Does engaging with an interactive adherence intervention improve time in therapeutic range compared to receiving an education intervention alone, among patients anticoagulated with warfarin in Cape Town, South Africa?

MASTER OF PUBLIC HEALTH MINOR DISSERTATION (PPH7015W)

CHRISELDA PILLAY (NDXCHR007)

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Does engaging with an interactive adherence intervention improve anticoagulation control in patients on warfarin in Cape Town, South Africa?

Chriselda Pillay[1], Morna Cornell[2], Gayle Tatz[1], Andrea Jorgensen[3], Catherine Orrell[4], Munir Pirmohamed[3], Catriona Waitt[3], Karen Cohen[1]

Abstract

Background:

Warfarin is the mainstay of oral anticoagulation in South Africa. There is wide variability between individual dose requirements. Regular International Normalised Ratio (INR) monitoring to guide dosing is required. Maintaining INR in therapeutic range is important for efficacy and safety. Time in Therapeutic Range (TTR) ≥65% is associated with better outcomes. The WarPATH study included an adherence intervention comprising patient education sessions and weekly interactive text messages with clinician contact details. We hypothesised that engaging with the interactive component of the intervention would improve TTR.

Objectives:

To identify predictors of higher TTR, to compare retention in INR monitoring between those who did and did not engage with the interactive component of the adherence intervention and to describe the content of those interactions.

Methods:

This analysis is nested in the WarPATH study, and we included South African WarPATH participants with sufficient INR results to calculate TTR (by Rosendaal method) in weeks 2-12 following warfarin initiation. We constructed a multivariable linear regression model to identify associations with higher TTR. We constructed a logistic regression model of associations with retention in INR monitoring in months four to seven following warfarin initiation (≥3 INR results, or documented warfarin stop by clinician between four and seven months if <3 INRs).

Results:

We included 61 participants, 51% men, median age 50 years (Inter-quartile range (IQR) 43-61). Median TTR was 40% (IQR 28-64%), only 14 (23%) achieved TTR≥65%. In a multivariable linear regression model, male sex (p= 0.04) and older age (p=0.02) were associated with higher TTR; adjusted for mobile phone ownership, anticoagulation indication and engagement with the interactive component of the adherence intervention. In 47% of telephonic interactions, participants requested assistance with systems challenges to anticoagulation care. Although TTR was not associated with engagement, in a multivariable logistic regression model (n=57), participants who engaged with the interactive component of the intervention were more likely to be retained in INR monitoring (Adjusted Odds Ratio 4.8, 95% Confidence Interval 1.32-21.1, p=0.02), adjusted for sex, age, anticoagulation indication, mobile phone ownership.

Conclusion:

Anticoagulation control in this cohort was poor. Participants who engaged with the interactive intervention were more likely to be retained in INR monitoring. Interaction content revealed multiple health system barriers to good anticoagulation control on warfarin. This adherence intervention is simple and scaling for public sector implementation should be explored alongside access to alternative oral anticoagulants requiring no laboratory monitoring or individualised dosing.

Manuscript

Background

Oral anticoagulation is required for treatment and prevention of several prevalent diseases in South Africa.[1] Long term oral anticoagulation is prescribed for patients with mechanical valve replacement and/or certain cardiac arrythmias. Short- to long-term oral anticoagulation is prescribed for thromboembolic conditions.[1-3] Warfarin, a Vitamin K antagonist (VKA), is the primary oral anticoagulant used in the South African public sector, and is included in the South African Essential Medicines List (EML).[1,4] Warfarin therapy is challenging due to its narrow therapeutic index and wide variability in individual daily dose requirements needed to achieve optimal anticoagulation.[1-3] Direct oral anticoagulants (DOACs) do not require laboratory monitoring or individualised dosing. However, access to DOACs in sub–Saharan Africa is limited due to high drug costs.[5]

Prothrombin time (a measure of clotting time) is the test used to determine the risk of bleeding and/or coagulation status of a VKA user.[6] The International Normalised Ratio (INR) which accounts for the inter-test variability due to the sensitivity of the materials used to perform the test, is the preferred test for measuring the current extent of anticoagulation.[7] INR results are compared to an indication-specific therapeutic range to determine if the current level of anticoagulation is adequate. Warfarin use requires regular INR monitoring with appropriate dose adjustment for optimal anticoagulation.[2,10] Stability on treatment is defined as achieving and maintaining an INR within therapeutic range at an unchanged dose over two consecutive INR tests.[4,10] INR levels on either side of the indication-specific therapeutic range may lead to significant morbidity and mortality.[1-3]

The Time in Therapeutic Range (TTR), calculated according the Rosendaal method, may be used to determine if optimal anticoagulation has been achieved for a period of warfarin use.[8-9] The ACTIVE-W trial, which included South African participants, found that a TTR of ≥65% is associated with a 2.29% reduction in stroke risk among patients anticoagulated for atrial fibrillation.[12] Anticoagulation control among South African warfarin users has been shown to be suboptimal in a number of studies.[1-3]

This adherence study is nested within the Warfarin Anticoagulation In Patients In Sub-Saharan Africa (WarPATH) project's study of a "bundle of care" to improve anticoagulation outcomes in South Africa and Uganda.[14] The bundle of care included: implementing a dosing algorithm, providing adherence support, conducting root-cause analysis of warfarin-related adverse events, implementing point-of-care (POC) INR testing, and providing staff training.

Improving treatment adherence in resource-limited settings has been studied extensively in antiretroviral therapy programmes.[15-16] To improve antiretroviral therapy adherence among people living with human immunodeficiency virus (HIV) in South Africa, studies have been carried out to explore utility of tools available in a resource-limited setting.[16-17] Interacting with a text message service has been shown to significantly reduce treatment interruption, improve adherence and viral suppression.[18] Notably, the two-way communication through text messages

were shown to be the driver of text message intervention success compared to interventions where recipients did not have the option to respond to or interact with the text message content.[18-19] Interactive adherence interventions for warfarin therapy have been implemented among other populations with variable results on TTR and adherence.[20-24]Warfarin therapy requires both regular INR monitoring and dose adjustment to achieve adequate anticoagulation.

We hypothesised that engaging with the interactive component of our adherence intervention would improve adherence to warfarin therapy, which would increase TTR and improve anticoagulation outcomes.

Objectives:

We aimed to (1) identify associations with higher TTR, and to determine whether interacting with an adherence intervention (by responding to text messages and/or making use of the call back service) improved TTR, (2) determine impact of the interactive component of the adherence intervention on retention in INR monitoring in months four to seven post warfarin initiation, (3)describe the interactions with the interactive component of the adherence intervention.

Methods:

The WarPATH study implemented a "bundle of care" to improve anticoagulation control in patients receiving warfarin in Uganda and South Africa. In South Africa, the prospective cohort study was conducted in Cape Town, Western Cape. We recruited participants between June 2021 and July 2022. We invited patients attending participating public healthcare facilities and being initiated on warfarin therapy for a VTE, valvular heart disease or atrial fibrillation to participate in the WarPATH study. We included patients who were 18 years and older and able to follow up at one of the participating study sites. We took consent from participants and their treating clinicians. WarPATH participation involved receiving a suggested starting dose of warfarin based on a dosing algorithm, adherence support and POC INR testing with dose adjustment at three-to-four-day intervals. The adherence intervention included education on warfarin use, receiving 12 interactive text messages and telephonic access to a research medical officer (RMO). Study participation lasted 12 weeks. We monitored participants until stability was achieved and referred them to their local healthcare facility to continue warfarin therapy according to the standard of care, during which time participants still had access to the WarPATH RMO and received weekly interactive text messages containing adherence support. Participants received an anticoagulation booklet documenting their INR readings and warfarin dose adjustments at WarPATH follow up and a comprehensive referral letter to their closest anticoagulation clinic. Participants were reimbursed for their travel expenses when attending WarPATH appointments with a cash voucher of ZAR150. As part of the WarPATH COVID-19 risk mitigation strategy, we offered participants option of a home visit if they were unable to follow up at a health facility.

The adherence intervention consisted of two components, both delivered to all WarPATH participants. All participants attended two one-on-one in-person education sessions conducted by a nurse or doctor. The first session gave information on warfarin use and healthy eating guidelines for warfarin therapy. A second education session to consolidate the information

followed within three days of the first. Both sessions provided the opportunity for questions and discussion. The verbal education was delivered in an easy-to-understand format in the participant's language of choice, together with a written summary (in English language) provided to each participant. This could be shared with treatment support partners (relatives/caregivers) and referred to throughout anticoagulation therapy.

The second component was designed to encourage interaction. WarPATH participants received one text per week for 12 weeks (using the short messenger service format), each with a cost-free opportunity to interact with the adherence support content in the text or request a call back from the RMO (supplementary table 1). We sent the texts in English language and conducted call conversations in English, isiXhosa or Afrikaans language. We used the automated function of a bulk text messenger service to send the text messages, programmed to be delivered at one-week intervals to the mobile phone number provided by the participant. We provided participants with the contact details for a mobile phone monitored by WarPATH RMOs. We considered responses to the text messages and/or making use of the call back service and/or making contact on the study mobile phone (which were optional) as engagement with the interactive component of the adherence intervention. The interactive messaging was not implemented at the Ugandan study sites because of logistic challenges.

We had planned to include support groups for WarPATH participants to discuss their experiences on warfarin therapy, but this was not implemented due to COVID-19 restrictions around gatherings.

Adherence may be quantified with a variety of tools, all of which have limitations. Dispensing data and pharmacy refill data for warfarin is difficult to interpret due to variable dose requirements and dose adjustments. We therefore used anticoagulation control as measured by TTR as a proxy for adherence to warfarin therapy.[25-27] We used all the INR results collected in the 2–12-week period to calculate TTR according to the Rosendaal method which assumes a linear relationship between consecutive INRs.[8] In this analysis, we included all participants in the South African WarPATH cohort with sufficient INR data to calculate a TTR in weeks 2-12 following warfarin initiation (figure 1). We excluded participants who had their warfarin stopped by their clinician, withdrew participation, demised or had insufficient INR result. We determined the target INR ranges according to the indication for anticoagulation and local guidelines, where Valvular Heart Disease (mechanical valve) requires an INR of 2.5-3.5[28-29] and VTE and Atrial Fibrillation require an INR of 2-3 to be therapeutic.[4]

We anonymised WarPATH participants by providing them with a unique Participant Identity Number, maintained throughout our analysis. We extracted demographic data, language of choice for counselling, indication for anticoagulation, mobile phone ownership and engagement with the interactive component of the adherence intervention from the WarPATH database. We also extracted data on the number and content of text and call interactions. For this analysis, we excluded texts and calls to arrange WarPATH follow-up appointments.

We visually explored the distribution of age, the only continuous variable in our dataset. As age was non-parametrically distributed, we used the Wilcoxon Rank-Sum test to determine if there

was a significant difference in medians between the two groups. We used the Chi-square test or Fisher's exact test (where $n \leq 5$ in one of the groups compared) to explore associations between categorical variables.

We extracted INR data for weeks 2-12 from the WarPATH database, and for months four to seven following warfarin initiation from the National Health Laboratory Service's online database (TrakCare). We classified participants as having insufficient INR data after checking for INR results on TrakCare and seeking results of POC INR testing from healthcare facility staff and/or participants, as POC testing results are not captured on TrakCare.

To explore retention in INR monitoring, in months four to seven after warfarin initiation, we analysed INR results in this period. We excluded participants who demised or were lost from care in the preceding 2–12-week period. We classified those who had ≥3 INRs and those who had <3 INRs with documented clinician decision to stop warfarin as retained in INR monitoring in months four to seven following warfarin initiation. For participants with <3 INR results, we contacted the participant and/the treating facility where possible to determine if they were being monitored with a POC machine, if their anticoagulation therapy was complete or if they chose not to be monitored.

We constructed a multivariable linear regression model of associations with higher TTR and included engaging with the interactive component of the adherence intervention, sex, age, indication for anticoagulation and mobile phone ownership in the model based on an *a priori* decision. We included engagement with the interactive component of the adherence intervention, sex and mobile phone ownership as binary variables and age as a continuous variable in 10-year increments. We constructed a multivariable logistic regression model of associations with achieving TTR≥65%. We included engagement with the interactive component of the adherence intervention, sex and mobile phone ownership as binary variables and age as a continuous variable in 10-year increments based on an *a priori* decision.

We constructed a multivariable logistic regression model of associations with retention in INR monitoring in months four to seven following warfarin initiation and included engagement with the interactive component of the adherence intervention, sex, age, indication for anticoagulation and mobile phone ownership in the model based on an *a priori* decision. We report crude and adjusted odds ratios (ORs) with 95% confidence intervals (CIs) and p-values. A p-value <0.05 was regarded as statistically significant throughout.

We performed the statistical analysis on R software version 4.2.3.

Ethical considerations

This study was approved by the Human Research Ethics Committee at the University of Cape Town (ref. no. (ref. no. 710/2020 and 652/2023).

Results

Study participants

The WarPATH study enrolled 81 participants from five participating public healthcare facilities (False Bay, Groote Schuur, Mitchells Plain, New Somerset and Victoria Hospitals) between June 2021 and July 2022 (Figure 1). Sixty-one WarPATH participants were eligible for this analysis; of whom 37 (61%) engaged with the interactive component of the adherence intervention (Table 1). Those who engaged with the interactive component of the adherence intervention were more likely to have chosen to be counselled in English than those who did not engage.

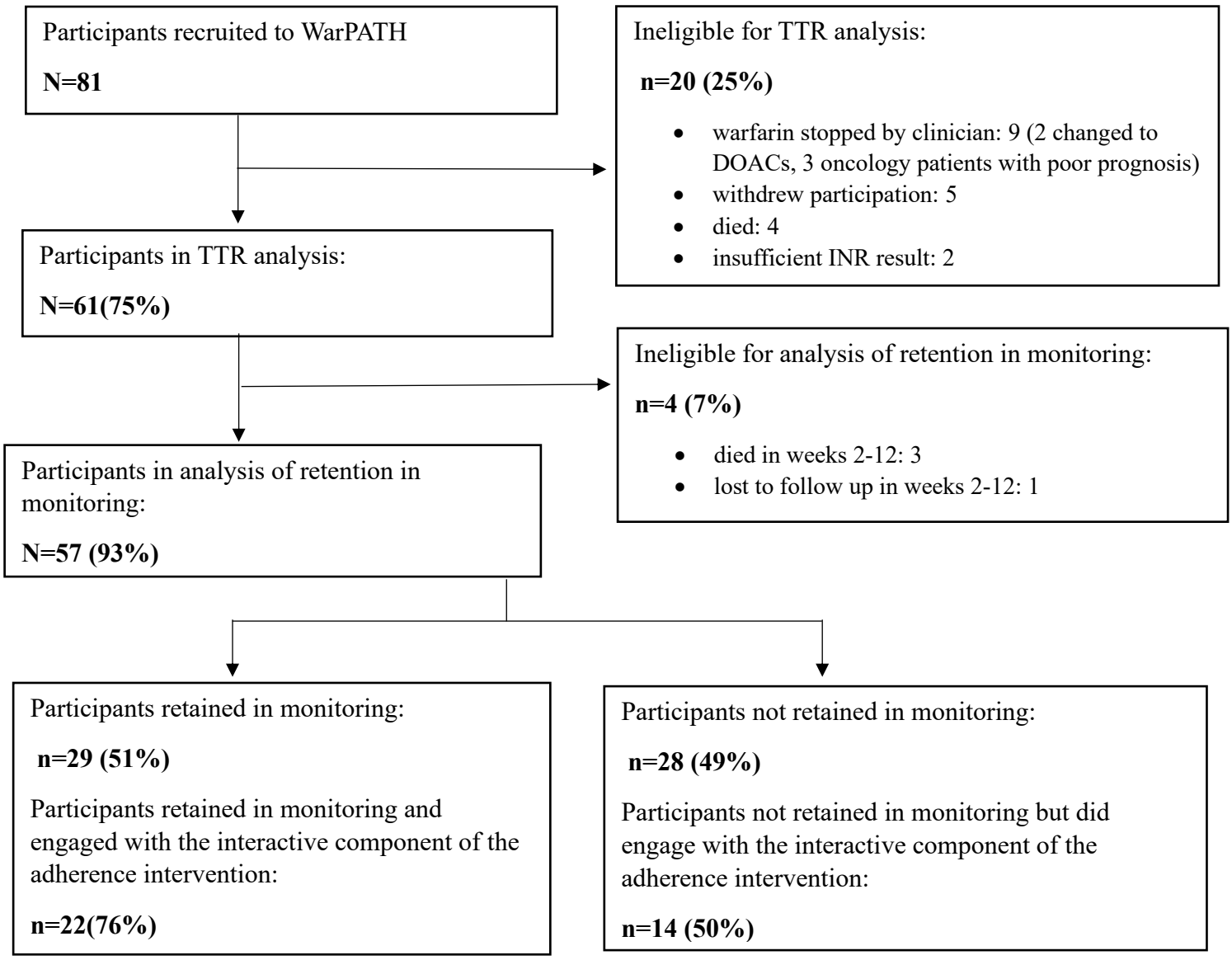

Figure 1: Flowchart summarising the participants included in this analysis.

Table 1: Characteristics of WarPATH study participants with TTR result, categorised by engagement with the interactive component of the adherence intervention (n=61)

Baseline Variable	Engaged with the interactive component of the intervention (n=37, 61%)	Did not engage with the interactive component of the intervention (n=24, 39%)	All participants with TTR results N=61	P-value
Sex, n (%)				
Male	17(46)	13(54)	30(49)	0.49**
Age (years)				
median (IQR)	52(44-61)	50(42-61)	50(43-61)	0.87***
Language chosen for counselling, n (%)				
English	35(95)	17(71)	52(85)	
Other*	2(5)	7(29)	9(15)	0.02****
Indication for anticoagulation, n (%)				
Venous Thromboembolism	24(65)	15(62)	39(64)	
Mechanical Valve	4(11)	5(21)	9(15)	
Atrial fibrillation	9(24)	4(17)	13(21)	0.52****
Owned mobile phone, n (%)	33(89)	16(67)	49(80)	0.09**

*IsiXhosa, Afrikaans, ** Chi square test, *** Wilcoxon rank-sum test, ****Fisher's exact test

Anticoagulation control in weeks 2-16 post warfarin initiation

The median TTR for the cohort was 40% (IQR 28-64%), only 14/61 (23%) achieved adequate anti-coagulation in weeks 2-12 post warfarin initiation. The median number of INR results in weeks 2-12 was 8 (IQR 5-12), with those achieving TTR ≥65% receiving a median of four INRs (IQR3-5) and those with TTR <65% receiving a median of nine INRs (IQR6-13).

Table 2: Multivariable linear regression model of associations with Time in Therapeutic Range (TTR) in WarPATH participants with TTR result for weeks 2-12(n=61)

	Univariable Linear Regression			Multivariable Linear Regression		
Explanatory variables	β co-efficient	95% Confidence Interval	P-value	β co-efficient	95% Confidence Interval	P-value
Constant				22,38	-5,65 to 50,42	0,12
Engagement with interactive component of adherence intervention:						
Did not engage	1			1		
Engaged	-10.62	-24.39 to 3.15	0.13	-12.38	-26.04 to 1.27	0.07
Sex:						
Female	1			1		
Male	12.82	-0.49 to 26.14	0.06	13.83	0.71 to 26.95	0.04
Age (in 10-year increments)	5.07	0.17 to 9.96	0.04	6.23	1.11 to 11.35	0.02
Indication for anticoagulation:						
Venous Thromboembolism	1			1		
Mechanical Valve	-4.04	-24.01 to 15.92	0.69	-10.2	-29.01 to 8.61	0.29
Atrial fibrillation	0.08	-17.20 to 17.37	0.99	-8.62	-26.01 to 8.76	0.32
Mobile phone access, n(%)						
Owned mobile phone	1			1		
Shared a mobile phone	-6.17	-23.95 to 11.60	0.49	-14.58	-31.90 to 2.74	0.10

Engagement with the interactive component of the adherence intervention

There were 45 responses via text to the adherence intervention text messages, received from 17 participants. (Supplementary table 1, Supplementary figure 1). Seventeen messages were answers to the question asked in the text message, 12 messages were "please call me" requests, 14 were assistance requests and two were to report INR results from POC testing.

There were 36 telephonic interactions, including 24 calls from 21 participants to the RMOs, and 12 calls to eight participants in response to a "please call me" text message. Telephone call content is summarised in Figure 2. In 17/36 (47%) of calls, participants requested assistance with addressing barriers to accessing anticoagulation care (access to warfarin tablets (19%) and INR

monitoring services (28%). In a further 17% of calls, participants requested assistance with accessing care for other conditions.

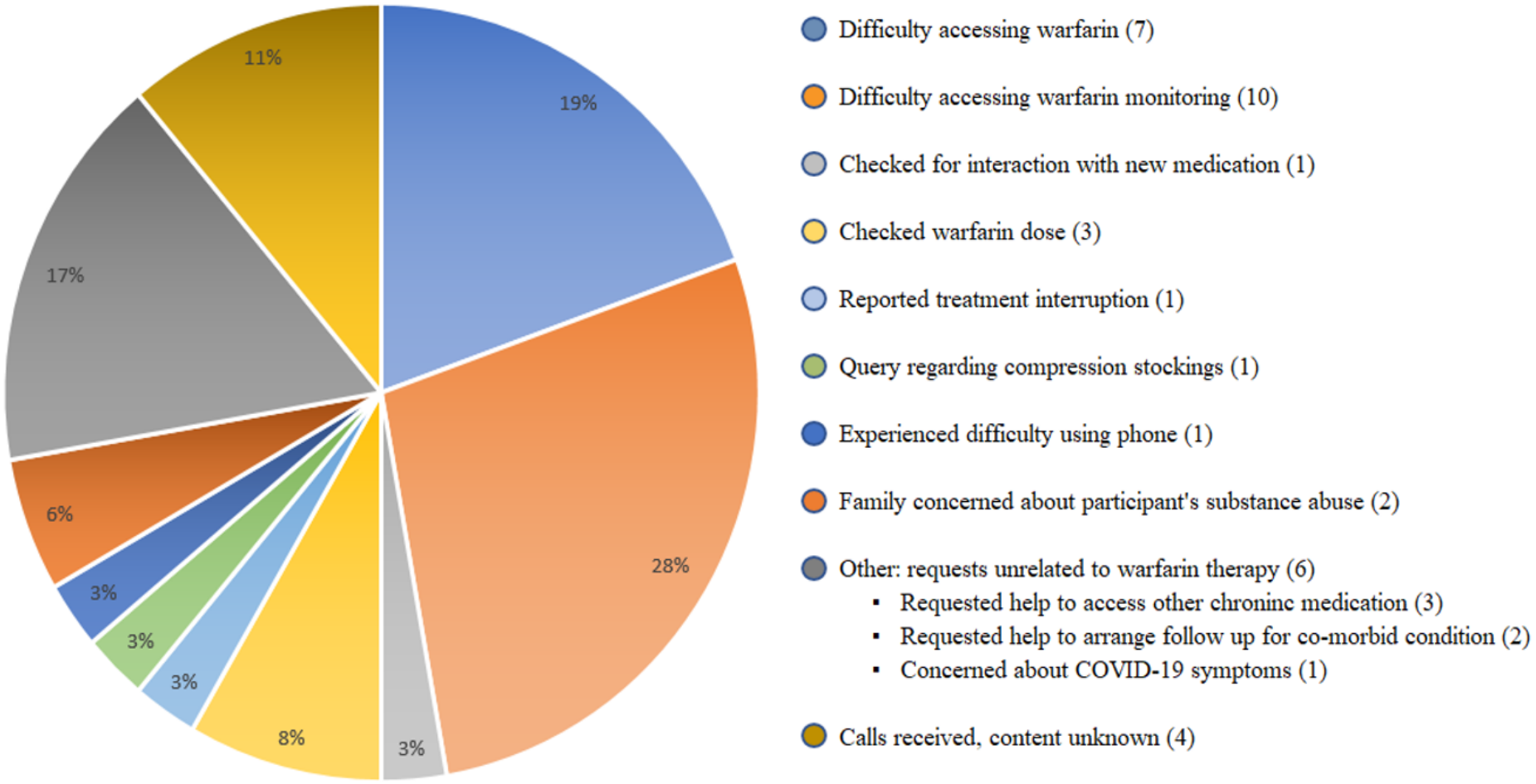

Figure 2: Content of 36 telephonic interactions with 29 WarPATH study participants

Associations with TTR

A multivariable linear regression model of associations with TTR in weeks 2-12 is shown in Table 2. Only Male sex and older age were associated with higher TTR. We constructed a multivariable logistic regression model of associations with TTR ≥65%. (Supplementary Table 2). We did not find any significant associations, which may be due to lack of power, as only 14 participants achieved a TTR ≥65%.

Retention in INR monitoring

We included 57/61 (93%) participants in the analysis of associations with retention in INR monitoring in months four to seven after warfarin initiation, of which 29 were retained (Figure 1). Median TTR in months four to seven post warfarin initiation was 12% (IQR 0-43%), with only three (5%) achieving TTR ≥65%. In a multivariable logistic regression model adjusted for sex, age, indication for anticoagulation and mobile phone ownership, participants who engaged with the interactive component of the adherence intervention had 4.8 times the odds of being retained in INR monitoring in months four to seven after warfarin initiation compared with those who did not engage (Table 3).

Table 3: Multivariable Logistic Regression Model of associations with retention in International Normalised Ratio (INR) monitoring in months four to seven after warfarin initiation among WarPATH participants (n=57)

Variable	Number retained in INR monitoring in months four to seven after warfarin initiation	Crude Odds Ratio (95% Confidence Interval)	p-value	Adjusted Odds Ratio (95% Confidence Interval)	p-value
Engagement with interactive component of adherence intervention:					
Did not engage	7/21(33%)	1		1	
Engaged	22/36(61%)	3.14(1.04-10.2)	0.05	4.77(1.32-21.1)	0.02
Sex, n(%)					
Female	17/29(59%)	1		1	
Male	12/28(43%)	0.53(0.18-1.50)	0.2	0.55(0.16-1.82)	0.3
Age (years)		0.97(0.93-1.01)	0.12	0.97(0.93-1.02)	0.3
Indication for anticoagulation, n(%)					
Venous Thromboembolism	20/36(56%)	1		1	
Mechanical Valve	6/9(67%)	1.60(0.36-8.53)	0.5	3.03(0.56-21.4)	0.2
Atrial fibrillation	3/12(25%)	0.27(0.05-1.06)	0.08	0.33(0.06-1.63)	0.2
Mobile phone access, n(%)					
Owned mobile phone	25/48(52%)	1		1	
Shared a mobile phone	4/9(44%)	0.74(0.16-3.11)	0.7	1.67(0.29-10.5)	0.6

Discussion

We found that male sex and older age were associated with better anticoagulation control on warfarin. In nearly half of the telephonic interactions prompted by the adherence intervention participants requested assistance with barriers to accessing anticoagulation care, drawing attention to multiple systems related challenges experienced by warfarin users. Anticoagulation control was poor, even under study conditions which included an adherence intervention. Engaging with the interactive component of the adherence intervention predicted retention in INR monitoring in the four months after the interactive adherence intervention ended. Language was a barrier to engaging with the adherence intervention, highlighting the need to be more inclusive when designing adherence support tools.[30]

Studies in South Africa and Sweden have found an association with increasing age and better TTR.[2,31]Younger participants are more likely to be economically active which may be a barrier to the regular monitoring required for warfarin therapy. Multiple studies have found better anticoagulation outcomes in men.[2,31-33] However, hypotheses to explain this finding conflict: in a South African study it was proposed that a diet rich in vitamin K (such as green leafy vegetables) may be responsible for women having poorer anticoagulation control, while investigators in Europe proposed the opposite i.e. that women may have a higher likelihood of being on a diet low in vitamin K leading to their poorer anticoagulation control.[2,32-34] No definitive explanation for this association has been found to date and future research should explore determinates of sex differences in anticoagulation outcomes.

Based on the content of telephonic interactions with participants, accessing INR monitoring services and warfarin treatment was limited by mechanisms that restricted participant access to the anticoagulation management team. We hypothesise that the poor anticoagulation control observed may be partly due to health systems level challenges. South Africa's health system is still influenced by historical political actions responsible for the differential distribution of services among the population. In this context, access to healthcare can be described as the opportunity to use services and includes appropriate service utilisation among sufficiently informed healthcare users who are empowered to exercise choice when navigating the health system.[35]. Challenges included not being able to communicate with their anticoagulation clinic, the de-escalation of routine services during the summer holiday (December/January period) and during COVID-19 waves (which occurred periodically during the study period). A warfarin supply shortage in March 2022 may have also impacted access to warfarin.[36] Warfarin therapy is challenging, requiring frequent monitoring which incurs costs to the user, including travel costs and working hours missed. WarPATH participants were compensated for their travel costs in the study but were responsible for their own travel costs on study exit. Barriers to accessing the appropriate care have been well documented among South African public healthcare users. [35,37-39] We identified similar barriers in our analysis, including poor understanding of referral pathways, fragmented health services and long waiting times posing barriers to accessing health services. [37-38]This intervention has the potential to identify health system barriers which may inform service design.

The poor TTR in this study was in keeping with the findings of three large studies which quantified TTR in South African participants, with mean TTRs of 46%,[12] 55%,[40] and 58%[41]. The WarPATH bundle of care was based on the rationale that anticoagulation control is dependent on multiple factors.[14] This analysis explores the impact of the interactive component of the adherence intervention on warfarin efficacy. However, there are multiple other factors impacting on efficacy, including pharmacogenetic factors, which have to date been poorly characterised in African patients. Results of the pharmacogenetic study component of WarPATH were not available at the time of our analysis.[14]

Those who engaged with the intervention were more likely to be retained in INR monitoring. An increase in healthcare seeking behaviour among those with poor response to treatment is not a common finding but has been observed among patients with tuberculosis and diabetes mellitus.[42-43] It has been suggested that this association occurs because of patient perception of disease severity, and good patient education, both of which may have been addressed in the WarPATH adherence intervention.[44-46]

Almost all participants who engaged chose English as the language of communication, suggesting that language may have been a barrier to engagement.[30] South Africa has 12 official languages and a population with varying levels of literacy; however, health education is still mostly delivered in the English language.[47-48] While participants were able to choose the language in which they received their verbal counselling, the educational tools and text messages were only available in English. A previous study including participants representative of the South African population served by the public healthcare sector found that patients may be able to read and pronounce medical words but could not comprehend the content. Findings from our root cause analysis of adverse events among patients on warfarin therapy in South Africa and Uganda (a component of the WarPATH bundle of care) showed how language barriers can cause morbidity. English language competency has been identified as protective against poor adherence among people living with HIV in South Africa.[49] Language proficiency may play a more crucial role than the level of education as a predictor of adherence.[50] The interactive component was leveraged off existing adherence interventions which were shown to be effective in the South African setting among people living with HIV. Text messages can improve linkage to care, deliver adherence reminders and retain patients in care through persistence, but are limited by the user's ability to maintain access to the mobile phone (reliable network coverage and keeping the mobile phone charged) and their literacy level.[20] It is likely that the linkage to care appealed to participants' desire for individualised care and accountability, and positively influenced their choice to continue anticoagulation monitoring.[51]A Kenyan study found that the weekly receipt of text reminders improved adherence to treatment, consistent with our finding of participants being retained in INR monitoring, which may be a surrogate for treatment adherence.[52]

A review of text message interventions for various conditions showed that the driver of success for text message-based interventions is the communication being two-way. In our study, all participants received the text messages, but those who responded were more likely to be retained in INR monitoring.[19] The need for two-way communication should be considered when developing differentiated models of care and telehealth services to support anticoagulation therapy.

This study has limitations. The WarPATH study period coincided with the COVID-19 pandemic. Risk mitigation strategies such as the de-escalation of routine healthcare services and a restriction on recruiting COVID-19 positive patients contributed to a smaller than planned sample size and resulted in this analysis being underpowered. Retention in anticoagulation therapy includes INR monitoring, collection of medicines, and adherence to prescribed warfarin dosing. However, pharmacy refill data for warfarin is very difficult to interpret because of variable dose requirements and multiple dose adjustments, and we had no access to warfarin prescribing and dispensing data after WarPATH ended. We only had access to INR monitoring results in months four to seven following warfarin initiation, allowing us to explore retention in INR monitoring, which may not necessarily translate into adherence to therapy. This is of particular concern as anticoagulation control was very poor. Some participants with < 3 INR results on TrakCare were not contactable and we found no record of them at the facility to which they had been referred. It is possible that these participants may have demised, attended a different healthcare facility that used POC monitoring, had warfarin stopped at a facility other than the one to which they had been referred, or continued treatment in the private healthcare sector. This may have resulted in misclassification and introduced bias into our analysis. Where possible, an isiXhosa speaking research nurse or Afrikaans speaking RMO responded to participants who indicated this as a preference. However, the call content and text responses presented here represent the concerns of those who engaged with the intervention, which may have been driven by English language competency. Our findings may not reflect the challenges of those who did not engage, who were less likely to be English speaking.

In addition to a larger sample size, sample selection of future studies should extend beyond urban and peri-urban healthcare users to be more representative of the South African population and account for transversal healthcare systems challenges. Future study designs should consider the multiple factors that contribute to good anticoagulation control and not be limited to patient dependent factors. The field of adherence studies in South Africa should shift towards exploring the impact of interventions delivered in the preferred language of the user. To determine the feasibility and sustainability of the intervention, the cost and efficacy of warfarin therapy should be compared to that of other oral anticoagulants under similar conditions where possible.

Where warfarin use is indicated, good anticoagulation control is necessary to reduce the risk of bleeding or thrombotic events. Older age alone should not be a reason for deferring warfarin initiation when indicated and consideration should be given to other supportive measures to mitigate risk. However, meeting the requirements for safe and effective anticoagulation such as regular INR monitoring with prompt warfarin dose adjustment is challenging in our public healthcare system, making warfarin use unfavourable. Interventions that encourage health-seeking behaviour invest in developing skills that empower healthcare users to take charge of their health beyond the acute period of illness. Management plans that incorporate this and address language barriers have the potential to strengthen healthcare provider and healthcare user relationships towards achieving better outcomes. The findings in this study can inform a more robust adherence intervention that strengthens health systems and improves services. Building this additional layer of support into anticoagulation therapy may guard against some of the consequences of systemic challenges.

Conclusion

Warfarin anticoagulation control remains poor under study conditions, making anticoagulation therapy an ongoing field of interest. This simple adherence intervention stimulated participant engagement with the healthcare team. The content of the interactions reveals systems' challenges which are barriers to good anticoagulation control. The scaling and implementation of this intervention to support the anticoagulation therapy service should be explored in further studies. These findings highlight the multiple challenges faced by warfarin-users in our setting, and prompt consideration of oral anticoagulants which require no monitoring or individualised dosing and may be more suitable in our resource-constrained healthcare system.

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Author Affiliations:

1. Division of Clinical Pharmacology, Department of Medicine, University of Cape Town, Cape Town, South Africa
2. Centre for Infectious Disease Epidemiology and Research, School of Public Health, University of Cape Town, Cape Town, South Africa
3. Wolfson Centre for Personalised Medicine, Institute of Translational Medicine, University of Liverpool, Liverpool, United Kingdom
4. Desmond Tutu HIV Foundation, University of Cape Town Medical School, Cape Town, South Africa

Author contact details

- Chriselda Pillay: chriselda.pillay@westerncape.gov.za
- Morna Cornell: morna.cornell@gmail.com
- Gayle Tatz: gayle.tatz@uct.ac.za
- Andrea Jorgensen: A.L.Jorgensen@liverpool.ac.uk
- Catherine Orrell: Catherine.Orrell@hiv-research.org.za
- Munir Pirmohamed: Munirp@liverpool.ac.uk
- Catriona Waitt: C.Waitt@liverpool.ac.uk
- Karen Cohen: karen.cohen@uct.ac.za

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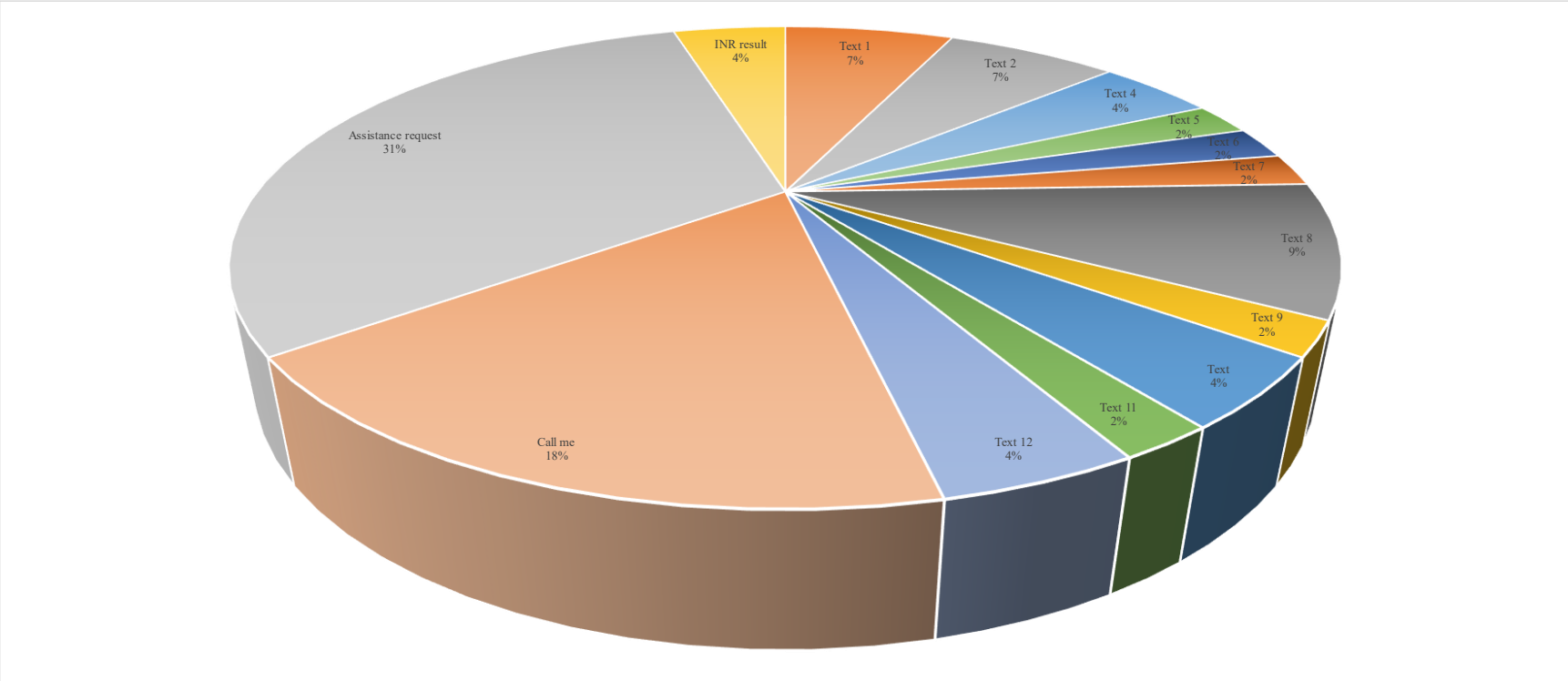
Supplementary material

Supplementary tables and figures

Supplementary Table 1: Message content used in the WarPATH interactive adherence intervention

Legend	Text Number	Number of Interactions	Text Content
	1	3	Thank you for choosing to take part in the WarPATH "Bundle of Care" study. Reply to this message with any questions or type "call me" and someone will phone you back. All replies are free!
	2	3	How was your first week of warfarin therapy? Do you have any bruising, bleeding or any other concerns? Reply "call me" for someone to phone you back.
	3	0	Getting your INR in range with the right dose of warfarin is different for each person. This may take time. Reply for free with any questions or "call me" for someone to phone you back.
	4	2	Speak to the doctor or nurse before using any other medication, even herbal medication or over-the-counter remedies. These treatments can cause problems when taken with warfarin. Would like a list of some examples. Reply "call me" for someone to phone you back.
	5	1	Different foods, especially green, leafy vegetables, can interfere with your warfarin. Instead of avoiding them, try to eat the same amounts every day and be consistent. Ask us if you would like a list. Reply "call me" for someone to phone you back.
	6	1	Alcohol can cause your INR to increase if you have more than 1 or 2 drinks. A high INR makes your risk of bleeding higher too. Ask us any questions about alcohol and warfarin. Reply "call me" for someone to phone you back.
	7	1	Are you planning a trip or holiday away from home? Make sure you have enough warfarin long before you go and can get your INR checked there if needed. Reply "call me" for someone to phone you back.
	8	4	How do you remember to take your warfarin every night? Tell us what helps you remember! Reply with your answer or any questions for free. Reply "call me" for someone to phone you back.
	9	1	Do you remember all the information that was given to you when you first started warfarin? Refresh your memory and see if you have any new questions. We can send the information again if you would like. Reply "call me" for someone to phone you back.
	10	2	You have been on warfarin for 10 weeks already! What has been the biggest change for you? Reply "call me" for someone to phone you back.
	11	1	If you forget to take a dose of your warfarin, don't take it at another time or double your dose. This can cause your INR to increase too much. Take your warfarin as normal the next day. Do you have any questions about how to take your warfarin? Reply "call me" for someone to phone you back.
	12	2	This is your last message from the WarPATH study. Thank you for participating! We hope you have learned a lot about warfarin. Tell us if you have any last questions. Reply "call me" for someone to phone you back.
	Call me	8	"call me" response, index message not recorded
	Assistance Request	14	accessing warfarin (4), accessing other medicines (2), warfarin dosing (4), other clinical problems (4),
	INR result	2	Report INR results from POC testing



Supplementary figure 1: Content 45 of text message interactions from 17 WarPATH participants (content description in supplementary table 1)

Supplementary Table 2: Multivariable Logistic Regression Model of associations with Time in Therapeutic Range (TTR) ≥65% among WarPATH participants with TTR, (N=61)

Variable	TTR≥65%	Crude Odds Ratio (95% Confidence Interval)	Adjusted Odds Ratio (95% Confidence Interval)	p-value
Engagement with interactive component of adherence intervention:				
Did not engage	8/24(33)	1	1	
Engaged	6/37(16)	0.39(0.11-1.30)	0.37(0.09-1.36)	0.14
Sex, n(%)				
Female	4/30(13)	1	1	
Male	10/31(32)	3.10(0.90-12.6)	2.90(0.79-12.4)	0.12
Age (in 10-year increments)		1.14(0.73-1.81)	1.08(0.64-1.87)	0.8
Indication for anticoagulation, n(%)				
Venous Thromboembolism	8/39(21)	1	1	
Mechanical Valve	2/9(22)	1.11(0.15-5.75)	0.73(0.08-4.28)	0.7
Atrial fibrillation	4/13(31)	1.72(0.39-6.94)	1.54(0.29-7.74)	0.6
Mobile phone access, n(%)				
Owned mobile phone	11/50(22)	1	1	
Shared a mobile phone	3/11(27)	1.33(0.26-5.53)	0.83(0.14-3.88)	0.8

Protocol

Study Protocol

Does engaging with an interactive adherence intervention improve Time in Therapeutic Range compared to receiving an education intervention alone, among patients anticoagulated with warfarin in Cape Town, South Africa?

Hypothesis:

Engaging with an interactive adherence intervention improves anticoagulation control

Summary of WarPATH study:

This study is a secondary analysis of data from the WarPATH study which was designed to evaluate whether implementation of the warfarin bundle improved anticoagulation control (Appendix A). The warfarin bundle included:

1. The use of a clinical dosing algorithm to determine the starting dose of warfarin
2. Providing adherence support through education sessions and text messages
3. Conducting root cause analysis of warfarin related adverse events
4. Implementing point of care monitoring
5. Providing staff training

There were two adherence interventions embedded in the study which were offered to all participants. In the first intervention, all participants received an in-person education session in the language of their choice with an information handout to retain (Appendix B1 and B2). The second intervention was the interactive component, where all participants received 12 interactive mobile text messages (Appendix C) and had telephonic access to a Research Medical Officer (RMO). All participants were offered the cost-free option to engage with the interactive component. Participants could engage by using one or both methods of interaction, namely, by responding to the text messages or requesting a call back option to the RMO.

Participants were followed up at 3-4 day intervals until stability was reached and then discharged to the local clinic to continue warfarin anticoagulation according to the normal standard of care. Participants were then followed up remotely for 90 days and blood results were recorded.

An additional six months of anticoagulation control results were collected following the participants' exit from the study.

Background:

Oral anticoagulation is necessary for the treatment and prevention of several prevalent diseases in South Africa. Long term oral anticoagulation is prescribed for patients with mechanical valve replacement and those with certain cardiac arrythmias. Short- to long-term oral anticoagulation is prescribed for thromboembolic conditions.[1] While the number of warfarin users in South Africa is

unknown, regional estimations for Sub-Saharan African (SSA) countries inform the drug utilisation. Deep Vein Thrombosis (DVT), a thromboembolic condition, has an incidence of 2.4% to 9.6% in postoperative patients, and 380 to 448 per 100 000 births per year in pregnant and postpartum women in SSA.[2,3] A hospital-based study in Soweto, South Africa, estimated the incidence of Atrial Fibrillation to be 5.6 cases per 100,000 population per year.[4] The burden of disease is estimated to increase as access to care improves.[5]

Warfarin, a Vitamin K antagonist, is the mainstay of oral anticoagulation as prescribed by the South African Essential Medicines List.[6] Warfarin therapy is challenging due to its narrow therapeutic index and wide variability on individual daily dose requirements needed to achieve stability.[7] Optimal warfarin anticoagulation is measured in two stages. The International Normalised Ratio (INR) is a standardised representation of prothrombin time which indicates the current level of anticoagulation.[8] INR results are compared to an indication-specific therapeutic range to determine if the current level of anticoagulation is adequate. The Time in Therapeutic Range (TTR), is calculated according the Rosendaal method and is the standard method of determining optimal anticoagulation therapy over the period of warfarin use.[9] Warfarin use requires regular INR monitoring with appropriate dose adjustment to optimise anticoagulation therapy.[10] Stability on treatment is defined as achieving and maintaining an INR within therapeutic range at an unchanged dose for a minimum clinically relevant period. [11] INR levels on either side of the indication-specific therapeutic range may lead to significant morbidity and mortality.[7] The optimal TTR used in this analysis is ≥65%, informed by extensive review of TTR and associated treatment outcomes.[12] The ACTIVE-W trial, which included South African participants, noted a TTR of ≥65% is associated with a 2,29% (95% CI 1,57-3,35; p<0,001) reduction in stroke risk.[13] Anticoagulation control among South African warfarin users remains suboptimal. [14,15] For this reason, safe and optimal warfarin therapy remains a relevant field of study.

As a Vitamin K antagonist, warfarin's mechanism of action is the depletion of functional Vitamin K reserves which will reduce the synthesis of active clotting factors.[16] Understanding this, and the importance of a Vitamin K controlled diet, are key to achieving optimal warfarin therapy. [17] This metabolic process may also be affected by certain medications (other classes of anticoagulants) and disease processes (liver, renal or cardiac impairment) which may interfere with warfarin's mechanism of action. These processes have the potential to amplify the anticoagulation effect of warfarin and require conservative prescription.[18-20] Having an awareness of this impact improves patient health literacy and empowers warfarin users to make informed decisions about their health.[21] To mitigate the risks of easy bleeding while being anticoagulated, certain lifestyle modifications should be made. Assessing fall risk and substance intoxication provides an opportunity to modify risks associated with the increased risk of bleeding.[22] Regular INR monitoring with appropriate warfarin dose adjustment provide opportunities to achieve safe and effective anticoagulation.[23] Warfarin therapy education at treatment initiation with revision at intervals can address patient perceptions and experiences.[24] This process is often neglected, due to the limited time spent with the patient in busy clinical settings.[25]

The WarPATH bundle of care is a novel approach to improving anticoagulation outcomes. It combines the traditional approach of education and counselling- based services with the benefits of information and communication technology enhanced solutions.

The adherence bundle is built around improving health literacy, which is the degree to which patients have the capacity to obtain, process and understand basic health information and services to make appropriate health decisions.[26] The education needs to be delivered in an easy to understand format and in the patient's language of choice to account for varying levels of literacy.[27-29] The adherence bundle consisted of two interventions which were delivered to all participants in the WarPATH study. The first intervention included an in-person education session which allowed for discussion and provided the opportunity for questions. A tool summarising the information was provided. This could be shared with treatment support partners and could be referred to regularly. The second intervention was designed for participant interaction. WarPATH study participants received one text per week for 12 weeks, each with a cost-free opportunity to interact with the adherence support content or request a call back from the RMO. Receiving patient education can be limited in an episode of acute illness, so the content was summarised into 12 interactive short message service (SMS) texts, with an opportunity to discuss treatment concerns.[30,31]. Interacting with the text messages and/or making use of the call back service was considered as engaging with the second intervention.

Improving treatment adherence in resource-limited settings has been an area of great interest, with a focus on antiretroviral therapy adherence in South Africa.[32] Interacting with a text message service has been shown to significantly reduce treatment interruption.[33] When studied in other resource-limited settings, text message services have been shown to improve adherence and viral suppression.[34] It is worth noting that two-way communication through text messages were shown to be the driver of text message intervention success.[35] Information- and communication technology-enhanced solutions have been cited as feasible adherence intervention tools.[36]

Interactive adherence interventions have been implemented in high resource settings, but there is limited evidence for Low to Middle Income Countries (LMIC). The COVID-19 pandemic showed a need for successful care plans that combined point of care treatment and remote management.[37]Studies that designed their intervention around a Telemedicine tool only included participants who displayed adequate control in the standard model of care. Those with a history of poor adherence, the absence of a reliable caregiver, an anticipated upcoming surgical procedure (requiring warfarin interruption), recent initiation/discontinuation of medication with documented major drug–drug interaction with warfarin, or three or more heart failure exacerbations requiring hospitalisation in the two years prior to transition date were excluded from the study.[38] These broad exclusion criteria do not reflect our burden of disease and patient profile.[39] Notably, similar interventions produced equivocal results.[40]

In this study, we aim to assess whether interacting with an adherence intervention (by responding to text messages and/or making use of the call back service) impacted on anticoagulation control, and what factors predicted adequate anticoagulation control. This analysis will contribute to the body of work that seeks to improve anticoagulation outcomes, with a focus on the role of interactive interventions in the South African setting.

Study objectives:

1. To describe the cohort in two groups: those who did or did not engage with the interactive intervention.
2. To determine whether there was any difference in short-term anticoagulation control between those who did and did not engage with the interactive intervention.
3. To determine whether there was any difference in long-term anticoagulation control between those who did and did not engage with the interactive intervention.
4. To determine predictors of adequate short- and long-term anticoagulation control

Methods:
Study design:

The WarPATH study is a prospective cohort study. As part of the bundle of care, all participants received counselling in the language of their choice, an educational handout, 12 weekly text messages over the duration of the study and contact details for the on-call Research Medical Officer (RMO). Responding to the text messages and using the RMO contact details were optional components and are classified as the interactive component of the intervention.

Participant eligibility:

The WarPATH cohort included patients who provided written consent for their participation, were 18 years and older, commencing warfarin treatment for the first time and were able to follow up at one of the participating sites. Indication for anticoagulation was restricted to Venous Thromboembolism, Atrial Fibrillation and Valvular and Valvular Heart Disease. Patients who were unwilling to participate, who were younger than 18 years old, pregnant, unable to follow up at the participating sites or considered unsuitable for the study by their treating clinician were not included in the WarPATH study.

In addition to the inclusion/exclusion criteria applied in the recruitment of the WarPATH study, we also excluded those who did not have enough INR data to calculate a TTR between weeks 2 and 6.

Study site:

WarPATH participants were recruited from Groote Schuur Hospital, New Somerset Hospital, Mitchell's Plain Hospital, Victoria Hospital and False Bay Hospital in Cape Town, Western Cape, South Africa.

Sample size calculation:

We will select the cohort for this analysis based a convenience sample. We will select participants from the WarPATH study who are eligible for this analysis.

Data Management:

The data used in this analysis was collected in the WarPATH study period. The additional month of INR results used to measure the long-term anticoagulation control was gathered from the National Health Laboratory Services' online results platform after gaining permission from the Human Research Ethics Committee at the University of Cape Town. In the WarPATH study, -participants were anonymised and assigned unique identification numbers. The same identification system will be used in this analysis to maintain participant's privacy. A single participant list is kept in a locked cupboard with restricted access. Participant correspondence by text or call was recorded in the Adherence Form (see Appendix) by the responsible RMO. The primary data sources were the Bulk SMS Application and the study phone's call and message logs. All interactions were collated onto an electronic spreadsheet and stored in a password-protected folder. Additional data (demographic data, potential confounders) will be extracted from the WarPATH electronic database which is stored on RedCAP.

Data Analysis:

We will describe the cohort according to whether participants engaged with the interactive intervention or not, using demographic data, indication for anticoagulation and site of treatment as proportions of the sample. All demographic data will be reported as categorical variables. Sex will be defined as a binary variable (male or female), age in years will be categorized according to quartiles (18-25, 26-35, 36-59, >60). Language is the language in which the counselling was delivered (English or other, where a translator was used). The site of anticoagulation therapy will be categorised according to the hospital where warfarin was initiated (Groote Schuur, New Somerset, Mitchell's Plain, Victoria and False Bay). We will categorise indication as Venous Thromboembolisms (VTE), mechanical valve or atrial fibrillation. Access to mobile device will be defined as a binary variable (access to own device indicates a personal device, no access to own device indicates the participant using someone else's device). We will report the summary statistics of each variable according to its distribution, as well as the TTR of the cohort.

We will build two logistic regression models to estimate the short- and long-term outcomes of adequate anticoagulation among those who did or did not engage with the interactive intervention to determine if engaging with the intervention is a predictor of adequate INR control. We define adequate coagulation as a binary outcome (reaching or not reaching a TTR of ≥65%). Variable selection for the models will be made *a priori*. We will adjust for potential confounders of the relationship between the decision to engage with the interactive component intervention and outcome including age, sex, language, access to own mobile device. We will report crude and adjusted odds ratios with 95% confidence intervals. These regression models will also identify predictors of adequate short and long-term anticoagulation, and will be defined as covariables with a significant adjusted odds ratio and a p-value of <0,05.

We will assess the association between engaging and not engaging with the interactive intervention and achieving adequate short-term anticoagulation for the four-week period in the WarPATH study. To standardise the period of comparison, we will assess anticoagulation between weeks 2 and 6 in the study period for all participants.

Next, we will assess the association between engaging or not engaging with the interactive intervention and achieving adequate long-term anticoagulation in the four-month period after exiting the WarPATH study. To determine the long-term impact of the intervention, we will gather INR results for each participant in the four months following their exit from the study. We will calculate a second TTR for each participant in this second time period and compare the results of the first and second TTRs of those who engaged with the intervention to those who did, to assess whether there was any lasting impact of the intervention. We will assess whether any other variables predicted short- or long-term INR.

We will perform a modified Intention to Treat Analysis, in which those with 2-6 weeks of data will be eligible for inclusion.

Dummy tables:

Table 1: Characteristics of participants who did and did not interact with an interactive adherence intervention to improve warfarin anticoagulation

	Participants who did not engage with the interactive intervention (n=X,%)	participants who engaged with the interactive intervention (n=X,%)
Sex, n(%) Male		
Age category (years) n(%) 18-25 26-35 36-59 >60		
Language, n(%) English		
Study site, n(%) A B C D E		
Indication for anticoagulation, n(%) Venous Thromboembolism Mechanical Valve Atrial fibrillation		
Access to own mobile device, n(%)		

Table 2: Multivariable Logistic Regression Model reporting the crude and adjusted odds of achieving adequate short-term anticoagulation (TTR ≥65%)

Variable	TTR≥65% n(%)	Crude Odds Ratio (95% Confidence Interval)	Adjusted Odds Ratio (95% Confidence Interval)	P-value
Level of engagement with the interactive intervention Did not engage with the interactive intervention n(%) Engaged with the interactive intervention n(%)				
Sex, n(%) Male Female				
Age category (years) n(%) 18-25 26-35 36-59 >60				
Language, n(%) English Other				
Study site, n(%) A B C D E				
Indication for anticoagulation, n(%) Venous Thromboembolism Mechanical Valve Atrial fibrillation				
Access to own mobile device, n(%) Yes No				

Table 3: Multivariable Logistic Regression Model of the crude and adjusted odds of achieving adequate long-term anticoagulation (TTR ≥65%)

Variable	TTR≥65% n(%)	Crude Odds Ratio (95% Confidence Interval)	Adjusted Odds Ratio (95% Confidence Interval)	P-value
Level of engagement with the interactive intervention Did not engage with the interactive intervention n(%) Engaged with the interactive intervention n(%)				
Sex, n(%) Male Female				
Age category (years) n(%) 18-25 26-35 36-59 >60				
Language, n(%) English Other				
Study site, n(%) A B C D E				
Indication for anticoagulation, n(%) Venous Thromboembolism Mechanical Valve Atrial fibrillation				
Access to own mobile device, n(%) Yes				

No				

Ethics:

Ethics approval was received for the WarPATH study (HREC 710/2020, valid until 30/05/2024)(Appendix D).

The data collected in the WarPATH study was anonymised and we will maintain this method of data handling as we perform our analysis.

We will submit an ethics application to the Human Research Ethics Committee at the University of Cape Town to access the additional INR results beyond the study period. We will request access to four months of INR results in the period following their exit from the study for each participant.

Risks and Benefits

This analysis does not require any further interaction with the participants and there are therefore no foreseeable health risks to the participants.

Upon recruitment to the WarPATH study, participants provided consent for the study team to access their medical records, both paper and electronic in order to extract information relevant to this study, of which this analysis is an objective (Appendix E). We will not breach confidentiality and will maintain participant privacy by using anonymised data. We will only request access to the relevant results; INR results in the four months following exit from the study. We will request permission for limited access to the NHLS database, agreeing to limit our database use to the relevant data and maintain patient privacy and confidentiality. When consenting to participation in the WarPATH study, participants were not guaranteed any direct benefit from their participation. They were informed that participating in the study would add to a body of work that may improve the management of similar patients in the future. This analysis is one such instance.

In performing this analysis we aim to:

- Inform policy makers regarding the outcomes of interacting with an adherence intervention
- Improve the standard of care in anticoagulation control

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Appendix A:
War-PATH study Synopsis

SYNOPSIS: Implementation of a "bundle of care" to improve anticoagulation control in patients receiving warfarin in Uganda and South Africa

Project: NIHR Global Health Research Group on warfarin anticoagulation in patients with cardiovascular disease in Sub-Saharan Africa (War-PATH)

BACKGROUND

This study is **phase four** of a project which aims to improve the quality of anticoagulation in Uganda and South Africa.

In phase 1 we audited the quality of anticoagulation across five services in the two countries and found that the median time in therapeutic INR range (TTR) was 41%.

In phase 2 we recruited patients on stable doses of warfarin to identify clinical and genetic factors which may influence warfarin dose and developed and validated a clinical warfarin dosing algorithm. Genetic analyses of the collected data are ongoing.

In phase 3 we will pilot-implement the clinical algorithm developed in phase 2 in a feasibility study. (Protocol entitled: Pilot implementation of a clinical algorithm for warfarin dosing in sub-Saharan African patients in the War-PATH Ugandan and South African clinical study sites. Ethical approval refs: Uganda – JC2919; South Africa – HREC REF: 788/2019). Phase 3 was halted due to the COVID-19 pandemic but will shortly resume as the situation has been steadily improving.

The current protocol (phase 4) describes a study with the aim to implement a warfarin "bundle of care" to improve the quality of anticoagulation, and thereby clinical outcomes, using a mixed methods approach. The bundle will include patient-centred and process-centred activities, namely (1) implementing dosing algorithms, (2) providing adherence support, (3) conducting root-cause analysis of warfarin-related adverse events, (4) implementing point-of-care INR testing, and (5) providing staff training. We anticipate that this warfarin bundle will result in better INR control than the current standard of care.

DESIGN

A mixed methods implementation study of a warfarin "bundle of care" to improve the quality of anticoagulation, and thereby clinical outcomes.

AIMS

The primary objective is to evaluate whether implementation of the warfarin bundle improves time in therapeutic range.

Secondary objectives are to evaluate whether implementation of the warfarin bundle improves time to achieving a therapeutic INR, whether implementation of the warfarin bundle affects the occurrence of adverse effects (death, bleeding, and thrombotic events), whether staff find the interventions contained in the bundle acceptable, and to explore patients' experiences and acceptability of the package of care, and whether the bundle represents good value for money.

OUTCOME MEASURES

Testing for improvement in anticoagulation control

We will measure time in therapeutic range (TTR) over the initial three months of warfarin therapy, using the Rosendaal linear interpolation method, similar to the approach in phase 1 and 3 of the project.

Primary Outcome

We will compare time in therapeutic INR range between prospectively followed participants who received the warfarin care bundle and a retrospectively reviewed patient group who did not receive the warfarin care bundle but instead received standard of care. This will give a combined estimate of the impact of the warfarin care bundle. It will not be possible to separate out the effect of the individual components of the warfarin care bundle on TTR.

Secondary Outcomes

- We will compare time to achieving a therapeutic INR in a prospectively followed group of participants who received the warfarin care bundle with the retrospectively reviewed patient group who received standard care.
- We will compare adverse events (death, bleeding, or thrombosis) in the prospectively followed participants who received the warfarin care bundle with the retrospectively reviewed patient group who received standard care.
- We will explore staff experiences and acceptability of the warfarin bundle using in-depth interviews at the end of the implementation period.
- We will explore participant experiences and acceptability of the warfarin bundle using focus group discussions at the end of the implementation period.
- Qualitative assessment of useful lessons learnt from root cause analysis that can be fed back into the warfarin bundle.

- We will perform cost effectiveness analyses from the perspective of the health service providers to judge whether the War-PATH warfarin bundle represents good value for money. These will be based on estimated costs associated with warfarin treatment, and health outcomes expressed as quality-adjusted, and disability-adjusted life-years (QALYs and DALYs). Resource use will include hospital admissions, outpatient clinic visits, phlebotomy, point-of-care and laboratory INR tests, additional blood tests and prescribed warfarin. The economic analysis will estimate the incremental costs per QALY gained, and DALY averted, and inform policy.

POPULATION AND STUDY DESIGN

- We will **retrospectively review** folders of 222 adult patients (111 in Uganda and 111 in South Africa) who initiated warfarin treatment before 31 December 2020. We will include all sequential patients chronologically backwards from 31 December 2020 until the required sample size is reached.
- We will also recruit 222 consenting adult participants (111 in Uganda and 111 in South Africa), who are being newly initiated on warfarin treatment for venous thromboembolism, atrial fibrillation or valvular heart disease and will follow these participants for 3 months **('implementation group')**.
- We will record self-reported ethnic background of participants. Participants of Black African ancestry will be initiated on a dose calculated using the **dosing algorithm** developed in Phase 2 of our current study, which takes account of patient age, weight, target INR and HIV status. Participants with non-black African ancestry will be initiated on a dose calculated using the published and validated International Warfarin Pharmacogenetics Consortium (IWPC) algorithm.

- The package of **adherence support** offered will include the following:

  - Data driven counselling
  - Peer support groups
  - Interactive weekly text messaging.

- **Root cause analysis** will be undertaken in all patients on warfarin at the INR clinic and/or hospital who are seen with a serious thrombotic or haemorrhagic event.

- We will make **point-of-care INR testing** a central part of improving the clinical pathway.
- **Staff training** will include co-design workshops discussing the rationale for the bundle and likely implementation issues with a team of clinicians involved in the provision of anticoagulation services. Discussions will be held with all clinical teams at each implementation site prior to commencement. This will enable the study team to identify the site's current routine processes, patient pathway and any changes that would be required to accommodate the bundle.
- **Co-design workshops** for the development of training material to be used in patient education will bring together patient or community representatives, healthcare staff, the research team and a representative from policy makers.

DURATION

1st October 2020 to 1st September 2021

SUMMARY

Title	Implementation of a "bundle of care" to improve anticoagulation control in patients receiving warfarin in Uganda and South Africa.
Short Title	War-PATH: Implementation of the warfarin bundle
Aims	To implement the warfarin bundle to improve the quality of anticoagulation, and thereby clinical outcomes using a mixed methods approach.
Hypothesis	Implementing the warfarin bundle is feasible and improves INR control of Ugandan and South African patients on warfarin
Methodology	A mixed methods approach of implementation of patient and process centred activities to improve the quality of anticoagulation in sub-Saharan African patients.
Study Duration	11 months
Study Centre(s)	**South Africa**: Groote Schuur and Tygerberg Hospitals and health care facilities in their drainage areas. **Uganda**: Uganda Heart Institute and Mulago National Referral Hospital and health care facilities in their drainage areas.
Objectives	The primary objective is to evaluate whether implementation of the warfarin bundle improves time in therapeutic range. Secondary objectives are: • to evaluate whether implementation of the warfarin bundle improves time to achieving a therapeutic INR, • whether implementation of the warfarin bundle affects the occurrence of adverse effects (death, bleeding, and thrombotic events), • whether staff find the interventions contained in the bundle acceptable, • to explore patients' experiences and acceptability of the package of care, and • whether the bundle represents good value for money.
Number of Participants	444 total (222 retrospective folder reviews. 222 prospectively recruited participants with individualised warfarin starting dose.)
Inclusion Criteria for retrospective folder review	1. Patients newly initiated on warfarin anticoagulation before 1 January 2021. 2. Indication for warfarin treatment is either venous thromboembolism (VTE), atrial fibrillation (AF) or valvular heart disease (VHD).

	3. Age 18 years or over at the time of initiation.
Inclusion Criteria for prospective recruitment	1. Patients newly initiated on warfarin anticoagulation. 2. Indication for warfarin treatment is either venous thromboembolism (VTE), atrial fibrillation (AF) or Valvular Heart Disease (VHD). 3. Age 18 years or over at the time of initiation. 4. Signed or witnessed written (witnessed thumbprint for illiterate participants) informed consent. 5. Participant resident in and willing to be followed up at a health facility in an area where follow-up is feasible in the opinion of the investigator
Inclusion Criteria for root cause analysis	1. Patient on warfarin (irrespective of duration of treatment) 2. Patient experienced bleeding or thrombotic episode during the timeframe of the study 3. Age 18 years or over.
Exclusion Criteria for prospective recruitment	1. Patient unwilling to take part. 2. Clinical staff feel that there is a clinical reason why the patient should be dosed with another anticoagulant 3. Pregnancy. 4. Received more than one dose of warfarin prior to recruitment.

Appendix B1: Patient Education

Patient Education Warfarin Introduction

What is warfarin?

Warfarin is a drug which thins your blood, meaning that it doesn't clot as easily as before.

What is warfarin used for?

People who need to thin their blood use warfarin, either for a short period of time or sometimes for the rest of their lives depending on which condition they have. If you are on warfarin for the rest of your life, it is because there is a risk of blood clots forming whenever you don't use warfarin. This makes stopping warfarin at any time, risky. Warfarin is commonly taken by people who have blood clots in the legs (deep venous thrombosis/ DVT), blood clots in the lungs (pulmonary embolus/PE), irregular heart rhythms like atrial fibrillation (AF) and for people who have had a valve in their heart replaced. There are some other reasons too but they are more rare.

How does warfarin prevent clots from forming?

Warfarin stops your body from producing clotting factors which help the blood to clot. The specific clotting factors it targets are those which need vitamin K to be produced. Eating food with high levels of vitamin K can decrease your INR when you are on warfarin. This means that your blood clots more easily.

What is the correct dose?

Not everyone takes the same dose of warfarin. Each person may need to increase or decrease their dose many times before they find the right one. Sometimes, even when someone has been on the same dose for a long time, the dose may change if things about that person change. This includes things like their weight, diet and medications that they are on. Smoking, alcohol, herbal medications, supplements, other illnesses like thyroid disease and heart failure and age can affect the required dose of warfarin.

What is an INR?

The INR stands for international normalised ratio, which doesn't really explain what it is at all! The INR is a test to see how thin or thick the blood is. A higher INR indicates thinner blood (bleeds more easily, does not clot easily) whereas a lower INR indicates thicker blood (clots more easily, does not bleed easily).

What should my INR be?

This depends on why you are taking warfarin. Different conditions require different treatment and so the target INR may be different for different people. Usually, it will be between 2 and 3 or between 2.5 and 3.5. Your INR will be checked every few days at the beginning when you start warfarin but once your INR is in the correct range, you won't have to check it as often. Most people check their INRs once a month.

What if my INR goes too high or too low?

If your INR is just a little out of range, you might stay on the same dose or have your dose adjusted. Before adjusting your dose, we will need to check that there aren't any other reasons why your INR is not in range. Examples of these reasons are: if you had forgotten to take your warfarin one or

more days recently, if you had started any other herbal remedy, medication or supplement recently, if you had food or drinks which interact with warfarin, if you were sick (diarrhoea or vomiting, infection, thyroid disease, heart failure) or if you had recently smoked, drank alcohol or used other drugs like marijuana.

If your INR is very high, you may need to stop your warfarin for 1 or more days before restarting (sometimes on a different dose). If it is extremely high, you may need treatment in hospital. Sometimes, vitamin K is given to try and decrease the INR.

When the INR is too low, it means your blood is too thick and can clot. This can be dangerous.

Signs of Over-anticoagulation

People on warfarin may experience some side-effects even when their INRs are in range. This may include bruising more easily and some women may complain that their periods/menses are heavier than they were before.

Signs that your INR might be too high are bleeding gums or nose bleeds and very extensive bruising. In cases where the INR is very high, larger bleeds such as in the stomach or brain, may occur. If you see blood in your urine or stool, vomit or cough blood or have any bleeding which does not stop, it is important to seek emergency treatment immediately.

Injuries and Activities

Injuries which may not have seemed serious before taking warfarin, can become more dangerous because the chances of bleeding are much higher on warfarin. If you hit your head or have any serious injury, it is better to check that there is no internal bleeding if you have any doubt.

High risk activities and contact sports must be avoided for this reason.

When should I take my warfarin?

It is best to take your warfarin at night. Most clinics will recommend that you take it at 6pm. This is so that when you have blood taken to check your INR early in the morning, you will get those INR results long before the next dose at 6pm so that there is still time to adjust your warfarin dose if needed.

What if I miss a dose of warfarin?

It is important that if you miss a dose of warfarin, you do not take that dose the next day on top of the next day's dose. If you take too much warfarin at once, your INR can increase and your risk of bleeding can increase as well. Instead, tell your doctor or nurse that you missed that dose the next time you see them.

Where should I store my warfarin?

Warfarin can be a very dangerous drug when it is taken by those who do not need it, especially in large amounts. If there are small children in the house, this is even more important to remember. Ensure that your warfarin is kept in a safe place out of reach of children and away from other medications so that nobody can confuse it for another tablet.

How do I remember to take my warfarin every day?

There are many ways to make sure you don't miss any doses of warfarin. Some helpful tips include:

- Ask someone you live with to help you remember.
- Set an alarm on your cell phone.
- Take you warfarin at the same time as something else eg. Your favourite TV programme, when you brush your teeth, when you get home from work in the evening.
- A pill box can help if you have many other medications to take as well

What if I want to fall pregnant?

If you are planning to fall pregnant in the future while you are taking warfarin, it is important to discuss this with your doctor first. Falling pregnant on warfarin without proper planning can be harmful to you and/or your baby.

Who should I tell that I'm on warfarin?

Any doctor, nurse or pharmacist à warfarin can interact with other medications. If your health provider doesn't know you are on warfarin, they may prescribe you medicine which interacts.
Anybody who may perform a surgery or procedure on youà surgeons and dentists will need to know that you are on warfarin long before the planned procedure. This is to ensure that your INR is not too high and there is time to allow it to decrease if needed.
Anyone attending to you in an emergency à you may not always be able to tell the relevant people about your warfarin in these situations. This is where a medic alert bracelet is very useful. Telling your immediate family or the people you live with can also be helpful but this is a personal choice is you would like to disclose.

Medic Alert Bracelets

A medic alert bracelet can be worn at all times to inform health providers of things like allergies, medical conditions and medications in situations when the person concerned cannot do so. It is also a good reminder even when it is not an emergency! You can apply for your medic alert bracelet by contacting the MedicAlert® Foundation on 086 111 2979 or via email: info@medicalert.co.za.

What can interact with warfarin?

There are many things which interact with your warfarin.

Medications

There are many different types of medicines which interact with warfarin. Some of them might increase the concentration of warfarin in your blood and some might decrease it. These are not just the medications prescribed by your doctor but can also include medications, supplements and herbs you can buy at the pharmacy or drug store without a prescription. This is why you should never take any medication without speaking to your doctor, pharmacist, or nurse first. Traditional medications from your traditional healer may also interact with warfarin. If you use traditional medications, it is important to tell your doctor, pharmacist, or nurse.
Examples of common medications which can interact include:

- Antibiotics (treating infections)
- Anti-inflammatories (for pain relief such as ibuprofen)
- Medications for heart disease
- Stomach ulcer and reflux medications
- Epilepsy medications
- TB treatment
- Aspirin (for pain or heart medication)
- Cough and cold remedies

Health Conditions

Health conditions which may alter your INR include:

- thyroid disease
- liver disease
- cardiac failure

Appendix B2: Dietary Advice

HEALTHY EATING GUIDELINES FOR PATIENTS ON WARFARIN

A healthy, balanced diet consists of a variety of foods. Eating a variety of foods ensures that the body receives all the nutrients it needs to function optimally.

Warfarin is a medicine that helps to prevent the formation of blood clots and is often prescribed in certain heart conditions or when there is an increased risk of blood clot formation. The effectiveness of Warfarin may be influenced by what we eat and drink.

The body uses Vitamin K to help with blood clotting, BUT Vitamin K is also needed for a healthy diet. There is no need to restrict Vitamin K rich foods or change your diet if you are on Warfarin. Instead, try and eat the same amount of these foods each day**. Do not eat a large amount the one day and nothing the rest, sudden changes in the amount of vitamin K in your diet can impact how your warfarin is working.**

Foods high in Vitamin K

Limit all foods below to a total of ½ cup per day, this is not ½ cup per each item per day but rather ½ cup of all of them together. For example: 1 kiwi fruit & ¼ cup spinach.

Asparagus	Chickpeas	Kale	Pine nuts	**Spices: Limit to 1 teaspoon per day**
Avocado	Chicory	Kiwi fruit	Raisins	Ginger
Beef liver	Chinese cabbage	Lentils	Seaweed	Tumeric
Blackberries	Collard greens	Lettuce	Soybeans	
Blueberries	Green leafy vegetables	Mango	Swiss chard	**Oils: Limit to 1 tablespoon per day**
Cabbage	Green beans	Mung beans	Watercress	Canola
Cauliflower	Green tea	Peas		

The following foods have a major effect on your warfarin levels and should be had less often than the others listed above:

Broccoli Brussel sprouts Cranberry or pomegranate juice Grapefruit Spinach

Alcohol

Large amounts of alcohol can affect warfarin, but sensible amounts are allowed. ***Avoid binge drinking*.**

Cannabis & CBD oil

Cannabidiol can result in increased warfarin levels, putting you at risk of bleeding. Consult your doctor first.

Vitamins, minerals, herbal- and other dietary supplements

DO NOT take any of these products: fish oil supplements, ginkgo biloba, Devil's claw, ginseng or multivitamins. Consult your doctor first.

GENERAL HEALTHY EATING GUIDELINES

Make starchy foods part of most meals

Starchy foods such as bread, rice, pasta, oats, maize meal and potatoes are good sources of energy. Many of these foods are high in fibre as well. Insoluble fibre found in whole wheat bread and bran flakes prevents constipation. Soluble fibre found in oats, legumes, and maize meal may help to reduce cholesterol and control blood glucose levels.

Protein foods

Meat, chicken, eggs, fish and dairy products (milk, cheese, and yoghurt) are excellent sources of protein. The body uses protein to build new tissue and to replace damaged tissue. Remember to choose low fat versions of these foods to control your total fat intake, e.g. low fat milk and yoghurt, lean minced meat & skinless chicken.

Eat fats sparingly

Sources of fat include margarine, butter, oil, nuts, coconut and avocado pears.
Total fat intake should be limited in order to prevent weight gain and to protect heart health. Most South Africans consume too much fat.

Follow these tips to reduce fat intake:

- **Eat less deep fried food & takeaways, processed meat (eg viennas, polony) and commercially baked products.**
- **Remove all visible fat on meat before cooking.**
- **Use less oil in cooking.**
- **Choose lean meat, chicken (cooked without skin), fish and legumes.**
- **Choose low fat dairy products.**
- **Steam, grill or bake instead of frying and roasting.**

Eat dry beans, peas, lentils and soya regularly

These foods are economical sources of protein and they are low in fat and high in fibre. They are good alternatives to meat, chicken and fish.

Eat plenty of fruit and vegetables every day

Fruits and vegetables contain a variety of vitamins and minerals, which boost the body's immunity and protect against infections.
Select a variety of colours as the colour usually indicates the type of vitamin it is rich in. Dark yellow (sweet potatoes, carrots, and butternut are Vitamin A rich. Oranges, tomatoes and guavas are rich in Vitamin C. The skins and pips of fruit are also sources of insoluble fibre, which helps to prevent constipation.

Use salt and foods high in salt sparingly


The use of salt is an acquired taste and just a habit.
Salt is found in almost all the food we eat. It is only needed in small amounts.

To lower salt intake:

- Reduce salt in cooking – use garlic, herbs or lemon juice instead (Maximum 1 tablespoon), to add flavour to food.
- Remove the salt cellar from the dinner table to avoid adding extra salt to cooked food.
- Avoid convenience foods such as canned and packet soups, processed meat and cheese spreads, commercial sauces and spreads and fast foods.

Be Active

Department of Dietetics
Groote Schuur Hospital
TEL: (021) 404 4471


Physical activity has many health benefits. It speeds up weight loss, lowers blood pressure and protects the health of your heart. Try to do about 30 minutes of moderate intensity exercise, such as brisk walking, every day.

Participant Text Messaging (12 weeks, one message per week)

1. Thank you for choosing to take part in the WarPATH “Bundle of Care” study. Reply to this message with any questions or type “call me” and someone will phone you back. All replies are free!

2. How was your first week of warfarin therapy? Do you have any bruising, bleeding or any other concerns? Reply “call me” for someone to phone you back.

3. Getting your INR in range with the right dose of warfarin is different for each person. This may take time. Reply for free with any questions or “call me” for someone to phone you back.

4. Speak to the doctor or nurse before using any other medication, even herbal medication or over-the-counter remedies. These treatments can cause problems when taken with warfarin. Would like a list of some examples. Reply “call me” for someone to phone you back.

5. Different foods, especially green, leafy vegetables, can interfere with your warfarin. Instead of avoiding them, try to eat the same amounts every day and be consistent. Ask us if you would like a list of . Reply “call me” for someone to phone you back.

6. Alcohol can cause your INR to increase if you have more than 1 or 2 drinks. A high INR makes your risk of bleeding higher too. Ask us any questions about alcohol and warfarin. Reply “call me” for someone to phone you back.

7. Are you planning a trip or holiday away from home? Make sure you have enough warfarin long before you go and can get your INR checked there if needed. Reply “call me” for someone to phone you back.

8. How do you remember to take your warfarin every night? Tell us what helps you remember! Reply with your answer or any questions for free. Reply “call me” for someone to phone you back.

9. Do you remember all the information that was given to you when you first started warfarin? Refresh your memory and see if you have any new questions. We can send the information again if you would like. Reply “call me” for someone to phone you back.

10. You have been on warfarin for 10 weeks already! What has been the biggest change for you? Reply “call me” for someone to phone you back.

11. If you forget to take a dose of your warfarin, don’t take it at another time or double your dose. This can cause your INR to increase too much. Take your warfarin as normal the next day. Do you have any questions about how to take your warfarin? Reply “call me” for someone to phone you back.

12. This is your last message from the WarPATH study. Thank you for participating! We hope you have learned a lot about warfarin. Tell us if you have any last questions. Reply “call me” for someone to phone you back.

Participant Information Sheet

Protocol Version this Information Accompanies: Version 1.1
Site: Cape Town, South Africa
Site Principal Investigator: A. Prof Karen Cohen
Site Principal Investigator contact number: (+27) 021 406 6293.

Introduction

You are being invited to take part in a research study. This study is shared work between the University of Liverpool, Bangor University, UK, the University of Cape Town, South Africa and the Infectious Disease Institute, Kampala, Uganda. Before you decide if you will take part, it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with others if you wish. Ask us if anything is unclear or if you would like more information.

Why have I been invited to participate in this study?

You have been invited to participate because you are about to start taking the drug warfarin**.What is the purpose of the study?**
Warfarin is a drug which "thins" the blood and makes it clot less. Warfarin prevents blood clots from forming in the veins and in the heart. If clots form, they can travel to the brain or lungs where they can cause serious damage.

Many different conditions are treated with warfarin. These include deep vein thrombosis (blood clot in a vein in the leg), pulmonary embolus (blood clot which has travelled to the blood vessels in the lung) and atrial fibrillation (irregular heartbeat). Warfarin is also given to some patients with heart valve disorders, and patients who have had heart surgery or have had heart valves replaced.

The International Normalised Ratio (INR) is a blood test that shows how well warfarin is working. The INR blood test is done regularly on all patients taking warfarin. Depending on the reason you are taking warfarin, your target INR will either be between 2 and 3 or between 2.5 and 3.5. It is important that the INR is kept in the target range. If the INR is too low, clots may form which may worsen your condition being treated. If the INR is too high, this may result in a bleed which can be very serious. Doctors use the results of the INR test to decide if you are on the correct dose of warfarin, and to guide a new dose if needed.

Different people need different doses of warfarin to reach the target INR. Researchers have developed clinical algorithms to help guide warfarin dosing. A clinical algorithm is a tool that a doctor can use to workout the correct warfarin dose for an individual patient by answering a set of questions about that patient. There are algorithms that are used to guide warfarin dosing in Europe and America, but these algorithms do not work well in black patients. We know from previous studies that the INR is not well controlled in Ugandan and South African patients.

Usually in South Africa all patients are started on the same dose of warfarin and the dose is changed if needed after testing the INR. Some people require a much higher warfarin dose and some people require amuch lower dose to achieve their target INR. If the starting dose of warfarin is too high or too low for thatpatient, this can cause the INR to be outside of the target range.

We have developed a new package of care (the warfarin bundle) which is a program of activities that aimsto improve the health of patients taking warfarin. The bundle includes:
an algorithm to calculate a personal starting warfarin dose.
using point of care devices for finger prick testing giving instant results, instead of sending a bloodsample to the laboratory for testing,
one-one counselling session/s to discuss your warfarin and how to take it
support groups that you will be invited to take part in which will provide more information onwarfarin together with other people on warfarin
a short questionnaire on when and how you take your medication.

We developed an algorithm using clinical information that we collected from a group of black patients taking warfarin in Uganda and South Africa who had an INR in the target range.

The algorithm uses four questions about a patient to work out the warfarin dose: weight, age, HIV status and target INR. If you decide to participate in this study and self-identify as being of black African ethnicity, we will use this algorithm to calculate your starting dose of warfarin. If you do not identify as ofblack African ethnicity, we will use a different algorithm to work out your warfarin dose (the InternationalWarfarin Pharmacogenetics consortium algorithm) which has been previously validated in a number of studies.

Your INR result will be available at the time of your appointment as the study will be using Point of Care testing devices, which involves a finger prick test meaning that you do not have to wait for the laboratory result for your INR test results. Once you are taking Warfarin, you will be invited to join support groups, which will be run by a project counsellor on your clinic day. They will provide information to you on the importance on taking your medication properly and to help with any questions you may have. We will alsoask you to complete some questions about when and how you take your medication.

We will compare your INR results with the INRs of other patients who did not receive this bundle of care package to see if all the components in this bundle helped to improve control of your INR. If this helps to improve INR control overall for the people who participated in this study, we may use it for others taking warfarin to help them with their INR control too. We will use information from this study to work out if use of the dosing algorithm impacts on the cost of treating patients with warfarin

HIV Testing

If you decide to participate in this study, we will ask you what your HIV status is, and use that information when we calculate your warfarin starting dose. If do not know your HIV status, we will offer you an HIV test. If you accept the HIV test, we will provide you with pre and post-test counselling which will include information about what HIV is and what a positive or negative result means. You can choose not to test for HIV. If you choose not to do the HIV test, you can still participate in the study. We will then record your HIV status as “unknown” when we calculate your dose

Collection of information about your ethnicity

There are 2 different warfarin dosing algorithms that we may use in this study. The first dosing algorithm which we are using was developed by us, using information collected from people taking warfarin who identify as black. We do not know how this algorithm will perform in people who do not self-identify as

black and therefore we will therefore only use this algorithm for those who do self-identify as of black African ethnicity. If you self-identify as of another ethnicity, we will use a different algorithm in which information about your ethnicity is needed to calculate the dose more accurately For this reason, we will ask you how you identify your ethnicity.

What will happen to me if I take part?

If you decide that you would like to participate in this study, a study doctor or nurse will meet with you, and will collect information about you, including your age, height, weight, ethnicity, past medical history and current medications. We will collect this information by speaking to you, and by reviewing your paperbased and electronic clinical and laboratory records. We will record your contact telephone number. We will also ask your permission to collect a blood sample for use in genetic research and for storage for futureresearch. We will give you a separate information sheet about this blood sample. You can decide not to give a blood sample and still participate in the main study.

We will calculate your warfarin starting dose using the dosing algorithm. We will discuss this starting dose with your doctor. Your doctor will decide whether to use the warfarin dose we have calculated.

If your doctor decides that they do not want to use the warfarin dose we have calculated, you will continue warfarin treatment and INR monitoring under their care, using the dose they select. You may still participatein the other components of the bundle of care. We will continue to collect information about your warfarin dosing, and other medicines that you receive, over the first 3 months of treatment with warfarin. We will collect your INR results during the first 3 months.

If your doctor agrees, you will start warfarin at the dose we have calculated. We will check on you regularly during the first 14 days of taking warfarin. We will check your INR every 2 to 3 days until it reaches the target range and stays in range at the next check. Your warfarin dose will need to be adjusted if your INR is outside the target range. We will recommend dose adjustments to your doctor. Your doctor will have thefinal decision about dose adjustments. At each check, we will record what dose of warfarin you are taking,and your INR results. We will record any new problems that you develop.

We will organise one of more counselling sessions with just you and a counsellor starting when you first begin taking warfarin, to discuss some of the important things you need to know to control your INR. They may also answer questions you have about taking warfarin.

During your clinic visits for the first 3 months, you will also be asked by a study team member to join weekly support groups to learn more about the drug you are taking and the importance of taking it properly.You will also be contacted by text message on a regular basis by the study team to make sure you are not having any problems taking your warfarin.

Once you reach the INR target, you will continue warfarin treatment at an outpatient clinic. This is usual clinical care. We will send information about the study and warfarin dosing with you to give to the clinic nurse or doctor. The healthcare staff will continue to monitor your INR. They will adjust your warfarin dose if needed.

We will continue to collect information from your medical records for 3 months after you started warfarin.We will record all your INR results and all your warfarin dose adjustments during the first 3 months of

taking warfarin. We will also collect information on medicines that you are taking and new problems thatyou develop, including hospital visits or admissions. We will collect this information from your clinical and laboratory records. We will contact you telephonically or meet you at the clinic at the end of the 3rd month, to find out how you are.

Do I have to take part in this study?

It is your choice to participate in this study or not. If you decide not to participate, you will receive usual clinical care following standard treatment guidelines.

If you decide to take part in the study, you will be given this information sheet to keep and be asked to signa consent form. You will still be free to withdraw at any time and without giving a reason. This will not affect the standard of care you receive.

If you do decide to withdraw from the study at a later stage, we would like to be able to use any research results obtained before your withdrawal of consent, however no further information will be collected. Please inform the study doctor if you want to withdraw your consent.

What are the side effects/ risks of taking part?

If your INR is too high, there is a risk of bleeding which can be serious, and if your INR is too low, there is a risk of clots forming which may lead to them traveling to the lungs or brain. These are the same risks as for patients who are started on the usual warfarin dose. It is the first time testing this new algorithm, so if your INR is calculated by using it, there is no guarantee that it will lead to an improvement in INR control.We will closely monitor you during the first 14 days, until your INR reaches the target range.

What are the possible benefits of taking part?

The study may not benefit you. We do not yet know if this bundle of care will improve control of your INR. The results of this study will hopefully contribute to improving warfarin dosing for other people in the future.

Will my taking part in this study be kept confidential?

Confidentiality will be maintained at all times. The clinical study team at The University of Cape Town will be the only people who will know your personal information (name and telephone number). This information will not be shared outside that team and will be stored in a locked cabinet in Old Main Building,Groote Schuur Hospital. Only the study team have the key to this cabinet. We will assign a code to be usedon any documents or databases containing your clinical details. Once the study has been completed, we willensure that no one can link your identity to your clinical details (anonymisation), and therefore it will not be possible to trace the information back to you. Your name or identifying information will not be publishedin any report of the study findings. Support groups may involve contact with other patients on warfarin whomost likely attend the same clinic as you. You may choose to introduce yourself and share any informationyou would like with the other participants in these groups however, no information about you will be sharedwith them by the study staff.

What will happen to the results of the research study?

We will combine all the results from the participants taking part in the study and publish any results in

medical journals. Research findings will also be communicated back to the doctors looking after you, and information will be available via the clinic you attend. You will not be specifically identified in any publication. As this is a collaborative study, we would like to send your anonymized information to the UK where they can analyse all of the data from both Uganda and South Africa. We would like to ask for your permission to send this information to them. This will be done electronically with password protected files and none of your personal information (name or telephone number) will be included.

Will I be paid to be in this study?

There is no payment to be a part of this study. If you have been discharged from hospital, we will reimburse you R150 for your transport costs to come back to the clinic for follow up within the first 14 days after discharge. You will not be reimbursed for clinic visits for reasons unrelated to this study. You will be responsible for your own transport costs for clinic and hospital visits after the first 14 days of follow up.

Who is organizing and funding the research?

This study is funded by the National Institute for Health Research through the University of Liverpool in the United Kingdom.

Who has reviewed the study?

This study has been reviewed by the UCT Faculty of Health Sciences Human Research ethics committee. You may contact the Chairman of the Research Ethics Committee if you have any questions regarding your rights as a study participant at any time.

Human Research Ethics Committee, Faculty of Health Sciences Old Main Building of Groote Schuur Hospital, Floor E53, Room 46, Observatory, 7925.

Thank you for reading the information about our research project. If you would like to take part,please read and sign this form.

Participant Consent

I, the undersigned, hereby agree that:

- The information in the participant information sheet and the written informed consent form was explained to me. All my questions about the study have been answered to my satisfaction.
- I understand that my participation is voluntary and I may withdraw from the study at any time, without giving a reason, and this will have no impact on my medical care
- I give permission to the researchers to have access to my medical records, both paper and electronic, to extract information relevant to this study
- I agree that the anonymised information collected about me may be transferred to the United Kingdom.
- I agree to allow the study staff to contact me directly by telephone and/or text message.
- I agree to take part in the study under the conditions as described in the participant information sheet.

☐ yes ☐ no

_____	_____	Date: _____ /_____/ _____
Name of Participant (printed)	Signature of Participant	Day Month Year

or if illiterate, make a thumbprint in the box below

**If the patient is unable to read and/or write, an impartial witness should be present during the informed consent discussion. After the written informed consent form is read and explained to the participant, and after they have orally consented to their participation in the study, and have either signed the consent form or provided their fingerprint, the witness should sign and personally date the consent form. By signing the consent form, the witness attests that the information in the consent form and any other written information was accurately explained to, and apparently understood by, the patient and that informed consent was freely given by the patient*

_____	_____	Date: _____ /_____/ _____
Name of Person Witnessing Consent (printed)	Signature of Person Witnessing Consent	Day Month Year

Deviations from protocol and justifications

We originally intended to calculate TTR from INR results in weeks 2-6 in the WarPATH study. Applying this inclusion criteria limited the number of participants eligible for analysis (as TTR requires ≥3 INR results) and would have further reduced study power. We decided to amend this to include INR data collected in weeks 2-12 which increased the number of participants eligible for analysis.

We aimed to build a logistic regression model of associations with adequate short-term anticoagulation control. Analysis of the data revealed poor TTR, with only 14/61 participants achieving adequate anticoagulation control, resulting in an underpowered logistic regression model. We decided to use a linear regression model for our primary analysis and determined predictors of higher TTR.

Similarly, our intention to build a logistic regression model to determine associations with adequate anticoagulation beyond the adherence intervention (in months four to seven after warfarin initiation) was underpowered with only 3/57 achieving adequate anticoagulation. We considered if there was any durable impact of the intervention by using the INR monitoring data we had access to. We explored retention in INR monitoring as a proxy for anticoagulation therapy adherence instead.

In view of the low TTR in this analysis, we explored the content of the interactions between the participants and the study team to gain insight into the possible reasons for poor anticoagulation.

Ethics Approval

Ethics Approval: Study

Ethics Approval: WarPATH

Journal Requirements

South African Medical Journal

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:

o **Background:** why the study is being done and how it relates to other published work.

o **Objectives:** what the study intends to find out

o **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.

o **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.

o **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.

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.

Turnitin Report