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Research Report

The prevalence of bleeding disorders in women with regular heavy menstrual bleeding at a secondary gynaecology clinic in central South Africa

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Submission

7 June 2021

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DECLARATION

I Motshidisi M. Deiker , declare that the coursework Masters Degree mini-dissertation that I herewith submit in a publishable manuscript format for the Master's Degree qualification at the University of the Free State is my independent work, and that I have not previously submitted it for a qualification at another institution of higher education.

Signed .....

Date ..... 1 June 2021

Place ..... Bloemfontein

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1 ABSTRACT

Background: Heavy menstrual bleeding (HMB) affects 10-15% of women. Studies from developed countries show that 20% of females with heavy menstrual bleeding have an underlying bleeding disorder. The prevalence of bleeding disorders in patients with HMB has not been determined in South Africa.

Objectives: To determine the prevalence of bleeding disorders in women with heavy menstrual bleeding in a tertiary gynaecology clinic in central South Africa and to evaluate the use of the Molecular and Clinical Markers for the Diagnosis and Management of Type 1 VWD bleeding assessment tool (MCMDM-1 VWD BAT) and the bleeding time in identifying women with HMB with underlying bleeding disorders.

Methods: This was a prospective descriptive study. Forty-one patients with heavy menstrual bleeding not attributable to other causes in the PALM-COEIN classification were recruited. Demographic data were collected, the MCMDM-1 VWD BAT was administered, a modified Ivy bleeding time was done, and routine laboratory testing was done to exclude non-haematological conditions. Screening tests for coagulation disorders were done.

Results: Forty-one patients were recruited for the study, but only 36 had a complete data set. None of the patients were identified to have an underlying bleeding disorder even though seven patients (19.4%) had an elevated MCMDM-1 VWD score, despite the lack of laboratory evidence of a bleeding disorder. One (2.5%) patient had an elevated bleeding time. All the patients were referred from primary healthcare clinics.

Conclusion: The prevalence of bleeding disorders in this study is low when compared to studies done elsewhere, even though there was selection bias. Half of the patients were already on contraceptives, which might have reduced their bleeding symptoms. Our functional Von Willebrand factor assays were dependent on ristocetin and may have overestimated the Von Willebrand factor concentration. The MCMDM-1 VWD bleeding assessment tool was easy to administer. The bleeding time did not contribute to the diagnosis. The study needs to be repeated in a primary care setting, using Von Willebrand factor assays that are independent of ristocetin. Such studies are indicated to determine to true prevalence of bleeding disorders in patients with heavy menstrual bleeding in South Africa.

Keywords: Heavy menstrual bleeding, bleeding disorders, bleeding assessment tool.

2 LIST OF ABBREVIATIONS

Abbreviation	Explanation
AUB	Abnormal uterine bleeding
BAT	Bleeding assessment tool
FIGO	International Federation of Gynaecology and Obstetrics
GnRHa	Gonadotropin releasing hormone analogues
HMB	Heavy menstrual bleeding
ISTH/SCC-BAT	The International Society on Thrombosis and Haemostasis/The Scientific and Standardization Committee
MCMDM-1 VWD	Molecular and Clinical Markers for the Diagnosis and Management of Type 1 VWD
NHLS	National Health Laboratory Service
PALM-COEIN	Polyps, Adenomyosis, Leiomyoma, Malignancy – Coagulopathy, Ovulatory dysfunction, Endometrial, Iatrogenic, Not yet classified
VW	Von Willebrand
VW:RCoF	Von Willebrand ristocetin co-factor activity
VWD	Von Willebrand disease

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6 CHAPTER 1: LITERATURE REVIEW

Introduction

Abnormal uterine bleeding (AUB) is defined as bleeding from the uterine corpus that is abnormal in regularity, volume, frequency, volume or duration in the absence of pregnancy.[1] The terminology previously used to define abnormal uterine bleeding was revised by the International Federation of Gynaecology and Obstetrics (FIGO).[2] Menorrhagia, which was previously defined as excessive bleeding from the uterine corpus of more than 80 mL, was replaced by the term heavy menstrual bleeding (HMB). FIGO classifies the causes of abnormal uterine bleeding into structural and non-structural causes. The following classification system is used: PALM COEIN.

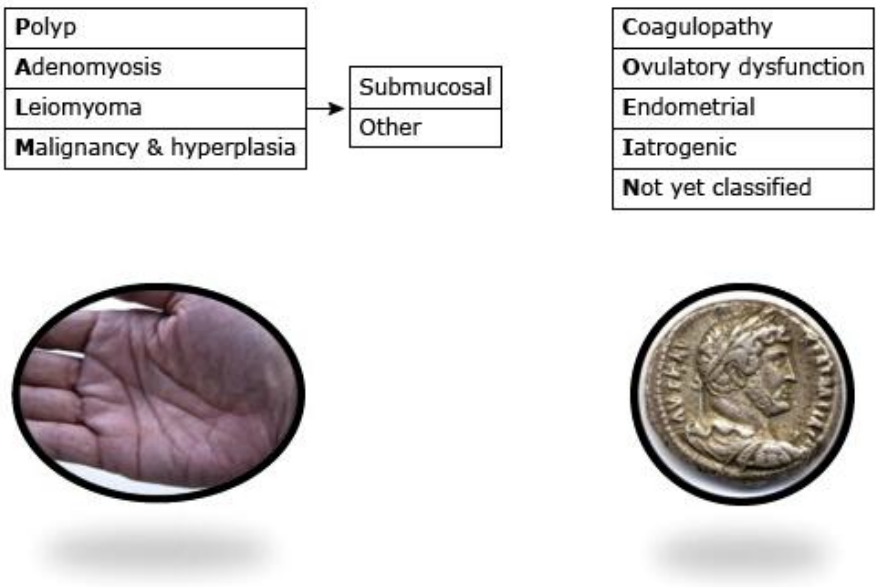

Fig 1: PALM-COEIN classification system for abnormal uterine bleeding in non-gravid reproductive-age women.[1,2]

6.1 HEAVY MENSTRUAL BLEEDING

Heavy menstrual bleeding is defined as excessive menstrual blood loss which interferes with a women's physical, social, emotional and or material quality of life.[3] This patient centred definition is endorsed by the Royal College of Obstetrics and Gynaecologist (RCOG) and the American College of Obstetrics and Gynaecologist.

Heavy menstrual bleeding (HMB) is one of the most common symptoms of women with bleeding disorders. The prevalence of HMB in women with Von Willebrand disease is 74-94%, conversely the prevalence of VWD in women with HMB is 5-24%.[4] The most common bleeding disorders that affect women are: Von Willebrand disease, platelet dysfunction defects and deficiencies of coagulation factors e.g. haemophilia A (Factor VIII), Haemophilia B (Factor IX), Factor XI, rare bleeding disorders. [4]

6.2 ENDOMETRIAL HAEMOSTASIS AND MENSTRUATION[5,6]

Before defining the different bleeding disorders; one needs to understand how the endometrial cycle is regulated and how menstruation can present haemostatic challenges in patients with an underlying bleeding disorder. During menstruation, there is a complex interaction between tissue growth, blood vessel growth, bleeding, coagulation and fibrinolysis.[5, 6]

The menstrual cycle is regulated centrally by the pituitary and the hypothalamus. Gonadotropins , namely luitenizing hormone and follicle stimulating hormones are secreted in a pulsatile manner. These hormones act on the ovary. The main function of the ovary is to produce a mature ovum that will be used for fertilisation and implantation. The endometrium is prepared for possible implantation of a fertilized ovum by the steroid hormones, namely oestrogen and progesterone; produced by the ovary during the different stages of folliculogenesis.

The endometrium is a complex multicellular dynamic tissue, which undergoes structural changes during a menstrual cycle. The endometrium consists of a functional and a basal layer. The endometrial layers undergo changes such as proliferation and shedding during the menstrual cycle. The changes are mediated by the steroid hormones secreted by the ovary. The purpose of these changes is to prepare the endometrium for implantation and pregnancy. When pregnancy does not occur, the functional layer will shed at the end of each cycle and regenerate again, while the basal layer remains intact. The functional and basal layer is rich in blood vessels, namely the radial and spiral arteries that supply the endometrial glands and stroma.[5-7]

Changes to the endometrium are divided into two phases; the proliferative phase and the secretory phase. The proliferative phase is where there is rapid re-growth of the functional layer of the endometrial and this occurs parallel to the follicular phase in the ovary. This proliferative phase is accompanied by progressive revascularization of the endometrium. Ovulation takes place mid-cycle and this phase is followed by the secretory phase on the endometrial layers. This is a hormone mediated process. In the late secretory phase, levels of progesterone and estrogen begin to reduce and decidualisation occurs. Menstruation is the end result of a cycle in which implantation failed to occur. Menstrual debris consists of, stromal, glandular tissue and blood that undergoes coagulation and fibrinolysis.[7] In instances where there is an imbalance of haemostatic factors, heavy menstrual bleeding can occur.

There is a disruption of blood vessels in the endometrium that occurs during menstruation, vasoconstriction and activation of the clotting cascade then takes place to attain haemostasis.[5-7] The coagulation cascade is activated in two pathways ; the extrinsic and intrinsic pathway :[6] This is depicted below.

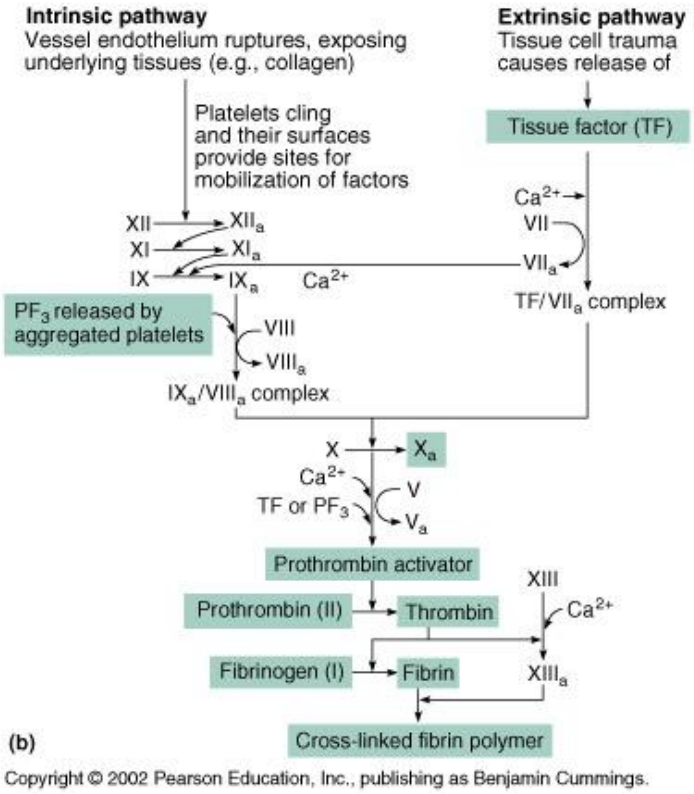

Figure 2. Outline of the coagulationpathway (http://www.apsubiology.org/anatomy/2020/2020_Exam_Reviews/Exam_1/CH17_Hemostasis_II_Coagulation.htm)

The extrinsic and intrinsic pathways culminate in conversion of factor X to Xa, which assists in the conversion of pro-thrombin to thrombin, leading to the formation of a fibrin clot. The fibrin clot undergoes degradation by the fibrinolytic system.[5-7] Haemostatic abnormalities that occur interfere with this system, causing a haemostatic defect that may clinically manifest as heavy menstrual bleeding in women.

6.3 BLEEDING DISORDERS

Bleeding disorders are more prevalent in women with heavy menstrual bleeding and heavy menstrual bleeding is more common among women with bleeding disorders. Up to, 20% of females with heavy menstrual bleeding are thought to have an underlying bleeding disorder.[4]

6.3.1 Von Willebrand Disease

The prevalence of HMB in women with Von Willebrand disease (VWD) is 74-92%, this is a significant finding.[4] Von Willebrand disease is an inherited disease, affecting males and females with equal frequency. If a women has an underlying bleeding disorder it manifests clinically during the haemostatic challenges of menstruation and childbirth.

VWD is caused by a deficiency in, or a dysfunction of, von Willebrand factor.[4] VWF has two main haemostatic functions. In primary haemostasis it functions at the site of injured vessel walls, by facilitating platelet adhesion to the subendothelial structures (e.g. exposed collagen fibres). It further supports platelet aggregation and thrombus formation. In secondary haemostasis, VWF functions as a carrier protein for coagulation factor VIII.

VWD is classified into various subtypes; Type 1 VWD results from the deficiency of VWF. Type 2 VWD results from abnormal VWF. Four subtypes of Type 2 include: Type 2A (deficiency of normal multimers of VWF), type 2B (VWF with enhanced platelet binding with affected individuals can present with thrombocytopenia), Type 2M (VWF with reduced platelet binding) and Type 2N (VWF with reduced binding to FVIII, which allows FVIII to be proteolyzed). Type 3 VWD results from the absence of VWF.[8]

Type 3 is rare and severe. People with Type 1 disease have bleeding that is mild to moderate in severity; these patients do not require routine blood transfusion or other treatment. Type 1 VWD is not life threatening.

6.3.1.1 Low von Willebrand factor levels

There is a subset of patients that present with reduced plasma VWF antigen levels (30-50 IU/dL). These patients do not present typically as patients with established Type1, 2 or 3 von Willebrand disease that are described above. There is a partial quantitative deficiency of plasma von Willebrand factor and these patients can present with significant bleeding symptoms. Patients that present with high bleeding scores on the bleeding assessment tool and plasma VWF levels in the range described above need particular attention as they may need treatment in the form of antifibrinolytic agents, VWF containing concentrates as well as DDAVP.[9-11] The 2021 guidelines for the diagnosis of Von Willebrand disease recommend that the cut-off limit for the diagnosis of Von Willebrand disease is <30 IU/dL for non-bleeding patients and 50 IU/dL for symptomatic patients.[12]

6.3.2 Factor deficiencies

Haemophilia is an X-linked recessive disorder, which is characterized by a deficiency of coagulation factor VIII (Haemophilia A) or a deficiency of factor IX (haemophilia B). Women can be carriers of haemophilia. Obligatory carriers are the daughters of a father with haemophilia, and the mothers of sons with haemophilia.

Carriers can be symptomatic, this occurs in those women with factor levels resembling mild haemophilia, this places these women at an increased tendency for bleeding.[13] This variation occurs because of the process of Lyonisation where one of the pair of X chromosomes in a cell is randomly inactivated. Some carriers may have most of the X chromosomes with the haemophilia gene inactivated, while others may have most of the normal X chromosomes inactivated. Haemophilia is defined as severe moderate or mild according to the factor concentration. In severe haemophilia the levels are between 0-1% of normal (<0.01 IU/mL), in moderate between 1% and 5% of normal (0.01-0.05 IU/mL), and in mild haemophilia the levels are between 5% and 40% of normal (>0.05-0.40 IU/mL).[14]

6.3.3 Disorders of platelets; disorders of primary haemostasis.

Some of the more common inherited platelet disorders include the following

Bernard-Soulier syndrome — characterized by a defect in any of the components of the glycoprotein (GP) Ib/IX/V complex, giant platelets, and greater than expected bleeding for the degree of thrombocytopenia

Glanzmann thrombasthenia — characterized by a defect in the GP IIb/IIIa complex, normal platelet counts, normal platelet morphology, and abnormal in vitro platelet aggregation.

Storage pool diseases — these include Wiskott-Aldrich syndrome, thrombocytopenia with absent radii syndrome, Chediak–Higashi syndrome, and Hermansky-Pudlak syndrome.

6.3.4 Rare bleeding disorders

Inherited deficiencies of coagulation factors: FI (Fibrinogen), FII, FV, FVII, FX, FXI, FXIII as well as combined deficiencies of FV and FVIII, multiple vitamin K-dependent coagulation and factor deficiency. These accounts for about 3-5% of all inherited bleeding disorders. They are autosomal recessive conditions.[4]

6.4 Mobility spectrum disorder

Hypermobility is a broad term and is not uncommon, and it is mostly associated with normal, or near-normal, coagulation assays. Patients with mobility spectrum disorder also present with HMB. Examples of connective tissue disorders that cause hypermobility syndromes include Ehlers Danlos syndrome, Marfan syndrome and osteogenesis imperfecta. Typically patients will present clinically with joint hypermobility. Due to vascular fragility that is present in patients with collagen disorder they may present with bleeding abnormalities. An association between increased joint mobility and heavy menstrual bleeding has been reported in several studies, after other PALM-COEIN causes of HMB had been excluded. Although the focus of this study is clear, it is important to note this fact.[19-21]

6.5 DIAGNOSIS OF BLEEDING DISORDERS [1]

The identification of women with bleeding disorders is of paramount importance. This is directly related to morbidity that is associated with heavy menstrual bleeding. Thus a bleeding disorder should be considered as part of the differential diagnosis in all women presenting with heavy menstrual bleeding. A thorough history and clinical assessment is essential in the initial assessment of women who present with heavy menstrual bleeding. The following history should be taken into consideration; a detailed gynaecological history, to assess for causes other than coagulation defects.

A family history of bleeding disorders and a medication history, including contraceptive, anticoagulant, antiplatelet and iron therapy should be noted. A gynaecological examination, followed by an abdomino-

pelvic ultrasound should be performed on the patient to exclude any structural causes that may be associated with HMB. This is to exclude other causes on the PALM COEIN list (see Fig 1).

A bleeding assessment tool (BAT) is useful as it is used to objectively quantify the bleeding symptoms that a patient experiences. A thorough history regarding the bleeding symptoms of a patient can be obtained from administering this tool to the patient. Various tools have been validated to be used in the assessment of bleeding symptoms of a patient. A BAT (bleeding assessment tool) generates a score that can be used to guide haemostatic testing in a patient with bleeding symptoms. The International Society on Thrombosis and Haemostasis/The Scientific and Standardization Committee, (ISTH/SCC-BAT) and the Molecular and Clinical Markers for the Diagnosis and Management of Type 1 VWD , (MCMDM-1 VWD) are examples of bleeding assessment tools that have been validated to be used in women that present with heavy menstrual bleeding.[17,22,21] Please refer to Appendix 2 for an example of a BAT.

Laboratory tests should then be performed. These include:[1]

- Complete full blood count (including the platelet count and a blood smear)
- Thyroid function testing (thyroid stimulating hormone as a screening test)
- Prothrombin time
- Activated partial thromboplastin time
- Assays of von Willebrand factor activity
- VWF antigen and levels of other clotting factors
- Platelet function tests
- Peripheral blood smear to analyse platelet morphology

6.6 MANAGEMENT[3]

Recognition of bleeding disorders in females leads to improvement in the quality of life of these patients, as appropriate management is implemented. The management of patients that suffer from heavy menstrual bleeding secondary to a bleeding disorder is a multidisciplinary approach. Clinicians involved in the management of patients with a bleeding disorder with heavy menstrual bleeding are general gynaecologists, haematologists, and in the reproductive years when a patient is pregnant the obstetrician and neonatologist. When effective treatment is instituted these patients will not be subjected to unnecessary procedures, hospitalisations and maternal mortality and morbidity will be decreased, women will not have limitations in daily activities of living, and they will have a better quality of life.

Management strategies are dependent on the woman's wish to preserve fertility. If a woman would like to preserve fertility and fall pregnant as soon as possible, haemostatic measures can be used. These include antifibrinolytic drugs such as tranexamic acid, clotting factor replacement and intranasal DDAVP (desmopressin, 1-desamino-8-D-arginine vasopressin) which is currently not available in South Africa. The timely recognition and assessment of women with heavy menstrual bleeding that have an underlying bleeding disorder plays an important role when these women fall pregnant. The incidence of postpartum haemorrhage, which is currently listed among the top five causes of preventable maternal deaths in South Africa will be reduced. Management of patients with underlying bleeding disorders in pregnancy necessitates multidisciplinary care that includes: foetal medicine specialists, geneticists, haematologists, neonatologists. These patients are cared for and delivery should take place in tertiary level hospitals with the necessary expertise to reduce morbidity and mortality related to the haemostatic challenges that these patients often face.

In women who want to preserve fertility but do not wish to fall pregnant immediately, hormonal measures can be used.[1] Combined oral contraceptives have been proven to reduce the incidence of unacceptable heavy menstrual bleeding in patients with underlying bleeding disorders. The mechanism of action is by suppression of ovulation and endometrial proliferation, which in turn will reduce menstrual blood loss. Second line hormonal treatment includes the levonorgestrel intra-uterine system, which works by acting locally on the endometrium by preventing proliferation. Gonadotropic releasing hormone analogues (GnRHa) stops production of the steroid hormones; in the majority of patients bleeding will stop. The side effect profile of using GnRHa for prolonged periods needs to be kept in mind. These patients end up in a reversible menopausal state, due to the decreased levels of oestrogen. Patients need to be counselled with regards to the side effect profile of each hormonal drug.[3]

In patients whom hormonal therapy is contra-indicated or has failed; a minimally invasive surgical procedure can be offered: endometrial ablation. Endometrial ablation is a hysteroscopic procedure. The functional layer of the endometrium is destroyed or removed. This is aimed at reducing blood loss during menstruation. A strict selection criterion exists; the women should have completed her family. She should be willing to continue with contraception as the procedure is not a contraceptive method. In some women the functional layer of the uterus may proliferate again, causing recurrence heavy menstrual bleeding. Complications of operative hysteroscopy, such as fluid overload, pulmonary oedema, electrolyte abnormalities should be known and explained to the patient prior to embarking on this treatment modality.[3]

In women who do not wish to preserve fertility, particularly those with other pelvic gynaecological pathology and in those women in whom medical therapy has failed, hysterectomy can be offered to the patient. Abdominal hysterectomy or laparoscopic hysterectomy can be done. The complications of both procedures should be discussed extensively with the patient.

6.7 STUDY MOTIVATION

The prevalence of bleeding disorders in patients that present to gynaecological clinics with heavy menstrual bleeding is unknown in South Africa. Primary evaluation and management of these women is hampered by lack of research in the field. Major advances in multidisciplinary care; including the involvement of gynaecologists, haematologists as well as obstetricians, is needed in patients that present with HMB secondary to an underlying bleeding disorder. The awareness of the impact of bleeding disorders in women needs much improvement in South Africa.

It is important to know the prevalence of bleeding disorders in women with heavy menstrual bleeding as this will afford gynaecologists with a holistic view of diseases, particularly bleeding disorders that can otherwise be managed conservatively in collaboration with a haematologist. This affords better management of the patients, equating to an improved quality of life for women with bleeding disorders.

Furthermore advances made in identifying these women will make a positive impact on improving care when these individuals fall pregnant as the incidence of postpartum haemorrhage will be anticipated and treated accordingly. See detailed research methodology in Appendix 1, which is the protocol.

6.8 AIM

The primary aim of the study is to determine the prevalence of bleeding disorders in women with regular heavy menstrual bleeding at a secondary gynaecology clinic in central South Africa.

A secondary aim is to evaluate the sensitivity and specificity of the MCMDM-1 VWD BAT and the bleeding time in identifying women with regular HMB with underlying bleeding disorders.

6.8 Conclusion

Research data from around the world with regards to the prevalence of underlying bleeding disorders in patients with heavy menstrual bleeding is abundant. However in our setting the prevalence is unknown. HMB, secondary to an underlying bleeding disorder affects the quality of life of a patient adversely. It is therefore important to identify and to manage these patients appropriately.

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7 CHAPTER 2: PUBLISHABLE MANUSCRIPT

This manuscript will be submitted to the South African Medical Journal for possible publication. The author guidelines set out by the SAMJ are stipulated in Annexure 6.

Title page

The prevalence of bleeding disorders in women with heavy menstrual bleeding at a tertiary gynaecological clinic in central South Africa.

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ABSTRACT

Background: Heavy menstrual bleeding (HMB) affects 10-15% of women. Studies from developed countries show that 20% of females with heavy menstrual bleeding have an underlying bleeding disorder. The prevalence of bleeding disorders in patients with HMB has not been determined in South Africa.

Objectives: To determine the prevalence of bleeding disorders in women with heavy menstrual bleeding in a tertiary gynaecology clinic in central South Africa and to evaluate the use of the MCMDM-1 VWD (Molecular and Clinical Markers for the Diagnosis and Management of Type 1 VWD) bleeding assessment tool (BAT) and the bleeding time in identifying women with HMB with underlying bleeding disorders.

Methods: This was a prospective descriptive study. Forty-one patients with heavy menstrual bleeding not attributable to other causes in the PALM-COEIN classification were recruited. Demographic data were collected, the MCMDM-1 VWD BAT was administered, a modified Ivy bleeding time was done, and routine laboratory testing was done to exclude non-haematological conditions. Screening tests for coagulation disorders were done.

Results: Forty-one patients were recruited for the study, but only 36 had a complete data set. None of the patients were identified to have an underlying bleeding disorder even though seven patients (19.4%) had an elevated MCMDM-1 VWD score, despite the lack of laboratory evidence of a bleeding disorder. One (2.5%) patient had an elevated bleeding time. All the patients were referred from primary healthcare clinics.

Conclusion: The prevalence of bleeding disorders in this study is low when compared to studies done elsewhere, even though there was selection bias. Half of the patients were already on contraceptives, which might have reduced their bleeding symptoms. Our functional Von Willebrand factor assays were dependent on ristocetin and may have overestimated the Von Willebrand factor concentration. The MCMDM-1 VWD bleeding assessment tool was easy to administer. The bleeding time did not contribute to the diagnosis. The study needs to be repeated in a primary care setting, using Von Willebrand factor assays that are independent of ristocetin. Such studies are indicated to determine to true prevalence of bleeding disorders in patients with heavy menstrual bleeding in South Africa.

Keywords: Heavy menstrual bleeding, bleeding disorders, bleeding assessment tool.

MAIN BODY OF TEXT

Introduction

Heavy menstrual bleeding is defined as excessive menstrual blood loss which interferes with a women's physical, social, emotional and or material quality of life.It affects 10-15% of women.[1,2,3] It is one of the most common presenting symptoms in women with bleeding disorders.[3,4] The prevalence of heavy menstrual bleeding (HMB) in women with Von Willebrand disease (VWD) is 74-94%, while the prevalence of VWD in women with HMB is 5-24%.[2,3] The most common bleeding disorders that affect women are: VWD, platelet function defects and deficiencies of coagulation factors, for example, haemophilia A, haemophilia B, factor XI deficiency and rare bleeding disorders.[2]

The prevalence of bleeding disorders in women with HMB in South Africa is unknown. The prevalence of VWD is lower in African American women, namely 1-2%, but this may be a laboratory artefact.[2-8]

The International Federation of Gynaecology and Obstetrics (FIGO) have revised the terminology of abnormal uterine bleeding.[1] Menorrhagia, the term previously used to define HMB, was replaced by HMB. The FIGO PALM COEIN classification system for abnormal uterine bleeding in non-gravid reproductive-age women is used to determine the cause of abnormal uterine bleeding (see Table 1).

Table 1. FIGO PALM COEIN classification[1]

Structural causes
Polyps
Adenomyosis
Leiomyoma
Malignancy and hyperplasia
Non-structural causes
Coagulopathy
Ovulatory dysfunction
Endometrial
Iatrogenic
Not yet classified

The identification of women with HMB that have an underlying bleeding disorder will enable the appropriate management of these patients, so reducing their related morbidity and improving their quality of life.[9,6] The evaluation of women with HMB with a suspected underlying bleeding disorder includes a personal and family history of bleeding tendencies, and a complete clinical and gynaecological evaluation to exclude other causes using the PALM-COEIN system. Only if the history suggests a bleeding disorder should one test for bleeding disorders.

Various bleeding assessment tools (BATs) are used to simplify the assessment of bleeding symptoms and to identify patients with a high likelihood of a bleeding disorder. The International Society on Thrombosis and Haemostasis/The Scientific and Standardization Committee BAT (ISTH/SCC-BAT), the Molecular and Clinical Markers for the Diagnosis and Management of Type 1 VWD (MCMDM-1) BAT and the condensed MCMDM-1 BAT were developed to identify patients with VWD. These tools have been widely used as a predictor of bleeding disorders in women with HMB.[10-12] The condensed MCMDM-1 questionnaire is robust and is easily administered in 5-10 minutes.

Objectives

The aims of the study were to determine the prevalence of bleeding disorders in women with HMB in a gynaecology clinic in a tertiary hospital in central South Africa. Secondary aims were to evaluate the sensitivity and specificity of the MCMDM-1 VWD bleeding assessment tool, and a point of care bleeding time to identify women with HMB that have an underlying bleeding disorder.

Methods

A prospective cross-sectional study was conducted to assess the prevalence of bleeding disorders in patients with HMB that presented to the gynaecology clinic at Pelonomi Hospital, Bloemfontein, South Africa. The study was conducted from November 2018 to November 2020. Ethics approval was obtained from the Health Sciences Research Ethics Committee, University of the Free State (UFS-HSD 2018/0158/2509).

As the prevalence of VWD in South Africa is unknown, convenience sampling was used. Forty-one adult study participants with unexplained HMB were included, after other PALM-COEIN causes had been excluded. Pregnant and post-menopausal women were excluded from the study. The MCMDM-1 VWD questionnaire was administered. A modified Ivy bleeding time (Surgicutt, Ortho, Milan, Italy) was done, followed by formal laboratory coagulation testing. Of the 41 patients, four had missing laboratory data, and there was blood sampling failure in one of the patients. Thirty-six laboratory tests were performed at the Universitas National Health Laboratory Service (NHLS) in Bloemfontein. The tests included prothrombin time, partial thromboplastin time, thrombin time, fibrinogen level, Von Willebrand (VW) antigen level, ristocetin co-factor activity (VW:RCoF), collagen-binding assay and VW factor multimer analysis. These assays were performed on an automated coagulation instrument using the manufacturer's reagents. All assays were done according to the Universitas Service Laboratory standard operating procedures, except for the VW factor assays, which were done according to various in-house assays developed by the Special Haemostasis Laboratory.

Statistical Analysis

The data was reviewed and processed by the Department of Biostatistics at the University of Free State. Numerical values were be summarised by means, standard deviations or medians and percentiles. Categorical variables were summarised by frequencies and percentages. The sensitivity and specificity of screening tests were summarised by percentages with 95% confidence intervals.

Results

Forty-one patients were included, but only 36 had complete data sets (see Figure 1). The median age of the thirty-six patients was 28 (range 17-47). Twenty-seven (75.0%) were African (see Table 2). The results of screening tests are shown in Table 3, and those of the Von Willebrand factor assays in Table 4.

Fig 3: Overview of study participants and results

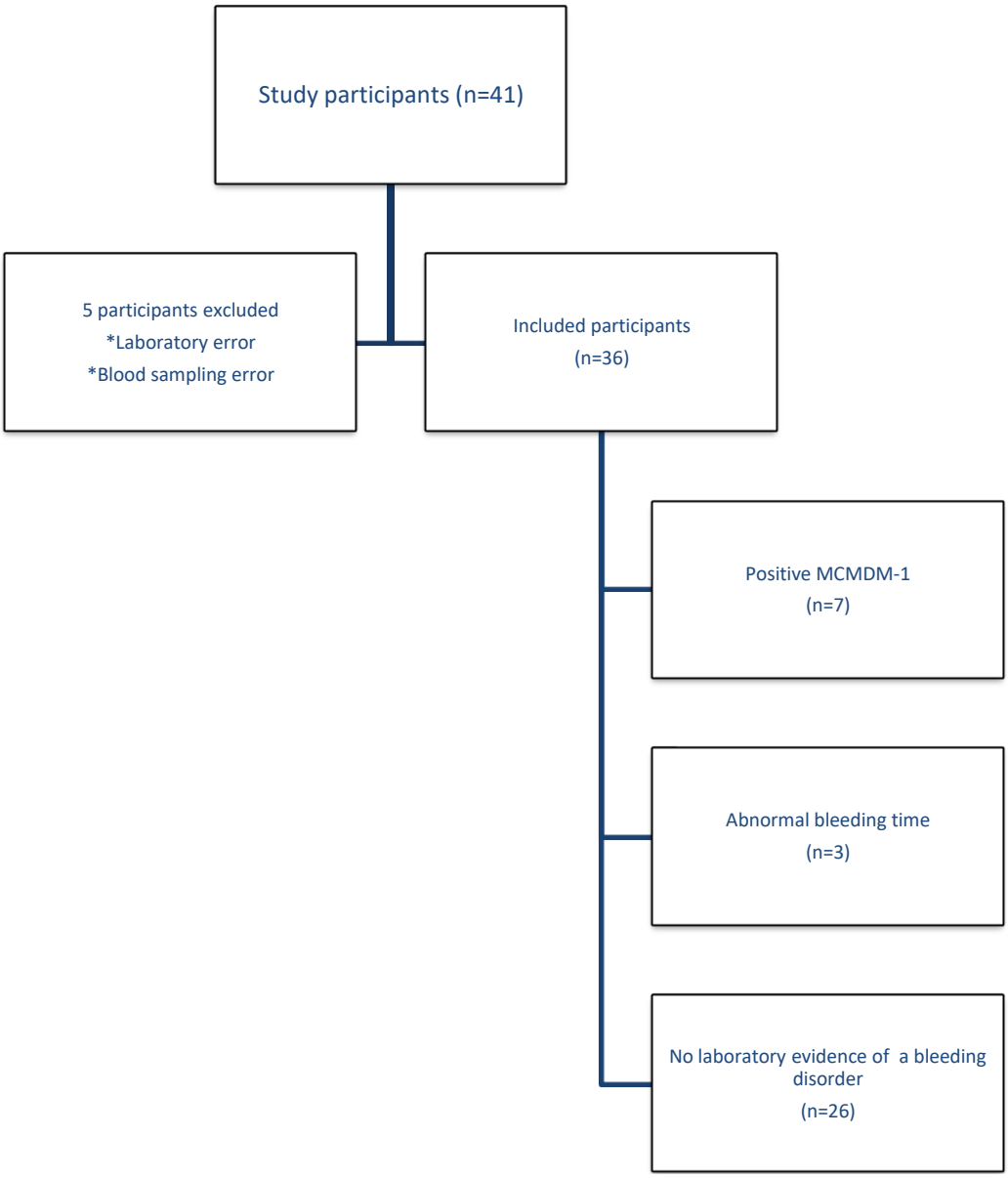

Table 2. Demographic and clinical data (*N=36*)	
Characteristics	***n* (%)**
Race	
African	27 (75.0)
White	9 (25.0)
Coloured	2 (5.6)
Indian	1 (2.8)
Duration of symptoms	
6-12 months	10 (27.8)
Since menarche	26 (72.2)
Parity	
Nulliparous	17 (47.2)
Multiparous	19 (52.8)
Contraception use	
Combined oral contraceptives	13 (36.1)
LNG-IUS (Mirena)	1 (2.8)
Depo Provera	4 (11.1)
Nonusers of contraception	5 (13.9)
Unknown status	13 (36.1)
Co-morbidities	
Hypertension	5 (13.9)
Diabetes mellitus	3 (8.3)
Positive bleeding assessment tool	7 (19.4)
Prolonged bleeding time	1(2.8)

Table 3. Screening tests for bleeding disorders		
Parameter	**Median (lower;upper quartile)**	**Reference interval**
Prothrombin time	12 (11;13)	9.9 - 12.3 s
Partial thromboplastin time	26 (23;27)	21.6 - 28.7 s
Thrombin time	17 (16;17)	14 – 21 s
Fibrinogen	3 (2;4)	1.7 - 4.2 g/L

Table 4. Von Willebrand factor assays		
Parameter	**Median (lower;upper quartile)**	**Reference interval**
Von Willebrand antigen	109 (84;133)	51 – 143%
Ristocetin cofactor activity	91(72;110)	50 – 150%
Collagen binding assay	101 (79;133)	49 – 157%
Multimeric analysis	Normal for all patients	

None of the patients were identified to have an underlying bleeding disorder.

Discussion

None of the patients that presented with HMB in this study were found to have an underlying bleeding disorder. One patient was a carrier of haemophilia. However, she did not fit the coagulation definition of having a bleeding disorder. She had a strong family history of haemophilia, presented with HMB and had an elevated MCMDM-1 VWD BAT score. The low prevalence of bleeding disorders in patients with HMB reported in this study differs significantly from the prevalence reported in the developed world. Since the seminal publication of Kadir et al.[5] studies with a similar study design have reported a prevalence of inherited bleeding disorders of 5-20% in women presenting with HMB.[2,4]

Shankar et al.[13] and Dilley et al.[14] showed a lower prevalence of 1.3% of underlying bleeding disorders in African American women versus 15.9% in Caucasians. In our sample, 75% of the patients were African, reflecting a population that consists mainly of Africans.[15] This difference in the ethnicity of our sample may partially explain our divergent results. Sukhu et al.[16] have also reported such ethnic differences in Von Willebrand factor levels in a study of 310 control individuals in KwaZulu-Natal. However, Flood et al.[17] have shown that the P1467S mutation in a known ristocetin-binding region of the A1 domain of VWF causes a false increase in ristocetin co-factor results. This variant appears to be common in people of African descent. Newer assays[18] no longer use ristocetin and would reveal a more accurate prevalence of VWD in Africa.[19]

Most patients with abnormal uterine bleeding present to primary level clinics where tranexamic acid and hormonal therapy are prescribed. Patients are only referred to higher-level clinics if their HMB does not respond to primary treatment, or if the HMB has a structural cause. Therefore, our study probably suffered from selection bias. The bias might have been avoided if patients who presented with HMB to primary health clinics were screened. Eighteen patients (50.0%) were already using a contraceptive method when they were reviewed at the clinic. Combined oral contraceptives alone reduce the number of patients with unacceptable HMB by between 12-77%.[20]

The use of bleeding assessment tools is recommended in the 2021 guideline for the diagnosis of VWD.[21] Seven patients had a positive BAT, however, the laboratory tests could not demonstrate a bleeding disorder. Bowmen et al.[12] reported a sensitivity of 100% and a specificity of 87% for the use of the MCMDM-1 VWD to predict bleeding disorders in a patient with bleeding symptoms in Canada. The researcher is both fluent in Sesotho and Afrikaans, which are the primary languages in central South Africa, and the patients seemed to understand the questions easily. However, the BAT has not been used extensively in our setting. The condensed MCMDM-1 VWD bleeding assessment tool can be comfortably used in gynaecological practice to identify patients that may have an underlying bleeding disorder and prompt haemostasis testing.

Only one patient had an elevated bleeding time, but the laboratory assays indicated no bleeding disorder. The bleeding time is affected by a large number of diseases, drugs, physiologic factors, test conditions, not all of them related to platelets.[21] In our study, the bleeding time was not a helpful test. It is also not recommended as a preoperative screening test for bleeding disorders.[22]

Limitations of the study included the following: small sample size and recruitment that was hampered by the COVID-19 pandemic. The patients had also been referred from primary health care clinics where the prescription of tranexamic acid and contraceptives might have confounded the results. We also did not screen for patients with hypermobility spectrum disorder which is increasingly reported and a cause of HMB.[23]

Currently, gynaecologists do not appear to be aware of underlying bleeding disorders as a cause of HMB. Chi et al.[24] showed that only 2% of female reproductive specialists would offer testing for

VWD when reviewing a patient with HMB in adolescents and older women. Dkeidek et al.[25] reported that in an Australian teaching hospital, only half of the expected number of patients with HMB were referred for screening for bleeding disorders.

Even though no underlying bleeding disorders were identified in this study population, identifying and managing women with HMB due to underlying bleeding disorders is important. The study needs to be extended to women with HMB who present to primary care. Awareness of the possibility that HMB can be attributed to an underlying bleeding disorder needs to be promoted. The true prevalence of VWD (which a common cause of HMB) needs to be determined in Africa using VWF tests which are independent of ristocetin.[19] The prevalence of P1467S mutation[17] in the ristocetin-binding region of the A1 domain of VWF in South Africa needs to be determined.

Declaration. None.
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Author contributions. LH and MJC conceived the study design. MMD wrote the protocol. MMD and LH collected the data. SMB provided supervision. All authors approved the final version.
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Conflicts of interest. None.

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8 Appendix 1: Protocol approved by HSREC

RESEARCH PROTOCOL

SUMMARY IN LAY TERMS

Heavy menstrual bleeding is a common complaint of many women attending gynecology clinics. Heavy menstrual bleeding is defined as abnormally heavy menstrual blood loss that interferes with a woman's physical, social, emotional and /or material quality of life. Heavy menstrual bleeding has many different causes, but in this study, the researchers will focus on heavy menstrual bleeding caused by bleeding disorders. The researchers would like to investigate whether some of the women presenting with this complaint might have undiagnosed bleeding disorders.

The research project will take place in the Gynaecology clinic at Pelonomi Hospital once approval has been given by the University of the Free State Health Research Ethics Committee and the Free State Department of Health.

Participants of the study will be women that have the symptom of heavy menstrual bleeding, are older than 18 years of age and have no other apparent cause that could explain abnormal menstrual bleeding. Informed consent will be obtained from all of these women. The study entails a full gynaecological history, physical examination and ultrasound evaluation, as is the norm in any secondary gynaecology clinic. In addition to this, the participants of the study will answer a questionnaire, which is known as the MCMDM-1 BAT. This is a bleeding assessment tool (BAT) which serves to evaluate bleeding symptoms in patients with a suspected bleeding disorder. Lastly, the blood samples will be taken from the participants to perform the necessary laboratory tests that will diagnose possible bleeding disorders.

Ultimately, this research aims to identify the number of women with heavy menstrual bleeding due to bleeding abnormalities. It will afford the researchers the opportunity to manage them appropriately and establish new protocols in evaluating a woman with heavy menstrual bleeding in the gynaecology clinic.

Introduction

Abnormal uterine bleeding is a common gynaecological complaint with an estimated 10-35% of women reporting heavy menstrual bleeding during their lifetime.(1,2) Its importance and prevalence of reporting is most likely a function of the impact on women's quality of life. Heavy menstrual bleeding carries a high morbidity with increased healthcare costs related to medical complications and contributes to school and work absenteeism.(1)

The International Federation of Gynaecology and Obstetrics (FIGO) revised the terminology system of abnormal uterine bleeding (AUB) in non-pregnant reproductive aged women in 2011.(3) The goal was to avoid poorly defined terms previously used to describe AUB, e.g. menorrhagia, menometrorrhagia, oligomenorrhoea. Ultimately the term heavy menstrual bleeding replaced menorrhagia.

Heavy menstrual bleeding is defined as excessive menstrual blood loss which interferes with a women's physical, social, emotional and /or material quality of life.(4) The Royal College of Obstetricians and Gynaecologists (RCOG) and the American College of Obstetricians and Gynaecologists (ACOG) also prefer this patient centred definition of heavy menstrual bleeding. For clinical purposes this definition of heavy menstrual bleeding is structured in such a way that it is subjective. Women report any menstrual abnormalities if they perceive it as abnormal.

Heavy menstrual bleeding is also defined as regular bleeding that is heavy or prolonged and refers only to cyclic (ovulatory) menses or blood loss over 80 ml per menstrual cycle, with anaemia, low ferritin levels, passing clots greater than a 50 pence coin in size and soaking of bed clothes through a pad/tampon within one hour.(3) This is a more objective definition, mostly used for research purposes as direct methods for determining menstrual volume are used.

Abnormal uterine bleeding can be caused by a wide variety of local and systemic diseases. The most common of these aetiologies are bleeding associated with pregnancy, structural uterine pathology, anovulation, bleeding disorders or neoplasia. In addition to the newer and better descriptive terminology, FIGO developed a new classification system to categorise the cause of abnormal uterine bleeding (Figure 1).

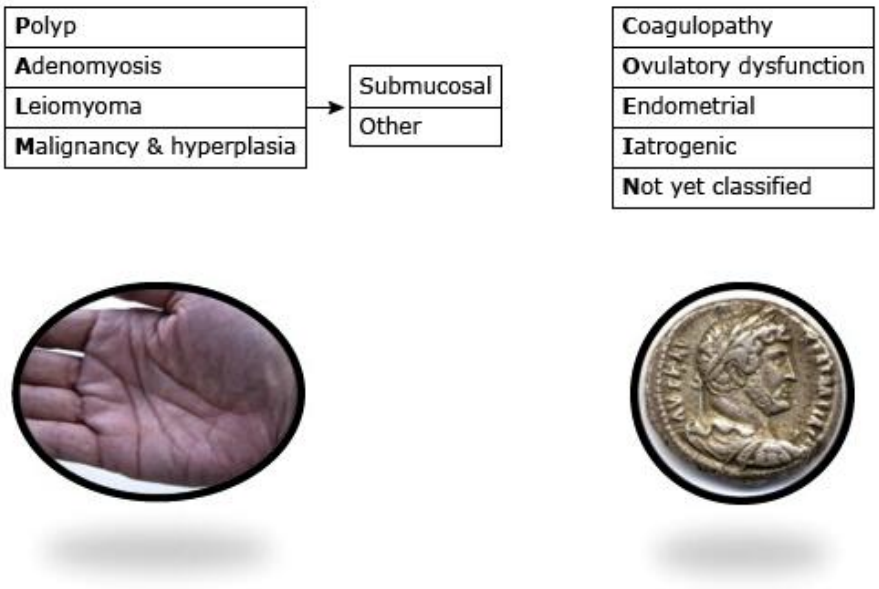

Figure 1. PALM-COEIN classification system for abnormal uterine bleeding in non-gravid reproductive-age women. (3)

The system comprises four categories that are defined by visually objective structural criteria (PALM: polyp, adenomyosis, leiomyoma, and malignancy and hyperplasia), four that are unrelated to structural anomalies (COEI: coagulopathy, ovulatory dysfunction, endometrial, iatrogenic), and one reserved for entities that are not yet classified (N). The leiomyoma category (L) is subdivided into patients with at least one submucosal myoma (LSM) and those with myomas that do not impact the endometrial cavity (LO).(3)
As appreciated by the PALM-COEIN classification women with inherited and acquired coagulopathies are at a high risk of suffering from HMB. Up to 20% of females with heavy menstrual bleeding are thought to have an underlying bleeding disorder.(5) Conversely, heavy menstrual bleeding is one of the most common symptoms of women with bleeding disorders. The most common bleeding disorders that affect women are: Von Willebrand disease (VWD), platelet function defects and deficiencies of coagulation factors e.g. haemophilia A (Factor VIII), Haemophilia B (Factor IX), Factor XI and rare bleeding disorders.(6) The prevalence of heavy menstrual bleeding in women with VWD is 74-94% and the prevalence of VWD in women with heavy menstrual bleeding is 5-24%.(6)

Evaluation of a woman with heavy menstrual bleeding with a suspected underlying bleeding disorder should include the consideration of personal and family history of bleeding tendencies and the complete clinical and gynaecological evaluation to exclude other causes related to PALM-COEIN. Furthermore, a full medication history including contraceptives, anticoagulants, antiplatelet therapy and iron supplementation should be taken.

The Pictorial Bleeding Assessment Chart allows women to track the number of pads or tampons used for a menstrual period as well as the degree of soiling.(7) The PBAC aims to identify women with menstrual

blood loss of >80 ml. Once identified, these women can then undergo assessment of HMB as described above. The PBAC is not specific in identifying underlying coagulopathies.

Should the history and clinical examination deem an underlying coagulopathy likely, laboratory testing should be undertaken.(2) Laboratory assessment includes a full blood count, blood group evaluation, thyroid function testing, prothrombin time, activated thromboplastin time, assays of Von Willebrand factor (VWF), as well as levels of other clotting factors and platelet function tests. Laboratory testing is expensive and if not directed appropriately will only add to the health cost burden of women with HMB. Selecting women in whom HMB is coagulopathy related has been a research field of interest for many years. This has led to the development and validation of various bleeding assessment tools aimed at identifying both HMB and underlying bleeding disorders.

The various bleeding assessment tools (BAT) serve as a simplified evaluation assessing bleeding symptoms in patients with a suspected bleeding disorder or HMB. ISTH/SSC-BAT (International Society on Thrombosis and Haemostasis/The Scientific and Standardization Committee Bleeding Assessment Tool), is a bleeding assessment tool that was established by a working group within the framework of the ISTH/SSC Subcommittees on VWF and on Perinatal/Paediatric Haemostasis during the 53rd SSC annual meeting held in Geneva in 2007.(8) The ISTH/SCC-BAT is specifically designed to identify patients with underlying coagulopathy and direct further laboratory evaluation of the suspected bleeding disorder.

The Molecular and Clinical Markers for the Management and Diagnosis of type 1 VWD study (MCMDM-1) and the condensed MCMDM-1 bleeding questionnaire have also been used as a predictor of bleeding disorders in women with heavy menstrual bleeding.(9,10) The MCMDM-1 is a detailed questionnaire, which takes approximately 40 minutes to administer. A condensed version focuses directly on the details that affect the bleeding score and takes 5-10 minutes to administer. The condensed MCMDM-1 VWD bleeding questionnaire can distinguish between women with heavy menstrual bleeding secondary to a bleeding disorder and those that do not have a bleeding disorder and assists to determine the severity of the bleeding disorder.(9,10) In this study the researcher will make use of the condensed MCMDM-1 VWD bleeding questionnaire (Annexure A).

As noted with international research data; the prevalence of women with heavy menstrual bleeding who have an underlying bleeding disorder is up to 20%.(5) It is not the researchers' experience that the same prevalence has been reported in the same population of patients in the gynaecology clinic at Pelonomi Hospital. This therefore suggests that cases of women with heavy menstrual bleeding secondary to a bleeding disorder likely go undiagnosed.

Evaluation and management of women with heavy menstrual bleeding with an underlying bleeding disorder in central South Africa is hampered by a lack of research in the field. Major advances in the multidisciplinary management of HMB are urgently needed and the awareness of the impact of bleeding disorders on HMB needs to be advocated.

The real world prevalence of HMB associated with bleeding disorders in the researchers' clinic will improve the management of these women. Furthermore, the role of haematologists in the conservative medical management of these patients will contribute greatly to the multidisciplinary approach these women warrant. Advances made in identifying women with bleeding disorders will make a positive impact on improving obstetric care of these individuals as well.

Research Aim

The primary aim of the study is to determine the prevalence of bleeding disorders in women with regular heavy menstrual bleeding at a secondary gynaecology clinic in central South Africa.
A secondary aim is to evaluate the sensitivity and specificity of the MCMDM-1VWD BAT and the bleeding time in identifying women with regular HMB with underlying bleeding disorders.

Methodology

Study design

This is a prospective cross-sectional study.

Sample/Study Participants

Participants of the study will be women who have been referred to Pelonomi Gynaecology clinic for work up of heavy menstrual bleeding. Consecutive sampling will be used.

Sample size of 50 patients.
The time frame for data collection is 6 months, from April 2018 – September 2018. Two to three cases are anticipated per week.

Inclusion criteria

- All non-pregnant females referred to Pelonomi Hospital Gynaecology clinic with the main complaint of heavy menstrual bleeding at their first visit.
- Women aged 18 years and above.
- Pre-menopausal women. Menopause will be defined as the permanent cessation of menstrual periods, determined retrospectively after a woman has experienced 12 months of amenorrhoea without any other obvious pathological or physiological cause.
- First visit.

Exclusion criteria

- Pregnant woman. In the Gynaecology clinic in Pelonomi Hospital a point of care urine HCG test is used to determine whether a patient is pregnant, a formal β-HCG is done only when there is a discrepancy between the clinical presentation and the urine HCG.
- Post-menopausal women.
- Women known to have bleeding disorders.
- Those already diagnosed with an identifiable cause as on the PALM-COEIN classification.

Measurement

Women that are referred to Pelonomi Hospital's Obstetrics and Gynaecology clinic with the history of heavy menstrual bleeding will be participants of the study. There will be strict adherence to the inclusion and exclusion criteria. The gynaecology clinic takes place every Monday to Friday; therefore, data can be collected daily depending on the patients that are present that qualify to be participants of the study. Referring clinics from greater Bloemfontein and surrounding towns contact the clinic for appointments for the patients, therefore the participants of the study will be given a date to come to the clinic and will then be seen by the researcher.

A standard gynaecological work up for the cause of heavy menstrual bleeding will be done for the participants of the study. Participants that fall in the category of unexplained HMB will then continue to form part of the research project. Please see the outline of the research project below. The participants of the study will be asked to come back at a later date to collect and review their results with the researcher.

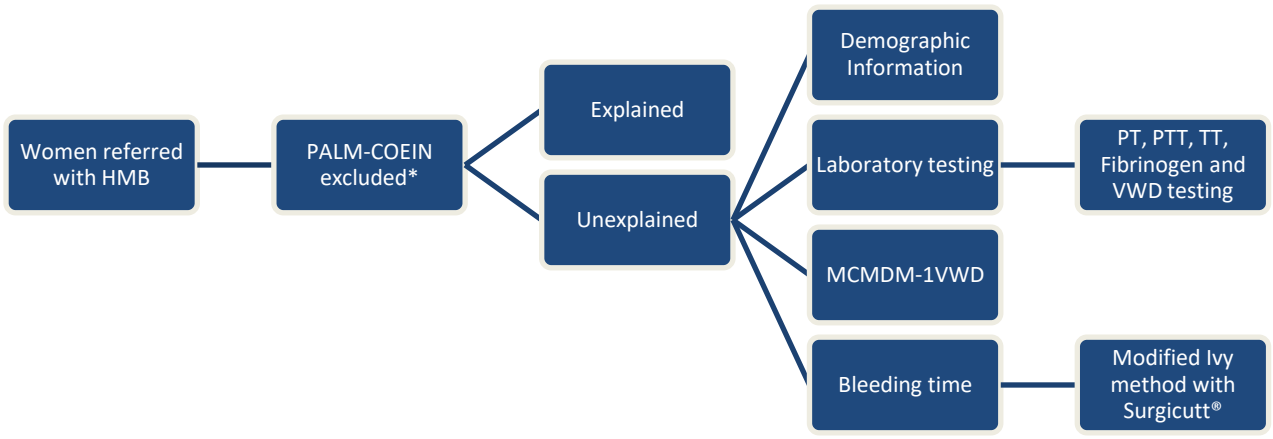

Figure 2. Diagrammatic representation of the study design.

** "C" for coagulation will not be excluded.*

Exclusion of PALM-COEIN

HISTORY

The history will consist of the main complaint, age at menarche, duration and characteristics of menstrual pattern, any previous gynaecological surgery, any non-gynaecological surgery previously performed on the patient, any known medical illnesses, a sexual history and a full medications history including contraceptive use.

CLINICAL EXAMINATION

Measurement of vitals, calculation of BMI. A systematic abdominal examination, a speculum examination and bimanual vaginal examination.

SPECIAL EXAMINATIONS

Abdominal and/or vaginal ultrasound:

A gynaecological ultrasound will be done to rule out any structural abnormalities that can explain heavy menstrual bleeding.

Routine laboratory tests:

Basic blood tests done at the Pelonomi Gynaecology Clinic are the following:

- Human Chorionic gonadotropin, to exclude pregnancy. A urine point of care test can be done in this regard to minimise costs.
- Full blood count and ferritin, especially in women with symptoms and signs of anaemia.
- Additional testing is selective and depends upon the information obtained on history and physical examination: thyroid stimulating hormone, follicle stimulating hormone (FSH), luteinizing hormone (LH), oestrogen levels, prolactin levels, androgen levels and coagulation studies (which will be performed in the unexplained HMB subgroup).

Unexplained HMB

Once a gynaecological cause of heavy menstrual bleeding has been excluded, the researcher will assign this patient to the unexplained HMB category and proceed to do the following:

The MCMDM-1VWD BAT

The researcher will complete the MCMDM-1 BAT (see Annexure A) on all patients with unexplained HMB. The researcher will use an interpreter where necessary.

The Bleeding Time

The bleeding time will be performed on all women with unexplained HMB. The modified Ivy's method using a Surgicutt® device will be used. This will be performed at the first clinic visit by an experienced NHLS technologist and/or the researcher.

Laboratory coagulation testing:

Laboratory testing to identify women with underlying bleeding disorders will be performed on all patients with unexplained HMB. Two citrate tubes will be drawn. One tube will be allocated for testing the following parameters:

- Prothrombin time
- Partial thromboplastin time
- Thrombin Time
- Fibrinogen

These assays will be performed on the Siemens Sysmex CS 2100i automated coagulation instrument (Siemens Healthcare Diagnostics, Tarrytown, USA(Siemens®) using the manufacturer's reagents. All assays will be performed following Universitas Service Laboratory standard operating procedures to assure good laboratory practise. A laboratory request form specifically generated for the research project will be used to identify and mark blood samples (Annexure D). This will assure billing onto a research entity and prohibits charges on the Department of Health accounts. This laboratory form with the blood samples will be sent to the central Universitas NHLS reception.

The above tests are screening tests and will not specify any particular bleeding disorder. Should the above screening tests elude to an underlying bleeding disorder requiring further investigation, the additional tests will be as for routine care of any patient with abnormal coagulation screening tests. An example includes a patient with an isolated prolonged PTT for which clotting factor levels (like factor VIII) should be investigated. A second example is a prolonged bleeding time that is not explained by the finding of VWD, where formal platelet function testing is indicated. These tests will be performed at subsequent visits and will not form part of the budget for this study. The results of these test will be used in the final data set (please see informed consent document).

The second tube will be stored at -80°C for VWD testing which will include:

- Von Willebrand antigen
- Ristocetin cofactor activity
- Collagen binding assay
- Multimeric analysis

The VWF assays will be performed on various in house assays developed by the Special Haemostasis Laboratory.

The blood will be taken to the Special Haemostasis Laboratory at Department of Haematology and Cell Biology within six hours by the researcher personally. The researcher responsible for identifying patients, examining them and drawing the blood, will be the principle researcher. The co-supervisor will be responsible for overseeing laboratory testing.

Methodological and measurement errors

Bleeding Assessment Tool:

- Language barriers

The researcher is fluent in Sesotho, Afrikaans and English and will be able to explain the informed consent and patient information document to the participants of the study in these three languages.

- Intra-observer and inter-observer variability

The researcher is a registrar in the Department of Obstetrics and Gynaecology and will be collecting the data. The researcher is well trained to perform the measurements of the research project. Regular checks during the data collection process will be facilitated by the supervisors of the study to make sure that measurements are being made correctly.

The researcher will be the only one collecting data from the research participants, therefore inter-observer variability will be of minimal significance in this regard.

Bleeding time:

- Intra-observer and inter-observer variability.

  Only the researcher and a single experienced NHLS technologist will be responsible for measuring the bleeding time. If possible both the researcher and the technologist will be present to observe the bleeding time. This aims to limit both intra- and inter-observer variability. The researcher will be trained by both the second co-supervisor (a haematologist) and the experienced NHLS technologist to be awarded competency to perform the measurement of a bleeding time.
- Reproducibility

  The modified Ivy's method with the use of a Surgicutt® bleeding time device assures optimal reproducibility of the bleeding time as the device delivers identical incisions. The bleeding time will also be performed with strict adherence to the NHLS standard operating procedure.

Laboratory testing:

- Standardisation/Quality assurance

  The instruments used within the Special Haemostasis Laboratory are regularly calibrated and partake in external quality assurance programs as required for laboratory accreditation. The instruments will be checked daily to assure internal quality control materials deliver satisfactory results. All the laboratory samples will be performed in batches on the same day to limit inter-run variability.

- Lability of samples

  The blood samples will be taken to the Special Haemostasis Laboratory at Department of Haematology and Cell Biology within six hours of collecting the blood by the researcher personally, so as to minimize any sample degradation. The samples will also be frozen at -80°C to assure viability of the samples for an extended period and allow for the batching of laboratory testing.

Pilot study

A pilot study will be conducted in March 2018 pending approval of the Ethics Committee and the Free State Department of Health. The first five study participants will be included. If no adjustments are deemed necessary, these five participants will be included in the final data set.

Analysis of data

The researcher will enter the data into an Excel spreadsheet. Data will be reviewed and processed by the Department of Biostatistics at the University of Free State. Numerical values will be summarised by means, standard deviations or medians and percentiles. Categorical variables will be summarised by frequencies and percentages. Sensitivity and specificity of screening tests will be summarised by percentages with 95% confidence intervals.

Implementation of findings

The aim of the researcher is to use the findings of this study to:

- Write new departmental protocols for the management of HMB, in particular to identify candidates for coagulation testing. Both the bleeding time and the MCMDM-1VWD will be considered as candidate tools to incorporate into such protocols. The researchers deem both tools to be cost effective gatekeepers to full coagulation testing.

- Formulate new treatment strategies for women with fertility wishes, who have been found to have an underlying bleeding disorder, focussing on improved antenatal and postpartum care. Planning obstetric management in advance can greatly minimise the bleeding risks involved.

- Facilitate a multidisciplinary approach for management of women with bleeding disorders who have HMB between gynaecology and haematology.

- Facilitate further research in this spectrum; i.e. assessment of perceived improved quality of life in women with heavy menstrual bleeding secondary to a bleeding disorder who have been managed conservatively.

- Present and findings at congresses and attempt to publish the report.

Time Schedule

- Protocol submission to Health Sciences Research Ethics Committee of the University of the Free Sate: 16 February 2018.
- Submission to Free State Department of Health: March 2018.
- Data collection: April to August 2018.
- Laboratory testing: September 2018.
- Data submission and analysis: October 2018.
- Writing of original article for publication: November 2018
- Completion of MMed Dissertation: November 2018.

Budget

Application for funding will be done once approval has been granted from the Ethics Committee.
The University of the Free State Special Haemostasis Laboratory has offered to sponsor the VWF antigen, VWF multimeric analysis and collagen binding assays which together amounted to R81 084 of the total budget. The researchers will apply for funding for the remaining budget, from the Postgraduate Committee.

Item	Cost per Item
Prothrombin time @ R44.76	R2238
Partial thromboplastin time @ R49.57	R2478.50
Fibrinogen @ R32.36	R1618
Thrombin Time @ R63.97	R3198.50
Bleeding Time @ R52.22	R2611
VWF Antigen @ R540.56	R27028.00
Ristocetin Cofactor @R287.93	R14396.50
VWF multimer @ R540.56	R27028.00
VWF Collagen binding@R540.56	R27028.00
Full Blood Count @ R52.00	R2600
Stationery: 1. Patient information document: 50 sheets @ R0.35 × 2 = R35 2. Patient consent forms: 50 sheets @ R0.35 = R17.50	R175

3. Patient data sheets 50 sheets @ R0.35 = R17.50 4. MCMMDM-1VWD Bleeding Questionnaire 50 questionnaires (6 pages per questionnaire) @ R0.35×6 = R105	
TOTAL (excluding sponsored money from Special Haemostasis laboratory)	R 29 315.50

Please note, further directed coagulation testing to classify bleeding disorders will be done on subsequent clinic visits as part of routine patient care. The costs of these tests will not form part of this budget. These tests include individual factor levels and formal platelet function testing. The researchers predict that these costs to be small, because similar studies reported that only 6-10% of patients will require further tests.(9)

Ethical aspects

All research projects must be approved by the Health Sciences Research Ethics Committee of the University of the Free State before the study commences.

Permission to conduct the study will be obtained from (Annexure G):

- Free State Department of Health
- Head: Department of Obstetrics and Gynaecology, UFS: Professor SM. Baloyi
- Head of Clinical Unit Obstetrics and Gynaecology Pelonomi Hospital : Dr. Nondabula
- Head of School of Pathology: Dr J Naicker

Informed consent will be obtained from all the participants in this study. The purpose, risks involved and benefits of the study will be explained to the patients in the language of their choice. A copy of the information leaflet with all the details pertaining to the study will be given to each participant (see Annexure E).

Personal information of the participants will be kept confidential. Only the researcher will have access to the participants' identity and contact information to assure confidentiality. The researcher will collect participant identifying information (hospital number) for the sole purpose of furthering appropriate care after completion of the study.

Participants in the study that have been found to have a bleeding tendency will be informed duly and treated accordingly.

All study samples will be kept for a minimum of two years after completion of the study, but it is highlighted that stored plasma samples contain no genetic material as they are largely acellular and thus DNA free. After the minimum storage period the samples will be exposed of as per NHLS standard operating procedures.

Participants will be made aware that there may be organizations that may inspect and/or copy research records for data analysis and quality assurance, these include the National Health Research Ethics Council (NHREC).

Reference List

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10. Bowman M, Mundell G, Grabell J, Hopman WM, Rapson D, Lillicrap D, et al. Generation and validation of the Condensed MCMDM-1VWD Bleeding Questionnaire for von Willebrand disease. J Thromb Haemost. 2008;6(12):2062–6.

8.1 Appendix 2: Bleeding Assessment Tool: Molecular and Clinical Markers for the Diagnosis and Management of Type 1 VWD

CONDENSED MCMDM-1 BLEEDING QUESTIONNAIRE:

Age _____ **Date of Birth** _____ **(DD/MO/YYYY)**

Presenting complaint of bleeding or bruising today	**Yes**	☐ **No**	☐
Personal history of bleeding or bruising	**Yes**	☐ **No**	☐
Ever been diagnosed with a bleeding disorder?	**Yes**	☐ **No**	☐

Diagnosis: _____

Family history of bleeding (at least one family member)	**Yes**	☐ **No**	☐

If yes, what was the diagnosis? _____
Pedigree:

Are you currently taking Oral Contraceptive Pills? **Yes** ☐ **No** ☐

If yes, brand name _____

Are you pregnant? _____ **Gestation time** _____

Specify any herbals and/or medications that you have taken in the past 30 days:

Name	**Dose**	**Route**	**Frequency**	**Duration**

Nosebleeds **Yes** ☐ **No** ☐

Number of episodes/year

☐ **< 1** ☐ **6 - 12**
☐ **1 – 5** ☐ **> 12**

Duration of average episode

☐ **< 1 minute**
☐ **1 – 10 minutes**
☐ **> 10 minutes**

Medical attention ☐ **Yes** ☐ **No**

☐ **Consultation only**
☐ **Cauterization/packing**
☐ **Antifibrinolytics**
☐ **DDAVP**
☐ **Transfusion/Replacement**

Bruising **Yes** ☐ **No** ☐

Location ☐ **Exposed sites**
☐ **Unexposed sites**

Size of average ☐ **< 1 cm**
☐ **1 – 5 cm**
☐ **> 5 cm**

Minimal or no trauma **Yes** ☐ **No** ☐

Medical attention **Yes** ☐ **No** ☐

If yes, please specify _____

Bleeding from minor wounds **Yes** ☐ **No** ☐

Number per year ☐ **< 1**
☐ **1 – 5**
☐ **6 or more**

Duration of average episode ☐ **< 5 minutes**
☐ **> 5 minutes**

Medical attention ☐ **Yes** ☐ **No**
☐ **Consultation only**
☐ **Surgical hemostasis**
☐ **Blood transfusion/DDAVP/Replacement**

Oral cavity bleeding Yes ☐ No ☐

☐ Tooth eruption
☐ Gums, spontaneous
☐ Gums, after brushing
☐ Bites to lip and tongue

Medical attention ☐ Yes ☐ No

☐ Consultation only
☐ Surgical hemostasis/Antifibrinolytic
☐ Blood transfusion/DDAVP/Replacement

Post-dental extraction Yes ☐ No ☐

☐ No bleeding in at least 2 extractions
☐ None done, or no bleeding in 1 extraction

Medical attention ☐ Yes ☐ No

☐ Consultation only
☐ Resuturing or packing
☐ Blood transfusion/DDAVP/Replacement

Gastrointestinal Bleeding Yes ☐ No ☐

☐ Ulcer, portal hypertension, hemorrhoids
☐ Spontaneous
☐ Surgery/Blood transfusion/DDAVP/Antifibrinolytic

Surgery Yes ☐ No ☐

☐ No bleeding in at least 2 surgeries
☐ None done, or no bleeding in 1 surgery

Post-op medical attention Yes ☐ No ☐

☐ Consultation only
☐

Surgical hemostasis/Antifibrinolytic

☐ **Blood transfusion/DDAVP/Replacement**

Menorrhagia **Yes** ☐ **No** ☐

Duration of average menstruation _____ days

Duration of heavy menstruation _____ days

How often do you change your pads/tampons

on heaviest days _____ hours

on average days _____ hours

What type of feminine product do you use? (i.e. panty liner, super absorbency tampon etc.)

_____

Medical attention ☐ **Yes** ☐ **No**

- ☐ **Consultation only**
- ☐ **Pill use/Antifibrinolytics**
- ☐ **Dilatation & curettage**
- ☐ **Iron therapy**
- ☐ **Blood transfusion/DDAVP/Replacement**
- ☐ **Hysterectomy**

Post-partum hemorrhage **Yes** ☐ **No** ☐

- ☐ **No bleeding in at least 2 deliveries**
- ☐ **No deliveries, or no bleeding in 1 delivery**

Medical attention ☐ **Yes** ☐ **No**

- ☐ **Consultation only**
- ☐ **D&C/Iron therapy/Antifibrinolytics**
- ☐ **Blood transfusion/DDAVP/Replacement**
- ☐ **Hysterectomy**

Muscle hematomas **Yes** ☐ **No** ☐

☐

Post-trauma, no therapy

☐ Spontaneous, no therapy

☐ Spontaneous or traumatic requiring DDAVP or Replacement

☐ Spontaneous or traumatic requiring surgical Intervention or transfusion

Hemarthrosis Yes ☐ No ☐

☐ Post-trauma, no therapy

☐ Spontaneous, no therapy

☐ Spontaneous or traumatic requiring DDAVP or Replacement

☐ Spontaneous or traumatic requiring surgical Intervention or transfusion

Central Nervous System Bleeding Yes ☐ No ☐

☐ Subdural, any intervention

☐ Intracerebral, any intervention

Other _____

_____

Medical attention Yes ☐ No ☐

☐ Consultation only

☐ Surgical hemostasis/Antifibrinolytic

☐ Blood transfusion/DDAVP/Replacement

Scoring Key

Symptom	Score -1	0	1	2	3	4
Epistaxis	--	No or trivial (less than 5)	> 5 or more than 10’	Consultation only	Packing or cauterization or antifibrinolytic	Blood transfusion or replacement therapy or desmopressin
Cutaneous	--	No or trivial (< 1cm)	> 1 cm and no trauma	Consultation only	--	--
Bleeding from minor wounds	--	No or trivial (less than 5)	> 5 or more than 5’	Consultation only	Surgical hemostasis	Blood transfusion or replacement therapy or desmopressin
Oral cavity	--	No	Referred at least one	Consultation only	Surgical hemostasis or antifibrinolytic	Blood transfusion or replacement therapy or desmopressin
Gastrointestinal bleeding	--	No	Associated with ulcer, portal hypertension, hemorrhoids, angiodysplasia	Spontaneous	Surgical hemostasis, blood transfusion, replacement therapy, desmopressin, antifibrinolytic	--
Tooth extraction	No bleeding in at least 2 extractions	None done or no bleeding in 1 extraction	Reported, no consultation	Consultation only	Resuturing or packing	Blood transfusion or replacement therapy or desmopressin
Surgery	No bleeding in at least 2 surgeries	None done or no bleeding in 1 surgery	Reported, no consultation	Consultation only	Surgical hemostasis or antifibrinolytic	Blood transfusion or replacement therapy or desmopressin
Menorrhagia	--	No	Consultation only	Antifibrinolytics, pill use	Dilation & curettage, iron therapy, ablation	Blood transfusion or replacement therapy or desmopressin or hysterectomy
Postpartum hemorrhage	No bleeding in at least 2 deliveries	None done or no bleeding in 1 surgery	Consultation only	Dilation & curettage, iron therapy, antifibrinolytics	Blood transfusion or replacement therapy or desmopressin	Hysterectomy
Muscle hematomas	--	Never	Post trauma, no therapy	Spontaneous, no therapy	Spontaneous or traumatic, requiring desmopressin or replacement therapy	Spontaneous or traumatic, requiring surgical intervention or blood transfusion
Hemarthrosis	--	Never	Post trauma, no therapy	Spontaneous, no therapy	Spontaneous or traumatic, requiring desmopressin or replacement therapy	Spontaneous or traumatic, requiring surgical intervention or blood transfusion
Central nervous system bleeding	--	Never	--	--	Subdural, any intervention	Intracerebral, any intervention

Scoring Key: A few small changes in wording from the original MCMDM-1 scoring key are indicated in the boxes. For tooth extraction and surgery a score of 1 was previously for "Referred in <25% of cases" and a score of 2 was previously for "Referred in >25% of cases". For the menorrhagia category we added ablation therapy (which was not included in the original) at the same level as D&C and iron therapy.

9 Appendix 3: Permission letters

9.1 Permission letter from the HSREC

UNIVERSITY OF THE FREE STATE
UNIVERSITEIT VAN DIE VRYSTAAT
YUNIVESITHI YA FREISTATA

UFS·UV
HEALTH SCIENCES
GESONDHEIDSWETENSKAPPE

Health Sciences Research Ethics Committee

29-Aug-2018

Dear Dr Motshidisi Deiker

Ethics Clearance: **The prevalence of bleeding disorders in women with unexplained heavy menstrual bleeding at a secondary gynaecology clinic in central South Africa.**
Principal Investigator: **Dr Motshidisi Deiker**
Department: **Obstetrics and Gynaecology Department (Bloemfontein Campus)**

APPLICATION APPROVED

Please ensure that you read the whole document

With reference to your application for ethical clearance with the Faculty of Health Sciences, I am pleased to inform you on behalf of the Health Sciences Research Ethics Committee that you have been granted ethical clearance for your project.

Your ethical clearance number, to be used in all correspondence is:**UFS-HSD2018/0158/2509**

The ethical clearance number is valid for research conducted for one year from issuance. Should you require more time to complete this research, please apply for an extension.

We request that any changes that may take place during the course of your research project be submitted to the HSREC for approval to ensure we are kept up to date with your progress and any ethical implications that may arise. This includes any serious adverse events and/or termination of the study.

A progress report should be submitted within one year of approval, and annually for long term studies. A final report should be submitted at the completion of the study.

The HSREC functions in compliance with, but not limited to, the following documents and guidelines: The SA National Health Act. No. 61 of 2003; Ethics in Health Research: Principles, Structures and Processes (2015); SA GCP(2006); Declaration of Helsinki; The Belmont Report; The US Office of Human Research Protections 45 CFR 461 (for non-exempt research with human participants conducted or supported by the US Department of Health and Human Services- (HHS), 21 CFR 50, 21 CFR 56; CIOMS; ICH-GCP-E6 Sections 1-4; The International Conference on Harmonization and Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH Tripartite), Guidelines of the SA Medicines Control Council as well as Laws and Regulations with regard to the Control of Medicines, Constitution of the HSREC of the Faculty of Health Sciences.

For any questions or concerns, please feel free to contact HSREC Administration: 051-4017794/5 or email EthicsFHS@ufs.ac.za.

Thank you for submitting this proposal for ethical clearance and we wish you every success with your research.

Yours Sincerely

Dr. SM Le Grange
Chair : Health Sciences Research Ethics Committee

Health Sciences Research Ethics Committee
Office of the Dean: Health Sciences
T: +27 (0)51 401 7795/7794 | E: ethicsfhs@ufs.ac.za
IRB 00006240; REC 230408-011; IORG0005187; FWA00012784
Block D, Dean's Division, Room D104 | P.O. Box/Posbus 339 (Internal Post Box G40) | Bloemfontein 9300 | South Africa

9.2 Permission from the Department of Health

health
Department of Health
FREE STATE PROVINCE

26 July 2018

Dr M Deiker
Dept. of Obstetrics and Gynaecology
UFS

Dear Dr M Deiker

Subject: The prevalence of Bleeding disorders in women with unexplained heavy menstrual bleeding at a secondary gynaecology clinic in central South Africa.

- Please ensure that you read the whole document, Permission is hereby granted for the above mentioned research on the following conditions:
- Participation in the study must be voluntary.
- A written consent by each participant must be obtained.
- Serious Adverse events to be reported to the Free State department of health and/ or termination of the study
- Ascertain that your data collection exercise neither interferes with the day to day running of Pelonomi Hospital nor the performance of duties by the respondents or health care workers.
- Confidentiality of information will be ensured and please do not obtain information regarding the identity of the participants.
- **Research results and a complete report should be made available to the Free State Department of Health on completion of the study (a hard copy plus a soft copy).**
- Progress report must be presented not later than one year after approval of the project to the Ethics Committee of The University of the Free State and to Free State Department of Health.
- Any amendments, extension or other modifications to the protocol or investigators must be submitted to the Ethics Committee of The University of the Free State and to Free State Department of Health.
- **Conditions stated in your Ethical Approval letter should be adhered to and a final copy of the Ethics Clearance Certificate should be submitted to** szbeelats@fshealth.gov.za or lithekanyi@fshealth.gov.za **before you commence with the study**
- No financial liability will be placed on the Free State Department of Health
- Please discuss your study with the institution manager/CEOs on commencement for logistical arrangements
- Department of Health to be fully indemnified from any harm that participants and staff experiences in the study
- Researchers will be required to enter in to a formal agreement with the Free State department of health regulating and formalizing the research relationship (document will follow)
- You are encouraged to present your study findings/results at the Free State Provincial health research day
- Future research will only be granted permission if correct procedures are followed see http://nhrd.hst.org.za

Trust you find the above in order.
Kind Regards

Dr D Motau
HEAD: HEALTH
Date: 27/07/18

Head : Health
PO Box 227, Bloemfontein, 9300
4th Floor, Executive Suite, Sophia House, cnr Maitland and, Harvey Road, Bloemfontein
Tel: (051) 405 1646 Fax: (051) 403 1556 e-mail: motaud@fshealth.gov.za/chkeaving@fshealth.gov.za
www.fs.gov.za

Appendix 3: Participant information documents

9.3 English Participant information document

Patient information leaflet (English)

PARTICIPANT'S INFORMATION LEAFLET

TITLE OF STUDY:

The prevalence of bleeding disorders in women with regular heavy menstrual bleeding at a secondary gynaecology clinic in central South Africa

Dear Ms/Mrs,

1) THE PURPOSE OF THIS STUDY:

We are doing this study to identify and diagnose women presenting to the gynaecology clinic with heavy menstrual bleeding and who also have an underlying undiagnosed inherited bleeding disorder. By doing so we are able to identify these women and determine how common/uncommon inherited bleeding disorders are in our population. The prevalence of inherited bleeding disorders in South African women with heavy menstrual bleeding is unknown.

Identifying these women will give the health workers treating these women a better understanding of the disease and in turn these women will be treated appropriately.

We are inviting you to participate in a research study.

2) What is involved in the study?

This study involves answering a questionnaire which will be provided by the researcher, a gynaecological examination, a gynaecological pelvic ultrasound and blood tests. The gynaecological pelvic ultrasound is used to assess the uterus for any abnormalities that might be the cause of heavy menstrual bleeding. The blood tests involved are used to test for any bleeding disorders that a participant might have. Participation in the study will take place over two clinic visits. The first visit is for the examination and the tests described above; the second visit will be for you to come and collect your results and to discuss the findings with the researcher.

The blood will be discarded as with blood for any other test after the tests have been completed. No genetic material will be collected or stored.

3) Risks of being involved in the study:

The only possible risk and discomfort involved is the standard gynaecological examination, including imaging with the ultrasound. Taking of blood from a vein could cause discomfort and carries a risk.

4) Benefits of being in the study:

Gynaecological evaluation of heavy menstrual bleeding that is part of this study is the basic assessment that is done on all patients that attend the gynaecology clinic. A patient that is identified to have any gynaecological problem will be treated appropriately. The patients that have a haematological illness will be afforded the opportunity to be referred to a specialist and be treated for the specific illness.

5) Official approval for the study:

The plan of the study has been submitted to the Faculty of Health Sciences Research Ethics Committee, University of Free State for approval. The study has been approved by the Head of Obstetrics and Gynaecology, UFS, Professor Baloyi. The study has also been approved by the Head of Clinical Services, Obstetrics and Gynaecology Pelonomi Hospital.

6) Non participation or withdrawal from the study

Should you wish not to participate in the study, you will receive the standard clinic treatment for heavy menstrual bleeding. You can decide to withdraw from the study at any time. There will be no discrimination against you. You will receive the standard clinic treatment for heavy menstrual bleeding.

7) Results of the study

You will be asked to come back on a date that is your clinic day to come and collect your results and discuss findings with the researcher. Please note that the follow-up test results for clotting can also be used in this study.

8) Participation is voluntary

Participation is voluntary and refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled. The subject may also discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.

9) Reimbursement for "out of pocket" expenses.

The participants will not be reimbursed for any expenses.

10) Confidentiality:

All records obtained during this research project will be regarded as confidential. All results obtained will be published and presented in a confidential manner. Once you have entered the research study a number will be allocated to you and your blood samples so that no direct link exists between the participant and information. Organizations that may inspect and/or copy your research records for quality assurance and data analysis include groups such as the Health Sciences Research Ethics Committee.

11) Contact details of researcher(s)

If you have any questions concerning this study contact: Dr Deiker
Tel: (051) 405 1435 Cell: 0823576494

12) Contact details of HSREC Secretariat and Chair – for reporting of complaints/problems.

The Chairperson: Health Sciences Research Ethics Committee (HSREC)
For Attention: Mrs MGE Marais
Francois Retief Building
Faculty of Health Sciences
University of the Free State
Bloemfontein 9300. T: +27 51 401 7795

9.4 Sesotho Participant information document

Patient information leaflet (Sesotho)

Ho ata a mafu a madi bathong ba Bo-Mmeba ba tswang madi a mangata ha ba le Matsatsing (Sebaka Secondary Gynaecology clinic in Central South Africa)

The prevalence of bleeding disorders in women with heavy menstrual bleeding at a secondary gynaecology clinic in central South Africa.

Dear Ms/Mrs

1) Lebaka le Bohlokwa ba dipatlisiso

Re etsa dipatlisiso tsena hore re kgone ho bona hore lebaka le etsang hore ho be le madi a sa tlwaelehang a mangata ho bo-MME ha ba le Matsatsing ke lefeng Sepetleleng sa gynaecology. Re tlo kgona ho bona hore ke Bo-mme ba jwang ba hlaelwang ke ntho ena hara bohle ba dulang sebakeng sena.Re kgone ho bona hape hore e tlwaelehile ho le hokae. Ho ata ha lefutso la bothata ba madi a tswang a le mangata Bo-MMeng ba south Africa ha ba le matsatsing ha le so tsejwe. Ho kgona ho bona Bo-MME bana ho tla fana ka Tlhaiso leseding basebetsing bohle ba dipetlele mme batla tseba le mokgwa wa ho ba hlokomela.

Re ya ho amohela hore o nke karolo dipatlisisong tsena

2) Ho nka karolo ho bolelang

O tlo botswa dipotso ke mookamedi wa dipatlisiso, o etsuwe ditlhatlhobo tsa Gynae,Ditlhatlhobo tsa Modumo wa pelvic le Ditlhatlhobo tsa madi.Di Tlhatlhobo tsa modumo wa pelvic di thusa ho bontsha Bothata bo ka bang teng ba popelo bo ka etsang hore madi a tswe a le mangata.Di Tlhatlhobo tsa madi di thusa ho bona Bothata Mading.

Madi a lahluwa ha ho qetuwe ho etsa ditlhatlhobo ka wona.Diphatsa tsa lefutso le tsona ha di bolokoe hohang

3) Dikotsi tsa ho Nka Karolo

Kotsi e teng ke ho se Phuthulohe ha ho tswa Ditlhatlhobo tsa Gynae le ha ho nkuwa setshwantsho kapa sona senepe sa ultrasound. Ho nka Madi Pela methapo ho utlwisa bohloko e bile ho kotsi.

4) Melemo ya ho nka karolo

Ditlhatlhobo tse bontshang madi a mangata ha bo-mme ba le matsatsing di bonolo haholo e bile di estuwa nako e kgolo le nyane dipetleleng tsa Gynae.Mokudi ya nang le bothata ba gynae o kgona ho hlokomeleha hantle.bakudi batla fumanwa bana le bothata ba haematology batla romellwa ho setsebi sa haematology ho lo hlahlubuwa.

5) Tumello ya Molao ka Dipatlisiso

Dithero tsa dipatlisiso di romelletswe phaphosing ya Health Science Research Committee ya UFS Hore di dumellwe di be molaong.Dipatlisiso di dumelletswe ke Hloho ya Obstetrics le Gynaecoloqy,UFS, Professor Baloyi.Di patlisiso di dumellestwe hap eke Hloho ya Clinical Services,Obstetrics and Gynaecology Pelonomi Hospital

6) Ho se nke karolo kapa ho itokolla dipatlisisong

Ha o ikgethela ho se nke karolo dipatlisisong o tla fumana tlhatlhobo e tlwaeleheileng ya madi a bo-mme ba matsatsing.o ka ikgethela ho itokolla dipatlisisong ka nako e kgethuweng ke wena.ha ho no ba le Kgethollo mabapi le wena, o tla fumana tlhatlhobo e tlwaeleheileng ya madi a bo-mme ba matsatsing.

7) Bopaki ba dipatlisiso

O tla fumantshwa letsatsi la clinic le o tlang ka lona hore o fumane bopaki , e bile o tla buisana ka bopaki boo le mookamedi wa dipatlisiso. Ka kopo tseba hore ho kaba le ditlhatlhobo tse ding tsa ho kwalana ha madi tse ka etsuwang.

8) Wa ithaopa ho nka karolo

Ho nka karolo ke ho ithaopa, ha o hana o ntse o tla fumana melemo ya dipatlisiso e oetshepisitsweng.se sesebediswa se ka itokolla ka nako e sebatlang ka yona. Ha o itokolla hana o ntse o tla fumana melemo ya dipatlisiso e oetshepisitsweng.

9) Ho Buseletswa ka ditjhelete tsa ditshenyehelo tsa pokoto

Moithaupi ha a Buseletswe ditjhelete tsa ditshenyehelo

10) Sephiri

Dipanmpiri kaofela tsa dipatlisiso tsena ke Sephiri.Bopaki ba di patlisiso bo tla phatlalatswa sephiring.ha o kgetha ho nka karolo ya dipatlisiso o tla fumana nomoro ya hao le nomoro ya madi a hao, hore ho se bonahale hore moithaupi ke mang.Mokhatlo o kgonang o kgonang ho sheba kapa ho qopitsa ditokomane tsa dipatlisiso, ke o tshwanang le Health sciences Research Ethics Committee

11) Dinomoro tsa Mookamedi wa Dipatlisiso

Ha o na le dipotso founela DR. Deiker Tel: (051) 405 1435 Cell:082 3576 494

12) Dinomoro tsa HSREC Secretariat and chair- ya ho tlaleha mathata le ditletlebo

Chairperson: Health Science Research Committee
Attention:Mrs MGE Marais
Francois Retief Building
Fuculty of health sciences
University of the Free State
Bloemfontein 9300: Tel: 051 401 7795

9.5 Afrikaans Participant information document

Patient information leaflet (Afrikaans)

PATIENT INLIGTINGSTUK

Titel van die studie: Die voorkoms van bloedingsiektes in vrouens met gereelde swaar menstruele bloeding by 'n sekondêre ginekologie kliniek in Sentraal Suid Afrika.

The prevalence of bleeding disorders in women with regular heavy menstrual bleeding at a secondary gynaecology clinic in Central South Africa

Geagte Mej/Mev,

26) Die doel van hierdie studie:

Ons voer hierdie studie uit om vrouens te diagnoseer wat na hierdie ginekologie kliniek verwys word met swaer menstruele bloeding en wat moontlik 'n bloedingsiekte mag hê. Ons beoog ook om die algehele voorkoms van bloedingsiektes in Suid Afrikaanse vrouens in ons kliniek vas te stel aangesien dit grootendeels onbekend is. Deur bloedingsiektes op te tel in ons pasiente kan ons gesondheidswerkers bewus maak en oplei ten opsigte van die behandeling van hierdie pasiente en ten einde pasient sorg verbeter.

Ons nooi u uit om deel te neem aan hierdie studie.

27) Waaruit bestaan hierdie studie?

Die studie sluit in 'n kort vraagstuk wat aan u gevra sal word deur die ondersoeker, 'n ginekologiese ondersoek, 'n pelviese sonar en bloedtoetse (indien geindikeer). Die pelviese sonar word gebruik om moontlike baarmoeder problem wat die swaar menstruele bloeding kan verklaar op te tel. Die bloedtoetse word gebruik om hormonale en stollings probleme te diagnoseer.

Alle bloedmonsters word toepaslik vernietig nadat die studie voltooi is. Geen genetiese material sal gestoor word nie.

28) Wat is die risiko verbonde aan die studie?

Die enigste moontlike ongemak verbonde is die pelviese sonar en ginekologiese ondersoek. Bloedtrek vir laboratorium ondersoeke kan kortdurende ongemak veroorsaak.

29) Voordele van deelname in die studie:

Grootendeels is die fisiese ondersoek en spesiale ondersoeke standaard soos vir enige pasient wat verwys word vir verdure uitwerk van swaer menstruele bloeding. Bykomend sal daar spesiale laboratorium ondersoeke op u uitgevoer word wat 'n moontlike bloedingsiekte by u kan diagnoseer. Indien 'n bloedingsiekte by u gediagnoseer word, sal u verwys word na 'n spesialis om die korrekte behandeling vir die spesifieke siekte te ontvang.

30) Goedkeuring vir die uitvoer van hierdie studie:

Die plan van hierdie studie is goedgekeur deur die etiese kommitee van die Universiteit van die Vrystaat en die Vrystaat se Departement van Gesondheid. Dit is ook deur die Hoof van Obstetrie en Ginokologie ,UVS, Dr Baloyi, goedgekeur sowel as die Hoof van Kliniese Dienste, Obstetrie en Ginokologie, Pelonomi Hospitaal.

31) Deelname weiering of onttrekking vanuit die studie:

Sou U besluit om nie aan die studie deel te neem nie, sal u steeds die nodige sorg verkry soos vir enige ander pasiënt wat verwys word met u simptome. U kan enige tyd onttrek uit die studie en daar sal nie teen u gediskrimineer word nie. Jy sal die standard behandeling kry vir swaar menstruele bloeding.

32) Uitslae van die studie:

U uitslae sal met u bespreek word tydens u opvolgafspraak by die ondersoeker. Let asseblief daarop dat opvolg stollingsuitslae ook gebruik kan word in die studie.

33) Vrywillige deelname:

Deelname is vrywillig en weiering om deel te neem sal geensins lei tot penalisering of verlies van voordele wat die pasiënt toekom. Deelname kan enige tyd gestaak word sonder dat die pasiënt voordele wat haar toekom verloor.

34) Vergoeding vir uitgawes:

Deelname aan die studie is gratis, en u word ook nie vergoed of betaal vir u deelname aan die studie nie.

35) Vertroulikheid:

Alle bloeduitslae en persoonlike inligting word streng vertroulik hanteer. Sodra u vir die studie inskryf word ‘n nommer aan u persoonlike inligting en bloedmonsters toegeken sodat geen direkte verbintenis tussen die deelnemer en die inligting bestaan nie. Organisasies wat jou rekords mag inspekteer of afskrifte daarvan maak vir kwaliteitdoeleindes en data analise sluit groepe in soos die Gesondheids Wetenskap Navorsing Etiese Komitee.

36) Kontak besonderhede van ondersoeker:

As u enige verdere inligting benodig, kontak gerus:
Dr. Deiker
Tel: (051) 405 1435 Cell: 0823576494

37) Kontak besonderhede van die Etiek Komitee:

The Chairperson: Health Sciences Research Ethics Committee (HSREC)
For Attention: Mrs MGE Marais
Francois Retief Building
Faculty of Health Sciences
University of the Free State
Bloemfontein 9300. T: +27 51 401 7795

10 *Appendix 4: Informed consent documents*

10.1 English Informed consent document

You have been asked to participate in a research study:

The prevalence of bleeding disorders in women with regular heavy menstrual bleeding at a secondary gynaecology clinic in Central South Africa

I have been informed about the study by …….. and have had a chance to read through the information leaflet and I have had all my questions answered to my satisfaction. I understand what procedures will be performed on me and what the risks and benefits are.

I understand that participation is entirely voluntary. I will not be penalized or lose benefits if I refuse to participate or decide to terminate participation.

I have been informed that there is no financial compensation.

I may contact Dr M Deiker at (051) 405 1435 or 0823576494 anytime if I have questions about the research or if I am injured as a result of the research.

I may contact the Secretariat of the Health Sciences Research Ethics Committee, UFS, at telephone number (051) 4017794/5 if I have questions about my rights as a research subject.

If I agree to participate, I will be given a signed copy of this document as well as the participant information sheet, which contain a written summary of the research.

The research study, including the above information, has been verbally described to me. I understand what my involvement in the study means and I voluntarily agree to participate.

_____ _____

Signature of Participant Date

_____ _____

Signature of Witness Date
(Where applicable)

_____ _____

Signature of Translator Date
(Where applicable)

10.2 Sesotho Informed consent document

Informed consent document (Sesotho)

Kopo ya ho ba karolo ya di patlisiso tsa bo ithuto, mabapi le **ho ata a mafu a madi bathong ba Bo-Mme ba ba tswang madi a mangata ha ba le Matsatsing (Sebaka Secondary Gynaecology clinic in Central South Africa)**

Ke bolelletswe ka dipatlisiso Ke …….. ya Mphileng monyetla wa ho bala pampiri ya tlhaloso ka di patlisiso e bile dipotso tsaka di arabuwe kaofela ho ya ka kgotsofalo yaka.Ke utlwisisa dintho tse tlo etsuwa ho nna,hape ke utlwisisa tsohle ka ditlamorao tse ntle le tse mpe.

Ke ya Dumela hore ke Mo ithaupi di patlisitsong tsena.Ha ke no lahlehelwa ke letho ho tse ntshwanetseng ha ke sa Dumele ho ba karolo kapa ha ke tlohela mahareng.

Ke bolelletswe hore ha hona moputso wa tjhelete

Nka founela DR M Deiker Nomorong ena (051) 405 1435/082 3576 494 nako engwee le engwee ha kena le dipotso mabapi le dipatlisiso kapa ha ke utlwile bohloko ka lebaka la dipatlisiso.

Nka founela Sekeretari ya Health Science Research Ethics Committee(UFS) (051) 401 77 94/5 ha kena le dipotso mabapi le ditokelo tsaka jwalo ka se sebediswa dipatlisitsong tsena.

Ha ke Dumela ho Nka Karolo ke tla fuwa pampiri ena e saennweng hape le pampiri e kentseng ditho tse ngotsweng fatshe ka bokgutshwane ka patlisiso ena.

Dipatlisiso tsena tsa boithuto le dipuo tse seng di boletswe ka hodimo, ke di bolelletswe ka molomu.Ke utlwisisa karolo yaka dipatlisisong tsena Mme ke ya dumela ho nka karolo.

Mosaeno oa morupelouoa

Mosaeno wa bapaki

10.3 Afrikaans Informed consent document

Informed consent document (Afrikaans)

U is gevra om deel te neem aan ‘n studie:

Die voorkoms van bloedingsiektes in vrouens met gereelde swaar menstruele bloeding by ‘n sekondêre ginekologie kliniek in Sentraal Suid Afrika

The prevalence of bleeding disorders in women with regular heavy menstrual bleeding at a secondary gynaecology clinic in Central South Africa

Ek is voldoende ingelig oor die studie deur ……. en ek het ook die pasient inligtingstuk gelees. Al my vrae is beantwoord. Ek verstaan wat op my uitgevoer kan word en wat die risiko’s en voordele daaraan verbonde is.

Ek verstaan dat deelname vrywillig is. Ek sal nie gepenaliseer word as ek deelname weier of ontrek nie.

Ek is ingelig dat my deelname geen finansiele voordeel inhou nie.

Ek mag enige tyd Dr Deiker kontak by (051) 405 1435 of 0823576494 as ek enige vra het oor die studie of as ek enige besering opgedoen het tydens deelname aan die studie.

Ek mag die sekretaresse van die Gesondheids Wetenskappe Navorsings Etiek Kommitee kontak by (051) 4017794/5 indien ek verdere vrae het oor my regte as ‘n navorsings deelnemer.

As ek instem om deel te neem aan die studie, sal ek ‘n getekende afskrif van hierdie dokument ontvang asook die pasient inligtingstuk wat ‘n geskrewe opsomming van die studie bevat.

Die navorsingstudie asook die bogenoemde inligting is duidelik aan my gekommunikeer en ek verstaan wat my deelname in hierdie studie vereis en ek stem in om deel te neem aan die studie.

_____	_____
Handtekening van deelnemer	Datum
_____	_____
Handtekening van waarnemer	Datum
_____	_____
Handtekening van vertaler *(Indien toepaslik)*	Datum

11 *Appendix 5: Participant data sheet*

Patient Data Collection Sheet

Participant no.	Hospital no. (PM no)	Contact number/s	Age	Menarche	Family Hx of Bleeding disorders (Y/N)	Co-dx	Gravidity	Parity	Duration of symptoms	BMI	Referring HCW (GP,MO,Specialist gynae)

12 *Appendix 6: Laboratory work sheet*

Laboratory Results Sheet

Study Number	PT	PTT	TT	Fibrinogen	Bleeding Time	VWF:Ag	RCo	ColB	Multimeric Analysis

13 *Appendix 7: Author guidelines, South African Medical Journal*

SAMJ Article Guidelines

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

General:

- Manuscripts must be written in UK English.
- The manuscript must be in Microsoft Word format. Text must be single-spaced, in 12-point Times New Roman font, and contain no unnecessary formatting (such as text in boxes).
- Please make your article concise, even if it is below the word limit.
- Qualifications, ***full*** affiliation (department, school/faculty, institution, city, country) and contact details of ALL authors must be provided in the manuscript and in the online submission process.
- Abbreviations should be spelt out when first used and thereafter used consistently, e.g. 'intravenous (IV)' or 'Department of Health (DoH)'.
- Include sections on Acknowledgements, Conflict of Interest, Author Contributions and Funding sources. If none is applicable, please state 'none'.
- Scientific measurements must be expressed in SI units except: blood pressure (mmHg) and haemoglobin (g/dL).
- Litres is denoted with an uppercase L e.g. 'mL' for millilitres).
- Units should be preceded by a space (except for % and ºC), e.g. '40 kg' and '20 cm' but '50%' and '19ºC'.
- Please be sure to insert proper symbols e.g. µ not u for micro, a not a for alpha, b not B for beta, etc.
- Numbers should be written as grouped per thousand-units, i.e. 4 000, 22 160.
- Quotes should be placed in single quotation marks: i.e. The respondent stated: '...'
- Round brackets (parentheses) should be used, as opposed to square brackets, which are reserved for denoting concentrations or insertions in direct quotes.
- If you wish material to be in a box, simply indicate this in the text. You may use the table format – this is the *only* exception. Please DO NOT use fill, format lines and so on.

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

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

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

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

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

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

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

Preparation notes by article type

Research

Guideline word limit: 4 000 words

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

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

Do not replicate data in tables and in text .

Structured abstract

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

Here is an example of a good abstract.

Main article

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

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

- Objectives (within Introduction/Background): a clear statement of the main aim of the study and the major hypothesis tested or research question posed

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

Results

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

Discussion

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

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

Conclusions

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

Editorials

Guideline word limit: 1 000 words

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

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

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

CME (by invite only)

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

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

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

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

For queries about these guidelines please feel free to contact the CME editor, Dr Bridget Farham, by email (ugqirha@iafrica.com) or telephone (+27 (0)21 789 2331).

Review process

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

Guest editorials

Guideline word limit: 1 000 words

- Include the guest editor's personal details (qualifications, positions, affiliation, e-mail address, and a short personal profile (50words)).
- If possible, include a photograph of the author(s) at high enough resolution for print. It is preferable to provide two guest editorials, one for each issue, so that the content of the articles in each issue is covered.

Articles

Guideline word limit: 2 000 - 3 000 words

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

Personal details

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

In Practice

Guideline word limit: 2 000 - 3 000words

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

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

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

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

- Author affiliations and qualifications: to be the same as for Research. Provide all authors' names and initials, qualifications and full affiliations, and corresponding author.
- Short abstract: does not need to be structured, but should capture the essential features of the article
- Introduction: the reason for the article and the issue being addressed
- Recent research, discussion, local policy around the issue – include your own research where appropriate
- All statements should be referenced and, if opinion only, this should be stated
- Discussion: how this article adds to the discussion around a particular topic
- If a clinical practice or policy point is at issue, this needs to be emphasised, using a box with highlights if appropriate.

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

Case reports

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

Please use the following format for case reports:

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

14 *Appendix 8: Turnitin report*

MM Deiker Chap 2 no bio

ORIGINALITY REPORT

19%	9%	17%	6%
SIMILARITY INDEX	INTERNET SOURCES	PUBLICATIONS	STUDENT PAPERS

PRIMARY SOURCES

1	"Management of Bleeding Patients", Springer Science and Business Media LLC, 2021 Publication	2%
2	Submitted to University of the Free State Student Paper	2%
3	H. Marieke Knol, André B. Mulder, Dick H. Bogchelman, Hanneke C. Kluin-Nelemans, Ate G.J. van der Zee, Karina Meijer. "The prevalence of underlying bleeding disorders in patients with heavy menstrual bleeding with and without gynecologic abnormalities", American Journal of Obstetrics and Gynecology, 2013 Publication	2%
4	"Abstracts", Journal of Thrombosis and Haemostasis, 2015. Publication	1%
5	Brooke O'Brien, Jane Mason, Rebecca Kimble. "Bleeding Disorders in Adolescents with Heavy Menstrual Bleeding: The Queensland Statewide Paediatric and Adolescent	1%