

- Test Strips
- Code Chip
- Package Insert

Materials Required But Not Provided:

- PT/INR Meter
- Latex Gloves
- Capillary Transfer Tubes (optional)
- Safety Lancets
- Gauze for Puncture Site
- Control Solution
- Alcohol Swab

DIRECTIONS FOR USE

The Mission® PT/INR Test Strip uses either fresh capillary or fresh venous whole blood. Refer to the User's Manual for blood specimen collection before use.

1. Insert the code chip contained in the Mission® PT/INR Test Strip box into the Mission® PT/INR Meter as described in the User's Manual.
2. Open a foil pouch. Remove the test strip.
   Note: Each time before opening a test strip foil pouch, check the expiration date on the foil pouch. Do not use if the expiration date has passed.
3. Insert the test strip into the meter. The meter will automatically turn on and beep, if the sound is enabled. The meter will then go through a warm-up cycle. Check to ensure the displayed code number matches the number on the strip box. Select 'Blood' for a blood specimen, 'EC Tst' for an electronic control test, or 'CS Tst' for a liquid control specimen. When the meter displays the "ADD SPECIMEN" icon, prepare to collect the specimen.
4. Collect the blood specimen and apply the specimen to the Mission® PT/INR Test Strip according to the instructions in the User's Manual. The entire white circle in the center of the target area must be filled with one drop of blood. If the specimen well is only partially covered, repeat the test with a new strip.
5. Follow the displayed prompt to close the optics cover. The optics cover should be closed within 20 seconds of specimen application to the test strip.
6. The PT/INR meter will perform the test for about 2 minutes and "beep" when complete if the sound is enabled. Once complete, the meter will display the final INR value and Prothrombin Time if INR+PT is selected. Remove and discard the test strip. The meter will store the INR value in the memory, along with the date and time.
7. Carefully discard any materials that came in contact with blood according to proper biohazard control guidelines.

Note: Specimen may also be applied using a capillary transfer tube.

EXPECTED VALUES

The Mission® PT/INR Monitoring System displays the results in the International Normalized Ratio (INR units). Normal Prothrombin Time results can vary from person to person however, an INR of 1.0 usually corresponds to a normal value. Patients receiving anticoagulant therapy must be monitored carefully, with their physician establishing the appropriate INR range based upon the underlying clinical condition.

The Mission® PT/INR Monitoring System will display the following values when a test is completed:

INR Range	Display
INR < 0.7	INR <
0.7 ≤ INR ≤ 7.0	Measured INR Value
INR > 7.0	INR >

The recommended therapeutic range for warfarin is most commonly between INR 2 and 4 depending upon the underlying clinical condition.[3]

Normal Range

Normal PT levels, expressed as an INR, were determined for capillary whole blood collected from 120 healthy, warfarin-free individuals. Based upon the study performed, the reference INR range for the Mission® PT/INR Monitoring System is the following:

Specimen Type	95 % Range
Capillary Whole Blood	0.8 to 1.4

UNEXPECTED VALUES

Unexpected results may include results that fall outside the therapeutic range defined by the physician or results that fall within the therapeutic range but is associated with unusual clinical situations (such as abnormal symptoms of bleeding or bruising).

Possible causes for unexpected results:

- A hematocrit that is higher (above 60%) or lower (below 25%) than the validated operating range of the Mission® PT/INR Monitoring System. Hematocrit levels outside this range or individuals with severe anemia can cause inaccurate results.
- Patients with severe, congenital or autoimmune hypo-fibrinogenemia, dysfibrinogenemia, hypoprothrombinemia or disprothrombinemia, results may differ from a clinical reference assay system.
- Patients receiving an intravenous infusion therapy should not have their specimen taken from the arm receiving the IV.
- Certain prescription or over-the-counter drugs (e.g. pain relievers) may affect the action of oral anticoagulants and the INR value.
- Lupus may falsely prolong the INR level.[4]
- Changes in diet (e.g. taking nutritional supplements such as gingko biloba) and lifestyles may affect the action of oral anticoagulants and the INR value.

Upon receiving abnormal results or encountering unusual clinical conditions, please refer to a health care professional immediately and arrange for an alternative testing method.

PERFORMANCE CHARACTERISTICS

Measuring Range

The Mission® PT/INR Monitoring System has a numeric PT measuring range of 0.7 to 7.0 INR. Specimens below INR 0.7 are displayed as "INR < ". Specimens above INR 7.0 are displayed as "INR > ".

Verified Clinical Range. In clinical trials, patients tested in the INR 0.7 to 7.0 range. Performance outside of this range has not been verified.

Sensitivity

The Mission® PT/INR Monitoring System is sensitive to deficiencies of Factors II, V, VII and X at the following levels (3 lot averages):

Factor II	Factor V	Factor VII	Factor X
25%	35%	42%	28%

Thromboplastin. The Mission® PT/INR Monitoring System uses recombinant human thromboplastin. The thromboplastin reagent has an approximate average International Sensitivity Index (ISI) of 1.0 as determined by the Sysmex CA-530 coagulation analyzer.

Accuracy

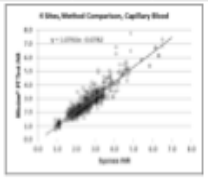
The Mission® PT/INR Monitoring System was compared against the *Sysmex*® analyzer, using human thromboplastin as a reference. The following accuracy data were obtained:

Capillary Whole Blood (INR)	Venous Whole Blood (INR)
Mission® PT/INR Monitoring System vs. Sysmex CA-530 Reference n = 606 Regression line: y = 1.070x - 0.078 r = 0.924	Mission® PT/INR Monitoring System vs. Sysmex CA-530 Reference n = 619 Regression line: y = 1.050x -0.068 r = 0.936

606 Capillary specimens were collected from 219 outpatients at four external sites. Capillary whole blood specimens were assayed on the Mission® PT/INR Meter with the Mission® PT/INR Test Strips, and venous specimens were measured on the Sysmex CA-530 Analyzer. The results are as follows:

Capillary Whole Blood

Site	N	Slope	Intercept	R
1	209	1.056	-0.073	0.965
2	184	1.091	-0.084	0.887
3	74	0.908	0.070	0.930
4	139	1.246	-0.436	0.865
All	606	1.078	-0.078	0.924

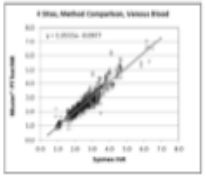


Capillary Data from All Sites: 606 Specimens from 219 patients

619 venous specimens were collected from 219 outpatients at four external sites. The INR of each specimen was compared to the INR of venous plasma specimens measured on the Sysmex CA-530 Analyzer. The results are as follows:

Venous Whole Blood

Site	N	Slope	Intercept	R
1	212	1.074	-0.092	0.972
2	191	1.060	-0.182	0.972
3	77	0.937	0.044	0.932
4	139	1.305	-0.617	0.909
All	619	1.055	-0.068	0.936



Venous Data from All Sites: 619 Specimens from 219 patients

Precision

Precision studies were done using control solutions level 1 and level 2 on 3 lots of strips. The within day precision study included 8 tests on 3 lots at 2 levels. Day to day precision included 2 tests, 2 runs per day for 20 days.

INR Scale	Within-Day 3 Strip Lots		Day-To-Day (Between Day) 3 Strip Lots	
	Level 1	Level 2	Level 1	Level 2
n	27	27	240	240
Mean	1.04	2.96	1.16	2.88
SD	0.05	0.11	0.01	0.03
CV	4.7%	3.8%	0.6%	1.0%

QUALITY CONTROL

Daily control testing is good laboratory practice and may be required in your location. Always check with the appropriate licensing or accrediting bodies to ensure your quality control program meets the established standards.

The recommended control solutions Mission® PT/INR Control Solution Level 1 and Level 2 should be tested when:

- A new shipment of test strips is received
- A new lot of test strips is opened
- Improper storage or handling of the test strips is suspected
- Patient PT results are unusually low or high

Control tests are performed in a very similar way to blood tests, using the commercially available liquid controls instead of blood. The User's Manual and control solution insert should be read before using the controls. The system is working properly if the control value displayed by the meter is within the acceptable range for the control solution tested. The acceptable control range can be found on the pouch label. If the value is not acceptable, please contact local distributor for assistance.

LIMITATIONS

- Hematocrit ranges between 25% and 60% have no significant effect on results. Hemolyzed specimens up to 500 mg/dL of hemoglobin in plasma have no significant effect on results.
- Bilirubin concentrations up to 20 mg/dL have no significant effect on results.
- Triglycerides concentrations up to 3000 mg/dL have no significant effect on results.
- Heparin and Low Molecular Weigh Heparin do not interfere with results up to 2 U/ml.
- Fondaparinux at the concentration ≥ 0.1 mg/dL, or therapeutic level could falsely increase the INR level compared with laboratory reference method.
- The Mission® PT/INR Monitoring System was designed to provide a quantitative measurement of Prothrombin Time for patients on warfarin therapy. Self-testing patients should be stabilized on warfarin therapy for at least 6 weeks.
- The Mission® PT/INR Monitoring System should not be used on individuals with severe coagulopathies such as disseminated intravascular coagulation (DIC) and other conditions with rapid changes in coagulation status (e.g. severe sepsis, septic shock, and hypotensive shock).
- A full hanging drop of blood should always be applied on to a test strip. Never apply a second drop of blood onto the same test strip. Always use a new test strip when performing a new test.
- Low specimen volume (typically under 10µL) will cause a specific error message.

BIBLIOGRAPHY

1. Coumadin® is a registered trademark of the Bristol Myers Squibb Pharma Company.
2. Coumadin® Official Package Insert. Rev. October 2011.
3. Cunningham, Mark et. al. "The Reliability of Manufacturer-determined Instrument-specific International Sensitivity Index Value for Calculating the International Normalized Ratio." Am. Jrnl. Clin. Pathol. July 1994. Volume 102, Number 1:128-133.
4. Sanfelippo, M.J et. al. "Falsely elevated INRs in warfarin-treated patients with the lupus anticoagulant." WMJ. 2000 Jun; 99(3):62-4, 43.

Index of Symbols

	Consult instructions for use		Use by	CODE	Code Number
IVD	For in vitro diagnostic use only	LOT	Lot Number	CTRL	Control Range
2-30 °C	Store between 2-30 °C		Manufacturer	REF	Catalog #
	Contents sufficient for <n> tests	EC REP	Authorized Representative	2	Do not reuse

ACON Laboratories, Inc.
10125 Mesa Rim Road
San Diego, CA 92121, USA

CE 0123

EC REP
MDSS GmbH
Schiffgraben 41
30175 Hannover, Germany

Number: 1150866901
Effective date: 2016-06-17

APPENDIX 5: HREC approval letter

UNIVERSITY OF CAPE TOWN
Faculty of Health Sciences
Human Research Ethics Committee

Room E53-46 Old Main Building
Groote Schuur Hospital
Observatory 7925
Telephone [021] 406 662
Email: shuretta.thomas@uct.ac.za
Website: www.health.uct.ac.za/fhs/research/humanethics/forms

13 November 2018

HREC REF: 730/2018

A/Prof Liesl Zuhlke
Paediatrics Cardiology
ICH Building, room 2.17
Red Cross War Memorial Children's Hospital

Dear A/Prof Zuhlke

PROJECT TITLE: INTERNATIONAL NORMALISED RATIO MONITORING IN CHILDREN: COMPARING THE ACCURACY OF PORTABLE POINT-OF-CARE MONITORS TO STANDARD OF CARE LABORATORY MONITORING AT RED CROSS WAR MEMORIAL CHILDREN'S HOSPITAL (MMED Candidate - Dr R Moore)

Thank you for submitting your study to the Faculty of Health Sciences Human Research Ethics Committee.

It is a pleasure to inform you that the HREC has **formally approved** the above-mentioned study subject to correcting the contact number of the HREC on the Consent form.

Approval is granted for one year until the 30 November 2019.

Please submit a progress form, using the standardised Annual Report Form if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.
(Forms can be found on our website: www.health.uct.ac.za/fhs/research/humanethics/forms)

Please quote the HREC REF in all your correspondence.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Please note that for all studies approved by the HREC, the principal investigator **must** obtain appropriate institutional approval, where necessary, before the research may occur.

The HREC acknowledge that the student Dr Ryan Moore will also be involved in this study.

Yours sincerely

Signature Removed

PROFESSOR M BLOCKMAN
CHAIRPERSON, FHS HUMAN RESEARCH ETHICS COMMITTEE
Federal Wide Assurance Number: FWA00001637.

UNIVE

FACULTY OF HEALTH SCIENCES
Human Research Ethics Committee

FHS016: Annual Progress Report / Renewal

HREC office use only (FWA00001637; IRB00001938) This serves as notification of annual approval, including any documentation described below.			
☑ Approved	Annual progress report	Approved until/next renewal date	30/11/2020
☐ Not approved	See attached comments		
Signature Chairperson of the HREC	Signature Removed	Date Signed	18/11/2019

Comments to PI from the HREC

Principal Investigator to complete the following:

1. Protocol information

Date (when submitting this form)	11 November 2019		
HREC REF Number	730/2018	Current Ethics Approval was granted until	30 Nov 2019
Protocol title	International Normalised Ratio Monitoring in Children: Comparing the accuracy of portable point-of-care monitors to standard of care laboratory monitoring at Red Cross War Memorial Children's Hospital		
Protocol number (if applicable)			
Are there any sub-studies linked to this study?	☐ Yes ☐ x No		
If yes, could you please provide the HREC Ref's for all sub-studies? Note: A separate FHS016 must be submitted for each sub-study.			
Principal Investigator	Prof Lies Zuhlke		
Department / Office Internal Mail Address	Dept of Paediatrics - Red Cross WMC Hospital, Room 2.17 ICH Building		

1.1 Does this protocol receive US Federal funding?	☐ Yes	☐ ✓No

HUMAN RESEARCH ETHICS COMMITTEE
16 NOV 2019
HEALTH SCIENCES FACULTY
UNIVERSITY OF CAPE TOWN

(Note: Please complete the Closure form (FHS010) if the study is completed within the approval period)

APPENDIX 6: INSTRUCTIONS TO AUTHORS (SAMJ)

Author Guidelines

The *SAMJ* has launched a new submission and tracking system. Authors will be required to register a profile on the Editorial Manager platform in order to submit a manuscript.

To submit a manuscript, please proceed to the *SAMJ* Editorial Manager website:

www.editorialmanager.com/samj

To access and submit an article already in production, please see the guidelines here.

Author Guidelines

Please view the Author Tutorial for guidance on how to submit on Editorial Manager.

Please take the time to familiarise yourself with the policies and processes below. If you still have any questions, please do not hesitate to ask our editorial staff (tel.: +27 (0)21 532 1281, email: submissions@hmpg.co.za).

SAMJ policies

- Types of articles considered by the SAMJ
- Article Processing Charges
- Authorship
- Conflict of interest
- Research ethics committee approval
- Clinical trials
- Protection of patient's rights to privacy
- Copyright notice
- Privacy statement
- Ethnic classification
- CPD

Manuscript preparation

- Preparing an article for anonymous review
- General article format/layout
- Preparation notes by article type
- Illustrations
- Tables
- References

From submission to acceptance

- Submission and peer-review
- Production process
- Changing contact details or authorship

Publication

- Online versus print
- Errata and retractions
- Indexing

SAMJ Policies

Type of articles considered by the SAMJ

The *SAMJ* will no longer limit the articles accepted to those that have 'general medical content', but is intending to capture the spectrum of medical and health sciences, grouped by relevance to the country's burdens of disease. This content will include research in the social sciences and economics that is relevant to the medical issues around our burden of disease. Please see 'A new vision for the *SAMJ* – and a call for papers' for a full discussion of the new directions for the *SAMJ*.

We accept the following types of articles:

Research
Reviews
Clinical trials
Editorials
In Practice (Previously Forum incl. Case Reports)
Correspondence
Obituaries
Book reviews
Ad hoc supplements e.g. guidelines, conference/congress abstracts, Festschrifts*

The following articles are by invitation only:

Guest editorial
Continuing Medical Education (CME)

*Contact claudian@hmpg.co.za for information on submitting ad hoc/commissioned supplements, including guidelines, conference/congress abstracts, Festschrifts, etc.

Publication Fees

All articles published in the *South African Medical Journa*l are open access and freely available online upon publication. This is made possible by applying a business model to offset the costs of peer review management, copyediting, design and production, by charging a publication fee of R5 565 (ex vat) for each research article published. The charge applies only to **Research** articles submitted after 1 March 2017. The publication fee is standard and does not vary based on length, colour, figures, or other elements.

When submitting a Research article to the *SAMJ*, the submitting author must agree to pay the publication fee should the article be accepted for publication. The publicaiton fee is

payable when your manuscript is editorially accepted and before production commences for publication. The submitting author will be notified that payment is due and given details on the available methods of payment. Prompt payment is advised; the article will not enter into production until payment is received.
Queries can be directed to claudian@hmpg.co.za.

Please refer to the section on 'Sponsored Supplements' regarding the publication of supplements, where a charge is applicable. Queries can be directed to dianes@hmpg.co.za or claudian@hmpg.co.za

Authorship

Named authors must consent to publication. Authorship should be based on: (*i*) substantial contribution to conceptualisation, design, analysis and interpretation of data; (*ii*) drafting or critical revision of important scientific content; or (*iii*) approval of the version to be published. These conditions must all be met (uniform requirements for manuscripts submitted to biomedical journals; refer to www.icmje.org)

If authors' names are added or deleted after submission of an article, or the order of the names is changed, all authors must agree to this in writing.

Please note that co-authors will be requested to verify their contribution upon submission. Non-verification may lead to delays in the processing of submissions.

Author contributions should be listed/described in the manuscript.

Conflicts of interest

Conflicts of interest can derive from any kind of relationship or association that may influence authors' or reviewers' opinions about the subject matter of a paper. The existence of a conflict – whether actual, perceived or potential – does not preclude publication of an article. However, we aim to ensure that, in such cases, readers have all the information they need to enable them to make an informed assessment about a publication's message and conclusions. We require that both authors and reviewers declare all sources of support for their research, any personal or financial relationships (including honoraria, speaking fees, gifts received, etc) with relevant individuals or organisations connected to the topic of the paper, and any association with a product or subject that may constitute a real, perceived or potential conflict of interest. If you are unsure whether a specific relationship constitutes a conflict, please contact the editorial team for advice. If a conflict remains undisclosed and is later brought to the attention of the editorial team, it will be considered a serious issue prompting an investigation with the possibility of retraction.

Research ethics committee approval

Authors must provide evidence of Research Ethics Committee approval of the research where relevant. Ensure the correct, full ethics committee name and reference number is included in the manuscript.

If the study was carried out using data from provincial healthcare facilities, or required active data collection through facility visits or staff interviews, approval should be sought from the relevant provincial authorities. For South African authors, please refer to the guidelines for submission to the National Health Research Database. Research involving

human subjects must be conducted according to the principles outlined in the Declaration of Helsinki. Please refer to the National Department of Health's guideline on Ethics in Health research: principles, processes and structuresto ensure that the appropriate requirements for conducting research have been met, and that the HPCSA's General Ethical Guidelines for Health Researchers have been adhered to.

Clinical trials

As per the recommendations published by the International Committee of Medical Journal Editors (ICMJE), clinical trial research is any research that assigns individuals to an intervention, with or without a concurrent comparison/control group to study the cause-and-effect relationship between the intervention and health outcomes. All clinical trials should be registered with the appropriate national clinical trial registry (or any international primary register, if relevant), and the trial registration number should be cited at the end of the abstract. All clinical trial reports must also contain a data sharing statement as per the recommendations of the ICMJE. Statements are to indicate:

- whether individual deidentified participant data will be shared;
- what data in particular will be shared; whether additional, related documents will be available;
- when the data will become available and for how long; by what access criteria data will be shared.

Please see the ICJME announcement for further details and illustrative examples of data sharing statements: ICMJE Data Sharing Statements for Clinical Trials

Since 1st December 2005, all clinical trials conducted in South Africa have been required to be registered in the South African National Clinical Trials Register. The SAMJ therefore requires that clinical trials be registered in the relevant public trials registry at or before the time of first patient enrollment as a condition for publication. The trial registry name and registration number must be included in the manuscript.

Please refer to the general guidelines for all papers at the top of this article for additional requirements with respect to ethics approval, funding, author contributions, etc. The format of original research articles should be followed for reporting of clinical trial results.

Patient Consent

Information that would enable identification of individual patients should not be published in written descriptions, photographs, and pedigrees unless the information is essential for scientific purposes and the patient (or parent or guardian) has given informed written consent for publication and distribution. We further recommend that the published article is disseminated not only to the involved researchers but also to the patients/participants from whom the data was drawn. Refer to Protection of Research Participants. The signed consent form should be submitted with the manuscript to enable verification by the editorial team.

Other individuals

Any individual who is identifiable in an image must provide written agreement that the image may be used in that context in the *SAMJ*.

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Material submitted for publication in the *SAMJ* is accepted provided it has not been published or submitted for publication elsewhere. Please inform the editorial team if the main findings of your paper have been presented at a conference and published in abstract form, to avoid copyright infringement. All research already published as 'Conference proceedings' needs to be substantially re-written, with a new title, a new abstract and new and important results to back up any study before it will be considered for a new publication. The *SAMJ* does not hold itself responsible for statements made by the authors.

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If an image/figure has been previously published, permission to reproduce or alter it must be obtained by the authors from the original publisher and the figure legend must give full credit to the original source. This credit should be accompanied by a letter indicating that permission to reproduce the image has been granted to the author/s. This letter should be uploaded as a supplementary file during submission.

Privacy statement

The *SAMJ* is committed to protecting the privacy of its website and submission system users. The names, personal particulars and email addresses entered in the website or submission system will not be made available to third parties without the user's permission or due process. By registering to use the website or submission system, users consent to receive communication from the *SAMJ* or its publisher HMPG on matters relating to the journal or associated publications. Queries with regard to privacy may be directed to publishing@hmpg.co.za.

Ethnic/race classification

Use of racial or ethnicity classifications in research is fraught with problems. If you choose to use a research design that involves classification of participants based on race or ethnicity, or discuss issues with reference to such classifications, please ensure that you include a detailed rationale for doing so, ensure that the categories you describe are carefully defined, and that socioeconomic, cultural and lifestyle variables that may underlie perceived racial disparities are appropriately controlled for. Please also clearly specify whether race or ethnicity is classified as reported by the patient (self-identifying) or as perceived by the investigators. Please note that is not appropriate to use self-reported or investigator-assigned racial or ethnic categories for genetic studies.

Continuing Professional Development (CPD)

SAMJ is an HPCSA-accredited service provider of CPD materials. Principal authors can earn up to 15 CPD continuing education units (CEUs) for publishing an article; co-authors are eligible to earn up to 5 CEUs; and reviewers of articles can earn 3 CEUs. Each month, *SAMJ* also publishes a CPD-accredited questionnaire relating to the academic content of the journal. Successful completion of the questionnaire with a pass rate of 70% will earn the reader 3 CEUs. Administration of our CPD programme is managed by Medical Practice Consulting. To complete questionnaires and obtain certificates, please visit MRP Consulting

Manuscript preparation

Preparing an article for anonymous review

To ensure a fair and unbiased review process, all submissions are to include an anonymised version of the manuscript. The exceptions to this are Correspondence, Book reviews and Obituary submissions.

Submitting a manuscript that needs additional blinding can slow down your review process, so please be sure to follow these simple guidelines as much as possible:

- An anonymous version should not contain any author, affiliation or particular institutional details that will enable identification.
- Please remove title page, acknowledgements, contact details, funding grants to a named person, and any running headers of author names.
- Mask self-citations by referring to your own work in third person

General article format/layout

Accepted manuscripts that are not in the correct format specified in these guidelines will be returned to the author(s) for correction, which will delay publication.

General:

- Manuscripts must be written in UK English.
- The manuscript must be in Microsoft Word format. Text must be single-spaced, in 12-point Times New Roman font, and contain no unnecessary formatting (such as text in boxes).
- Please make your article concise, even if it is below the word limit.
- Qualifications, ***full*** affiliation (department, school/faculty, institution, city, country) and contact details of ALL authors must be provided in the manuscript and in the online submission process.
- Abbreviations should be spelt out when first used and thereafter used consistently, e.g. 'intravenous (IV)' or 'Department of Health (DoH)'.
- Include sections on Acknowledgements, Conflict of Interest, Author Contributions and Funding sources. If none is applicable, please state ‘none’.

- Scientific measurements must be expressed in SI units except: blood pressure (mmHg) and haemoglobin (g/dL).
- Litres is denoted with an uppercase L e.g. 'mL' for millilitres).
- Units should be preceded by a space (except for % and ºC), e.g. '40 kg' and '20 cm' but '50%' and '19ºC'.
- Please be sure to insert proper symbols e.g. µ not u for micro, a not a for alpha, b not B for beta, etc.
- Numbers should be written as grouped per thousand-units, i.e. 4 000, 22 160.
- Quotes should be placed in single quotation marks: i.e. The respondent stated: '...'
- Round brackets (parentheses) should be used, as opposed to square brackets, which are reserved for denoting concentrations or insertions in direct quotes.
- If you wish material to be in a box, simply indicate this in the text. You may use the table format –this is the *only* exception. Please DO NOT use fill, format lines and so on.

SAMJ is a generalist medical journal, therefore for articles covering genetics, it is the responsibility of authors to apply the following:

- Please ensure that all genes are in italics, and proteins/enzymes/hormones are not.

- Ensure that all genes are presented in the correct case e.g. TP53 not Tp53.

**NB: Copyeditors cannot be expected to pick up and correct errors wrt the above, although they will raise queries where concerned.

- Define all genes, proteins and related shorthand terms at first mention, e.g. ‘188del11’ can be glossed as ‘an 11 bp deletion at nucleotide 188.’

- Use the latest approved gene or protein symbol as appropriate:

- Human Gene Mapping Workshop (HGMW): genetic notations and symbols
- HUGO Gene Nomenclature Committee: approved gene symbols and nomenclature
- OMIM: Online Mendelian Inheritance in Man (MIM) nomenclature and instructions
- Bennet et al. Standardized human pedigree nomenclature: Update and assessment of the recommendations of the National Society of Genetic Counselors. J Genet Counsel 2008;17:424-433: standard human pedigree nomenclature.

Preparation notes by article type

- Research
- Editorials
- CME
- In Practice and Case reports
- Reviews
- Clinical trials
- Correspondence
- Obituaries
- Book reviews
- Guidelines

Research

Guideline word limit: 4 000 words

Research articles describe the background, methods, results and conclusions of an original research study. The article should contain the following sections: introduction, methods, results, discussion and conclusion, and should include a structured abstract (see below). The introduction should be concise – no more than three paragraphs – on the background to the research question, and must include references to other relevant published studies that clearly lay out the rationale for conducting the study. Some common reasons for conducting a study are: to fill a gap in the literature, a logical extension of previous work, or to answer an important clinical question. If other papers related to the same study have been published previously, please make sure to refer to them specifically. Describe the study methods in as much detail as possible so that others would be able to replicate the study should they need to. Results should describe the study sample as well as the findings from the study itself, but all interpretation of findings must be kept in the discussion section, which should consider primary outcomes first before any secondary or tertiary findings or post-hoc analyses. The conclusion should briefly summarise the main message of the paper and provide recommendations for further study.

Select figures and tables for your paper carefully and sparingly. Use only those figures that provided added value to the paper, over and above what is written in the text.

Do not replicate data in tables and in text .

Structured abstract

- This should be 250-400 words, with the following recommended headings:
  - **Background:** why the study is being done and how it relates to other published work.
  - **Objectives:** what the study intends to find out
  - **Methods:** must include study design, number of participants, description of the intervention, primary and secondary outcomes, any specific analyses that were done on the data.
  - **Results:** first sentence must be brief population and sample description; outline the results according to the methods described. Primary outcomes must be described first, even if they are not the most significant findings of the study.
  - **Conclusion:** must be supported by the data, include recommendations for further study/actions.
- Please ensure that the structured abstract is complete, accurate and clear and has been approved by all authors.
- Do not include any references in the abstracts.

Here is an example of a good abstract.

Main article

All articles are to include the following main sections: Introduction/Background, Methods, Results, Discussion, Conclusions.

The following are additional heading or section options that may appear within these:

- Objectives (within Introduction/Background): a clear statement of the main aim of the study and the major hypothesis tested or research question posed
- Design (within Methods): including factors such as prospective, randomisation, blinding, placebo control, case control, crossover, criterion standards for diagnostic tests, etc.
- Setting (within Methods): level of care, e.g. primary, secondary, number of participating centres.
- Participants (instead of patients or subjects; within Methods): numbers entering and completing the study, sex, age and any other biological, behavioural, social or cultural factors (e.g. smoking status, socioeconomic group, educational attainment, co-existing disease indicators, etc)that may have an impact on the study results. Clearly define how participants were enrolled, and describe selection and exclusion criteria.
- Interventions (within Methods): what, how, when and for how long. Typically for randomised controlled trials, crossover trials, and before and after studies.
- Main outcome measures (within Methods): those as planned in the protocol, and those ultimately measured. Explain differences, if any.

Results

- Start with description of the population and sample. Include key characteristics of comparison groups.
- Main results with (for quantitative studies) 95% confidence intervals and, where appropriate, the exact level of statistical significance and the number need to treat/harm. Whenever possible, state absolute rather than relative risks.
- Do not replicate data in tables and in text.
- If presenting mean and standard deviations, specify this clearly. Our house style is to present this as follows:
- E.g.: The mean (SD) birth weight was 2 500 (1 210) g. Do not use the ± symbol for mean (SD).
- Leave interpretation to the Discussion section. The Results section should just report the findings as per the Methods section.

Discussion

Please ensure that the discussion is concise and follows this overall structure – sub-headings are not needed:

- Statement of principal findings
- Strengths and weaknesses of the study
- Contribution to the body of knowledge
- Strengths and weaknesses in relation to other studies
- The meaning of the study – e.g. what this study means to clinicians and policymakers
- Unanswered questions and recommendations for future research

Conclusions

This may be the only section readers look at, therefore write it carefully. Include primary conclusions and their implications, suggesting areas for further research if appropriate. Do not go beyond the data in the article.

Editorials

Guideline word limit: 1 000 words

These opinion or comment articles are usually commissioned but we are happy to consider and peer review unsolicited editorials. Editorials should be accessible and interesting to readers without specialist knowledge of the subject under discussion and should have an element of topicality (why is a comment on this issue relevant now?) There should be a clear message to the piece, supported by evidence.

Please make clear the type of evidence that supports each key statement, e.g.:

- expert opinion
- personal clinical experience
- observational studies
- trials
- systematic reviews.

CME (by invite only)

CME is intended to provide readers with practical, up-to-date information on medical and related matters. It is aimed at those who are not specialists in the field.

From January 2016, all CME articles will be printed in full in the *SAMJ*. Please try to adhere strictly to the guidelines on word count as we have a page limit for the print issue of the *SAMJ*. We reserve the right to place some tables and reference lists online if this is necessary for space.

In practice, this means that each CME topic usually covers two issues of the print issue of the *SAMJ*.

The guest editor, in consultation with the editor, is responsible for convening a team of authors, deciding on the subjects to be covered and for reviewing the manuscripts submitted. The suggestion is for 4 - 5 articles, although there is some room for flexibility contingent on discussions with the editor.

For queries about these guidelines please feel free to contact the CME editor, Dr Bridget Farham, by email (ugqirha@iafrica.com) or telephone (+27 (0)82 452 2860)

Review process

The guest editor reviews the articles and returns them to the CME editor for review and final approval.

Guest editorials

Guideline word limit: 1 000 words

- Include the guest editor's personal details (qualifications, positions, affiliation, e-mail address, and a short personal profile (50words)).

- If possible, include a photograph of the author(s) at high enough resolution for print. It is preferable to provide two guest editorials, one for each issue, so that the content of the articles in each issue is covered.

Articles

Guideline word limit: 2 000 - 3 000 words

- Each article requires an abstract of ±200 words.
- The editor reserves the right to shorten articles but will send a substantially shortened article back for author approval.

Personal details

Please supply: Your qualifications, position and affiliations and MP number (used for CPD points); Address, telephone number and fax number, and your e-mail address; and a short personal profile (50words)and a few words about your current fields of interest.

In Practice

Guideline word limit: 2 000 - 3 000words

This section includes articles that would previously have been accepted into the Forum section, and case reports.

In practice articles are those that draw attention to specific issues of clinical, economic or political interest regarding medicine and healthcare in southern Africa. They are assigned to a topic:

Case report
Clinical practice
Clinical alert
Issues in medicine
Issues in public health
Healthcare delivery
Medicine and the environment
Medicine and the law
Cochrane corner

An In Practice article should follow the following format – sub-headings are not necessary, but may be used for clarity:

- Author affiliations and qualifications: to be the same as for Research. Provide all authors' names and initials, qualifications and full affiliations, and corresponding author.
- Short abstract: does not need to be structured, but should capture the essential features of the article
- Introduction: the reason for the article and the issue being addressed

- Recent research, discussion, local policy around the issue – include your own research where appropriate
- All statements should be referenced and, if opinion only, this should be stated
- Discussion: how this article adds to the discussion around a particular topic
- If a clinical practice or policy point is at issue, this needs to be emphasised, using a box with highlights if appropriate.

Essentially In practice is an opportunity for a more discursive approach to topics of clinical, economic or political importance in southern African health systems. It is not an opportunity to put forward unsubstantiated opinions!

Case reports

The *SAMJ* has recently started to accept case reports. The cases must come from Africa, preferably southern Africa unless the condition is common to all African countries, and must be either a completely new description of a clinical condition or result (use Google!) or a case that highlights important practice or management issues.

Please use the following format for case reports:

- Title of case: do not include the words 'a case report' in the title
- Summary/abstract: up to 150 words summarising the case presentation and outcome
- Background: why is this case important and why did you write it up?
- Case presentation: presenting features, medical, social, family history as appropriate
- Case management: should be according to best practice, and if not, please explain why
- Investigations, if relevant: save space by simply saying 'normal' if, for example, renal function was completely normal, rather than listing normal results, highlight the abnormal – or indeed the normal if this is clinically significant
- Differential diagnosis, if relevant
- Treatment, if relevant
- Outcome and follow-up
- Discussion – a VERY BRIEF review of similar published cases
- Teaching points: 3 - 5 bullet points
- References: as per the *SAMJ* house style
- Tables and figures: keep to a minimum. Use clinical images where relevant – we need hi-res versions for print, and identifiable persons must have a consent form
- Patient consent: please include a statement about patient consent to a written case report. This should be uploaded as a supplementary file.

Clinical trials

Guideline word limit: 4000 words

As per the recommendations published by the International Committee of Medical Journal Editors (ICMJE), clinical trial research is any research that assigns individuals to an intervention, with or without a concurrent comparison/control group to study the cause-and-effect relationship between the intervention and health outcomes. All clinical trials should be registered with the appropriate national clinical trial registry (or any international

primary register, if relevant), and the trial registration number should be cited at the end of the abstract. Since 1st December 2005, all clinical trials conducted in South Africa have been required to be registered in the South African National Clinical Trials Register. The *SAMJ* therefore requires that clinical trials be registered in the relevant public trials registry at or before the time of first patient enrollment as a condition for publication. The trial registry name and registration number must be included in the manuscript.

Please refer to the general guidelines for all papers at the top of this article for additional requirements with respect to ethics approval, funding, author contributions, etc. The format of original research articles should be followed for reporting of clinical trial results.

Review articles

Guideline word limit: 4 000 words

These are welcome, but should be either commissioned or discussed with the Editor before submission. A review article should provide a clear, up-to-date account of the topic and be aimed at non-specialist hospital doctors and general practitioners.

Please ensure that your article includes:

- Abstract: unstructured, of about 100-150 words, explaining the review and why it is important
- Methods: Outline the sources and selection methods, including search strategy and keywords used for identifying references from online bibliographic databases. Discuss the quality of evidence.
- When writing: clarify the evidence you used for key statements and the strength of the evidence. Do not present statements or opinions without such evidence, or if you have to, say that there is little or no evidence and that this is opinion. Avoid specialist jargon and abbreviations, and provide advice specific to southern Africa.
- Personal details: Please supply your qualifications, position and affiliations and MP number (used for CPD points); address, telephone number and fax number, and your e-mail address; and a short personal profile (50 words) and a few words about your current fields of interest.

Correspondence (Letters to the Editor)

Guideline word limit: 500 words

Letters to the editor should relate either to a paper or article published by the SAMJ or to a topical issue of particular relevance to the journal's readership

- May include only one illustration or table
- Must include a correspondence address.

Book reviews

Guideline word limit: 400 words

Should be about 400 words and must be accompanied by the publication details of the book. Provide a hi-res image of the cover if possible (with permission from the copyright holder).

Obituaries

Guideline word limit: 400 words

Should be offered within the first year of the practitioner's death, and may be accompanied by a photograph.

Guidelines

Guidelines should always be discussed with the Editor prior to submission.

Because of the intensive review process required to ensure Guidelines are independent, evidence-based and free from commercial bias, they are usually published as a supplement to the *SAMJ*, the costs of which must be covered by sponsorship, advertising or payment by the guideline authors/association. We will provide a quote based on the expected length of the guideline and whether it is to appear online only, or in print, which must be accepted by the body putting the guidelines together before submitting the work to the SAMJ.

The Editor reserves the right to determine the scheduling of supplements. Understandably, a delay in publication must be anticipated dependent upon editorial workflow.

All guidelines should include a clear, transparent statement about all sources of funding and an explicit, clear statement of conflicts of interest of any of the participants in the guidelines about industry funding for lectures, research, conference participation etc.

All guidelines should be structured according to Agree II.

Please access this website before putting the guidelines together, download the Agree 11 instrument and use this to put the guidelines together.

All submitted guidelines will be sent to the local Agree II appraisal committee for review and must be endorsed by an appropriate body prior to consideration and all conflicts of interest expressed.

A structured abstract not exceeding 400 words (recommended sub-headings: *Background, Recommendations, Conclusion*) is required. Sections and sub-sections must be numbered consecutively (e.g. 1. Introduction; 1.1 Definitions; 2.etc.) and summarised in a Table of Contents.

Illustrations/photos/scans

- If illustrations submitted have been published elsewhere, the author(s) should provide consent to republication obtained from the copyright holder.
- Figures must be numbered in Arabic numerals and referred to in the text e.g. '(Fig. 1)'.
- Each figure must have a caption/legend: Fig. 1. Description (any abbreviations in full).
- All images must be of high enough resolution/quality for print.
- All illustrations (graphs, diagrams, charts, etc.) must be in PDF or jpeg form.
- Ensure all graph axes are labelled appropriately, with a heading/description and units (as necessary) indicated. Do not include decimal places if not necessary e.g. 0; 1.0; 2.0; 3.0; 4.0 etc.

- Scans/photos showing a specific feature e.g. *Intermediate magnification micrograph of a low malignant potential (LMP) mucinous ovarian tumour. (H&E stain).* –include an arrow to show the tumour.
- Each image must be attached individually as a 'supplementary file' upon submission (not solely embedded in the accompanying manuscript) and named Fig. 1, Fig. 2, etc.

Tables

- Tables should be constructed carefully and simply for intelligible data representation. Unnecessarily complicated tables are strongly discouraged.
- Large tables will generally not be accepted for publication in their entirety. Please consider shortening and using the text to highlight specific important sections, or offer a large table as an addendum to the publication, but available in full on request from the author
- Embed/include each table in the manuscript Word file - do not provide separately as supplementary files.
- Number each table in Arabic numerals (Table 1, Table 2, etc.) and refer to consecutively in the text.
- Tables must be cell-based (i.e. not constructed with text boxes or tabs) and editable.
- Ensure each table has a concise title and column headings, and include units where necessary.
- Footnotes must be indicated with consecutive use of the following symbols: * † ‡ § ¶ || then ** †† ‡‡ etc.

Do not: Use [Enter] within a row to make ‘new rows’:

Rather:
Each row of data must have its own proper row:

Do not: use separate columns for *n* and %:

Rather:
Combine into one column, *n* (%):

Do not: have overlapping categories, e.g.:

Rather:
Use <> symbols or numbers that don’t overlap:

References

NB: *Only complete, correctly formatted reference lists in Vancouver style will be accepted. Reference lists must be generated manually and not with the use of reference manager software. Endnotes must* ***not*** *be used.*

- Authors must verify references from original sources.
- Citations should be inserted in the text as superscript numbers between square brackets, e.g. These regulations are endorsed by the World Health Organization,[2] and others.[3,4-6]
- All references should be listed at the end of the article in numerical order of appearance in the Vancouver style (not alphabetical order).
- Approved abbreviations of journal titles must be used; see the List of Journals in Index Medicus.
- Names and initials of all authors should be given; if there are more than six authors, the first three names should be given followed by et al.
- Volume and issue numbers should be given.
- First and last page, in full, should be given e.g.: 1215-1217 **not** 1215-17.
- Wherever possible, references must be accompanied by a digital object identifier (DOI) link). Authors are encouraged to use the DOI lookup service offered by CrossRef:
  - On the Crossref homepage, paste the article title into the 'Metadata search' box.
  - Look for the correct, matching article in the list of results.
  - Click Actions > Cite
  - Alongside 'url =' copy the URL between { }.
  - Provide as follows, e.g.: https://doi.org/10.7196/07294.937.98x

Some examples:

- *Journal references:* Price NC, Jacobs NN, Roberts DA, et al. Importance of asking about glaucoma. Stat Med 1998;289(1):350-355. http://dx.doi.org/10.1000/hgjr.182
- *Book references:* Jeffcoate N. Principles of Gynaecology. 4th ed. London: Butterworth, 1975:96-101.
- *Chapter/section in a book:* Weinstein L, Swartz MN. Pathogenic Properties of Invading Microorganisms. In: Sodeman WA, Sodeman WA, eds. Pathologic Physiology: Mechanisms of Disease. Philadelphia: WB Saunders, 1974:457-472.
- *Internet references:* World Health Organization. The World Health Report 2002 - Reducing Risks, Promoting Healthy Life. Geneva: WHO, 2002. http://www.who.int/whr/2002 (accessed 16 January 2010).
- Legal references

  - Government Gazettes:

  National Department of Health, South Africa. National Policy for Health Act, 1990 (Act No. 116 of 1990). Free primary health care services. Government Gazette No. 17507:1514. 1996.

  In this example, 17507 is the Gazette Number. This is followed by :1514 - this is the notice number in this Gazette.

  - Provincial Gazettes:

  Gauteng Province, South Africa; Department of Agriculture, Conservation, Environment and Land Affairs. Publication of the Gauteng health care waste management draft regulations. Gauteng Provincial Gazette No. 373:3003, 2003.

  - Acts:

  South Africa. National Health Act No. 61 of 2003.

  - Regulations to an Act:

South Africa. National Health Act of 2003. Regulations: Rendering of clinical forensic medicine services. Government Gazette No. 35099, 2012. (Published under Government Notice R176).

- Bills:

South Africa. Traditional Health Practitioners Bill, No. B66B-2003, 2006.

- Green/white papers:

South Africa. Department of Health Green Paper: National Health Insurance in South Africa. 2011.

- Case law:

Rex v Jopp and Another 1949 (4) SA 11 (N)

Rex v Jopp and Another: Name of the parties concerned

1949: Date of decision (or when the case was heard)

(4): Volume number

SA: SA Law Reports

11: Page or section number

(N): In this case Natal - where the case was heard. Similarly, (C) woud indicate Cape, (G) Gauteng, and so on.

NOTE: no . after the v

- *Other references (e.g. reports) should follow the same format:* Author(s). Title. Publisher place: Publisher name, year; pages.
- Cited manuscripts that have been accepted but not yet published can be included as references followed by '(in press)'.
- Unpublished observations and personal communications in the text must **not** appear in the reference list. The full name of the source person must be provided for personal communications e.g. '...(Prof. Michael Jones, personal communication)'.

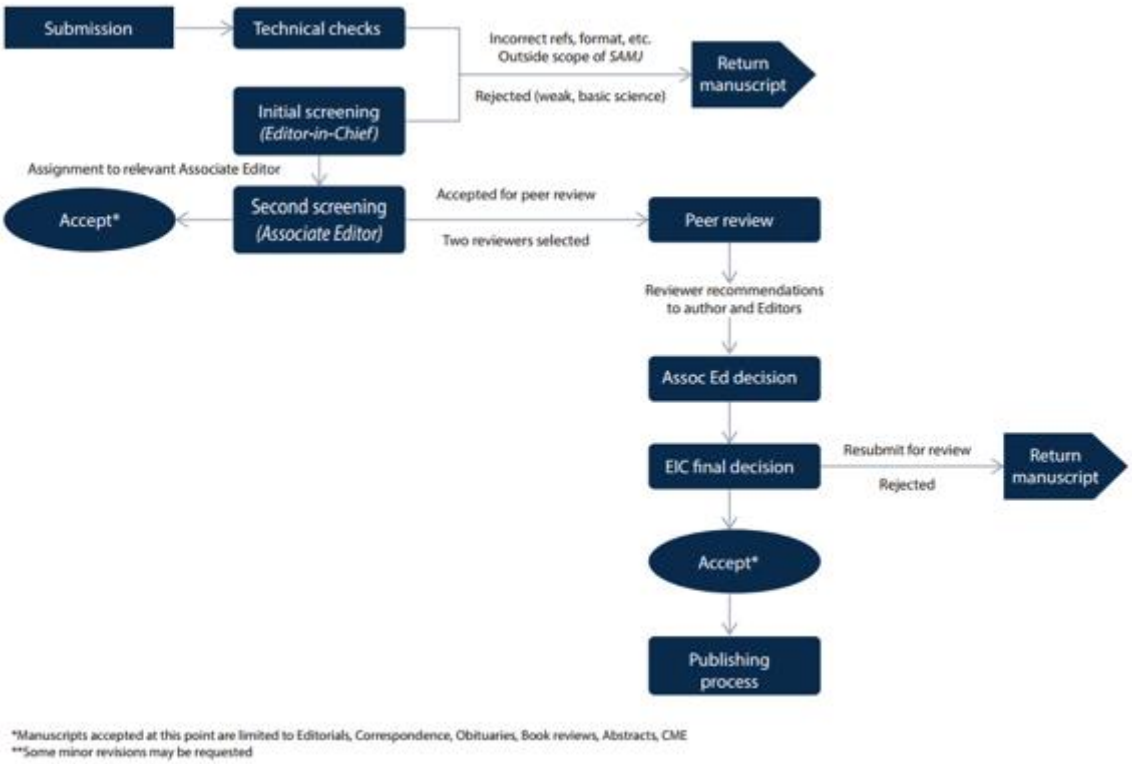
From submission to acceptance

Submission and peer-review

To submit an article:

- Please ensure that you have prepared your manuscript in line with the SAMJ requirements.
- All submissions should be submitted via Editorial Manager
- The following are required for your submission to be complete:
  - Anonymous manuscript (unless otherwise stated)
  - Manuscript
  - Any supplementary files: figures, datasets, patient consent form, permissions for published images, etc.
- Once the submission has been successfully processed on Editorial Manager, it will undergo a technical check by the Editorial Office before it will be assigned to an editor who will handle the review process. If the author guidelines have not been appropriately followed, the manuscript may be sent back to the author for correcting.

Peer-review process



Production process

Please note that there is a 6-month waiting time for publication, once an article has been sent to the production team.

The following process will follow:

1. An accepted manuscript is passed to a Managing Editor to assign to a copyeditor (CE).
2. The CE copyedits in Word, working on house style, format, spelling/grammar/punctuation, sense and consistency, and preparation for typesetting.
3. If the CE has an author queries, he/she will contact the corresponding author and send them the copyedited Word doc, asking them to solve the queries by means of track changes or comment boxes.
4. The authors are typically asked to respond within 1-3 days. Any comments/changes must be clearly indicated e.g. by means of track changes. Do not work in the original manuscript - work in the copyedited file sent to you and make your changes clear.
5. The CE will finalise the article and then it will be typeset.
6. Once typeset, the CE will send a PDF of the file to the authors to complete their final check, while simultaneously sending to the 2nd-eye proofreader.
7. The authors are typically asked to complete their final check and sign-off within 1-2 days. No major additional changes can be accommodated at this point.

8. The CE implements the authors' and proofreader's mark-ups, finalises the file, and prepares it for the upcoming issue.

Changing contact details or authorship

Please notify the Editorial Department of any contact detail changes, including email, to facilitate communication.

Publication

Online v. print

The *SAMJ* is an online journal. The online version of the journal is the one that has the widest circulation, is indexed by bibliographic databases including PubMed and SciELO, and is accessible in academic libraries. A printed edition , containing material selected by the Editor is also published each month and distributed to the membership of the South African Medical Association.

Online

- The full text of all accepted articles is published in full online, open access.
- Citation information of each article is based on its online publication.
- You may want to make use of the advantages of online publication e.g. specify web links to other sources, images, data or even a short video.

Print

- Not all articles will be selected for print.
- An article may be selected for print in a different month from that in which it was published online.
- Research articles will appear *in abstract form only*, if selected for a print edition.

Errata and retractions

Errata

Should you become aware of an error or inaccuracy in yours or someone else's contribution after it has been published, please inform us as soon as possible via an email to publishing@hmpg.co.za,including the following details:

- Journal, volume and issue in which published
- Article title and authors
- Description of error and details of where it appears in the published article
- Full detail of proposed correction and rationale

We will investigate the issue and provide feedback. If appropriate, we will correct the web version immediately, and will publish anerratum in the next issue. The correction will be indexed, as PubMed has a function for linking errata back to the original article. All investigations will be conducted in accordance with guidelines provided by the Committee on Publication Ethics (COPE).

Retractions

Retraction of an article is the prerogative of either the original authors or the editorial team of HMPG. Should you wish to withdraw your article before publication, we need a signed statement from all the authors.

Should you wish to retract your published article, all authors have to agree in writing before publication of the retraction.

Send an email to publishing@hmpg.co.za, including the following details:

- Journal, volume and issue to which article was submitted/in which article was published
- Article title and authors
- Description of reason for withdrawal/retraction.

We will make a decision on a case-by-case basis upon review by the editorial committee in line with international best practices. Comprehensive feedback will be communicated with the authors with regard to the process. In case where there is any suspected fraud or professional misconduct, we will follow due process as recommended by the Committee on Publication Ethics (COPE), and in liaison with any relevant institutions.

When a retraction is published, it will be linked to the original article.

Indexing

The *SAMJ* has an impact factor of 1.5.

Published articles are covered by the following major indexing services. As such articles published in the *SAMJ* are immediately available to all users of these databases, guaranteed a global and African audience:

- Index Medicus (Medline/PubMed)
- ExcerptaMedica (EMBASE)
- Biological Abstracts (BIOSIS)
- Science Citation Index (SciSearch)
- Current Contents/Clinical Medicine
- Scopus
- AIM
- AJOL
- Crossref
- Sabinet
- Scielo

Sponsored supplements

Contact claudian@hmpg.co.za for information on submitting ad hoc/commissioned supplements, including guidelines, conference/congress abstracts, Festschrifts, etc.

Submission Preparation Checklist

As part of the submission process, authors are required to check off their submission's compliance with all of the following items, and submissions may be returned to authors that do not adhere to these guidelines.

1. Named authors consent to publication and meet the requirements of authorship as set out by the journal.
2. The submission has not been previously published, nor is it before another journal for consideration. All research already published as 'Conference proceedings' needs to be substantially re-written, with a new title, a new abstract and new and important results to back up any study before it will be considered for a new publication.
3. The text complies with the stylistic and bibliographic requirements in **Author Guidelines**.
4. The manuscript is in Microsoft Word document format. The text is single-spaced, in 12-point Times New Roman font, and contains no unnecessary formatting.
5. Illustrations/figures are high resolution/quality (not compressed) and in an acceptable format (PDF or jpeg). These must be submitted individually as 'supplementary files' (not solely embedded in the manuscript).
6. For illustrations/figures or tables that have been published elsewhere, the author has obtained written consent to republication from the copyright holder.
7. Where possible, references are accompanied by a digital object identifier (DOI).
8. An abstract has been included where applicable.
9. The research was approved by a Research Ethics Committee (if applicable)
10. Any conflict of interest (or competing interests) is indicated by the author(s).

APPENDIX 7: STARD REPORTING GUIDELINES

STARD 2015

AIM

STARD stands for "Standards for Reporting Diagnostic accuracy studies". This list of items was developed to contribute to the completeness and transparency of reporting of diagnostic accuracy studies. Authors can use the list to write informative study reports. Editors and peer-reviewers can use it to evaluate whether the information has been included in manuscripts submitted for publication.

EXPLANATION

A **diagnostic accuracy study** evaluates the ability of one or more medical tests to correctly classify study participants as having a **target condition.** This can be a disease, a disease stage, response or benefit from therapy, or an event or condition in the future. A medical test can be an imaging procedure, a laboratory test, elements from history and physical examination, a combination of these, or any other method for collecting information about the current health status of a patient.

The test whose accuracy is evaluated is called **index test.** A study can evaluate the accuracy of one or more index tests. Evaluating the ability of a medical test to correctly classify patients is typically done by comparing the distribution of the index test results with those of the **reference standard**. The reference standard is the best available method for establishing the presence or absence of the target condition. An accuracy study can rely on one or more reference standards.

If test results are categorized as either positive or negative, the cross tabulation of the index test results against those of the reference standard can be used to estimate the **sensitivity** of the index test (the proportion of participants *with* the target condition who have a positive index test), and its **specificity** (the proportion *without* the target condition who have a negative index test). From this cross tabulation (sometimes referred to as the contingency or "2x2" table), several other accuracy statistics can be estimated, such as the positive and negative **predictive values** of the test. Confidence intervals around estimates of accuracy can then be calculated to quantify the statistical **precision** of the measurements.

If the index test results can take more than two values, categorization of test results as positive or negative requires a **test positivity cut-off**. When multiple such cut-offs can be defined, authors can report a receiver operating characteristic (ROC) curve which graphically represents the combination of sensitivity and specificity for each possible test positivity cut-off. The **area under the ROC curve** informs in a single numerical value about the overall diagnostic accuracy of the index test.

The **intended use** of a medical test can be diagnosis, screening, staging, monitoring, surveillance, prediction or prognosis. The **clinical role** of a test explains its position relative to existing tests in the clinical pathway. A replacement test, for example, replaces an existing test. A triage test is used before an existing test; an add-on test is used after an existing test.

Besides diagnostic accuracy, several other outcomes and statistics may be relevant in the evaluation of medical tests. Medical tests can also be used to classify patients for purposes other than diagnosis, such as staging or prognosis. The STARD list was not explicitly developed for these other outcomes, statistics, and study types, although most STARD items would still apply.

DEVELOPMENT

This STARD list was released in 2015. The 30 items were identified by an international expert group of methodologists, researchers, and editors. The guiding principle in the development of STARD was to select items that, when reported, would help readers to judge the potential for bias in the study, to appraise the applicability of the study findings and the validity of conclusions and recommendations. The list represents an update of the first version, which was published in 2003.

More information can be found on http://www.equator-network.org/reporting-guidelines/stard.

Section & Topic	No	Item
TITLE OR ABSTRACT		
	1	Identification as a study of diagnostic accuracy using at least one measure of accuracy (such as sensitivity, specificity, predictive values, or AUC)
ABSTRACT		
	2	Structured summary of study design, methods, results, and conclusions (for specific guidance, see STARD for Abstracts)
INTRODUCTION		
	3	Scientific and clinical background, including the intended use and clinical role of the index test
	4	Study objectives and hypotheses
METHODS		
Study design	**5**	Whether data collection was planned before the index test and reference standard were performed (prospective study) or after (retrospective study)
Participants	**6**	Eligibility criteria
	7	On what basis potentially eligible participants were identified (such as symptoms, results from previous tests, inclusion in registry)
	8	Where and when potentially eligible participants were identified (setting, location and dates)
	9	Whether participants formed a consecutive, random or convenience series
Test methods	**10a**	Index test, in sufficient detail to allow replication
	10b	Reference standard, in sufficient detail to allow replication
	11	Rationale for choosing the reference standard (if alternatives exist)
	12a	Definition of and rationale for test positivity cut-offs or result categories of the index test, distinguishing pre-specified from exploratory
	12b	Definition of and rationale for test positivity cut-offs or result categories of the reference standard, distinguishing pre-specified from exploratory
	13a	Whether clinical information and reference standard results were available to the performers/readers of the index test
	13b	Whether clinical information and index test results were available to the assessors of the reference standard
Analysis	**14**	Methods for estimating or comparing measures of diagnostic accuracy
	15	How indeterminate index test or reference standard results were handled
	16	How missing data on the index test and reference standard were handled
	17	Any analyses of variability in diagnostic accuracy, distinguishing pre-specified from exploratory
	18	Intended sample size and how it was determined
RESULTS		
Participants	**19**	Flow of participants, using a diagram
	20	Baseline demographic and clinical characteristics of participants
	21a	Distribution of severity of disease in those with the target condition
	21b	Distribution of alternative diagnoses in those without the target condition
	22	Time interval and any clinical interventions between index test and reference standard
Test results	**23**	Cross tabulation of the index test results (or their distribution) by the results of the reference standard
	24	Estimates of diagnostic accuracy and their precision (such as 95% confidence intervals)
	25	Any adverse events from performing the index test or the reference standard
DISCUSSION		
	26	Study limitations, including sources of potential bias, statistical uncertainty, and generalisability
	27	Implications for practice, including the intended use and clinical role of the index test
OTHER INFORMATION		
	28	Registration number and name of registry
	29	Where the full study protocol can be accessed
	30	Sources of funding and other support; role of funders