International normalised ratio control in a non-metropolitan setting in Western Cape Province, South Africa

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Declaration

I, Dawid Nicolaas Prinsloo, hereby declare that the work on which this dissertation/thesis is based is my original work (except where acknowledgements indicate otherwise) and that neither the whole work nor any part of it has been, is being, or is to be submitted for another degree in this or any other university. No part of this work has been reported or published prior to registration for the abovementioned degree.

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Format and contributions

This thesis is presented in the Published/Publication-ready format. The findings of this research were published in a manuscript with the title *“International normalised ratio control in a non-metropolitan setting in Western Cape Province, South Africa”* in the South African Medical Journal (Citation: *Prinsloo DN, Gould TJ, Viljoen CA, Basera W, Ntsekhe M. International normalised ratio control in a non-metropolitan setting in Western Cape Province, South Africa. S Afr Med J. 2021;111(4):355-360. https://doi.org/10.7196/SAMJ.2021.v111i4.15171*).

DN Prinsloo conceptualised the study, collected and analysed the data and wrote the manuscript. TJ Gould assisted with conceptualisation of study, and with reviewing and editing of the manuscript. CA Viljoen assisted with data analysis and editing of the manuscript. W Basera assisted with data analysis and reviewing of the manuscript. M Ntsekhe assisted with conceptualisation of study and with the analytical approach, and revised and edited the manuscript.

Note regarding official name change of “Eden District” to “Garden Route District”

At the time of the original application for ethical and provincial approval for this research the current “Garden Route District Municipality” was still named as the “Eden District Municipality”. Subsequently the name was changed by the Western Cape Provincial Government. The former name appears on the study protocol title and the ethical approval documents as well as the provincial approval document as these documents were submitted before the name change. A name change of the original title of the dissertation was requested as it still referred to the “Eden District”. Where the former “Eden District” is mentioned in the protocol or on documents in the appendices it refers to the “Garden Route District”.

List of abbreviations

Time in Therapeutic Range (TTR)

Primary Healthcare Clinic (PHC)

Interquartile range (IQR)

National Health Laboratory Service (NHLS)

Point-of-care (PoC)

Venous thromboembolism (VTE)

Odds Ratio (OR)

Confidence Interval (CI)

Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET AF)

Randomised Evaluation of Long-Term Anticoagulation Therapy trial (RE-LY)

Clopidogrel Trial with Irbesartan for prevention of Vascular Events (ACTIVE W)

American College of Chest Physicians (ACCP)

Non-vitamin K oral anticoagulant (NOAC)

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1. Published manuscript

International normalised ratio control in a non-metropolitan setting in Western Cape Province, South Africa

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Abstract

Background

The quality of international normalised ratio (INR) control determines the effectiveness and safety of warfarin therapy. Data on INR control in non-metropolitan settings of South Africa (SA) are sparse.

Objectives

To examine the time in therapeutic range (TTR) and its potential predictors in a sample of Garden Route District Municipality primary healthcare clinics (PHCs).

Methods

INR records from eight PHCs were reviewed. The TTR and percentage of patients with a TTR >65% were determined. A host of variables were analysed for association with TTR.

Results

The median (interquartile range (IQR)) age of the cohort (*N*=191) was 56 (44 - 69) years. The median (IQR) TTR was 37.2% (20.2 - 58.8); only 17.8% of patients had a TTR ≥65%. Compared with patients aged >50 years, those aged <50 had worse INR control (median (IQR) TTR 26.6% (16.1 - 53.0) v. 43.5% (23.5 - 60.1); *p*=0.01). Patients hospitalised for any reason during the study period had worse INR control than patients not hospitalised (median (IQR) TTR 26.2% (16.2 - 50.2) v. 42.9% (23.5 - 62.0); *p*=0.02). On multivariable regression analysis, participants on warfarin for atrial fibrillation/flutter had better INR control than those with other indications for warfarin (odds ratio 2.21; 95% confidence interval 1.02 - 4.77; *p*=0.04), but the control was still very poor.

Conclusions

INR control, as determined by TTR and proportion of TTR ≥65%, in these non-metropolitan clinics was poor. Age and hospitalisation as a marker of illness predicted poor control. There was a difference in control between groups, depending on the

indication for warfarin. Evidence-based measures to improve the quality of INR control in patients on warfarin therapy need to be instituted as a matter of urgency.

Introduction

Warfarin is the most commonly used anticoagulant worldwide. The effectiveness of warfarin therapy in reducing morbidity and mortality related to thromboembolic disease is well established.[1] The degree of anticoagulation effected by warfarin is determined by measuring the prothrombin time and is reported as the international normalised ratio (INR).[1] The INR is influenced by a variety of factors that contribute to the complexity of warfarin therapy.[1] Warfarin has a narrow therapeutic index; in order to maximise the benefit from warfarin therapy while avoiding the risk of bleeding, the INR needs to be maintained within a target range for a period above a minimum amount of time.[2,3] This is known as the time in therapeutic range (TTR). A minimum TTR of 65% is required for warfarin therapy to be regarded as effective. Below this value, warfarin is unlikely to prevent thromboembolic disease effectively, and the risk of bleeding complications increases.[4,5] The TTR is a useful, albeit imperfect, parameter by which the quality of anticoagulation is estimated.[6]

Warfarin is the only readily available oral anticoagulant in the public health sector in South Africa (SA). There is a paucity of data regarding the quality of INR control, as well as the complications associated with poor INR control, in non-metropolitan and rural SA settings. Previous studies conducted in metropolitan areas in SA and in the wider sub-Saharan Africa region have shown INR control to be poor.[4,7-14] The quality of INR control in non-metropolitan and rural primary healthcare clinic (PHC) settings in SA is largely unknown. This lack of data is particularly important in light of the relative scarcity of resources and facilities and limited ability to manage complications related to poor INR control such as bleeding, stroke, peripheral emboli and valve thromboses in these settings.

The Garden Route District Municipality is situated in the south-eastern part of Western Cape Province, SA. There are no dedicated anticoagulation clinics in the district, and patients requiring anticoagulation therapy are referred to their nearest PHC for initiation and/or continuation of warfarin therapy. INR testing is offered 24 hours a day at George Regional Hospital by the National Health Laboratory Service (NHLS). There are no standardised manual or computer-based algorithms regulating dosage adjustments or

follow-up. Point-of-care (PoC) testing and self-testing are not currently available in the district. Samples are transported daily from distant PHC facilities and satellite clinics to George Regional Hospital for analysis, with some clinics >90 km away from the laboratory. The resultant delay in processing of samples often leads to delayed adjustment of warfarin dosage, as well as questionable results in some instances. Patients are often required to return to their local clinics on another day to obtain their results and have adjustments made to their therapy.

Objectives

To examine the quality of INR control in PHC clinics in a non-metropolitan/rural setting in SA and assess the relationship between INR control and specific demographic and clinical factors over a 12-month period. The specific objectives were to calculate the TTR and the proportion of patients with a TTR ≥65%; to analyse INR control stratified by age (≥50 years), sex, employment status, government support grant status and indication for warfarin; and to determine the influence of all-cause hospital admissions during the study period on INR control. Furthermore, the association between TTR and the frequency of INR testing and early follow-up of out-of-range results with repeat testing was assessed. No outcomes of INR control were assessed in this study.

Methods

Study design

The study was a retrospective review of the records and available results of patients who underwent INR testing for the purpose of monitoring warfarin therapy at PHCs in the Garden Route District Municipality between July 2016 and June 2017.

Participating clinics

In order to represent different non-metropolitan and rural settings in the Garden Route District Municipality, eight PHCs were non-randomly selected. Four clinics from small town centres, two clinics situated in townships and two rural satellite clinics were included.

Ethical considerations

Ethical approval for the study was granted by the University of Cape Town Human Research Ethics Committee (ref. no. 785/2017). Permission was obtained before data were made available from the NHLS. Permission for research and data collection in the PHCs was obtained from the Western Cape provincial government (ref. no. WC_201711_028). As this was a retrospective review with no patient interaction, informed consent was not obtained.

Patient population

All patients aged ≥18 years who were on warfarin therapy and had INR testing performed during the study period were eligible. Those with an unknown indication for warfarin and/or <2 INRs performed during the study period were excluded.

Data collection

INR values were obtained from the NHLS database. Patient files were extracted at the relevant healthcare facilities to obtain the age, sex, employment status, indication for warfarin therapy, and whether the patient required hospital admission during the study period. The records were deidentified and anonymised. The TTR was calculated using the Rosendaal method of linear interpolation, which assumes linear increases and decreases of the INR between successive INR values over time. From this assumption, the time period during which the INR falls within the predetermined therapeutic range can be calculated and can be converted to a percentage of total time.[6,15] For mechanical valve replacement an INR of 2.5 - 3.5 was regarded as therapeutic, and for all other indications a range of 2 - 3 was regarded as therapeutic.[16]

Statistical analysis

Statistical analysis was performed using Stata version 14.2 (StataCorp, USA). Descriptive statistics were used to summarise data. Continuous variables were summarised as means with standard deviations for parametric data or medians with interquartile ranges (IQRs) for non-parametric data. Categorical variables were

expressed as frequencies and percentages. Variables evaluated for association with INR control are shown in Table 1.

For age and TTR, categorical variables were created (age <50 years, TTR ≥65%). Continuous variables (i.e. TTR) were compared for age <50, sex and hospital admission during study period, using either Student's *t*-test for parametric data or the Wilcoxon rank-sum test for non-parametric data. Categorical variables (i.e. TTR ≥65%) were compared for age <50, sex and hospital admission during the study period using χ^2 and Fisher's exact tests. Univariable regression analysis was performed using the following variables: age <50, sex, employment status, indication for anticoagulation therapy, and hospital admission during the study period. Variables significantly associated with a TTR ≥65% (p<0.05) were used for the multivariable regression model. A fit of the model was assessed using the Hosmer-Lemeshow goodness-of-fit test. The association between TTR and the number of INRs per patient, the time interval between tests and the percentage of out-of-range INRs that were followed up within 7 days with a repeat test was measured with a Spearman rank test. An r^2 value approaching 1 showed high levels of correlation between TTR and the number of INR tests, time interval between tests and percentage of out-of-range tests followed up within 7 days with a repeat test. A p-value <0.05 was considered statistically significant.

Results

Study population

Of the 287 eligible participants, 191 met all the stipulated inclusion and exclusion criteria (Fig. 1). The median (IQR) age of the study population was 56 (44 - 69) years, and the majority of the participants (56.5%) were unemployed women on government support grants. In descending order, the three most common indications for warfarin therapy were atrial fibrillation/ flutter (42.4%), venous thromboembolism (VTE) (28.8%) and mechanical prosthetic heart valves (24.1%) (Table 2).

Over the study period, a total of 2 635 INR tests were available for analysis. The median (IQR) TTR was 37.2% (20.2 - 58.8). Only 17.8% of patients had a TTR ≥65%.

Table 3 outlines the TTR and percentage TTR ≥65% stratified by age (above and below 50 years), sex, employment status, grant status, indication for warfarin, and all-cause hospital admission during the study period.

Regarding the TTR for different indications for warfarin, patients with atrial fibrillation and flutter had a median (IQR) TTR of 44.5% (25.3 - 62.3), patients with VTE a median of 26.7% (9.6 - 53.0), patients with a mechanical valve replacement a median of 38.3% (20.0 - 58.7), patients with antiphospholipid syndrome a median of 34.9 (6.3 - 50.1) and those with a left ventricular thrombus a median of 48.2% (11.5 - 71.7). Patients who were employed had a median (IQR) TTR of 28.8% (15.4 - 51.9), unemployed patients a median of 29.3% (16.2 - 59.1) and those receiving a government support grant a median of 46.8% (27.1 - 62.0). The results of the univariable and multivariable regression analysis for demographic and clinical factors associated with a TTR ≥65% are summarised in Table 4.

The multivariable regression analysis showed better INR control for patients with atrial fibrillation or flutter compared with other indications (odds ratio (OR) 2.21; 95% confidence interval (CI) 1.02 - 4.77; p=0.04). Patients who were hospitalised during the study period had worse INR control than those who were not hospitalised (OR 0.39; 95% CI 0.15 - 0.98; p=0.05). However, this did not remain significant in the multivariable model (OR 0.39; 95% CI 0.15 - 1.03; p=0.06). As shown in Table 5, no significant associations were found between TTR and total INR tests, INR testing frequency, or percentage of repeat testing for out-of-range values within 7 days.

Discussion

This is the first comprehensive study to assess the quality of INR control in a non-metropolitan PHC setting in SA. There were two major findings. First, the quality of INR monitoring in the eight broadly representative PHCs included was poor, as evidenced by a median TTR of 37.2% and a TTR ≥65% of 17.8%. Second, we found that the only clinical, demographic or social predictors of poor INR control were age and the need for hospitalisation. Patients with atrial fibrillation/flutter had better INR control than those with other indications for warfarin, but the TTR was well below acceptable effective

levels. There was lack of a significant association between TTR and all other variables included in our models.

We did not assess patient outcomes in the study. However, given the well-established relationships between poor INR control and major adverse events, the finding that 82.2% of our patients were unlikely to derive any significant benefit from warfarin therapy, and were at increased risk of developing thrombotic and thromboembolic (as well as haemorrhagic) complications, is concerning.

Our findings correlate with a limited number of previous studies in SA and confirm that INR control in the public health sector in SA, and particularly in rural settings, is poor.[7-9] Importantly, our findings suggest that compared with INR control in urban and peri-urban anticoagulation clinics, INR control outside these settings is worse. In the Cape Town metropolitan area, Barth *et al*.[7] demonstrated a mean TTR of 42% in patients with rheumatic heart disease without previous mitral valve replacement surgery, and 67% in patients who had had a previous mitral valve replacement. However, the study sample was small and only 334 INRs were analysed. Sonuga *et al*.[9] demonstrated, in a cross-section-of-files review at a secondary-level hospital INR clinic in Cape Town, that 48.5% of INRs were outside the target range. Only 136 INR values were included in the analysis. Ebrahim *et al*.[8] compared the TTR at two INR clinics in the Cape Town metropolitan area and calculated a mean TTR of 47%, with only 25.1% of patients having a TTR ≥65%.[8]

Data from large multicentre international trials also give some insight into the quality of INR control for atrial fibrillation in SA. Three large international multicentre trials, namely the Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET AF), the Randomised Evaluation of Long-Term Anticoagulation Therapy trial (RE-LY), and the Clopidogrel Trial with Irbesartan for prevention of Vascular Events (ACTIVE W), all demonstrated mean TTRs <60% for patients in the SA cohorts. In all three trials there was little difference in INR control between SA public and private sites.[4,12,13]

The data from studies performed in developed countries, metropolitan settings or dedicated INR clinics cannot be assumed to apply to non-metropolitan or rural settings

where dedicated INR clinics are lacking and a unique set of challenges exist. Many patients in rural settings live more remotely from PHCs than their counterparts in metropolitan areas, and readily available transport to and from clinics is not guaranteed. Public infrastructure, such as roads, and public transport in many of these areas in SA are less well developed, posing a further challenge to regular easy access to healthcare, particularly for ill and frail patients who require care most. Many rural areas are serviced by satellite or mobile clinics for their health needs on an interval basis only. Community service medical officers and nurses play a vital role in staffing the rural and remote health facilities across SA. These staff members are required to practise in more remote areas with less clinical experience and supervision, and regular turnover of staff is commonplace.[17] Access to laboratory services and INR testing is a further challenge in rural areas. Samples need to be transported to distant laboratories, exposing the samples to degradation, and results are not always timeously available. Patients may need to return for results on different days in order for adjustments to be made to warfarin dosages. Cellphone and internet signal is not always available in rural areas for telephonic dose adjustments to be facilitated. These factors make our findings particularly relevant in the broader SA context. The vast majority of South Africans are dependent on government facilities for their healthcare. Furthermore, the healthcare needs of the majority of South Africans are serviced by PHCs, many of which are under-resourced, under-staffed and located far from the nearest regional or tertiary facility.[18]

Previous studies have looked at the association between various demographic and clinical factors and TTR. Factors found to be associated with poor INR control included younger age, patients from poorer communities, alcohol abuse, smoking and substance abuse.[19] Concurrent medication use, medical comorbidities (cancer, chronic liver or kidney disease) and increased hospitalisation were also associated with poor INR control, with increased hospitalisation in this context being an indirect measure of sicker patients with more drug interactions and comorbidities as opposed to an outcome variable related to poor INR control.[19,20] Our study confirms the finding of worse INR control in younger patients and patients hospitalised for any reason during the study period. The reasons why younger patients have worse INR control are likely complex and varied, and might have to do with HIV and Tuberculosis related VTE and conditions

such as antiphospholipid syndrome requiring anticoagulation as opposed to non-valvular atrial fibrillation. These conditions are chronic and complex with the potential for more drug-drug interactions during treatment and difficulties with polypharmacy and adherence to therapy.

In our study, only 22.2% of out-of-range tests were followed up with a repeat test within 7 days. There is limited evidence guiding the optimal frequency of INR testing. The frequency of testing is influenced by the stability of the INR over time, the INR response to dose adjustment, and whether a patient is admitted or managed as an outpatient.[21] After initiation of therapy or dose adjustments as an outpatient, the American College of Chest Physicians (ACCP) recommends more frequent INR testing until the INR is stable and then at least every 4 weeks.[22] The ACCP furthermore recommends a monitoring frequency of up to once every 12 weeks in patients with stable INRs who have required no dose adjustments for a period of 3 months.[16] It has been shown that shorter intervals between INR tests are associated with better INR control.[22] In our study, no association could be shown between more frequent INR testing and TTR. A larger sample size would be required to further investigate the association between the frequency of INR testing and TTR, as well as clinical outcomes.

Standardised protocols recommending algorithm-based dosage adjustments of warfarin therapy, instead of adjustments based on clinical experience, have been associated with improvements in TTR. [13,23] Furthermore, standardized counselling before warfarin initaiation and the provision of information by means of patient information leaflets regarding important dietary considerations while on warfarin could also potentially improve patient understanding and involvement during treatment with warfarin. Algorithm-based computer programs recommending dose adjustments and scheduling follow-up testing have also been shown to improve TTR.[24,25] In the Garden Route District Municipality, standardised algorithms and protocols are not used to guide decision-making regarding warfarin therapy, and dose adjustments are made at the discretion of the treating clinician.

Self-testing and self-monitoring of the INR in appropriately selected patients using PoC devices has been associated with improved patient satisfaction and TTR, and a

reduction in clinical thromboembolic events with no increase in adverse events.[16,26-28] PoC testing is an appealing alternative to the routine laboratory measurement of the INR, particularly in rural resource-limited settings. In settings similar to the Garden Route District Municipality, specimens often need to be transported long distances for analysis. Furthermore, patients often need to come back to the facility on a different day to get their INR result for dosage adjustments to be made. A number of PoC devices are on the market. There have been concerns about the reliability of PoC INR results across different devices and compared with laboratory measurements. However, PoC testing is accepted as a reliable option for INR monitoring, with specific advantages over routine laboratory testing.[29] It is important to note that PoC INR values that are out of range, particularly above range, do become discrepant from laboratory values and need confirmation with laboratory testing.[30] PoC testing may play an important role in improving the effectiveness of warfarin therapy in SA.

Finally, a number of non-vitamin K oral anticoagulants (NOACs) are available in SA (rivaroxaban, dabigatran, apixaban). As a class, these agents have been shown to be non-inferior or superior to warfarin therapy in patients with non-valvular atrial fibrillation, with significantly better safety profiles, and are the preferred agents for the treatment of VTE.[31-34] Patients with valve lesions were excluded from these pivotal trials. The advantages of the use of these agents instead of warfarin include a much quicker onset of therapeutic levels of anticoagulation, a fixed drug dose with predictable levels of anticoagulation, fewer food and drug interactions, and absence of the need for regular monitoring of the INR. These agents should not be used in patients with prosthetic heart valves or valvular atrial fibrillation, or in pregnant patients, and caution needs to be exercised in patients with renal failure.[34,35]

Study strengths and limitations

Our study has several limitations. It was a retrospective observational study, and limited conclusions can be drawn regarding cause and effect. Many variables known to influence warfarin therapy and TTR were not analysed, including co-administration of medications, alcohol and drug use, smoking, dietary factors and comorbidities. The sample size was small, and bigger studies are needed to confirm the findings. Although

the clinics were selected to represent patients from varying demographic settings in the Garden Route District Municipality, the findings are not generalisable throughout the diverse society of SA. Patient compliance with therapy was not accounted for in the study. The contribution of patients defaulting follow-up and not taking their treatment undoubtedly plays a role in the quality of INR control. Outcomes of INR control were not assessed.

The method used to assess the quality of anticoagulation has limitations. Because of the assumption of a linear increase or decrease in INR between consecutive tests in the Rosendaal method, large time gaps between tests (>60 days) can give an incorrect representation of the TTR. However, the percentage of tests in range was also assessed and is not influenced by this assumption. Although care was taken to exclude patients having INRs tested at different facilities, patients moving around between different clinics and districts or between the private and public sectors for INR monitoring could not be fully accounted for. Whether patients were already established on warfarin therapy or newly initiated was not taken into account. Newly initiated patients will require time for the INR to stabilise in the therapeutic range.

Conclusions

This study is the first to give insight into the current status of warfarin therapy in a non-metropolitan PHC setting in SA, which included rural clinics. We showed that the quality of INR control in this setting is poor and that very few patients are likely to derive any benefit from warfarin therapy, with younger and hospitalised patients having the highest likelihood of poor INR control. Despite the unique challenges regarding anticoagulation therapy in rural areas, there are clear gaps in warfarin management that can be addressed by instituting basic interventions. The adoption of dose adjustment protocols and training of staff in their use may improve INR control. Investment in computer-based algorithms and required infrastructure could also be beneficial, with the cost weighed against the cost of poor INR control. PoC testing will improve the turnaround time of INR tests and negate the need for patients to return to PHCs on different days, and will further avoid the need for telephonic dose adjustments. On a societal level, access to healthcare can be improved by ensuring adequate roads, public transport and

infrastructure in rural areas. The expanded use of NOACs may prove to be uniquely beneficial in settings where challenges with INR testing abound that were not accounted for in the non-inferiority trials comparing these agents with warfarin. While the cost of NOACs, compared with effective warfarin therapy, is seen as prohibitive for their expanded use, the cost of ineffective warfarin therapy is largely unaccounted for. At the very least, increasing the availability of NOACs in the public sector for selected patients (e.g. those with non-valvular atrial fibrillation/ flutter and VTE) in whom INR control is proving to be a problem despite good adherence, needs to be considered. Future research is needed to assess the effect of the implementation of potential changes to improve the quality of INR control, such as dose adjustment protocols, PoC testing, and standardized information and education regarding warfarin therapy. A prospective study that assesses outcomes of poor INR control as well as the effect of specific intevntions to improve INR control will be valuable.

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References

1. Ansell J, Hirsh J, Poller L, Bussey H, Jacobson A, Hylek E. The pharmacology and management of the vitamin K antagonists. Chest 2004;126(3):204s-233s. https://doi.org/10.1378/ chest.126.3_suppl.172s

2. Reynolds MW, Fahrbach K, Hauch O, et al. Warfarin anticoagulation and outcomes in patients with atrial fibrillation: A systematic review and metaanalysis. Chest 2004;126(6):1938-1945. https://doi.org/10.1378/chest.126.6.1938

3. Oake N, Jennings A, Forster AJ, Fergusson D, Doucette S, van Walraven C. Anticoagulation intensity and outcomes among patients prescribed oral anticoagulant therapy: A systematic review and meta-analysis. Can Med Assoc J 2008;179(3):235-244. https://doi.org/10.1503/cmaj.080171

4. Connolly SJ, Pogue J, Eikelboom J, et al. Benefit of oral anticoagulant over antiplatelet therapy in atrial fibrillation depends on the quality of international normalised ratio control achieved by centers and countries as measured by time in therapeutic range. Circulation 2008;118(20):2029-2037. https://doi.org/10.1161/circulationaha.107.750000

5. Baumgartner H, Falk V, Bax JJ, et al. 2017 ESC/EACTS guidelines for the management of valvular heart disease. Eur Heart J 2017;38(36):2739-2791. https://doi.org/10.1093/eurheartj/ehx391

6. Schmitt L, Speckman J, Ansell J. Quality assessment of anticoagulation dose management: Comparative evaluation of measures of time-in-therapeutic range. J Thromb Thrombolysis 2003;15(3):213-216. https://doi.org/10.1023/b:thro.0000011377.78585.63

7. Barth DD, Zuhlke LJ, Joachim A, Hoegger T, Mayosi BM, Engel ME. Effect of distance to health facility on the maintenance of INR therapeutic ranges in rheumatic heart disease patients from Cape Town: No evidence for an association. BMC Health Serv Res 2015;15:219. https://doi.org/10.1186/s12913-015- 0890-4

8. Ebrahim I, Bryer A, Cohen K, Mouton JP, Msemburi W, Blockman M. Poor anticoagulation control in patients taking warfarin at a tertiary and district-level prothrombin clinic in Cape Town, South AfricaS Afr Med J 2018;108(6):490-494. https://doi.org/10.7196/SAMJ.2018.v108i6.13062

9. Sonuga BO, Hellenberg DA, Cupido CS, Jaeger C. Profile and anticoagulation outcomes of patients on warfarin therapy in an urban hospital in Cape Town, South Africa. Afr J Prim Health Care Fam Med 2016;8(1):e1-e8. https://doi.org/10.4102/phcfm.v8i1.1032

10. Fenta TG, Assefa T, Alemayehu B. Quality of anticoagulation management with warfarin among outpatients in a tertiary hospital in Addis Ababa, Ethiopia: A retrospective cross-sectional study. BMC Health Serv Res 2017;17(1):389. https://doi.org/10.1186/s12913-017-2330-0

11. Mwita JC, Francis JM, Oyekunle AA, Gaenamong M, Goepamang M, Magafu M. Quality of anticoagulation with warfarin at a tertiary hospital in Botswana. Clin Appl Thromb Hemost 2018;24(4):596-601. https://doi.org/10.1177/1076029617747413

12. Singer DE, Hellkamp AS, Piccini JP, et al. Impact of global geographic region on time in therapeutic range on warfarin anticoagulant therapy: Data from the ROCKET AF clinical trial. J Am Heart Assoc 2013;2(1):e000067. https://doi.org/10.1161/jaha.112.000067

13. Van Spall HG, Wallentin L, Yusuf S, et al. Variation in warfarin dose adjustment practice is responsible for differences in the quality of anticoagulation control between centers and countries: An analysis of patients receiving warfarin in the randomised evaluation of long-term anticoagulation therapy (RE-LY) trial. Circulation 2012;126(19):2309-2316. https://doi.org/10.1161/circulationaha.112.101808

14. Manji I, Pastakia SD, Do AN, et al. Performance outcomes of a pharmacist-managed anticoagulation clinic in the rural, resource-constrained setting of

Eldoret, Kenya. J Thromb Haemost 2011;9(11):2215- 2220. https://doi.org/10.1111/j.1538-7836.2011.04503.x

15. Rosendaal FR, Cannegieter SC, van der Meer FJ, Briet E. A method to determine the optimal intensity of oral anticoagulant therapy. Thromb Haemost 1993;69(3):236-239. https://doi. org/10.1055/s-0038-1651587

16. Holbrook A, Schulman S, Witt DM, et al. Evidence-based management of anticoagulant therapy: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest 2012;141(2 Suppl):e152S-e184S. https://doi.org/10.1378/chest.11-2295

17. Reid SJ, Peacocke J, Kornik S, Wolvaardt G. Compulsory community service for doctors in South Africa: A 15-year review. S Afr Med J 2018;108(9):741-747. https://doi.org/10.7196/SAMJ.2018.v108i9.13070

18. National Department of Health, South Africa. White paper on National Health Insurance. Government Gazette No. 39506:1230. 11 December 2015. https://www.gov.za/documents/national-health-insurance- 10-dec-2015-0000# (accessed 12 March 2020).

19. Rose AJ, Hylek EM, Ozonoff A, Ash AS, Reisman JI, Berlowitz DR. Patient characteristics associated with oral anticoagulation control: Results of the Veterans AffaiRs Study to Improve Anticoagulation (VARIA). J Thromb Haemost 2010;8(10):2182-2191. https://doi.org/10.1111/j.1538-7836.2010.03996.x

20. Macedo AF, Bell J, McCarron C, et al. Determinants of oral anticoagulation control in new warfarin patients: Analysis using data from Clinical Practice Research Datalink. Thromb Res 2015;136(2):250-260. https://doi.org/10.1016/j.thromres.2015.06.007

21. Ansell J, Hirsh J, Hylek E, Jacobson A, Crowther M, Palareti G. Pharmacology and management of the vitamin K antagonists: American College of Chest

Physicians Evidence-Based Clinical Practice Guidelines (8th edition). Chest 2008;133(6 Suppl):160s-198s. https://doi.org/10.1378/chest.08-0670

22. Rose AJ, Ozonoff A, Berlowitz DR, Ash AS, Reisman JI, Hylek EM. Reexamining the recommended follow-up interval after obtaining an in-range international normalised ratio value: Results from the Veterans Affairs study to improve anticoagulation. Chest 2011;140(2):359-365. https://doi.org/10.1378/ chest.10- 2738

23. Kim YK, Nieuwlaat R, Connolly SJ, et al. Effect of a simple two-step warfarin dosing algorithm on anticoagulant control as measured by time in therapeutic range: A pilot study. J Thromb Haemost 2010;8(1):101-106. https://doi.org/10.1111/j.1538-7836.2009.03652.x

24. Manotti C, Moia M, Palareti G, Pengo V, Ria L, Dettori AG. Effect of computer-aided management on the quality of treatment in anticoagulated patients: A prospective, randomised, multicenter trial of APROAT (Automated PRogram for Oral Anticoagulant Treatment). Haematologica 2001;86(10):1060-1070.

25. Poller L, Keown M, Ibrahim S, et al. An international multicenter randomised study of computer-assisted oral anticoagulant dosage vs. medical staff dosage. J Thromb Haemost 2008;6(6):935-943. https://doi. org/10.1111/j.1538-7836.2008.02959.x

26. Matchar DB, Jacobson A, Dolor R, et al. Effect of home testing of international normalised ratio on clinical events. N Engl J Med 2010;363(17):1608-1620. https://doi.org/10.1056/nejmoa1002617

27. Ryan F, Byrne S, O'Shea S. Randomised controlled trial of supervised patient self-testing of warfarin therapy using an internet-based expert system. J Thromb Haemost 2009;7(8):1284-1290. https://doi. org/10.1111/j.15387836.2009.03497.x

28. Heneghan C, Ward A, Perera R, et al. Self-monitoring of oral anticoagulation: Systematic review and meta-analysis of individual patient data. Lancet 2012;379(9813):322-334. https://doi.org/10.1016/s0140- 6736(11)61294-4

29. Shiach CR, Campbell B, Poller L, Keown M, Chauhan N. Reliability of point-of-care prothrombin time testing in a community clinic: A randomised crossover comparison with hospital laboratory testing. Br J Haematol 2002;119(2):370-375. https://doi.org/10.1046/j.1365-2141.2002.03888.x

30. Biedermann JS, Leebeek FW, Buhre PN, et al. Agreement between Coaguchek XS and STA-R Evolution (Hepato Quick) INR results depends on the level of INR. Thromb Res 2015;136(3):652-657. https://doi. org/10.1016/j.thromres.2015.06.037

31. Patel MR, Mahaffey KW, Garg J, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. N Engl J Med 2011;365(10):883-891. https://doi.org/10.1056/nejmoa1009638

32. Connolly SJ, Ezekowitz MD, Yusuf S, et al. Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med 2009;361(12):1139-1151. https://doi.org/10.1056/nejmoa0905561

33. Granger CB, Alexander JH, McMurray JJ, et al. Apixaban versus warfarin in patients with atrial fibrillation. N Engl J Med 2011;365(11):981-992. https://doi.org/10.1056/nejmoa1107039

34. Kearon C, Akl EA, Ornelas J, et al. Antithrombotic Therapy for VTE Disease: CHEST Guideline and Expert Panel Report. Chest 2016;149(2):315-352. https://doi.org/10.1016/j.chest.2015.11.026

35. Almarshad F, Alaklabi A, Bakhsh E, Pathan A, Almegren M. Use of direct oral anticoagulants in daily practice. Am J Blood Res 2018;8(4):57-72.

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Figure 1: Study participants selection diagram (INR = International Normalised Ratio)

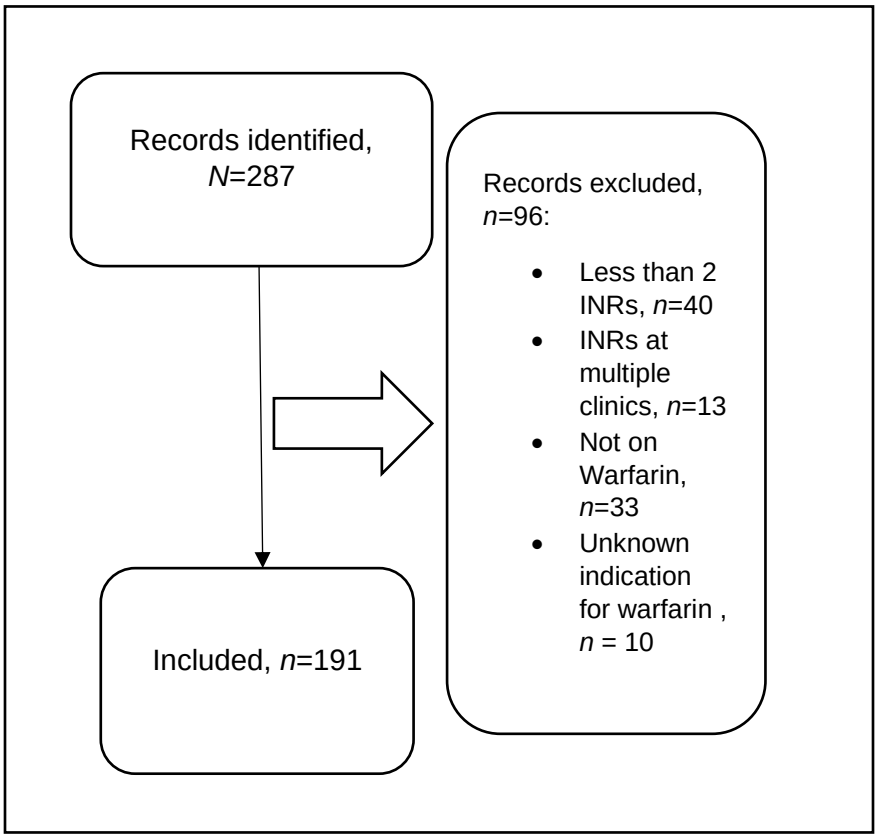

Table 1. Variables compared for assessment of association with improved or worse INR control

Demographic variables
Age
Sex
Employment status (employed, unemployed, government support grant)
Clinical variables
Indication for warfarin therapy (atrial fibrillation/flutter, venous thromboembolism, mechanical prosthetic valve, antiphospholipid syndrome, left ventricular thrombus)
Hospital admission during study period for any indication
Total number of INR tests per patient
Average time interval between tests (days)
Percentage of out-of-range INRs followed up within 7 days with repeat test

INR = international normalised ratio

Table 2: Baseline characteristics of study population (*N*=191)

Age (years), median (IQR)	56 (44-69)
Female, median (IQR)	108 (56.5)
Employment status, *n* (%)	
Employed	32 (16.8)
Unemployed	59 (30.9)
Government support grant	60 (31.4)
Unknown employment status	40 (20.9)
Indication for warfarin, *n* (%)	
Atrial flutter/fibrillation	81 (42.4)
Venous thromboembolism	55 (28.8)
Mechanical valve replacement	46 (24.1)
Antiphospholipid syndrome	6 (3.1)
Left ventricular thrombus	3 (1.6)
All cause hospital admission during study period, *n* (%)	62 (32.5)
INR tests per patient, median (IQR)	13 (7-19)
Duration of INR testing (months), median (IQR)	10.1 (6.6-11.36)
Time interval between INR tests (days), median (IQR)	21.4 (14.33-31.64)
Percentage INR tests in range (%), median (IQR)	33.3 (16.7-47.4)
Percentage of out-of-range tests above range (%), median (IQR)	33.3 (14.8-50)
Percentage of out-of-range tests below range (%), median (IQR)	66.7 (50.0-85.2)
Percentage of out-of-range INRs followed up within 7 days with repeat INR (%), median (IQR)	22.2 (0-45.5)
TTR (%), median (IQR)	37.2 (20.2-58.8)
Percentage TTR > 65%, n (%)	34 (17.8)

IQR = interquartile range; INR = international normalised ratio; TTR = time in therapeutic range.

Table 3: Patient related variables and TTR

	TTR (%), median (IQR)	p-Value	TTR ≥65%. *n/N* (%)	p-value
Age				
< 50	26.7 (16.1-53.0)	0.01	97/71 (12.7)	0.15
≥ 50	43.5 (23.5-60.1)		25/120 (20.8)	
Sex				
Female	32.0 (19.1-55.4)	0.1	14/108 (13.0)	0.06
Male	46.6 (20.7-63.0)		20/83 (21.1)	
All cause admission during study period				
Admitted	26.2 (16.2-50.2)	0.02	6/62 (9.7)	0.04
Not admitted	43.0 (23.5-62.0)		28/129 (21.7)	

TTR = time in therapeutic range; IQR = interquartile range.

Table 4: Univariable and multivariable regression analysis of demographic and clinical factors associated with a TTR≥65%*

	Univariable regression analysis			Multivariable regression analysis		
	Unadjusted OR	95% CI	p-value	Adjusted OR	95% CI	p-value
Age < 50	0.55	0.24-1.26	0.16			
Female	0.47	0.22-1	0.05	0.48	0.22-1.03	0.06
Employed	0.43	0.12-1.49	0.18			
Unemployed	0.77	0.34-1.77	0.54			
Government support grant	1.44	0.67-3.13	0.35			
Atrial fibrillation/flutter	2.24	1.05-4.78	0.04	2.21	1.02-4.77	0.04
Mechanical valve replacement	0.63	0.24-1.62	0.34			
VTE	0.47	0.18-1.21	0.12			
APS	0.92	0.1-8.14	0.94			
Hospital admission	0.4	0.15-0.99	0.05	0.4	0.15-1.03	0.06

TTR = time in therapeutic range; OR = odds ratio; CI = confidence interval; VTE = venous thromboembolism; APS = antiphospholipid syndrome.

*Demographic and clinical variables that were considered for the regression analysis included age <50 years, female sex, employment status, government support grant, atrial fibrillation/ flutter, mechanical valve replacement, VTE, APS, and hospital admission during the study period. Variables that were significantly associated with a TTR ≥65% (p<0.05) were retained in the multivariable model.

Table 5: Association between TTR and total INR tests, INR testing frequency and repeat testing for out-of-range values and Time in Therapeutic Range

	r^2	p-value
Total number of INR tests during study period	0.01	0.16
Time between INR tests (days)	0.04	0.01
Percentage of out-of-range tests followed up within 7 days with repeat test	0.02	0.08

r^2 is the square of the Spearman Rho value

2. Appendices and supporting material

2.1 Research Protocol

Title of study: INR Monitoring of Warfarin Therapy in Primary Healthcare Facilities in the Eden District, Western Cape, South Africa: A Retrospective Observational Study

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Co-supervisor:	**Professor M. Ntsekhe (Head of Cardiology Unti Groote Schuur Hospital)**

1. Purpose of the study

Primary aims of the study:

1. To determine the quality of International Normalised Ratio (INR) control as a measure of the effectiveness of warfarin therapy in the Eden District
2. To determine the prevalence of known predictors of poor INR control and the relationship between INR control and these known demographic and clinical predictors of poor INR control in the Eden District

Hypotheses:

1. The quality of INR control for warfarin therapy is expected to be poor and a low Time in Therapeutic Range is anticipated in the Eden District.

2. The predictors of poor INR control in the Eden District are expected to be common and in keeping with ineffective warfarin therapy, and an association between known predictors of poor INR control is expected to be found.

2. Background and rationale for the study

Warfarin is the most common anticoagulant used for the prevention and treatment of thromboembolic disease worldwide. [1] The beneficial effects of warfarin use in terms of reducing morbidity and mortality for arterial and venous thromboembolic conditions are well established. [1-5] Warfarin reduces the risk of ischaemic stroke in patients with non-valvular atrial fibrillation by 68%. [2] The risk of major thromboembolism associated with mechanical heart valve replacement is reduced by 75% with the use of warfarin compared to 40% with aspirin. [3] Long-term low intensity warfarin therapy has been shown to reduce the risk of recurrent venous thromboembolism by 64%. [4]

Anticoagulation is commonly used for various different indications in South Africa. Atrial fibrillation is the most common cardiac arrhythmia and is associated with an increased risk of stroke, requiring anticoagulation to reduce the stoke risk. [5,6] Hypertension, the most common risk factor for atrial fibrillation, is prevalent in Africa and is more likely to be poorly controlled and untreated with up to 40% of patients with hypertension demonstrating evidence of left ventricular hypertrophy. [5]. Despite advances in medicine and the development of novel anticoagulants warfarin remains the most common therapy used to prevent stroke in atrial fibrillation in South Africa and access to Non-Vitamin K Oral Anticoagulants (NOACs) is limited. [7] Human Immunodeficiency Virus (HIV) infection and tuberculosis are common in South Africa and increase the risk for venous thrombosis and pulmonary embolism [8]. The use of anti-mycobacterial drugs complicates the use of warfarin due to drug interaction making INR control challenging. [9] Valvular heart disease and mechanical heart valve replacement are other common indications for warfarin therapy in South Africa. [10]

2.1. Problems with the use of warfarin

Despite vast amounts of experience in the use of warfarin and a thorough understanding of the pharmacology, monitoring, limitations and side effects the clinical use of the drug remains plagued with the risks related to poor INR monitoring.

Warfarin has a narrow therapeutic window, wherein the benefit and risks associated with its use is closely related to the quality of the INR control. [11] Over anticoagulation leads to a significant bleeding risk while under anticoagulation is associated with thrombotic complications. Warfarin anticoagulation therefore requires frequent measurement of the INR to ensure an appropriate level of anticoagulation. [11] Depending on the indication for anticoagulation, the goal is to maintain the INR within a specific therapeutic window.

2.2 Monitoring of warfarin therapy and the quality of anticoagulation

The quality of INR control can be measured by calculating the Time in Therapeutic Range (TTR). [11-12] Several large studies have demonstrated a strong relationship between TTR and both thromboembolic events and haemorrhagic complications. [13] The benefit of warfarin therapy depends on the ability to maintain the INR in the therapeutic range.

The TTR that can be achieved with warfarin therapy varies significantly by population and country and is influenced by various factors. [5-7,13,14] Factors other than geographic region which influence the TTR include adherence to dose adjustment algorithms, self-monitoring and self-management compared to INR clinic monitoring. [15]

3. The Eden District and anticoagulation management

The Eden district in the Western Cape of South Africa is serviced by several level 1 facilities, including district hospitals and local Primary Healthcare Clinics which refer to George Regional Hospital, the local level 2 centre. Clinics within the George sub-district refer directly to George Regional Hospital since there is no local district hospital serving

these clinics. The level 3 referral facility for the Eden District, namely Groote Schuur Hospital, is more than 400km away.

The communities served by these clinics include patients from a non-metropolitan urban background as well as patients from an isolated rural background. Many patients live and work in rural areas that are far from their local clinics, including farms in the area. Transport to and from health facilities is often problematic and few patients have their own private transport. This brings about unique challenges regarding regular access to clinics and hospitals for anticoagulation management and INR control. Access to and from health facilities is often further limited by the underlying disease process that is being managed and that requires follow up. Follow up as regularly as weekly for INR testing is often problematic.

Patients that are diagnosed with conditions that require anticoagulation at George Regional hospital are initiated on warfarin therapy at George Regional Hospital, and all such patients are then down referred to their local level one facility for INR follow up. Many patients are also initiated on warfarin therapy at district hospitals and local clinics. There are no dedicated INR clinics in the district. No point-of-care INR analysers exist in the district, and INR measurement is offered by National Health Laboratory Service (NHLS) laboratory at George Regional Hospital. Knysna Provincial Hospital does not offer INR testing and the samples are tested at George Regional Hospital. This has the implication that samples for INR testing need to be transported more than 90km for analysis for some clinics in the Eden District. Facilities for self-management or self-monitoring of anticoagulation do not exist in this system. The fact that there are no point of care INR analysers at the health facilities means that patients cannot go to the clinic, have their INR tested and get their result on the same day. In a system where access to clinics is already often challenging, this causes even further difficulties in INR management. Telephonic feedback of INR results and warfarin dose adjustment after testing is feasible in some cases, but many patients do not have reliable contact numbers and have to be called back to the clinic for their results and warfarin adjustment.

Complications of warfarin therapy and poor INR control are common in the Eden district. Both haemorrhagic and thrombotic complications are regularly seen and many are referred for further management to George Regional Hospital. No formal data exists for the rate of minor or major haemorrhage. Some of the patients are managed at the district level and are not referred to George Regional Hospital for further treatment. Data from the Internal Medicine Department's monthly mortality and morbidity statistics show that during the period from 1 October 2015 until 30 September 2016 a total of 6 patients died in George Regional Hospital due to intracranial haemorrhage related to warfarin toxicity. This translates to 2.5% of the total mortality of patients admitted to medical wards in George Regional Hospital. This however does not account for patients dying in the community or at district hospitals in the Eden district. Furthermore, no data is available for the rate of non-fatal complications related to sub-therapeutic or supra-therapeutic INR's.

There is no data available regarding the TTR for the Eden district in the Western Cape. Data from the Clopidogrel Trial with Irbesartan for prevention of Vascular Events (ACTIVE W), the Randomised Evaluation of Long-Term Anticoagulation Therapy trial (RE-LY) and the Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET AF) consistently showed TTR values below 60% for South Africa. [5,6,13] A study done by Sonuga et al. in an INR clinic in Victoria Hospital in Cape Town also demonstrated a TTR of 48% [10]. It is difficult to extrapolate the data from studies performed in urban or first world settings to the patient population that is served in the Eden district where unique challenges with INR monitoring distinguish the patient population from those served in metropolitan and urban areas. The challenges with INR monitoring in the Eden district are not unique in the South African health care system. Many places are more rural and remote, adding further challenges to INR testing and warfarin dose adjustment.

4. The need for a study of quality of anticoagulation management in the Eden District

Previous studies consistently confirmed suboptimal quality of anticoagulation and INR control in South Africa. Extrapolating the data from these studies to the Eden district is difficult due to the unique challenges that exist locally. An understanding of the TTR as a measure of the quality of INR control and anticoagulation management will serve as the cornerstone from which changes can be implemented to improve anticoagulation management in the district and other similar settings in the Western Cape and South Africa. Furthermore, factors associated with poor INR control (both patient and healthcare system issues) can be identified and remedied. Potential solutions include the introduction of point of care INR analysers and the implementation of a universal protocol for INR management in the district. Patient factors resulting in poor INR control must be taken into consideration prior to selecting the valve prosthesis used at cardiac valve replacement surgery.

5. Aims and Objectives

AIM 1:

Determine the effectiveness of warfarin therapy in the Eden District

OBJECTIVES (AIM 1):

1. Determine the Time in Therapeutic Range (TTR) at 8 Primary Healthcare Clinics in The Eden District
2. Determine the percentage of out-of-range tests above the therapeutic range and below the therapeutic range

AIM 2:

Determine the influence of factors known to be associated with INR control on the effectiveness of warfarin therapy in the Eden District.

OBJECTIVES (AIM 2):

1. Determine the total number of INR tests per patient during the study period
2. Determine the average number of INR tests per month (frequency of testing)
3. Determine the percentage of out-of-range INR tests that are followed up within 7 days with a repeat test
4. Determine the indications for warfarin therapy in the Eden District
5. Determine whether and/or how the TTR is influenced by the following factors:
    a. Sex
    b. Age group (age less than or more than 50 years)
    c. Employment status
    d. Indications for warfarin therapy
    e. All cause hospital admission during the study period
    f. Total number of INR tests performed
    g. Frequency of INR testing (time between INR tests)
    h. Rate of early follow up of out-of-range INR tests with repeat test (within 7 days)

6. Methods

6.1 Design

This will be a cross sectional observational study by means of a retrospective record review.

6.2 Calculation of TTR

There are 3 common methods used to calculate the TTR. [11-12] The first method is the fraction of INR's in range. In this method the number of INR's in range is divided by the number of INR tests and expressed as a percentage. [12] With the second method the TTR of a cohort of patients on warfarin is calculated by looking at a cross-section of values on a given date and the proportion of the most recent INR's in those files that are within range. [12] The third method is the most commonly used method for calculating TTR and is known as the Rosendaal linear interpolation method. This method assumes a linear increase and decrease in INR between INR tests and dose adjustment. [16] The TTR is then expressed as the number of days that the INR is within the therapeutic range divided by the total number of days the patient is on warfarin, and this number is then converted to a percentage (i.e. percentage time in therapeutic range). [11,12,16]

6.3 Data collection method and analysis

Study population:

The following broadly representative level 1 facilities in the Eden District will be included:

1. Pacaltsdorp clinic
2. Sedgefield clinic
3. Herold satellite clinic
4. Kwanokothula clinic
5. Rosemoor clinic
6. Touwsranten clinic
7. Knysna Town clinic
8. Thembalethu clinic

6.4 Study sample

All the INR's collected at these 8 clinics over the period from 1 July 2016 to 30 June 2017 will be obtained from the National Health Laboratory Service (NHLS) following the correct procedure to do so. The file numbers of the patients who had INR testing done during this period will be retrieved from the NHLS Central Data Warehouse and the folders of each patient will be used for further for further data collection. Through an informal survey the number of patients on warfarin at each facility over the period of a year is estimated to be between 10 at the smaller satellite clinics to up to 50 at the bigger clinics.

Inclusion criteria: All files where INR testing was done during the predetermined period. Adults over the age of 18 years will be included.

Exclusion criteria: All files where 1 or less INR tests were done during the predetermined period. All records where INR testing was not done for the purpose of monitoring warfarin therapy will be excluded. Records where the age of the patient is less than 18 years will be excluded.

6.5 Data analysis

The diagnosis and desired therapeutic range for each patient's INR will be determined. The folder number, age, sex, diagnosis, desired therapeutic range, INR levels and collection dates, employment status will be determined. The data will be deidentified and anonymised. Using this data the TTR, INR's per month and average time between INR's will be calculated. The TTR for each patient will be determined using the Rosendaal method for calculating the percentage time of the INR in therapeutic range. [15] To determine whether an INR out of the target range resulted in an appropriate response from the healthcare provider, the time from when a sub- or supra-therapeutic INR measurement was performed until the next INR measurement will be calculated, and if this period is more than 7 days the response will be regarded as inadequate. If the out-of-range value was followed up with a repeat test within 7 days, it will be recorded as such and the percentage of out-of-range values followed up adequately will

be calculated. Statistical analysis will be done with the help of an expert biostatistician from the University of Cape Town.

Statistical analysis will be performed using Stata version 14.2 (StataCorp, USA). Descriptive statistics will be used to summarise data. Continuous variables will be summarised as means with standard deviations for parametric data or medians with interquartile ranges (IQRs) for non-parametric data. Categorical variables will be expressed as frequencies and percentages. Variables that will be evaluated for association with INR control include demographic variables (age, sex and employment status) and clinical variables (indication for warfarin, all cause hospital admission during study period, total number of INR tests per patient, average time between tests, and percentage of out-of-range tests followed up within 7 days with a repeat test).

Continuous variables will be compared using either Student's *t*-test for parametric data or the Wilcoxon rank-sum test for non-parametric data. Categorical variables will be compared using the χ^2 and Fisher's exact tests. To assess demographic and clinical variables associated with a TTR of ≥ 65% a univariable regression analysis will be performed for the selected variables. The variables with significant association (i.e $p<0.05$) will be tested further for association with a multivariable model. The association between TTR and the number of INRs per patient, the time interval between tests and the percentage of out-of-range INRs that were followed up within 7 days with a repeat test will be assessed with a Spearman rank test. An r^2 value approaching 1 will be assessed as showing increased levels of correlation between TTR and the selected variables. A *p*-value <0.05 was considered statistically significant.

6.6 Data safety management

The data will be stored on the personal computer of the principal investigator that is password protected and kept locked away in the residence of the principal investigator.

6.7 Ethical considerations

Ethical approval will be obtained from the University of Cape Town's Health Research Ethics Committee and the Provincial Government of the Western Cape. No external sources of funding are anticipated. Permission will be obtained from the Western Cape provincial government before commencing data collection. Data will be requested from the NHLS Central Data Warehouse Following the correct application process. No conflicts of interest are anticipated. No informed consent will be required as this will be a retrospective folder review without direct patient participation.

7. References

1. Pirmohamed M. Warfarin: almost 60 years old and still causing problems. Br J Clin Pharmacol. 2006 Nov; 62(5):509–511. https://doi.org/10.1111/j.1365-2125.2006.02806.x
2. Hart RG, Benavente O, McBride R, Pearce LA. Antithrombotic therapy to prevent stroke in patients with atrial fibrillation: A meta-analysis. Ann Intern Med. 1999; 131(7):492-501. http://dx.doi.org/10.7326/0003-4819-131-7-199910050-00003
3. Cannegieter SC, Rosendaal FR, Briët E. Thromboembolic and bleeding complications in patients with mechanical heart valve prostheses. Circulation. 1994; 89(2):635-641. http://dx.doi.org/10.1161/01.cir.89.2.635
4. Ridker PM, Goldhaber SZ, Danielson E, Rosenberg Y, Eby CS, Deitcher SR, et al. Long-term, low-intensity warfarin therapy for the prevention of recurrent venous thromboembolism. N Engl J Med. 2003 Apr 10;348(15):1425-1434. http://dx.doi.org/10.1056/nejmoa035029
5. Oldgren J, Healy JS, Ezekowitz M, Commerford P, Avezum A, Pais P, et al. Variations in cause and management of atrial fibrillation in a prospective registry of 15400 emergency department patient in 46 countries: The RE-LY atrial

fibrillation registry. Circulation. 2014; 129(15):1568-1576. http://dx.doi.org/10.1161/circulationaha.113.005451

6. Connoly SJ, Pogue J, Eikelboom J, Flaker G, Commerford P, Franzosi MG, et al. Benefit of Oral Anticoagulant Over Antiplatelet Therapy in Atrial Fibrillation Depends on the Quality of International Normalized Ratio Control Achieved by Centres and Countries as Measured by Time in Therapeutic Range. Circulation. 2008; 118(20):2029-2037. http://dx.doi.org/10.1161/circulationaha.107.750000

7. Van Spall HGC, Wallentin L, Yusuf S, Eikelboom JW, Nieuwlaat R, Yang S, et al. Variation in Warfarin Dose Adjustment Practice Is Responsible for Differences in the Quality of Anticoagulation Control Between Centers and Countries. Circulation. 2012; 126(19):2309-2316. http://dx.doi.org/10.1161/circulationaha.112.101808

8. Bibas M, Biava G, Antorini A. HIV-associated Venous Thromboembolism. Mediterr J Hematol Infect Dis. 2011; 3(1):e20111030. http://dx.doi.org/10.4084/mjhid.2011.030

9. Yew WW. Clinically significant interactions with drugs used in the treatment of tuberculosis. Drug Saf. 2002; 25(2): 111-133. http://dx.doi.org/10.2165/00002018-200225020-00005

10. Sonuga BO, Hellenberg DA, Cupido C, Jaeger C. Profile and anticoagulation outcomes of patients on warfarin therapy in an urban hospital in Cape Town, South Africa. Afr J Prim Health Care Fam Med. 2016; 8(1). http://dx.doi.org/10.4102/phcfm.v8i1.1032.

11. Ansell J, Hirsch J, Dalen J, Bussey H, Anderson D, Poller L, et al. Managing oral anticoagulant therapy. Chest. 2001; 119(1):22S-38S. http://dx.doi.org/10.1378/chest.119.1_suppl.22s

12. Schmitt L, Speckman J, Ansell J. Quality assessment of anticoagulation dose management: comparative evaluation of measures of Time-in Therapeutic

Range. J Thromb Thrombolysis. 2003; 15(3):213-216. http://dx.doi.org/10.1023/b:thro.0000011377.78585.63

13. Singer DE, Hellkamp AS, Piccini JP, Mahaffey KW, Lokhnygina Y, Pan G, et al. Impact of global geographic region on time in therapeutic range on warfarin anticoagulant therapy: Data from ROCKET AF clinical trial. J Am Heart Assoc. 2013; 2(1):e000067. http://dx.doi.org/10.1161/jaha.112.000067

14. Wieloch M, Själander A, Frykman V, Rosenqvist M, Eriksson N, Svensson PJ. Anticoagulation control in Sweden: reports of time in therapeutic range, major bleeding, and thrombo-embolic complications from the national quality registry AuriculA. Eur Heart J. 2011; 32(18):2282-2289. http://dx.doi.org/10.1093/eurheartj/ehr134

15. Heneghan C, Ward A, Perera R. Self-monitoring of oral anticoagulation: systematic review and meta-analysis of individual patient data. Lancet. 2012; 379(9813):322-334. http://dx.doi.org/10.1016/s0140-6736(11)61294-4

16. Rosendaal FR, Cannegieter SC, van der Meer FJ, Briet E. A method to determine the optimal intensity of oral anticoagulant therapy. Thromb Haemost. 1993; 69(3):236-239. http://dx.doi.org/10.1055/s-0038-1651587

2.2 Western Cape Provincial approval letter

Western Cape Government
Health

Health Impact Assessment
Health Research Sub Directorate
Health.Research@westerncape.gov.za
Tel: +27 21 483 0866; fax: +27 21 483 9895
5th Floor, Norton Rose House, 8 Riebeek Street, Cape Town, 8001
www.capegateway.gov.za)

REFERENCE: WC_201711_028
ENQUIRIES: Dr Sabela Petros

University of Cape Town

Anzio Road

Observatory

Cape Town

7925

For attention: Dr Dawid Prinsloo, Prof Mpiko Ntsekhe, Dr Trevor Gould

Re: INR Monitoring of Warfarin Therapy in Primary Healthcare Facilities in the Eden District, Western Cape, South Africa: A Retrospective Observational Study.

Thank you for submitting your proposal to undertake the above-mentioned study. We are pleased to inform you that the department has granted you approval for your research. Please contact **Dr Terence Marshall on 044 803 2752** to assist you with any further enquiries in accessing the following sites:

Great Brak River Clinic

Herold Satellite Clinic

Karatara Satelite Clinic

Knysna Town Clinic

Kwanokathula Clinic

Pacaltsdorp Clinic

Rosemoor Clinic

Sedgefield Clinic

Thembalethu Clinic

Touwsranten Clinic

Kindly ensure that the following are adhered to:

1. Arrangements can be made with managers, providing that normal activities at requested facilities are not interrupted.
2. Researchers, in accessing provincial health facilities, are expressing consent to provide the department with an electronic copy of the final feedback (**annexure 9**) within six months of completion of research. This can be submitted to the provincial Research Co-ordinator (Health.Research@westerncape.gov.za).

3. In the event where the research project goes beyond the *estimated completion* date which was submitted, researchers are expected to complete and submit a progress report (**Annexure 8**) to the provincial Research Co-ordinator (Health.Research@westerncape.gov.za).

4. The reference number above should be quoted in all future correspondence.

Yours sincerely

MS A VAN DEN BERG

ACTING DIRECTOR: HEALTH IMPACT ASSESSMENT

DATE: 2017/12/21

CC: **H SCHUMANN** **DIRECTOR: EDEN/CENTRAL KAROO**

2.3 Ethics approval

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 6626
Email: shuretta.thomas@uct.ac.za
Website: www.health.uct.ac.za/fhs/research/humanethics/forms

13 November 2017

HREC REF: 785/2017

Dr Trevor Gould
Internal Medicine
George Regional Hospital

Dear Dr Gould

PROJECT TITLE: INR MONITORING OF WARFARIN THERAPY IN PRIMARY HEALTHCARE FACILITIES IN THE EDEN DISTRICT, WESTERN CAPE, SOUTH AFRICA: A RETROSPECTIVE OBSERVATIONAL STUDY

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.

Approval is granted for one year until the 30 November 2018.

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.

Yours sincerely

PROFESSOR M BLOCKMAN
CHAIRPERSON, FHS HUMAN RESEARCH ETHICS COMMITTEE
Federal Wide Assurance Number: FWA00001637.
Institutional Review Board (IRB) number: IRB00001938
This serves to confirm that the University of Cape Town Human Research Ethics Committee complies to the Ethics Standards for Clinical Research with a new drug in patients, based on the Medical Research Council (MRC-SA), Food and Drug Administration (FDA-USA), International Convention on Harmonisation Good Clinical Practice (ICH GCP), South African Good Clinical Practice Guidelines (DoH

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 6338
Email: lamees.emiedi@uct.ac.za
Website: www.health.uct.ac.za/fhs/research/humanethics/forms

05 March 2019

HREC REF: 785/2017

Dr T Gould
Internal Medicine
George Hospital

Dear Dr Gould

PROJECT TITLE: INR MONITORING OF WARFARIN THERAPY IN PRIMARY HEALTHCARE FACILITIES IN THE EDEN DISTRICT, WESTERN CAPE, SOUTH AFRICA: A RETROSPECTIVE OBSERVATIONAL STUDY (MMed Candidate Dr Dawid Prinsloo)

Thank you for submitting your annual progress report and study deviation form to the Faculty of Health Sciences Human Research Ethics Committee.

Annual re-approval has been granted until 30 March 2020.

The HREC acknowledges that MMed Candidate, Dr Dawid Prinsloo, is also part of this study.

Supervisors: Dr Trevor Gould & Prof Mpiko Ntsekhe.

Please quote the HREC reference number in all your correspondence.

Yours sincerely

PROFESSOR M BLOCKMAN
CHAIRPERSON, FHS HUMAN RESEARCH ETHICS COMMITTEE

UNIVERSITY OF CAPE TOWN

HUMAN RESEARCH ETHICS COMMITTEE
08 OCT 2020
HEALTH SCIENCES FACULTY
UNIVERSITY OF CAPE TOWN

FACULTY OF HEALTH SCIENCES
Human Research Ethics Committee

FHS017: Annual Progress Report / Renewal

Record Reviews/Audits/Collection of Biological Specimens/Repositories/Databases/Registries

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	30.10.2021
☐ Not approved	See attached comments		
Signature Chairperson of the HREC		Date Signed	8/10/20

Principal investigator to complete the following: Thanks for deviation decision

1. Protocol information

Date (when submitting this form)	5/10/2020		
HREC REF Number	785/2017	Current Ethics Approval was granted until	
Protocol title	INR Monitoring of warfarin therapy in Primary Healthcare Facilities in the Eden District, Western Cape, South Africa: A Retrospective Observational Study		
Principal Investigator	Dr TJ Gould		
Department / Office Internal Mail Address	George Hospital David.Prins@gmail.com Trevor.gould@westerncape.gov.za		
1.1 Does this protocol receive US Federal funding?		☐ Yes	☑☐ No

2. Protocol status (tick ✓)

☐	Research-related activities are ongoing
☐✓	Data collection is complete, data analysis only

Please indicate (in the block below) the titles and HREC reference numbers of any projects currently making use of the Database/register/repository.

3. Protocol summary

Total number of records or specimens collected, reviewed or stored since the original approval		191
Total number of records or specimens collected, reviewed or stored since last progress report		0
Have any research-related outputs (e.g. publications, abstracts, conference presentations) resulted from this research? If yes, please list and attach with this report.	☐✓Yes	☐ No

4. Signature

Signature of PI		Date	28/09/2020

UNIVERSITY OF CAPE TOWN

HUMAN RESEARCH ETHICS COMMITTEE
0 8 OCT 2020
HEALTH SCIENCES FACULTY

FACULTY OF HEALTH SCIENCES
Human Research Ethics Committee

Form FHS011: Study deviation

HREC office use only (FWA00001637; IRB00001938)			
This serves as acknowledgement of a protocol deviation as described below.			
Chairperson of the HREC signature/ Designee		Date	8/10/2020

Note: Please note that incomplete submissions will not be reviewed.
Please email this form and supporting documents (if applicable) in a combined pdf-file to hrec-enquiries@uct.ac.za.

Please clarify your plan for research-related activities during COVID-19 lockdown

Principal investigator to complete the following:

1. Protocol information

Date (when submitting this form)	6/10/2020
HREC REF Number	785/2017
Project Title	INR Monitoring of warfarin therapy in Primary Healthcare Facilities in the Eden District, Western Cape, South Africa: A Retrospective Observational Study
Protocol number	
Principal Investigator	Dr TJ Gould/Prof M Ntsekhe
Department / Office Internal Mail Address	George Hospital Dawid.Prins@gmail.com Trevor.gould@westerncape.gov.za

2. Protocol deviation description

Please describe the deviation below, including the reason why the deviation occurred.
Renewal form submitted electronically during COVID lockdown before expiry date of active approval, but was not processed by ethics committee. Now form is resubmitted.

3. Follow-up actions

3.1 Please describe any follow-up action(s) taken or planned as a result of this deviation e.g. DSMB reporting, report to sponsor, informing participants.
None indicated
3.2 Please describe what action(s) have or will be taken to prevent similar deviations in future.

4. Principal investigator's acknowledgement of responsibility

UNIVERSITY OF CAPE TOWN
IYUNIVESITHI YASEKAPA • UNIVERSITEIT VAN KAAPSTAD

HUMAN RESEARCH ETHICS COMMITTEE
- 6 MAY 2021
HEALTH SCIENCES FACULTY
UNIVERSITY OF CAPE TOWN

FACULTY OF HEALTH SCIENCES
Human Research Ethics Committee

Form FHS010: Study Closure Report

HREC office use only (FWA00001637; IRB00001938)			
Noted and filed. This serves as acknowledgement that this study is closed.			
☑ Approved	Study closure report		
☐ Not Approved	Study closure report		
Chairperson of the HREC signature/Designee		Date	6/5/2021

Note: Please note that incomplete submissions will not be reviewed.
Please email this form and supporting documents (if applicable) in a combined pdf-file to hrec-enquiries@uct.ac.za.

Please clarify your plan for research-related activities during COVID-19 lockdown

1. Principal Investigator to complete the following:

Date (when submitting this form)	04/05/2021
HREC REF Number	785/2017
Protocol Title	INR Monitoring of warfarin therapy in Primary Healthcare Facilities in the Eden District, Western Cape, South Africa: A Retrospective Observational Study
Protocol number (if applicable)	N/A
Principal Investigator	Dr TJ Gould
Department / Office Internal Mail Address	Dawid.prins@gmail.com

2. Please confirm (tick ✓)

This study is closed to enrollment	☐ ✓ Yes	☐ No
Participants have completed all research-related interventions	☐ ✓ Yes	☐ No
Participants have completed all research-related follow-up	☐ ✓ Yes	☐ No
Data analysis is complete	☐ ✓ Yes	☐ No

Your sponsored protocol is closed	☐ Yes N/A	☑ No N/A
If you answered 'no' to any of the above questions, you must keep your study open until all research activity is completed.		

3. What is the reason for closing the study? (tick ✓)

Research completed	✓	No time	
Terminated due to toxicity/adverse event		PI left UCT or affiliated sites	
Slow accrual		Insufficient funding	
Loss of interest		Research never began	
Other. Please specify:			

4. For clinical trials, please describe the arrangements for provision of care after research, including (where applicable) post-trial access to the investigational product.

N/A

5. Please explain how the research findings have been disseminated to participants, communities, and/or stakeholders.

Published findings in South African Medical Journal

6. Please confirm (tick)

Have you submitted a final report to the Provincial Health Research Committee?	☐ ✓Yes	☐ No	☐ N/A
Please note: Researchers must submit final reports to the relevant research co-ordinator/research directorate at City Health Department, GSH, RXH, TBH, PGWC (for non-tertiary hospitals) within six months of completion of the study and may be required to report the findings of the study to other relevant authorities including the PHRC.			

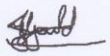
7. Please indicate how, and for how long, the data will be stored and protected.

Data stored on password protected computer under lock and key accessible only to PI. Data will be destroyed by means of permanent deletion from the hard drive within 5 years after publication.

8. Please list or attach any papers, abstracts, presentations or other outputs generated from this study.

Journal article published in South African Medical Journal. (Attached)

9. Signatures

Signature of PI		Date	04 May 2021

2.4 Author guidelines: South African Medical Journal (Abbreviated)

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

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.

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)'.

2.5 Reviewer comments and responses

Reviewer #1 comments
This is a relevant and valuable article and one of the first (possibly only) assessment of INR monitoring in a rural area. It will add significantly to the medical knowledge. Its methods, results and conclusions (that are correctly drawn from the results) are sound, but can be improved upon. It will assist with clinical decision making by informing clinicians of the difficulties facing INR monitoring in a rural area. Yes, it is suited to the SAMJ, since warfarin is used by a wide variety of specialities to manage several illnesses.
Thank you for reviewing the manuscript and the constructive feedback. We have made some changes as suggested.
Yes, the research question is well stated. The population is well described, but the variables correlated with INR should be listed (tabulated) clearly in the Methods section. If this is done the results would be easier to interpret. This is an article of an extraordinary number of abbreviations! A table of all abbreviations in the Methods section might be useful. The statistical methods are sound.
Thank you for the suggestion. After reading the manuscript with this comment in mind it was clear that there were far too many unnecessary abbreviations, and a number of abbreviations were only used once in the manuscript. The following changes were made: 1. Removed numerous abbreviations, particularly ones used only once or infrequently in manuscript to make reading easier: Prothrombin Time (PT); George Regional Hospital (GRH); Central data warehouse (CDW); Garden Route District Municipality (GRDM); National health laboratory service (NHLS); Mitral valve replacement (MVR); Sub-Saharan Africa (SSA); Standard deviation (SD); Odds ratio (OR) [in text]; Left ventricular thrombus (LV thrombus) 2. A table listing the clinical and demographic variables compared for association with INR control was added as suggested.
Yes the population is well described, but the challenges facing the patients to enable robust INR testing could be expanded upon. A cryptic reference is made to a "unique set of challenges" - it is critical to differentiate the challenges pertinent to a rural population from those of a urban population. Also add any challenges that are specific to this rural area and clinics. It would be useful to include a very brief description of the "Rosendaal method." It is mentioned in the Discussion and context is important
Thank you for the comments. We have made the following changes: 1. A description of the Rosendaal method was added. *"The TTR was calculated using the Rosendaal method of linear interpolation which assumes linear increases and decreases of the INR between successive INR values over time. From this assumption the time period that the INR falls within the predetermined therapeutic range can be calculated and can be converted to a percentage of total time."* 2. A more detailed description of the specific challenges patients in rural settings experience was added in the discussion.
The Discussion could be strengthened by commenting on some of the issues mentioned above. The article is unique since it describes a difficult problem in a rural setting and this should possibly be expanded on.
Thank you. As mentioned with the previous comment we expanded on the challenges that patients face in a rural setting that makes INR monitoring more difficult.
Yes, briefly, but in rather abstract terms that do not give guidance to resolution of these issues. I suspect that there are societal and infrastructural issues that add significantly to poor INR testing protocols and those could be mentioned.
Thank you for the comment. We have expanded the discussion and conclusion and gave more detailed suggestions regarding possible interventions that may improve INR control in rural settings.

This is a relevant and valuable article and one of the first (possibly only) assessment of INR monitoring in a rural area. It will add significantly to the medical knowledge in this setting. Its methods, results and conclusions (that are correctly drawn from the results) are sound, but can be improved upon. It will assist with clinical decision making by informing clinicians of the difficulties facing INR monitoring in a rural area. Not only the technical issues, but societal and infrastructural issues that add significantly to these poor INR testing outcomes and protocols could be mentioned (even speculatively). With these corrections, this paper could be a very powerful contribution to this common and serious problem.
Thank you for the constructive feedback. We have made numerous changes to the manuscript based on the suggestions given, and added a more detailed discussion regarding the challenges faced regarding INR monitoring in a rural setting as opposed to an urban environment, and also added suggestions for improving INR monitoring outcomes.