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PREVALENCE OF COMORBID PSYCHIATRIC ILLNESS AND QUALITY OF LIFE IN ADULTS WITH INHERITED BLEEDING DISORDERS IN CENTRAL SOUTH AFRICA

BY

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DECLARATION OF AUTHORSHIP

I, Heinrich Tertius Koekemoer, declare that the coursework Master's Degree mini-dissertation and interrelated publishable article that I herewith submit for the degree in MMed (Psychiatry) at the University of the Free State are my own independent work and that I have not previously submitted it for a qualification at another institution of higher education. Where help was sought, it has been acknowledged.

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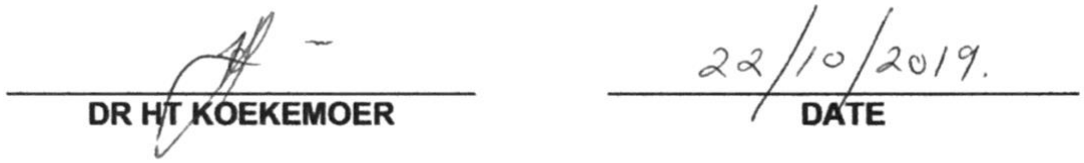

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ABSTRACT

Introduction: Inherited bleeding disorders (IBDs) appear to be relatively uncommon, but they pose unique health-related challenges. IBDs are acquired through inheritance of mutations that cause abnormal bleeding. Due to their chronic nature, one would expect similar psychosocial problems as seen in other chronic diseases. The purpose of this study was to obtain information about the psychiatric comorbidities of patients with inherited bleeding disorders in order to be able to sensitize health workers and to promote holistic care in order to better patients' health-related quality of life (HR-QoL).

Aim: To achieve this, the researchers aimed to establish the prevalence of psychiatric comorbidities in patients with IBDs, as well as their QoL. Furthermore, risk factors associated with psychiatric comorbidity and HR-QoL were evaluated.

Methods: A quantitative, cross-sectional, observational study was conducted using a questionnaire, the EQ-5D assessment tool, the Mini International Neuropsychiatric Interview - M.I.N.I. 7.0.2 (8/8/16 version), a functional assessment with the aid of the Functional Independence Score in Hemophilia (FISH) tool and also from patients' clinical records. At the Bloemfontein and the Kimberley Haemophilia Treatment Centres respectively there were 57 and 12 adult patients who attended regularly. Forty adult patients were consecutively sampled from these two sites.

Results: The median age of the sample was 29.5 years (range 18 to 65). The majority were male (83%), unemployed (75%), receiving a disability grant (53%) and had never been married (65%). The majority of patients had haemophilia (73%), followed by hereditary haemorrhagic telangiectasia (HHT) (23%), Von Willebrand Disease (VWD) (2.5%) and Bernard-Soulier syndrome (BSS) (2.5%). The prevalence of both hepatitis C virus (HCV) and human immunodeficiency virus (HIV) was 10%. Twenty-three percent of patients reported bleeding more than three times per month. The lifetime prevalence of comorbid psychiatric illness in patients with IBDs was high - 43% had one or more psychiatric comorbidity. Major depressive disorder (MDD) was particularly common, with a lifetime prevalence of 30%. The prevalence of anxiety disorders and substance use disorders were both 15%, followed by post-traumatic stress disorder (PTSD), schizophrenia and suicidality, all present in 2.5% of the sample. The group of patients with severe haemophilia carried most of the burden of psychiatric illness (53%) when compared to mild/moderate haemophilia, HHT and the other IBDs. The total sample had greater impairment in HR-QoL in all domains, but anxiety/depression compared to normative data. The severe haemophilia

subgroup was the only subgroup with worse anxiety/depression when compared to normative data. The deficit in HR-QoL was more pronounced in all domains (except pain/discomfort) in the severe haemophilia group when compared to the mild/moderate group. Functional assessments showed that actions such as squatting, stair climbing, and running are the most severely affected domains of functionality. No significant risk factors could be established for the development of psychiatric illness, but patients with a higher level of education were less likely to develop a mental illness compared to patients with lower levels of education. Higher bleeding frequencies, as well as perceiving family as unsupportive were significant risk factors for impaired HR-QoL. Never having been married was associated with the development of psychiatric illness in the haemophilia subgroup.

Conclusion: Patients with IBDs in central South Africa have a high prevalence of psychiatric illnesses, especially MDD (30%), compared to the 9.8% in the general population of South Africa. No demographic or clinical characteristics were associated with the development of psychiatric illness but optimizing measures to limit the bleeding frequency and educating and supporting family members might improve functioning and HR-QoL. Screening for comorbid psychiatric illness in patients with IBDs is recommended.

Keywords

Haemorrhagic disorders, inherited blood coagulation disorders, haemophilia, hereditary haemorrhagic telangiectasia, mental disorders, prevalence, MINI, health-related quality of life, developing countries, depression.

Word count: 3314

LIST OF ABBREVIATIONS

ABR	Annual bleeding rate
ADLs	Activities of daily livings
AVM	Arteriovenous malformation
BDI	Beck depression inventory
BHTC	Bloemfontein Haemophilia Treatment Centre
BPA	Bypassing agent
BSS	Bernard-Soulier syndrome
CI	Confidence interval
DSM-5	Diagnostic & Statistical Manual of Mental Disorders, Fifth Edition
EQ-5D	Euroqol-5 Dimensions
EuroQoL	European Quality-of-Life Questionnaire
FISH	Functional Independence Score in Hemophilia
GDP	Gross domestic product
GP	Glycoprotein
HBV	Hepatitis B virus
HCV	Hepatitis C Virus
HHT	Hereditary Haemorrhagic Telangiectasia
HR-QoL	Health-Related Quality of Life
HIV	Human Immunodeficiency Virus
HTC	Haemophilia Treatment Centre
IBD	Inherited Bleeding Disorder
KHTC	Kimberley Haemophilia Treatment Centre
MDD	Major depressive disorder
MDE	Major depressive episode
MINI	Mini International Neuropsychiatric Interview
PCL-5	PTSD-Checklist 5
PHQ-9	Patient Health Questionnaire 9
PWH	People/Patient with Haemophilia
PTSD	Post-traumatic stress disorder
QALY	Quality-adjusted Life Year
SF-36	Short form 36
STAI-Y	State-Trait Anxiety Inventory
SPD	Storage pool disorders
UFS	University of the Free State
VAS	Visual analogue scale
VWD	Von Willebrand disease
VWF	Von Willebrand factor
YA-PWH	Young adult patient with haemophilia

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CHAPTER 1

LITERATURE REVIEW

1. INTRODUCTION

1.1 INHERITED BLEEDING DISORDERS

Normal blood flow is regulated by the synchronous action of procoagulant and anticoagulant factors that prevent abnormal bleeding on the one side and haemostasis on the other. In response to endothelial damage, haemostasis occurs in three rapid steps: (i) vasoconstriction, (ii) platelet plug formation (primary haemostasis), (iii) stabilization of the blood clot through fibrin cross-linking (secondary haemostasis), and afterward, dissolution of the clot by the fibrinolytic system.[1] Although inherited bleeding disorders (IBDs) are rather uncommon, patients who are affected by them are often faced with unique health-related problems and treatment challenges which necessitates treatment at a tertiary healthcare facility such as a haemophilia treatment centre (HTC). IBDs encompass a group of disorders with multiple different aetiologies that lead to a tendency to bleed abnormally. They range from coagulation disorders (such as haemophilia A, haemophilia B and Von Willebrand Disease, abbreviated as VWD), to disorders of primary haemostasis, including vessel wall abnormalities (such as hereditary haemorrhagic telangiectasia (HHT)) and platelet functional disorders (such as Bernard-Soulier syndrome (BSS)).[2]

Haemophilia A affects 1 in 5 000 males worldwide and it is caused by insufficient levels of factor VIII as a result of many different defects in the X-linked factor VIII gene. Haemophilia B results from insufficient levels of factor IX as a result of mutations in the X-linked factor IX gene and affects about 1 in 25 000 people.[2] The diagnosis is dependent on a family history of bleeding disorders inherited in an X-linked pattern, clinical examination of joints, a blood work-up and radiological assessment of the musculoskeletal system. Coagulation disorders are characterized by soft tissue bleeds as well as haemarthroses affecting the knee, elbow, ankle and hip joints most commonly. Bleeding into joints is painful and repeated bleeding leads to synovial damage, hypertrophy and neovascularization. Left untreated, joint dysfunction with pain will ensue from the damage to cartilage and articular surfaces.[1,2] Haemophilia should ideally be confirmed by genotyping. Due to resource challenges, inversion intron 22 testing in haemophilia A is the only genotyping done in this centre, as it is most commonly associated with severe haemophilia A. Haemophilia severity depends on the circulating level of the procoagulant factor with mild disease correlating with

6 - 40%, moderate with 1 - 5% and severe < 1% of normal circulating factor.[3] South African blood products have always come from voluntary nonremunerated, predominantly repeat donors along with universal serological testing for HIV-1 and 2, hepatitis C, and syphilis combined with HIV p24 and hepatitis B surface antigen testing as these became available until 1999. From 1999 nucleic acid testing was introduced. The only South African haemophilia patients who contracted HIV from clotting factor products were those who used unsafe imported plasma products. In 1985 the then Natal Bioproducts Institute (now the National Bioproducts Institute) introduced solvent detergent processing of plasma products. There has been no documented transmission of HIV, hepatitis B or hepatitis C from their products since then.[2,4] The current standard of care in PWH is the prevention of bleeds by raising the deficient clotting factor level prophylactically with intravenous infusion of recombinant or plasma-derived factor, so as to reduce hospitalizations and complications. In low-income countries, the use of prophylactic regimens is limited by the high cost associated with factor replacement and patients often use infused factor concentrates on an on-demand basis only.[1] This can be done as home therapy[5], provided the family is capable[2], or at decentralized clinics. Perhaps the most feared treatment-related complication of haemophilia is the development of inhibitors - antibodies that develop in response to infused factor concentrates, rendering them ineffective. They occur in approximately 10-15% of patients with haemophilia A and 1-3% of haemophilia B patients.[6] The treatment of persons with haemophilia (PWHs) with inhibitors include the use of bypassing agents (BPAs) for acute bleeds and eradication of inhibitors.[1] Relatively recently enthusiasm has arisen over the possibility of a cure for haemophilia A and B involving treatment with gene therapy.

The most common coagulation disorder (affecting around 1.3% of people in some populations) is VWD,[7,8] even though the prevalence in South Africa currently appears to be far lower. This condition arises from insufficient levels or functional defects of Von Willebrand factor (VWF) due to defects of the VWF gene on chromosome 12. VWF acts by facilitating platelet aggregation by binding to sub-endothelial collagen and platelet glycoprotein Ib (GPIb) receptors, prolonging the half-life of FVIII and anchoring platelets at sites of injury. Larger VWF molecules facilitate better anchoring of platelets. VWD can thus present with mucocutaneous bleeding, such as epistaxis and menorrhagia, easy bruising and excessive bleeding after tooth extraction, depending on the type and the severity of defects. Patients often have a family history of bleeding disorders inherited in an autosomal dominant manner. VWD is subtyped into six subgroups dependent on the type of defect and the type of dysfunction of the VWF. Treatment consists of normalization of VWF and FVIII before surgical procedures, usually achieved with desmopressin (DDAVP) or

exogenous VWF concentrate infusion. Other rarer bleeding diatheses include FV, FVII, FX, FXI, FXIII and fibrinogen, as well as protease inhibitor deficiencies.[1]

Platelets are responsible for primary haemostasis through four successive steps: (i) platelet adhesion at the injury site, promoted by the platelet GP1b, which stimulates (ii) granule release, leading to a conformational change of the GPIIb/IIIa receptor, with the fibrinogen forming cross-linkages between platelets, leading to (iii) platelet aggregation. The activated platelets from the platelet plug expose phospholipids, providing a (iv) procoagulant surface and the formation of a secondary clot.[9] Therefore, even in the presence of normal platelet counts, patients with platelet dysfunction – such as Bernard-Soulier syndrome (BSS) - can present with platelet-type bleeding which can manifest in symptoms ranging from recurrent mucocutaneous bleeds from the gastroesophageal and the genitourinary tract to excessive postoperative bleeding.[2] It is a rare disorder (1:1 000 000) originating from a defect in the platelet GPIb-IX-V complex due to a mutation that is inherited in an autosomal recessive pattern. Treatment is supportive and antifibrinolytics, e.g. tranexamic acid, are used as adjuncts. Desmopressin is effective in storage pool disorders, which is a rare inherited platelet disorder, caused by dense granule deficiency, and might be beneficial in BSS.[10] Other inherited platelet disorders are beyond the scope of this manuscript, but include Glanzmann thrombasthenia, other secretory disorders, May-Hegglin anomaly and Scott syndrome.[1]

HHT is somewhat different from other IBDs as bleeding results from abnormalities in the blood vessel wall structure, rather than defective coagulation and, thus, the screening tests are usually normal. It arises from inherited mutations in the endothelial cell genes resulting in aberrant vascular modelling and the formation of aneurysms, as well as arteriovenous malformations (AVMs). It is inherited in an autosomal dominant fashion and affects about 1 in 5 000–10 000 people. Mutations in at least three different loci can cause HHT. It presents with recurrent mucocutaneous bleeds and iron-deficiency anaemia. Almost all patients (90-95%) will develop epistaxis by adulthood and up to 25% will present with gastrointestinal bleeding. The mainstay of treatment consists of iron replacement and screening for large and dangerous arteriovenous malformations (AVMs). AVMs are found in the lungs of 40% of patients, and the brains of up to 20% of patients. Liver AVMs are common, but rarely cause symptoms.[1,2]

1.2 PSYCHIATRIC COMORBIDITIES AND QUALITY OF LIFE IN CHRONIC DISEASES

There is a large body of evidence that demonstrates the psychosocial impact of chronic

diseases. Diabetes mellitus has been associated with psychiatric/psychological problems such as depression, anxiety[11-14] and distress.[15] Rheumatoid arthritis has also been strongly associated with the development of depression.[16] In addition, comorbid psychiatric illness can affect the control, adherence and the general health of patients suffering from chronic illnesses such as diabetes, rheumatoid arthritis, and asthma[16,17-21]. Evidence reveal that early treatment of comorbid psychiatric illness can greatly impact the course of chronic diseases.[17] Although IBDs are not polygenic like most common chronic diseases, they are chronic in nature and one would expect a similar psychosocial burden in light of the regular follow-up needed, chronic use of medication and health services, discrimination, stigma, health concerns and other factors.

1.3 PSYCHIATRIC COMORBIDITIES AND QUALITY OF LIFE IN BLEEDING DISORDERS

Outcome measures used in haemophilia trials, and medicine as a whole, now stretch beyond laboratory evaluations and clinical outcomes to include outcomes such as functionality and quality of living.[22] When conducting interventional trials, the National Institute for Clinical Excellence (NICE) recommends measuring health benefits in terms of the Quality-Adjusted Life Years (QALY's) gained.[23] A systematic review by Boehlen *et al*[22] determined that the Short Form Survey 36 (SF-36) are the most widely used generic assessment tool in haemophilia studies and that the NICE guidelines recommend the use of the EQ-5D questionnaire. Disease-specific QoL rating tools, such as the Haemo-QoL, have also been validated for use in haemophilia patients.[24] The adult haemophilia-specific (HAEMO-QoL-A) tool has demonstrated good internal consistency[25] and has the added benefit of assessing outcomes that are feasible and valuable to PWH, specifically. Generic measures, on the other hand, have the added benefit of comparing HR-QoL between different diseases and measuring disease progression over time.[22] The drawback of generic HR-QoL tools is that they do not differentiate whether changes in HR-QoL are due to clinical, economic or social factors.[23,26]

Research on the psychosocial impact of IBDs are limited, but this topic is receiving increasing attention due to higher standards of care. Available studies demonstrate impaired health-related quality-of-life (HR-QoL),[27-36] high levels of distress, social[31,34] and psychological problems,[27,35] pain, physical functioning,[35] as well as exposure to stigmatisation and discrimination[31,37,38] (see Table 1 for a list of recent published articles on the psychosocial aspects of IBDs).

Factors associated with the HR-QoL of persons with haemophilia (PWHs) specifically,

include: bleeding frequency,[39] disease severity,[32,34,36] orthopaedic status,[34,35] pain,[32,35,40] negative thoughts about pain,[40] limitations in lifestyle and activities of daily living (ADLs),[32-35] comorbid disease,[41] lack of social support, and unemployment.[42] Age has been associated both positively and negatively with HR-QoL.[36,41] Furthermore, severe haemophilia is associated with higher rates of unemployment, probably partly due to early retirement[43] and partly due to poor functioning.[27,34] Seventy-six to eighty percent of PWH from the Hemophilia Experiences, Results and Opportunities (HERO) study[21,27,44] reported a negative impact on employment. Drake *et al*.[45] reported similar rates of graduation from school between PWH and healthy subjects, contrasting results of similar studies done ten years earlier (when prophylactic treatment regimens were not yet prescribed), and holistic care was not yet provided via HTCs. The rate of self-reported psychological or psychiatric comorbidities in young adult patients (18-30 years of age) with haemophilia (YA-PWHs) is 43%, of which 26% are directly ascribed to haemophilia.[44] Thirty-two to 37% of PWHs screened positively for depression and/or anxiety, with unemployment, lack of social support, as well as impaired functioning being significant risk factors. Anxiety is often related to financial uncertainty.[31,42] Depression has been associated with comorbid blood-borne infections in the elderly population (>65 years of age),[35] but not with a younger, HIV infected cohort (mean age of 30.6 years) of men with haemophilia, where BDI, as well as STAI-Y scores, paralleled those of a healthy control group.[46] Further screening also revealed that 9% of patients struggled with drug and alcohol problems, when these were used to alleviate pain.[31] A PWH is prone to have lower self-esteem compared to healthy subjects and this, as noted by Canclini *et al*.[47] could further the risk of developing anxiety and/or depression. Comorbid depression, in turn, is associated with a poorer health-related quality of life (HR-QoL).[35,48] Predictors of a better quality of life are the personality traits of ‘agreeableness' and ‘openness'[48] and participation in sports activities.[49]

Studies have examined the efficacy of different treatment regimens in order to best improve HR-QoL. Preventing bleeds, and thus pain and impairment, early on, is the rationale behind prophylactic treatment regimens. A systematic review, conducted by Oladapo *et al*.[50] in 2015, reported that three out of the four available studies showed a significant improvement in perceived HR-QoL as measured by a visual analogue scale (EQ-5D$_{VAS}$). However, only one out of the four studies demonstrated significant improvement in functioning as measured by each of the 5 domains of quality of life (the EQ-5D$_{domains}$).[51-57] (The design of measuring tools are described in chapter 2). A report from a 2018 prospective, non-interventional study (NIS) by Mahlangu *et al*.[58] and Kruse-Jarres *et al*.[59] demonstrated that, compared to episodic treatment regimens, prophylactic regimens do decrease annual bleeding rates (ABRs) in PWHs type A (PwHAs), without inhibitors (1.9; [95% confidence

interval: 0.0–8.2] vs 31.1 [19.8–51.6]) and in PwHAs with inhibitors (16.8 [10.1-36.2] vs 21.7 [14.1-40.4]). This is in line with prior studies reporting improvement in HR-QoL in PWHs on prophylactic regimens and is ascribed to the improvement in perception of general health,[51] pain, physical activities[52,53] and absenteeism.[56,57] Although prophylactic treatment regimens decrease median ABRs, bleeding remains a problem, especially in persons with inhibitors (PWIs), necessitating better treatment strategies.

HHT is a disorder that can be very disruptive due to frequent nose bleeds, chronic tiredness and regular follow-up for haematinic treatment, yet the research done on the psychosocial impact of HHT is limited compared to other chronic diseases. Zarrabeitia *et al*.[60] found comparable impairment in quality of life between HHT and other chronic diseases. Excessive epistaxis seems to be a large contributor to impaired quality of living,[60-64] especially in elderly patients,[65] causing higher levels of anxiety/depression (44%) and pain/discomfort (48%). A large cross-sectional study by Chaturvedi *et al*.[66] found a prevalence rate of 88.7% for depression and 28% for PTSD resulting from traumatic bleeding episodes. HHT can present with symptoms that mimic depression, i.e. fatigue and headache related to anaemia and hypoxia; and sleeping abnormalities related to the stress and uncertainty HHT carries, posing a diagnostic challenge. Furthermore, sustaining a stroke is a notable risk in patients with HHT, either resulting from ruptured brain AVMs, resulting in haemorrhage, or ischaemic strokes caused by emboli originating from pulmonary AVMs,[67] which in turn is a known risk factor for the development of depression.[68,69] It is therefore imperative to differentiate symptoms of HHT from mood and anxiety disorders so as to ensure appropriate treatment. Symptoms of a major depressive episode (MDE) will have additional affective and cognitive symptoms, including irritability, excessive worry or anxiety, feelings of hopelessness or worthlessness, excessive guilt or self-criticism, poor concentration, indecisiveness, and suicidality.[70] In most countries, including South Africa, health care services for patients with IBDs are delivered by multi-disciplinary teams of professionals through the networks of HTCs. Forsyth *et al*.[71] reported a large-scale psycho-social study, involving PWHs from 10 different countries. They found that they were mostly treated by haematologists (89%), followed by haemophilia nurses, physiotherapists, general practitioners, social workers, counsellors or psychologists, and complementary therapists, using techniques such as acupuncture.

1.4 THE EFFECT OF PSYCHIATRIC MEDICATION ON THE HAEMOSTATIC SYSTEM

Lastly, a brief discussion on the effects of psychopharmacological agents and their effect on the haematological system will now follow. Almost all psychoneuroleptics carry a risk of

haematological side-effects. Antidepressants, especially selective serotonin reuptake inhibitors (SSRIs), have been associated with increased upper gastro-intestinal bleeding in different study designs,[72-74] although two other studies failed to demonstrate this association.[75,76] Other adverse effects of SSRIs include increased hospitalization[77] and need for transfusion of blood products during orthopaedic surgery.[78] Not only do the SRIs work at the neuronal synaptic level, but also at the platelet level, where serotonin (5-HT) is stored within platelet granules which are released upon platelet aggregation (caused by endothelial damage). Plasma 5-HT exerts a haemostatic effect by causing vasoconstriction, binding to 5-HT2A receptors expressed on platelet membranes, potentiating and facilitating platelet aggregation, enhancing platelet activation, and ultimately causing a change in platelet shape, priming the platelet surface for interactions with clotting factors.[79] SSRIs, especially fluoxetine, sertraline, and paroxetine, have been associated with prevention of 5-HT reuptake by platelets - leading to vasoconstriction of damaged coronary arteries,[80] interference of platelet aggregation[81] and abnormal bleeding.[82] No guidelines for the use of antidepressants in patients with bleeding disorders exist, but Demian and Guido[83] proposed that due to the decrease in platelet aggregation and functioning, non-SSRI antidepressant medication is advised in patients with known VWD and haemophilia. Patients on an SSRI, should be closely monitored and switched to a non-SSRI compound should bleeding occur. Any patient presenting with abnormal bleeding after the initiation of an SSRI should be investigated for a bleeding disorder, especially platelet function disorders.

1.5 PREVIOUS STUDIES OF QUALITY OF LIFE AND PSYCHIATRIC COMORBITIES IN CENTRAL SOUTH AFRICA

Between 2004 and 2007 there were 17 haemophilia treatment Centres (HTCs) in South Africa, of which 11 were fully functional and where 2205 patients with bleeding disorders were cared for. Mahlangu[84] reported that the most common bleeding disorder was haemophilia A (59%) followed by VWD (21%), haemophilia B (12%) and other bleeding diatheses (7.8%). Sixty-two percent were classified as severe, 18.6% as moderate and 19.4% as mild haemophilia; and 8.6% were affected by inhibitors. Forty percent of patients have been on home therapy. The health care workforce involved with patient care include doctors, nurses, physiotherapists, geneticists, dentists, social workers, and other staff. The expected number of PWHs in South Africa is more than five thousand if the population is expected to be around 50 million. The two HTCs in the Free State and Northern Cape provinces serve a population of approximately 4 million people,[85] thus the expected number of patients with haemophilia in central South Africa alone is around 400. To our knowledge, there is limited published data available on the prevalence of psychiatric comorbidities in

patients with IBDs in South Africa. Most of the available studies use screening tools for depression, anxiety, substance use disorders or other conditions such as PTSD. An unpublished study,[86] conducted in 2011 at the Bloemfontein Haemophilia Treatment Centre (BHTC) and the Kimberley Haemophilia Treatment Centre (KHTC), measured health-related quality of life in 14 adults with any form of haemophilia with the aid of the A36 Haemophilia-QoL® questionnaire. This study demonstrated an overall good quality of life in this sample, which had a median age of 22.5 years, but found that 'emotional functioning' and 'mental health' were the main factors affecting the quality of life in those scoring lower. 'Physical health' and 'daily activities' were the other important domains affecting the quality of life in study participants.

Another unpublished study,[87] similar to this study, was conducted at the BHTC in 2005. It included 30 adult patients suffering from haemophilia. At the time 80% were mentally healthy and 10% had major depression, with 73% not regarding haemophilia as a health stressor. Twenty-two (73%) of the respondents had had a major depressive episode (MDE), of which nine reported more than five MDEs. Thirteen had contemplated suicide, but no attempts were made. Seven had previously used antidepressants. Seventy percent indicated that they would have liked psychological intervention as part of their management. Despite having haemophilia, 83% had adequate levels of functioning.

2. IDENTIFICATION OF RESEARCH GAPS

International data on the psychosocial impact of IBDs, like haemophilia, are limited[26] and even more so in South Africa. Furthermore, even though unpublished data on the quality of life and psychiatric comorbidities of patients with haemophilia at the Bloemfontein and Kimberley HTCs are available from prior reports, the profile of patients and delivery of care has changed in the past twelve years. To our knowledge, this was one of the first studies investigating the prevalence of comorbid psychiatric illness and the quality of life in patients with IBDs in South Africa, using an objective, structured interview, as well as the potential risk factors.

3. AIM

To investigate the prevalence of comorbid psychiatric conditions and HR-QoL, and secondly, to evaluate possible factors that contribute to the development of psychiatric conditions and impaired HR-QoL in patients with IBDs visiting the BHTC and KHTC, South Africa, from 5 February 2018 to 28 February 2019.

4. OBJECTIVES

The objective was to evaluate:

1. The prevalence of psychiatric illness in patients with IBDs with the use of the MINI questionnaire
2. The HR-QoL in patients with IBDs using the EQ-5D questionnaire
3. The possible factors that contribute to the development of psychiatric conditions and impaired HR-QoL. These factors include demographic and clinical factors, as well as level of functioning. This data was obtained from patients' files, a standardized questionnaire and the FISH tool.

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TABLE 1 Summary of recent published literature on the psychosocial aspects of inherited bleeding disorders

Authors	Year	Disorder	Design	n (control)	Instrument	Impaired QoL[a]	Prevalence of mental illness (%)
Miners et al.[4]	1999	Haemophilia	Case-control	166 (1466)	EQ-5D SF-36	Yes*** Mixed	Depression/ anxiety (33)
Molho et al.[42]	2000	Haemophilia	Cross-sectional	116	SF-36	Yes	-
Solovieva[16]	2001	Haemophilia VWD FXIII def.	Cohort	150	SF-36	Yes*	-
Royal et al.[43]	2002	Haemophilia	Cohort	903	SF-36	Yes**	-
Canclini et al.[22]	2003	Haemophilia	Case-control	60 (78)	BDI[b]	-	Depression (8)
Beeton et al.[44]	2005	Haemophilia	Qualitative	11			-
Talaulikar et al.[5]	2006	Haemophilia VWD	Cross-sectional	30	SF-36	No	-
Barlow et al.[12]	2007	Haemophilia VWD	Descriptive, qualitative	9	[c]	-	Depression/ anxiety
Barlow et al.[6]	2007	Haemophilia VWD	Survey	309	[d]	-	Depression (32) Substance use (9)
Plug et al.[7]	2008	Haemophilia	Cross-sectional	1066	SF-36	Yes	-
Hartl et al.[18]	2008	Haemophilia	Case-control	53 (104)	SF-36	Mixed	-
Elander et al.[15]	2009	Haemophilia	Cross-sectional	209	SF-36	Yes	-
Siboni et al.[8]	2009	Haemophilia	Case-control	39 (43)	GDS		Depression*
Stieltjies et al.[9]	2009	Haemophilia	Survey	50	SF-36	Yes	-
Iannone et al.[17]	2012	Haemophilia	Cross-sectional	41	PHQ-9	-	Depression (37)
Kim et al.[23]	2013	Haemophilia	Cross-sectional	53	BDI		Depression
Carvalhosa et al.[18]	2014	Haemophilia	Cohort	71	WHOQOL-BREF SF-36	Yes Yes	- -
Forsyth et al.[19]	2015	Haemophilia	Cross-sectional	675	EQ-5D	Yes	-
Barry et al.[13]	2015	Haemophilia VWD	Cross-sectional	152	PHQ-2		Depression (10)

Authors	Year	Disorder	Design	n (control)	Instrument	Impaired QoL[a]	Prevalence of mental illness (%)
Caturvedi et al.[26]	2017	HHT	Cross-sectional	185	BDI-II PCL-5	-	Depression (88.7) PTSD (28.1)
Zarrabeitia et al.[25]	2017	HHT	Cross-sectional	187	EQ-5D	Yes	-
Gupta et al.[45]	2019	Haemophilia	Cross-sectional	282	EQ-5D	Yes	-

[a]Referring to overall impairment
[b]Modified version
[c]Semi-structured interview
[d]Non-standardized questionnaire
*<0.05, **<0.01, ***<0.001, used to measure strength of association where control groups were included or where results were compared to normative values in non-case-control studies.
BDI, Beck depression inventory; EQ-5D, FXIII def., Factor XIII deficiency; GDS, Geriatric depression scale; HHT, hereditary haemorrhagic telangiectasia; PCL-5, PTSD checklist 5; PHQ-9, Patient Health Questionnaire 9; PTSD, post-traumatic stress disorder; SF-36, Short form – 36; STAI-Y, State-trait Anxiety Inventory; VWD, Von Willebrand disease; WHOQOL-BREF, World Health Organisation quality of life brief version.

CHAPTER 2

PREVALENCE OF COMORBID PSYCHIATRIC ILLNESS AND QUALITY OF LIFE IN ADULTS WITH INHERITED BLEEDING DISORDERS IN CENTRAL SOUTH AFRICA

The article was prepared according to the journal submission guidelines for the *Haemophilia: The official journal of the World Federation of Hemophilia* (cf. Appendix O).

Title page

Prevalence of comorbid psychiatric illness and quality of life in adults with inherited bleeding disorders in central South Africa

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Running title
PREVALENCE OF MENTAL ILLNESS IN BLEEDING DISORDERS

Keywords
Haemorrhagic disorders, mental disorders, prevalence, MINI, health-related quality of life, developing countries, South Africa

Word count: 3362

Abstract

Introduction: Inherited bleeding disorders (IBDs) appear to be relatively uncommon, but they pose unique health-related challenges. Due to their chronic nature, one would expect similar psychosocial problems as seen in other chronic diseases.

Aim: The aim of this study was to evaluate the prevalence of psychiatric comorbidities in a population with IBDs, and secondly, to evaluate for risk factors for mental illness and impaired health-related quality-of-life (HR-QoL).

Methods: We conducted a cross-sectional, observational study in two Haemophilia Treatment Centres (HTCs) in central South Africa by interviewing 40 adult patients with IBDs on their usual follow up dates. We collected demographic data using a standardized questionnaire and clinical data with the aid of the MINI, EQ-5D and FISH measuring instruments and by accessing patient files.

Results: The median age of the sample was 29.5 years (range 18 to 65). The majority were male (83%), unemployed (75%), receiving a disability grant (53%) and had never been married (65%). The majority had haemophilia (73%), followed by hereditary haemorrhagic telangiectasia (HHT) (23%), Von Willebrand disease (VWD) (2.5%) and Bernard-Soulier syndrome (BSS) (2.5%). In our sample 43% had one or more psychiatric disorders and the lifetime prevalence

Abstract

of major depressive disorder (MDD) was 30%. Bleeding frequency and family support were significant predictors of HR-QoL, most notably in the domains of self-care, usual activities and pain/discomfort.

Conclusion: The prevalence of psychiatric disorders is high in the population suffering from IBDs in central South Africa and routine screening is justified. HR-QoL might improve by limiting bleeding frequency and by psycho-educating families.

Keywords

Haemorrhagic disorders, Mental disorders, Prevalence, MINI, Health-related Quality of life, Developing countries, Hereditary haemorrhagic telangiectasia

Word count: 254 words

Main body of text

1. INTRODUCTION

Inherited bleeding disorders (IBDs) are a group of disorders with varying degrees of lifelong, abnormal bleeding events.[1] The literature on the psychosocial impact of IBDs are limited, but this topic is receiving increasing attention due to higher standards of care[2] (see Table 1). Available studies demonstrate impaired health-related quality-of-life (HR-QoL),[2-13] high levels of distress, social[6,9] and psychological problems,[2,10] pain, physical functioning,[10] as well as exposure to stigmatisation and discrimination.[6,12,13]

Table 1

Factors associated with the HR-QoL of persons with haemophilia (PWHs), specifically, include bleeding frequency,[14] disease severity,[4,5,7] orthopaedic status,[7,8] pain,[5,8,15] negative thoughts about pain,[15] limitations in lifestyle and activities of daily living (ADLs),[5,7-9] comorbid disease,[16] lack of social support and unemployment,[17] as well as financial concern.[18] Age has been associated both positively and negatively with HR-QoL.[4,16] Severe haemophilia is associated with higher rates of unemployment, probably partly due to early retirement[18] and partly due to poor functioning.[2,7] The Hemophilia Experiences, Results and Opportunities (HERO) study[19,20] reported that employment was affected negatively in 76-80% of PWHs. The rate of self-reported psychological or psychiatric comorbidities in young adult patients (18-30 years old) with haemophilia (YA-PWH) is 43%, of which 26% are directly ascribed to haemophilia.[20] Thirty-two to thirty-seven percent of PWHs screened positively for depression and/or anxiety, with unemployment, lack of social support, as well as

impaired functioning being significant risk factors.[6] Anxiety is often related to financial uncertainty.[17] Depression has been associated with comorbid blood-borne infections in the elderly population (>65 years of age),[8] but not with a younger, HIV infected cohort (mean age of 30.6 years) of men with haemophilia.[21] Barlow *et al*.[6] reported that up to nine percent of PWHs struggled with drug and alcohol problems, often when these are used in an attempt to alleviate pain. PWHs are prone to have lower self-esteem compared to healthy subjects and this, as noted by Canclini *et al*.[22] could increase the risk of developing anxiety and/or depression. Comorbid depression, in turn, is associated with a poorer HR-QoL.[8,23] Predictors of a better quality of living are the personality traits of 'agreeableness' and 'openness'[23] and participation in sports activities.[24]

Zarrabeitia *et al*.[25] demonstrated that severe epistaxis in HHT patients cause impairment in quality of life with levels comparable to other chronic diseases. A large cross-sectional study by Chaturvedi *et al*.[26] found a prevalence rate of 88.7% for depression and 28% for PTSD as a result of traumatic bleeding episodes related to HHT.

In 2007 there were 11 functioning haemophilia treatment Centres (HTCs) in South Africa, where 2205 patients with bleeding disorders were cared for.[27] Patients are treated by a multi-professional team that rarely includes psychological services. The two HTCs in the Free State and Northern Cape provinces serve a population of about 4 million people,[28] thus the expected number of patients with haemophilia in central South Africa alone is around 400.

To our knowledge, there are no published studies investigating the mental health of patients with IBDs in South Africa and we aimed to establish the prevalence of psychiatric comorbidity and, secondly, we assessed risk factors associated with psychiatric comorbidity and HR-QoL.

2. MATERIALS AND METHODS

2.1 Sample and method

This cross-sectional, observational study was conducted at two HTCs in central South Africa from 5 February 2018 to 28 February 2019. The Bloemfontein Haemophilia Treatment Centre (BHTC) serves the population of the Free State Province and the Kimberley Haemophilia Treatment Centre (KHTC) serves the population of the Northern Cape Province in central South Africa. There were 208 patients on record at the BHTC, of which 57 attended at least twice a year, and 12 at the KHTC. After ethics committee approval (UFS-HSD2017/1552), participants were recruited using consecutive sampling and data were captured on anonymised data forms. Patients eligible for inclusion were persons with an IBD, who were 18 years or older, and who gave informed consent. Patients with acquired bleeding disorders were excluded.

2.2 Measures

2.2.1 Standardized questionnaire

A standardized face-to-face questionnaire was used to gather demographic data as reported by patients. With regards to assessing the level of education, patients were categorized as (i) no education, (ii) special education (including inclusive education or schooling at a special needs facility), (iii) general education (grade R to grade 9 - in most instances referring to age 6 to 15 years), (iv) further education (grade 10 to 12 - ages 16 to 18 years) and (v) higher education (including certificates and any other higher qualifications).

2.2.2 Clinical data

Clinical data concerning the type of IBD, medical comorbidities and inhibitor status of PWHs, were obtained from patient files.

2.2.3 Psychiatric illness

The Mini International Neuropsychiatric Interview - M.I.N.I. 7.0.2 (8/8/16 version) - is a brief structured diagnostic tool validated for research surveys[29-31] which is available in English. It screens for the most common psychiatric conditions and consists of ‘yes’ or ‘no’ questions. Permission was granted for the reproduction of 40 questionnaires in the form of hard copies (Appendix A).

2.2.4 Health-related quality of life

The EQ-5D-5L questionnaire was used to assess the HR-QoL of participants.[32-35] This tool was used in stead of a disease specific one as it enables comparison between different diseases and is therefore recommended by the NICE guidelines.[23] It is a self-rated questionnaire that assesses five domains of functioning: (i) mobility, (ii) self-care, (iii) usual activities, (iv) pain or discomfort, and (v) anxiety or depression. The scoring in each domain ranged from 1 to 5, 5 being the worst impairment and a self-rated visual analogue scale scored from 0 to 100 (where 100 would the best imaginable state of health). The original tool had a three-level severity score (EQ-5D-3L), but this was changed to a 5-level one (EQ-5D-5L) to increase the sensitivity and limit the ceiling effect.[34] Permission to use the English, Afrikaans, and Sesotho versions of the questionnaire was granted by the EuroQol group (Registration ID: 22427).

2.2.5 Functional status

The level of functioning of haemophilia patients was measured using the FISH (Functional Independence Score in Hemophilia) score. It is a performance-based tool validated to assess the functional ability of patients with haemophilia.[36,37] It assesses the level of self-care, the ability to transfer, as well as locomotion, by observation. Patients are scored on a scale from 1 (being the worst level of functioning) through 4.

Questions from the MINI and standardized questionnaires were read out to patients, assisted by an interpreter when needed. Patients rated themselves on

the EQ-5D. A co-author, a consultant in the Department of Haematology and Cell Biology, assisted in the scoring of the FISH inventory. The entire session lasted 30-90 minutes per patient.

2.2.6 Analysis

Results were summarized by frequencies and percentages (categorical variables) and means and standard deviations or percentiles (numerical variables). 95% confidence intervals (CIs) were calculated for main outcomes. Associations between categorical variables were assessed using contingency tables with chi-squared or Fisher's exact tests (depending on the sparseness of cells). Comparisons of subgroups regarding numerical variables were done using non-parametric Mann-Whitney or Kruskall- Wallis tests due to skewness of data.

3. RESULTS

3.1 Study population

Forty patients with bleeding disorders were enrolled in the study, 31 from the BHTC and nine from the KHTC (Table 2). The median age was 29.5 years (range 18-65). Eighty-three percent of patients were male. Three-quarters of patients were unemployed and almost half, 53% of patients, were receiving government disability grants. Eighty percent held a general or further education and 65% of the sample never married. Most patients had haemophilia (73%) (Table 3).

Almost one quarter, 23%, of patients reported a bleeding frequency of more than three times per month. Almost half (48%) of patients had missed one or more appointments in the preceding year, the most common reasons being a lack of available transport and/or personal responsibilities.

3.2 Outcome measures

3.2.1 Psychiatric illness

Forty-three percent of the sample fulfilled DSM-5 criteria for mental disorders as measured by the MINI questionnaire (Table 4), of which 25% had more than one diagnosis. A total of 12 patients fulfilled criteria for major depressive disorder (MDD) - three with a current episode (MDE) and 11 with previous MDEs. Two of the three currently depressed patients have also had at least one previous depressive episode. In total, six of the 12 patients had recurrent depression. Fifteen percent of the sample had an anxiety disorder (one half of these patients had a generalized anxiety disorder, and the other half had social anxiety disorder). The prevalence of substance use disorders was 15%, with alcohol and cannabis being the only two reported substances.

Regarding the haemophilia subgroup, 12 of the 29 patients fulfilled criteria for any mental disorder (41%), of which 24% fulfilled criteria for MDD, 17% for a substance use disorder, and 10% for an anxiety disorder. The severe

Table 4 &
Figure 1

haemophilia group had the highest prevalence of psychiatric illness (53%) and MDD (50%) when compared to the other groups (Figure 1).

3.2.2 Health-related quality of life

The results of the EQ5D questionnaire are summarized in Table 5. The median self-reported wellbeing on the EQ-5D$_{VAS}$ was 75 for the total sample.

3.2.3 Functional status

The results of the FISH scores are summarized in Table 6. The domains of functioning mostly impaired in PWHs was that of squatting and running. Sixty-two percent of PWHs were unable to squat at all while 45% were unable to run.

Table 5 & 6

3.2.4 Associations within the total sample

Psychiatric illness

There was no association between demographic or clinical characteristics and psychiatric illness, although the risk was lower in patients with higher educational qualifications (certificate and any other higher education) compared to those with a general (Gr. R – 9) or further (Gr. 10-12) educational qualification (13% vs 36% and 57%; *P* = 0.08). Patients with HIV were at an increased risk of developing depression compared to HIV non-reactive patients (75% vs 25%; *P* = 0.08). The

risk of depression was greater in patients receiving a disability grant, (43% vs 16%; *P* = 0.06).

Health-Related Quality of Life

When the EQ-5D scores were dichotomized between 'no problem' and 'any problem' (ranging from slight to severe/extreme), 70% of the total sample had problems with mobility, 18% with self-care, 38% with usual activities, 83% had pain or discomfort and 43% had anxiety or depression. Population norms were not available for South Africa and the patients' performance was therefore compared to the normative values of a country with a comparable GDP/capita, as advised by the questionnaire developers.[38,39] All the patients scored significantly lower than a healthy population in the domains of mobility and pain/discomfort (Table 7). Patients with a bleeding frequency of less than once per month reported significantly less problems in the domains of self-care and usual activities (0% and 13%, respectively) when compared to patients with a bleeding frequency of one to three times per month (25% and 56%, respectively, *P* = 0.048) and especially more than three times per month (33% and 44%, respectively, *P* = 0.042). Patients who perceived family and friends as supportive reported less impairment in the domain of pain/discomfort compared to patients who did not (80% vs 100%, respectively; *P* = 0.02). Neither age, ethnicity, employment status, family support nor HIV status was associated with HR-QoL.

Table 7

3.2.5 Associations in the haemophilia subgroup

Psychiatric illness

The risk of PWHs developing psychiatric illnesses was significantly lower in married patients than single or widowed patients (0% vs 52% and 100%; *P* = 0.02). Other demographic characteristics including age, education, race, employment status, and family history were not associated with the development of mental illness. None of the clinical characteristics were associated with the development of any mental disorder, although a bleeding frequency of more than three times per month were trending towards significance over one to three times per month and less than once a month (100% vs 23% and 50%; *P* = 0.08). This trend repeated when analyzing risks for the development of MDD in the haemophilia subgroup (50% vs 31% and 14%; *P* = 0.08).

Health-related quality of life

PWHs with a general education reported more problems with self-care than those with a further or a higher education (50% vs 6% and 0%; *P* = 0.04). Anxiety/depression was more prevalent in patients receiving on-demand treatment than prophylaxis (61% vs 27%; *P* = 0.13), treated at clinic than at home (67% vs 46%; *P* = 0.6), with higher bleeding frequencies than lower (100% if >3/month vs 38% if 1-3 times/month and 50% if less than once/month; *P* = 0.34), having a family history (50% vs 33%), with poor support (100% vs 42%), not feeling understood (100% vs 44%), having HIV (100% vs 48%) and having

medical comorbidities (67% vs 40%). None of these variables were significant predictors of high anxiety/depression levels.

Functional status

Age, bleeding frequency, treatment setting, comorbid illness and family support were all associated with functional outcomes. Patients above 65 years scored lower in the domains of dressing compared to patients aged 35 to 64 years and 18 to 34 years (Median FISH score: 1, 4 and 4; *P* = 0.03). Patients of younger age scored higher than the older two groups in the domain of squatting (2, 1 and 1, respectively; *P* = 0.047), but the middle age group scored lower than the other two age groups in the domain of stair climbing (3, 2 and 3; *P* = 0.03). Patients with a bleeding frequency of less than once a month scored lower than those with a bleeding frequency ranging from one to three times a month and more than three times a month in the domains of chair transfer (2, 4 and 4, respectively; *P* = 0.02), squatting (1, 2 and 2.5 respectively, *P* = 0.04) and in the domain of stair climbing (2, 3 and 4, respectively, *P* = 0.04). Patients receiving clinic-based therapy scored lower than those on home-based therapy in the domains of eating/grooming (3 vs 4; *P* < 0.01) and stair climbing (1 vs 3; *P* = 0.024). Patients with comorbidities and lack of perceived support scored lower in the domain of dressing compared to those without comorbidities and adequate social support (3 vs 4; *P* = 0.01 and 2 vs 4; *P* = 0.04).

4. DISCUSSION

Main body of text

Forty-three percent of patients with IBDs in central South Africa had one or more mental illness. The lifetime prevalence of MDEs was 30%. This compares favourably with findings from a survey including 307 patients with bleeding disorders from the UK Haemophilia Society. In this study Barlow *et al*[6], reported that 32% of its members had difficulty in managing depression and/or anxiety as measured with a non-standardized questionnaire. This percentage is also higher than the lifetime prevalence of depression (9.8%) of the general population in South Africa.[40] The prevalence of substance use disorders in our study was 15%, slightly higher than the nine percent reported in the aforementioned study[6]. Our results do not support the association between older age and a decreased HR-QoL directly as found by Solovieva *et al*.[16], but this could be due to the fact that this Finnish sample with coagulation disorders included a greater number of older subjects with a sample mean age of 43 years.

Regarding PWHs, we found a lifetime prevalence rate of MDD of 24%. This is comparable to a previous American study by Iannone *et al*.[17] that found a depression rate of 37% as measured by the PHQ-9. Canclini *et al*.[22] however, concluded after a case-control study using the Beck Depression Inventory (BDI) and the State-Trait Anxiety Inventory (STAI-Y), that the risk of anxiety and depression was not higher in PWHs.

The severe haemophilia subgroup from our study reported greater impairment in the QoL in all domains compared to normative data. When compared to patients

with severe haemophilia from a developed country[4] they reported less impairment in all domains except that of anxiety/depression. The comparison between these two studies is, however, complicated by the fact that the 3-level, not the 5-level, EQ-5D questionnaire was used in the study by Miners *et al*[4], but our results do suggest relatively good physical adjustment in this subgroup despite a lack of treatment resources. The higher anxiety/depression rates, on the contrary, emphasizes the psychological distress that severe PWHs in central South Africa suffer despite relatively good perceived health, and points to a possible need for psychosocial intervention. The association between age and HR-QoL reported by Miners *et al*.[4] was not replicated in our results, again, most probably due to the small number of elderly patients represented in our sample. Although the risk of depression was greater for severe than for mild/moderate PWHs (27% vs 14%) it did not reach statistical significance. While not significant, we found less problems associated with anxiety/depression, self-care and usual activites, as well as self-rated health status when patients were on a prophylactic regimen versus an on-demand regimen. As ADLs are associated with HR-QoL,[5,7-9] preventing bleeds remains a treatment priority. In a case-control study Hartl *et al*.[18] reported that PWHs were at a significantly greater risk of being unemployed compared to healthy subjects. Forsyth *et al.*[19] reported that unemployed patients were more likely to report problems with mobility (79% vs 53%), whereas our study found almost similar rates of mobility problems between unemployed and employed patients (70% vs 78%). The difference in our study results probably reflects the general higher rate of unemployment in South Africa of 27.6%,[41] making it very difficult for patients to obtain employment regardless

of health status. The nine patients with HHT from our study reported less anxiety/depression (22% vs. 44%), despite reporting comparable levels of pain/discomfort (44% vs. 48%) and greater impairment in physical domains (including mobility, self-care and usual activities) of QoL when compared to 187 Spanish patients with HHT, as reported by Zarrabeitia *et al*. in 2017.[25] Although only 22% of our subgroup reported problems with anxiety/depression, 44% of them fulfilled clinical criteria when measured by the MINI. We ascribe the discrepancy between self-rated and objectively measured psychological distress in our study to lack of patient awareness and knowledge of mental disorders – assuming their own psychiatric symptomatology to be normal, or lacking the insight as to the extent of the impairment caused in social and occupational functioning by their psychiatric symptomatology. Chaturvedi *et al*.[26] reported an 89% prevalence rate of MDD in another 2017 study on HHT patients. We ascribe this higher prevalence rate to the difference in measuring tools used and delivered. We are of the opinion that self-measuring tools such as the BDI and PCL-5, are subjective and carry the risk of capturing physical symptomatology, secondary to the primary bleeding disorder, as mental illness. Fatigue, anergia or sleep disturbances that is secondary to pain, poor physical health and/or anaemia could be captured as symptoms of primary mood disorders and, likewise, appropiate worrying about bleeding episodes, employment, finances and future health could be captured as anxiety disorders. The MINI questionnaire, delivered by a single clinician as a structured interview, presumably ensured greater consistency. Functionality was associated with dynamic risk factors such as bleeding frequency, comorbid illness, treatment setting and family support.

The strength of our study was the use of the MINI questionnaire, which ensured valid and objective results, with the range of data ensuring thorough analysis of risk factors. The use of a generic QoL measurement tool enables comparison between different disorders. This, however, may hamper the comparison of studies where disease-specific QoL measures were used. Limitations of the study include the absence of a control group and a small sample size, not representative of all ages. Our study was at risk of selection bias as only the patients who eventully came for follow up were included.

5. CONCLUSION

Psychiatric illnesses are common in patients with IBDs (42.5%), especially MDD and especially in patients with severe haemophilia. Because our study was limited to 40 patients, risk factors should be interpreted with the necessary caution. Our results, nonetheless, suggest that patients' level of functioning can be improved by decreasing the bleeding frequency, by the use of home-based treatment and by optimizing treatment of comorbidities. Families must receive adequate psychoeducation regarding IBDs and the risk of psychiatric illness. Despite a high level of mental illness, the majority of patients perceive their own health as realtively good. This sample had high rates of unemployment, poor education, and unmarried patients, and is probably representative of this and other developing countries. As these variables are risk factors for psychiatric

illness, screening for and appropriately referring patients with psychiatric comorbidities could improve HR-QoL and reduce morbidity.

Title page

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AUTHORSHIP

All authors contributed to the design and the discussion of the study. HK, MC and JJ reviewed the relevant literature and contributed to data gathering. GJ contributed to data analysis, interpretation and presentation. RN, JJ, MC and GJ contributed to the final review and editing.

DISCLOSURES

The authors have no conflict of interest to declare.

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Tables and Figures

TABLE 1 Summary of recent published literature on the psychosocial aspects of inherited bleeding disorders

Authors	Year	Disorder	Design	n (control)	Instrument	Impaired QoL[a]	Prevalence of mental illness (%)
Miners *et al*.[4]	1999	Haemophilia	Case-control	166 (1466)	EQ-5D SF-36	Yes*** Mixed	Depression/ anxiety (33)
Molho *et al*.[42]	2000	Haemophilia	Cross-sectional	116	SF-36	Yes	-
Solovieva[16]	2001	Haemophilia, VWD FXIII def.	Cohort	150	SF-36	Yes*	-
Royal *et al*.[43]	2002	Haemophilia	Cohort	903	SF-36	Yes**	-
Canclini *et al*.[22]	2003	Haemophilia	Case-control	60 (78)	BDI[b]	-	Depression (8)
Beeton *et al*.[44]	2005	Haemophilia	Qualitative	11			-
Talaulikar *et al*.[5]	2006	Haemophilia, VWD	Cross-sectional	30	SF-36	No	-
Barlow *et al*.[12]	2007	Haemophilia, VWD	Descriptive, qualitative	9	[c]	-	Depression/ anxiety
Barlow *et al*.[6]	2007	Haemophilia, VWD	Survey	309	[d]	-	Depression (32) Substance use (9)
Plug *et al*.[7]	2008	Haemophilia	Cross-sectional	1066	SF-36	Yes	-
Hartl *et al*.[18]	2008	Haemophilia	Case-control	53 (104)	SF-36	Mixed	-
Elander *et al*.[15]	2009	Haemophilia	Cross-sectional	209	SF-36	Yes	-
Siboni *et al*.[8]	2009	Haemophilia	Case-control	39 (43)	GDS		Depression*
Stieltjies *et al*.[9]	2009	Haemophilia	Survey	50	SF-36	Yes	-
Iannone *et al*.[17]	2012	Haemophilia	Cross-sectional	41	PHQ-9	-	Depression (37)
Kim *et al*.[23]	2013	Haemophilia	Cross-sectional	53	BDI		Depression
Carvalhosa *et al*.[18]	2014	Haemophilia	Cohort	71	WHOQOL-BREF SF-36	Yes Yes	 -
Forsyth *et al*.[19]	2015	Haemophilia	Cross-sectional	675	EQ-5D	Yes	-
Barry *et al*.[13]	2015	Haemophilia VWD	Cross-sectional	152	PHQ-2		Depression (10)

TABLE 1 continued

Authors	Year	Disorder	Design	n (control)	Instrument	Impaired QoL[a]	Prevalence of mental illness (%)
Caturvedi *et al*.[26]	2017	HHT	Cross-sectional	185	BDI-II PCL-5	-	Depression (88.7) PTSD (28.1)
Zarrabeitia *et al*.[25]	2017	HHT	Cross-sectional	187	EQ-5D	Yes	-
Gupta *et al*.[45]	2019	Haemophilia	Cross-sectional	282	EQ-5D	Yes	-

[a]Referring to overall impairment
[b]Modified version
[c]Semi-structured interview
[d]Non-standardized questionnaire
*<0.05, **<0.01, ***<0.001, used to measure strength of association where control groups were included or where results were compared to normative values in non-case-control studies.
BDI, Beck depression inventory; EQ-5D, FXIII def., Factor XIII deficiency; GDS, Geriatric depression scale; HHT, hereditary haemorrhagic telangiectasia; PCL-5, PTSD checklist 5; PHQ-9, Patient Health Questionnaire 9; PTSD, post-traumatic stress disorder; SF-36, Short form – 36; STAI-Y, State-trait Anxiety Inventory; VWD, Von Willebrand disease; WHOQOL-BREF, World Health Organisation quality of life brief version.

Tables and Figures

TABLE 2 Patient demographics

Patient demographics (n = 40)	**n (%)**
Age in years, median	29.5
Gender	
Male	33 (83)
Female	7 (17.5)
Place of residence	
Patients following up at BHTC	
Inside Mangaung	14 (35)
Outside Mangaung	16 (40)
Lesotho	1 (2.5)
Patients following up at KHTC	
Kimberley, NC	9 (22.5)
Working	
Yes	10 (25)
No	30 (75)
Education	
None	0 (0)
Special	0 (0)
General	11 (27.5)
Marital status	
Never married	26 (65)
Married	10 (25)
Separated	2 (5)
Widowed	2 (5)
Disability grant	
Yes	21 (52.5)
No	19 (47.5)

BHTC, Bloemfontein Haemophilia Treatment Centre; KHTC, Kimberley Haemophilia Treatment Centre; NC, Northern Cape

Tables and Figures

TABLE 3 Clinical characteristics

Variable	Total (n = 40)	Haemophilia (n = 29)
Type of IBD, n (%)		
Haemophilia A	20 (50)	
Haemophilia B	9 (22.5)	
VWD	1 (2.5)	
HHT	9 (22.5)	
BSS	1 (2.5)	
Haemophilia severity		
Mild		2 (6.9)
Moderate		5 (17.2)
Severe		22 (75.9)
Treatment setting		
Home		26 (89.7)
Clinic		3 (10.3)
Treatment regimen		
On-demand		18 (62.1)
Prophylaxis		11 (37.9)
History of inhibitors		
Yes		7 (24)
No		22 (76)
Hepatitis B virus, n (%)		
Never	30 (75)	28 (97)
Previous	0 (0)	0 (0)
Chronic	0 (0)	0 (0)
Unknown	10 (25)	1 (3)
Hepatitis C virus, n (%)		
Never	24 (60)	23 (79)
Previous	2 (5)	2 (7)
Chronic	2 (5)	2 (7)
Unknown	12 (30)	2 (7)
HIV, n (%)		
Yes	4 (10)	1 (3)
No	28 (70)	25 (86)
Unknown	8 (20)	3 (10)
Bleeding frequency, n (%)		
<1 time per month	15 (37.5)	
1 to <3 times per month	16 (40)	
≥3 times per month	9 (22.5)	
Missed appointments, n (%)		
Never before	21 (52.5)	
1 to <2 times per year	15 (37.5)	
≥2 times per year	4 (10)	
Family members affected, n (%)		
None	5 (12.5)	
1 to <2 members	8 (20)	
≥2 members	27 (67.5)	
Wearing MedicAlert® bracelet	**8 (20)**	
Family and friends supportive	**35 (87.5)**	
Feel understood	**37 (92.5)**	

BSS, Bernard-Soulier syndrome; HHT, Hereditary haemorrhagic telangiectasia; VWD, Von Willebrand disease.

Tables and Figures

TABLE 4 Prevalence of psychiatric illness in different groups of inherited bleeding disorders

Psychiatric illness	Total (n = 40)	95% CIs	Haemophilia			(HHT) (n = 9)	Other* (n = 2)
			Total (n = 29)	Severe (n = 22)	Moderate/ mild (n = 7)		
All, n (%)	17 (42.5)	27.0 - 59.1	12 (41.4)	9 (40.9)	3 (42.9)	4 (44.4)	1 (50)
MDD	12 (30)	16.6 - 46.5	7 (24.1)	6 (27.3)	1 (14.3)	4 (44.4)	1 (50)
Alcohol use disorder	6 (15)	5.7 - 29.8	5 (17.2)	2 (9.1)	3 (42.9)	1 (11.1)	0 (0)
GAD	3 (7.5)	1.6 - 20.4	1 (3.5)	1 (4.6)	0 (0)	1 (11.1)	1 (50)
SAD	3 (7.5)	1.6 - 20.4	2 (6.6)	2 (9.1)	0 (0)	1 (11.1)	0 (0)
PTSD	1 (2.5)	1.6 - 20.4	1 (3.5)	0 (0)	1 (14.3)	0 (0)	0 (0)
Cannabis use disorder	1 (2.5)	0.1 - 13.2	1 (3.5)	0 (0)	1 (14.3)	0 (0)	0 (0)
Schizophrenia	1 (2.5)	0.1 - 13.2	1 (3.5)	1 (4.6)	0 (0)	0 (0)	0 (0)
Suicidality	1 (2.5)	0.1 - 13.2	1 (3.5)	1 (4.6)	0 (0)	0 (0)	0 (0)

CI, confidence interval; GAD, generalised anxiety disorder; HHT, hereditary haemorrhagic telangiectasia; MDD, major depressive disorder; PTSD, post-traumatic stress disorder; SAD, social anxiety disorder.
*Other illnesses include Von Willebrand disease and Bernard-Soulier syndrome.

TABLE 5 EQ-5D questionnaire results

Domain	Total (n = 40)	Haemophilia (n = 29)		HHT (n = 9)	Other* (n = 2)
		Severe (n = 22)	Mild / moderate (n = 7)		
Mobility, n (%)					
No problems	12 (30)	5 (23)	3 (43)	4 (44)	0 (0)
Slight	17 (43)	12 (55)	1 (14)	4 (44)	0 (0)
Moderate	7 (18)	2 (9)	2 (29)	1 (11)	2 (100)
Severe	4 (10)	3 (14)	1 (14)	0 (0)	0 (0)
Unable	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Self-care, n (%)					
No problems	33 (83)	18 (82)	7 (100)	7 (78)	1 (50)
Slight	3 (8)	1 (5)	0 (0)	2 (22)	0 (0)
Moderate	1 (3)	1 (5)	0 (0)	0 (0)	0 (0)
Severe	3 (8)	2 (9)	0 (0)	0 (0)	1 (50)
Unable	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Usual activities, n (%)					
No problems	25 (63)	14 (64)	6 (86)	5 (56)	0 (0)
Slight	9 (23)	5 (23)	1 (14)	2 (22)	1 (50)
Moderate	4 (10)	3 (14)	0 (0)	1 (11)	0 (0)
Severe	1 (3)	0 (0)	0 (0)	1 (11)	0 (0)
Unable	1 (3)	0 (0)	0 (0)	0 (0)	1 (50)
Pain/discomfort, n (%)					
No problems	7 (18)	6 (27)	1 (14)	5 (56)	0 (0)
Slight	16 (40)	7 (32)	3 (43)	3 (33)	1 (50)

TABLE 5 (continued)

Domain	Total (n = 40)	Haemophilia (n = 29)		HHT (n = 9)	Other* (n = 2)
		Severe (n = 22)	Mild / moderate (n = 7)		
Moderate	11 (28)	7 (32)	1 (14)	1 (11)	0 (0)
Severe	5 (13)	1 (5)	2 (29)	0 (0)	1 (50)
Extreme	1 (3)	1 (5)	0 (0)	0 (0)	0 (0)
Anxiety/depression, n (%)					
No problems	23 (58)	10 (45)	5 (71)	7 (78)	1 (50)
Slight	13 (33)	10 (45)	1 (14)	1 (11)	1 (50)
Moderate	3 (8)	2 (9)	1 (14)	0 (0)	0 (0)
Severe	1 (3)	0 (0)	0 (0)	1 (11)	0 (0)
Extreme	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
EQ-5DVAS, median (p25-p75)	75 (45 - 85)	80	80	55	50

*Other illnessess include Von Willebrand disease and Bernard-Solier syndrome

TABLE 6 Functional Independence Score in Hemophilia results of the haemophilia subgroup

Functional domain	Total (n = 29) n (%)	Severe (n = 22) n (%)	Moderate / mild (n = 7) n (%)
Eating and grooming, mean (median)	**3.9 (4)**		
Unable	0 (0)	0 (0)	0 (0)
Uses uncommon/modifies implements / has difficulties / unable to groom	0 (0)	0 (0)	0 (0)
Takes breaks / prosthesis / abnormal postures to groom / pain / takes long time	3 (10.3)	3 (13.6)	0 (0)
No difficulty	26 (89.7)	19 (86.4)	7 (100)
Bathing, mean (median)	**3.8 (4)**		
Bed bath / mostly unable	0 (0)	0 (0)	0 (0)
Shower / modified bathroom / stool / occasional help	1 (3.4)	1 (4.5)	0 (0)
Unusual postures/discomfort	5 (17.2)	4 (18.2)	1 (14.3)
No difficulty	23 (79.3)	17 (77.3)	6 (85.7)
Dressing, mean (median)	**3.5 (4)**		
Requires complete help in >50% of activity	1 (3.4)	1 (4.5)	0 (0)
Requires complete help in <50% of activity	5 (17.2)	5 (22.7)	0 (0)
Discomfort / momentary support / adaptive maneuvers	1 (3.4)	0 (0)	1 (14.3)
No assistance needed	22 (75.9)	16 (72.7)	6 (85.7)
Chair transfer, mean (median)	**3.1 (3)**		
Unabe to get up from chair	0 (0)	0 (0)	0 (0)
Requires maximal support/crutches	9 (31)	6 (27.3)	3 (42.9)
Leans excessively forward/sits with extended knees	8 (27.6)	8 (36.4)	0 (0)
No difficulty	12 (41.4)	8 (36.4)	4 (57.1)
Squatting, mean (median)	**1.9 (1)**		
Unable to squat 12"* with support	18 (62.1)	14 (63.6)	4 (57.1)
Able to squat to height of 8"-12" with maximal help	3 (10.3)	3 (13.6)	0 (0)
Able to squat to height of 8"-12" with minimal help	2 (6.9)	2 (9.1)	0 (0)
Able to squat to height of 8" for 5 seconds	6 (20.7)	3 (13.6)	3 (42.9)
Walking, mean (median)	**3.1 (3)**		
Unable to walk 10 meters	2 (6.9)	2 (9.1)	0 (0)
Cane / brace	1 (3.4)	0 (0)	1 (14.3)
Stiff knee / gait	19 (65.5)	15 (68.2)	4 (57.1)

Normal	7 (24.1)	5 (22.7)	2 (28.6)

TABLE 6 (continued)

	Total (n = 29)	**Severe (n = 22)**	**Moderate / mild (n = 7)**
Stair climbing, mean (median)	**2.7 (2)**		
Unable to climb 14 steps on a flight of stairs	4 (13.8)	3 (13.6)	1 (14.3)
More than 14 seconds used to climb up or down	11 (37.9)	8 (36.4)	3 (42.9)
Limp / discomfort / up or down under 14 seconds	5 (17.2)	5 (22.7)	0 (0)
Climbs up / down under 9 seconds	9 (31)	6 (27.3)	3 (42.9)
Running, mean (median)	**2.2 (2)**		
Unable to walk briskly	13 (44.8)	10 (45.5)	3 (42.9)
Only walks briskly	6 (20.7)	5 (22.7)	1 (14.3)
Pain/runs part of distance only	1 (3.4)	1 (4.5)	0 (0)
Able to run 25 meters	9 (31)	6 (27.3)	3 (42.9)
Total score, mean (median)	24.1 (22)	(22)	(22)
Range (p25-p75)	14-32 (20-29)	14-32 (20-28)	19-32 (20-32)

*8 to 12 inches is equal to 20.32 to 30.48 cm.
FISH, Functional Independence Score for patients with haemophilia

TABLE 7 EQ-5D questionnaire percentages of any problems*

Domain, n (%)	Total (n=40)	Haemophilia		HHT (n=9)	Other† (n=2)	Norm‡ (n=1409)	P value	RR	95% CI
		Severe (n=22)	Mild/mod (n=7)						
Mobility	28 (70)	17 (77)	4 (57)	5 (56)	2 (100)	(29.8)	<0.01	2.3	1.9 - 2.9
Self-care	7 (18)	4 (18)	0 (0)	2 (22)	1 (50)	(9.2)	0.09	1.9	0.9 - 3.8
Usual activities	15 (38)	8 (36)	1 (14)	4 (44)	2 (100)	(25.9)	0.10	1.4	1.0 - 2.2
Pain/discomfort	33 (83)	16 (73)	6 (86)	4 (44)	2 (100)	(65.2)	0.02	1.3	1.1 - 1.5
Anx/depression	17 (43)	12 (55)	2 (29)	2 (22)	1 (50)	(47)	0.58	0.9	0.6 - 1.3
VAS, mean (median)	**69.6 (75)**	**74.8 (80)**	**69.9 (80)**	**60.3 (55)**	**52.5 (52.5)**	**78.9**	**-**	**-**	**-**
Index value	**0.626**	**-**	**-**	**-**	**-**	**0.706**	**-**	**-**	**-**

***Any problem equates to a score ranging from 2 to 5 on the EQ-5D (slight to severe/extreme).
†Other illnesses include Von Willebrand disease and Bernard-Soulier syndrome.
‡Thailand used as normative population as that of South Africa is not available. Thailand's GDP/capita resembles that of South Africa the best. CI, confidence interval; HHT, hereditary haemorrhagic telangiectasia; mod, moderate; RR, relative risk; VAS, visual analogue scale.

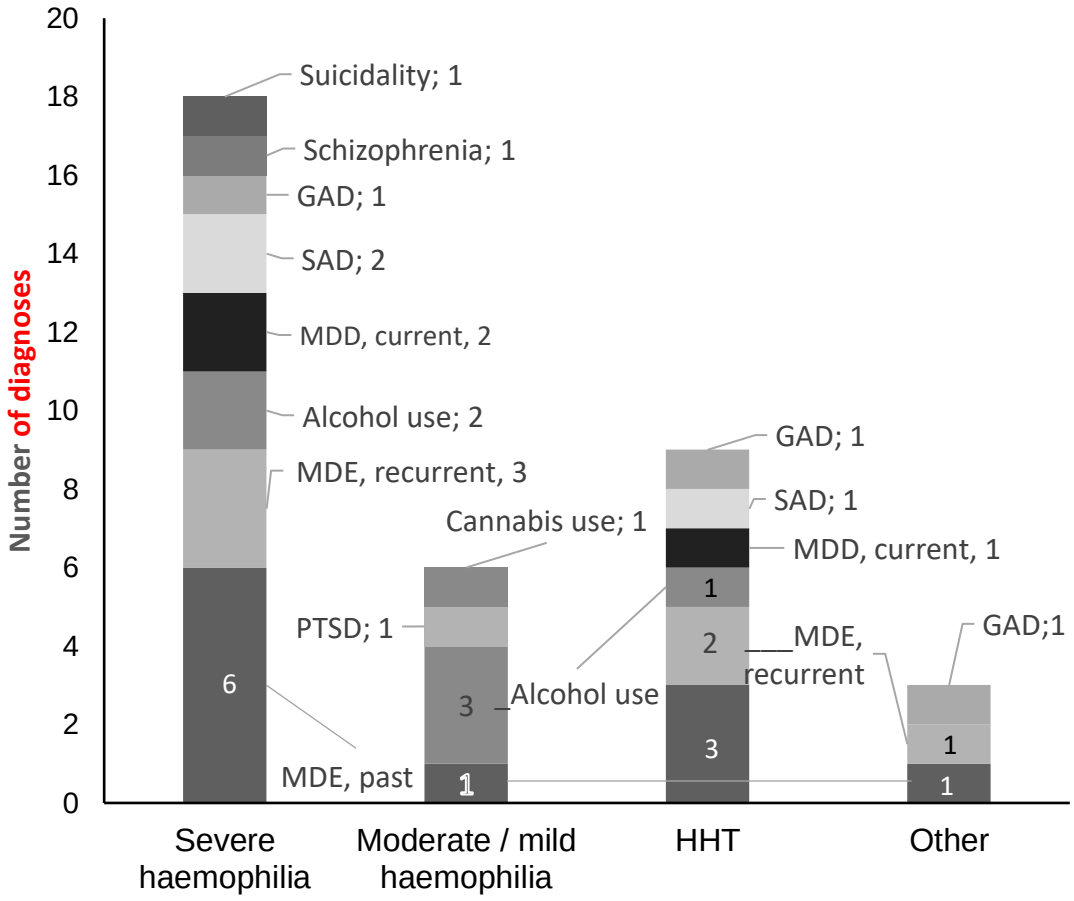

FIGURE 1 Number of psychiatric diagnoses per group of inherited bleeding disorders.
GAD, generalized anxiety disorder; HHT hereditary haemorrhagic telangiectasia; MDE, major depressive episode; MDD, major depressive disorder; PTSD, post-traumatic stress disorder; SAD, social anxiety disorder.

APPENDIX A

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Agreed and accepted:

David V Sheehan MD MBA — 12/11/17

Signature of Dr. David V. Sheehan, copyright holder — Date

For Dr Heinrich Koekemoer, the sponsoring company / CRO / healthcare provider / clinical care setting, requesting permission:

Signature — 27/11/2017 Date

Print Name and Title : Dr Heinrich Koekemoer
Phone: 0726520075
E-mail: heinrichkoekemoer@gmail.com

APPENDIX 1

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	Will the MINI be done at the screening visit after the informed consent form is signed?	(Yes) / No
Product/Compound	**Study Identification Number**	**Projected Number to be randomized to all study medications at baseline visit per protocol / clinical care setting**
Not applicable. This is an analytical, cross-sectinal study.	Awaiting ethical clearance. Health Sciences Research Ethics Committee number of protocol: UFS-HSD2017/1552	Not applicable. 40 participants projected to be enrolled in an analytical study.
Budget for Study being conducted using the MINI at no cost:* *US* *$___300_____*		**Projected number who will sign the informed consent form at the screening visit (typically this is a 3:1 or 2:1 ratio to those expected to be randomized to study medications at the baseline visit).** *This is the best estimate of the number of MINIs to be done at the screening visit.* **If in a clinical care setting rather than in a research study, how many MINIs will be administered, and how many MINIs are you requesting permission to use?**
		40 participants to be recruited in an analytical, cross-sectional study

David V Sheehan MD MBA
Signature of Dr. David V. Sheehan, copyright holder

12/11/17
Date

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LIST OF APPENDICES

APPENDIX A

LETTER OF PERMISSION: HEALTH SCIENCES RESEARCH ETHICS COMMITTEE, UFS

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

UFS·UV
HEALTH SCIENCES
GESONDHEIDSWETENSKAPPE

Health Sciences Research Ethics Committee

08-Mar-2018

Dear **Dr Heinrich Koekemoer**

Ethics Clearance: **Prevalence of comorbid psychiatric illness and quality of life in adults with bleeding disorders at the Bloemfontein Haemophilia Treatment Centre, South Africa.**

Principal Investigator: **Dr Heinrich Koekemoer**

Department: **Psychiatry (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-HSD2017/1552**

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

APPENDIX B

LETTER OF APPROVAL: PROVINCIAL HEALTH RESEARCH ETHICS COMMITTEE, NORTHERN-CAPE DEPARTMENT OF HEALTH

DEPARTMENT OF HEALTH
LEFAPHA LA BOPHELO BO BOTLE
DEPARTEMENT VAN GESONDHEID
ISEBE LEZEMPILO

Research and Development Unit
Executive Offices
Northern Cape Department of Health
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Tel: 053 830 2134
Fax: 086 485 3243
Email: BMashute@ncpg.gov.za/
EWorku@ncpg.gov.za

Enquiries: Dipatlisiso: Imibuzo: Navrae : Dr. E Worku

Date: Leshupelo: Umhla: Datum: 06 December 2018

Reference: Tshupelo: Isalathiso: Verwysing: *NC_201811_001*

Dr. H Koekemoer
PO Box 26260
Bloemfontein
9330

Dear Sir

Project Title: ***Prevalence of Comborbid Psychiatric Illness and the Quality of Life in Adults with Bleeding Disorders at the Bloemfontein Haemophilia Treatment centre, South Africa***

The application requesting permission to conduct the above-mentioned research study was received and reviewed by the Provincial Health Research Ethics Committee (PHREC) and the Acting Medical Director of Robert Mangaliso Sobukwe Hospital (formerly Kimberley Hospital)

Decision: Approval to conduct this study at Robert Mangaliso Sobukwe Hospital is granted

Your Provincial Ethics Reference Number is ***NC_201811_001,*** kindly use that reference number in correspondence with the PHREC administration

Please note the following

1) This approval is valid for a period of one year from the date of approval (i.e. 06 December 2018 to 05 December 2019)
2) The researcher(s) is hereby requested to make all necessary arrangements with the facility manger before visiting this facility, so that the provision of healthcare services is not affected by the activities of this research project.

Details of the CEO:
Name: Mr. Richard Jones
Tel: 053 802 2124

APPENDIX C1

LETTER OF CONSENT (ENGLISH)

Prevalence of comorbid psychiatric illness and quality of life in adults with inherited bleeding disorders in central South Africa

You have been invited to participate in this research study. You have been informed by Dr. Heinrich Koekemoer about the following aspects:

- ➢ The purpose of the study
- ➢ You will be asked questions and be asked to fill in a question form.
- ➢ Information about your health (like if you have HIV infection) will be obtained from your file.
- ➢ You will be asked to run over 50 meters and walk 14 steps on a flight of stairs as part of a physical examination, but do not have to if you do not feel up for it. This will be conducted as part of a well-researched evaluation system used internationally to measure disability in people with haemophilia. This system has proven to be safe and useful, with low bleeding risk. Medical help will be provided should you sustain any injuries during the research study.
- ➢ The evaluation would be approximately 60 minutes.
- ➢ The answers would be strictly confidential.
- ➢ The anonymous facts of this study may be used for a scientific article.
- ➢ No additional blood tests would be taken.
- ➢ Your participation in this study is voluntary. If you refuse to participate, it would not be held against you. It would also not interfere with further treatment.
- ➢ If you attend the clinic on a different day than your usual appointment date, we will pay the transport costs from your home to the clinic and back home according to the rates advised by NovoGo®. This does not include other costs such as food or accommodation spent on the same day.
- ➢ If you agree to participate, you will be given a signed copy of this document as well as the participant information sheet, which is a written summary of the research.
- ➢ Inquiries: You are welcome to contact Dr H Koekemoer at 0726520075. Free State Psychiatric Complex for any questions about the research.
- ➢ Complaints: You may contact the Ethics Committee secretariat, Maré Marais at 0514017795 if you have questions about your rights as a research participant.

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:

…… …….. ……. ……....
Patient Doctor Witness Interpreter (if applicable)

Name and surname:

……. ……. ……. …….
Patient Doctor Witness Interpreter (if applicable)

……..
Date

APPENDIX C2

LETTER OF CONSENT (SESOTHO)

Prevalence of comorbid psychiatric illness and quality of life in adults with inherited bleeding disorders in central South Africa

O memelwa ho nka karolo diphuputsong tsena tsa mahlale.
O tsebisitswe ke Dr Heinrich Koekemoer mabapi le dintlha tsena tse latelang:

- ➢ Sepheo sa diphuputso.
- ➢ O tla botswa dipotso mme o kopjwe ho tlatsa setlanka sa dipotso.
- ➢ O tla kopjwa ho matha dimitara tse mashome a mahlano mme o tsamaye mehato e le shome le metso e mene moahong wa mekato e le karolo ya hlahlobo ya mmele. Empa ha oa tlangwa ho etsa jwalo ha o se na tjantjello. Hona ho tla etswa e le karolo ya dihlahlobo tse fupuditsweng ka botlalo mme di sebediswa lefatshe- bophara ho lekanyetsa bofokodi bathong ba amehileng ke mafu a madi. Mokgwa ona wa dihlahlobo o bontshitse ho bolokeha ha bona mme kotsi ya ho tswa madi e tlase. Dithuso tsa bophelo bo botle di tla ba teng bakeng sa hao, ha ho ka etsahala hore ho be le temalo diphuputsong tsena.
- ➢ Hlahlobo e tla nka nako e lekanyetswang metsotso e mashome a tsheletseng.
- ➢ Dikarabo di tla tshwarelwa lekunutung.
- ➢ Dintlha tse tshireleditsweng tsa diphuputso tsena di ka sebediswa ho ngola tokomane ya tsa mahlale.
- ➢ Ho nka karolo ha hao diphuputsong tsena ho boithaopong. O ke ke wa qoswa ha o ka haana ho nka karolo mme hoo ha hona ho ama kalafo ya hao ho feta mona.
- ➢ Dipotso: O ka letsetsa Dr H. Koekemoer ho 0726520075, Free State Psychiatric Complex, ha o ena le dipotso tse ding mabapi le dipatlisiso tsena.
- ➢ Ditletlebo: O ka letsetsa Maré Marais wa Ethics Committee ho (051) 4017795 ha o ena le dipotso bakeng sa ditokelo tsa hao jwalo ka monka-karolo.

Ke hlaloseditswe ka diphuputso tsena tsa mahlale ha mmoho le ka dintlha tse ngotsweng kahodimo. Ke utlwisisa ho nka karolo ha ka ho bolela eng mme ke dumela ho nka karolo ka boithaopo.

Tekeno:

……. …… …… ……...
Mokudi Ngaka Paki Moqapulli (Ha ho hlokahala)

Lebitso le Sefane:

…… …….. …… …….
Mokudi Ngaka Paki Moqapulli (Ha ho hlokahala)

……..
Letsatsi

APPENDIX C3

LETTER OF CONSENT (AFRIKAANS)

Prevalence of comorbid psychiatric illness and quality of life in adults with inherited bleeding disorders in central South Africa

U word uitgenooi om deel te neem aan bogenoemde navorsing studie. U is ingelig deur Dr. Heinrich Koekemoer aangaande die volgende aspekte:

- ➢ Die doel van die studie.
- ➢ U word gevra om vrae te beantwoord en om ń vraelys in te vul.
- ➢ Inligting aangaande u gesondheid (Soos bv. of u HIV infeksie het) sal verkry word vanuit u pasiëntlêer.
- ➢ U sal gevra word om 50 meter te hardloop en om ongeveer 14 trappe te klim as deel van ń fisiese ondersoek, maar u hoef nie indien u nie gesond genoeg voel nie. Hierdie sal gedoen word as deel van ń goed nagevorsde evalueringstelsel wat internasionaal gebruik word om gestremdheid in mense met hemofilie te meet. Hierdie stelsel het geblyk om veilig en nuttig te wees, met ń lae bloedingsrisiko. U sal van mediese hulp verskaf word sou u beseer word tydens die studie.
- ➢ Die onderhoud en ondersoek sal om en by 60 minute duur.
- ➢ U antwoorde word vertroulik hanteer.
- ➢ Die anonieme inligting wat verkry word uit die studie kan gepubliseer word in n wetenskaplike joernaal.
- ➢ Geen bloedtoetse gaan gedoen word nie.
- ➢ U deelname is vrywillig en u sal nie gepenaliseer word as u weier om deel te neem nie. U kan teen enige tyd onttrek van die studie sonder enige vranderinge aan u sorg.
- ➢ U vervoer kostes vanaf u huis na die kliniek, en terug, sal deur ons gedek word indien u die kliniek op ń ander dag as u geröelde afspraak-datum bywoon volgens die tariewe aanbeveel deur NovoGo®. Ons sal nie ander onkostes soos kos, verblyf ens. dek nie.
- ➢ Indien u deelneem sal u ń getekende kopie van hierdie brief ontvang, asook ń inligting stuk wat ń opsomming is van hierdie studie.
- ➢ Navrae: U is welkom om Dr Koekemoer te kontak by 0726520075 by die Vrystaat Psigiatrie Kompleks indien u enige vrae het.
- ➢ Klagtes: Kontak, Maré Marais, sekretaresse by die Gesondheidswetenskap Navorsings Etiek Komitee by 0514017795 vir navrae aangaande u regte.

Die navorsingstudie, sowel as bogenaamde inligting, is aan my verduidelik. Ek verstaan wat my betrokkenheid by die studie behels en my deelname is vrywillig:

Handtekening:

…….. …….. ……. ……..
Pasiënt Dokter Getuie Tolk (indien van toepassing)

Naam en van:

…… …….. …… …….
Pasiënt Dokter Getuie Tolk (indien van toepassing)

……..
Datum

APPENDIX C4

INFORMATION LEAFLET (ENGLISH)

Prevalence of comorbid psychiatric illness and quality of life in adults with inherited bleeding disorders in central South Africa

Good day,

We, Dr Koekemoer and other researchers, are conducting research on patients with bleeding disorders. Research is the process to learn the answer to a question. In this study we want to establish how many people who have a bleeding disorder, like haemophilia, also have mental or psychological problems. We also want to establish how much these patients enjoy or do not enjoy their lives. Therefore, we are only collecting information and we will not change the regular treatment you usually receive here at the clinic.

We are inviting you to participate in this research study.

If you take part, we will ask you questions about your personal life (like ethnicity, gender, work, marital status, etc.) and your health. We will then ask you to complete a form about your quality of life, and we will also look in your personal file to see your diagnosis. We will also look in your file to see if you have infections such as hepatitis and HIV. You will also undergo a physical assessment to see how you function physically. This includes running over 50 meters and climbing 14 steps on a flight of stairs, but you do not have to do this if you do not feel up for it. It will last about 60 minutes in total to complete. About 40 patients attending this clinic (BHTC) will participate in this study. If you visit the clinic on a different day than your usual appointment date, and do not make use of the Free State Department of Health commuter service, we will pay the transport costs from your home to the clinic and back home according to the rates that NovoGo® advises. This does not include other extra costs like transport of a companion; or food or accommodation spent on the same day.

We don't foresee any risks to your health during this study. Appropriate medical help will be available should any problems occur during the study. This study has been approved by the Health Sciences Research Ethics Committee of the University of the Free State.

The benefit of participating in this study is that you will help us gather information to better help patients who have bleeding disorders.

You are welcome to contact me at any time if you want a copy of the results of the study.

You have the right to refuse to participate and will not be penalized. You may also tell me at any time that you don't want to continue with the study. You will then still be cared for the same way at the clinic as before.

All the information will be kept confidential, unless if for some reason, the law requires us to provide the information. The Health Sciences Research Ethics Committee which makes sure that research is done safely, might also seek access to the information in some cases.

The results of the study might be published in a medical journal and/or presented at a scientific meeting, but all information will be anonymous.

If you have any questions about the study you can call me, Dr Heinrich Koekemoer, at 0726520075.

You can also report any complaints to Maré Marais at the Ethics Committee at 0514017795.

APPENDIX C5

INFORMATION LEAFLET (SESOTHO)

Prevalence of comorbid psychiatric illness and quality of life in adults with inherited bleeding disorders in central South Africa.

Dumelang,

Nna, Dr Koekemoer le bafuputsi ba bang, re etsa diphuputso bakuding ba amehileng ke mafu a madi. Diphuputso tsa mahlale ke mokgwa wa ho fumana karabo ya potso e itseng. Phuputsong ena re batla ho fumana hore ke batho ba ba kae ba enang le mafu a madi, jwalo ka haemophilia, ba amehileng kelello le maikutlo. Mme re batla le ho netefatsa hore bakudi bana ba sa natefallwa ke bophelo ho le hokae. Ka hoo, re bokelletsa feela tlhahiso leseding mme re ke ke ra fetola kalafo ya kamehla eo le e fumantshwang kliniking mona.

Re o memela ho nka karolo diphuputsong tsena.

Ha o nka karolo, re tla o botsa dipotso mabapi le bophelo ba hao (bong, mosebetsi, tsa lenyalo, jwalo-jwalo), le mabapi le maemo a hao a bophelo. Kamora moo re tla o kopa hore o tlatse foromo mabapi le boleng ba bophelo, mme re

shebe le ka hara faele ya kliniki ho bona hore ke mofuta o feng wa lefu leo tshwerweng ke lona. Re tla sheba haape ka faeleng ya hao ho lekola hore na o na le mafu a kang Hepatitis (tshwaetso ya sebete) le HIV.

Hlahlobo ya mmele le yona e tla etswa ho lekola boemo ba hao mmeleng. Hona ho kenyelleditse ho matha dimitara tse ka tlolang mashome a mahlano le ho tsamaya mehato e leshome le metso e mene moahong wa mekato, empa ha oa tlangwa ho di etsa ha o sena tekatso ya seo.

Hona ho tla nka nako e ka bang metsotso e mashome a tsheletseng. Bakudi ba ka bang mashome a mane ba fumanang dithuso kliniking ena (BHTC) batla nka karolo diphuputsong tsena. Ha ho ka etsahala hore o tle kliniking ka letsatsing le eseng la hao la tlwaelo, mme o sa sebedise dipalangwang tsa mmuso tsa Lefapha la Bophelo Bo Botle, re tla lefa ditjeo tsa dipalangwang ho tloha lapeng la hao ho fihla kliniking le tsa ho kgutlela hae, ho ya ka ditekanyetso tse beuweng ke ba NovoGo®. Hona ha ho kenyelletse ditjeo tse ding tse kang ho palamisa motsamai-mmoho le wena, dijo kaapa madulo tse sebedisitsweng letsatsing leo.

Diphuputso tsena ha di a lebellwa ho beha bophelo ba hao kotsing ka tsela efe kaapa efe. Dithuso tse nepahetseng tsa bophelo bo botle di tla fumaneha ha ho ka ba le mathata a hlahang nakong ya diphuputso.Tetla ya ho etsa diphuputso

tsena e abuwe ke Health Sciences Research Ethics Committee ya Yunivesithi ya Foreisitata.

Molemo wa ko nka karolo ha hao phuputsong tsena ke hore o tla re thusa ho bokaletsa tlhahiso leseding e tla sebediswang ho ntlafatsa dithuso tse abelwang bakudi ba amehileng ke mafu a madi.

O dumelletswe ho itehanya le nna ka tsela enngwe le enngwe, nako efe kaapa efe ha o batla ho thola diphetho tsa diphuputso tsena.

O na le tokelo ya ho haana ho nka karolo mme o ke kebe wa qoswa bakeng sa hoo. Le ha o ka nka qeto ya ho emisa ho nka karolo ha hao, o ka mpolella ka nako efe kaapa efe. Mme le teng o tla tswella pele ho fumantshwa tlhokomelo e tshwanang le ya mehla kliniking ena.

Dintlha tsohle di tla tshwarelwa sephiring, ntle le ha molao o ka re hapelletsa ho faana ka ntlha tseo. Ba Health Sciences Research Ethics Committee, e leng bao ba netefatsang hore diphuputso tsena di etswa ka tsela e bolokehileng, le bona ba ka kopa ho fumantshwa tse ding tsa dintlha tsena.
Diphetho tsa diphuputso tsena di ka phatlalatswa dibukeng tsa mahlale a bophelo bo botle kaapa di ka tekelwa dikopanong tse kgolo tsa mahlale, empa dintlha tse lebaneng le bakudi di tla dula di tshirelediswe.

Ha eba o ena le dipotso mabapi le diphuputso tsena, o ka nna wa letsetsa nna Dr Koekemoer ho 0726520075.

Le ditletlebo o ka di lebisa ho Maré Marais wa Ethics Committee ho (051) 4017795.

APPENDIX C6

INFORMATION LEAFLET (AFRIKAANS)

Prevalence of comorbid psychiatric illness and quality of life in adults with inherited bleeding disorders in central South Africa

Goeie dag,

Ons, Dr Koekemoer en ander navorsers, doen navorsing op pasiënte met bloedingsiektes. Navorsing is die proses om die antwoord op ń vraag te vind. In die studie wil ons kyk hoeveel pasiënte met bloedingsiektes, soos hemofilie, lei ook aan geestes-, of psigiatriese siektes. Ons wil ook vasstel hoe baie of hoe min hierdie pasiënte hulle lewens geniet. Daarom gaan ons slegs inligting probeer kry en gaan geen veranderinge aan u behandeling by die kliniek maak nie.

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

Indien u deel neem, sal ons u vrae vra oor u persoonlike lewe, soos etniese agtergrond (ras), geslag, werk, huwelikstatus, ens., sowel as u gesondheid. Ons sal u dan vra om ń vraelys in te vul oor u kwaliteit van lewe, en ons sal in u lêer kyk om u diagnose te sien. Ons gaan in u lêer kyk of u enige infeksies (soos HIV) het. Ons sal u ook fisies ondersoek om te sien hoe u reg kom m*et al*ledaagse take. U sal gevra word om oor 50 meter te hardloop en ń stel van so 14 trappe te klim, maar u het volle reg om te weier, sou u verkies. Die hele onderhoud sal so 60 minute duur. Ons beplan om so 40 pasiënte by die kliniek te laat deelneem in die studie. Indien u op ń ander dag as u kliniek-datum kliniek toe kom, en nie gebruik maak van die Vrystaatse Gesondheidsdepartement se vervoer dienste nie, sal ons u vervoer kostes dek vanaf u huis na die kliniek, en terug, volgens die tariewe aanbeveel deur NovoGo®. Dit sluit nie kostes in soos vervoer van ń metgesel; of kos of akkommodasie wat u sou spandeer op dieselfde dag nie.

Ons verwag nie enige gevaar vir u gesondheid gedurende die studie nie. Mediese hulp is beskikbaar sou daar enige probleme wees tydens die studie. Hierdie studie is goedgekeur deur die Etiek Komitee van die Gesondheidswetenskappe Fakulteit by die Universiteit van die Vrystaat.

Die voordeel daarvan om aan die studie deel te neem is dat u ons sal help om inligting in te samel wat kan lei tot beter gesondheidsorg vir pasiënte met bloedingsiektes.

U is welkom om my te kontak as u ń kopie wil hê van die finale resultate van die studie.

U het die reg om deelname te weier sonder dat u gepenaliseer sal word. U mag ook enige tyd onttrek van die studie sonder dat u behandeling by die kliniek verander word.

Al die inligting word geheim gehou, tensy die wet vereis dat ons die inligting bekend maak vir veiligheidsredes. Die Gesondheidswetenskap Navorsings Etiek Komitee mag ook toegang tot die resultate van die studie vra vir etiese redes.

Die resultate van die studie mag in ń wetenskaplike tydskrif kom of aangebied word by vergaderings, maar u identiteit bly geheim.

Indien u enige vrae het oor die studie, kontak my, Dr Koekemoer, by die Vrystaat Psigiatrie Kompleks by 0726520075.

U kan enige klagte rig aan Me Maré Marais by die Gesondheidswetenskap Navorsings Etiekkomitee by 0514017795

APPENDIX D

LETTER OF PERMISSION: FREE STATE DEPARTMENT OF HEALTH

health
Department of Health
FREE STATE PROVINCE

20 February 2018

Dr H Koekemoer
Dept. of Psychiatry
Free State Psychiatric Complex
BFN

Dear Dr H Koekemoer

Subject: Prevalence of comorbid psychiatric illness and quality of life in adults with bleeding disorders at the Bloemfontein Haemophilia Treatment Centre, 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 Universitas 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 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 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** sebeelats@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: 21/3/2018

Head : Health
PO Box 227, Bloemfotein, 9300
4th Floor, Executive Suite, Bophelo House, cnr Maitland and, Harvey Road, Bloemfotein
Tel: (051) 408 1646 Fax: (051) 408 1556 e-mail:khusemj@fshealth.gov.za@fshealth.gov.za/chikobvup@fshealth.gov.za

APPENDIX E1

LETTER OF APPROVAL: HEAD OF ACADEMIC DEPARTMENT: HAEMATOLOGY

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

UFS·UV
HEALTH SCIENCES
GESONDHEIDSWETENSKAPPE

Head of Department Haematology & Cell Biology: Prof M Coetzee
Free State Psychiatric Complex
Bloemfontein
9301

15 November 2017

Re: Request for approval for conducting a study.

We wish to request permission to perform a study entitled: "Prevalence of comorbid psychiatric illness and quality of life of adults with bleeding disorders at the Bloemfontein Haemophilia Treatment Centre, South Africa". It will consist of interviewing and administering questionnaires to 40 participants with bleeding disorders and collecting data from their files at the above-mentioned facility. The study is expected to start 29 January 2018 and continue until end of November 2018. The results may be published in a scientific journal. The study protocol has been approved by the Health Sciences Research Ethics Committee (HSREC) of the University of the Free State.

A copy of the project proposal is attached.

Yours sincerely

Dr. H. Koekemoer
Registrar at FSPC (Dept. of Psychiatry)
Tel: +27 72 652 0075
Email: heinrichkoekemoer@gmail.com

Approved
MJ Coetzee
2017-11-23

Prof Maruis J Coetzee
MBChB, MMed(Path), FFPath(SA),DTM&H
MP 0217930
Dept. of Haematology & Cell Biology
Speed dail: 6357 / (051) 405 3911

Department of Psychiatry
T: +27(0)51 407 9294/6/7/382
F: +27(0)51 447 5370/
+27 (0) 51 448 3092
E: pretorpj@fshealth.gov.za

Free State Psychiatric Complex
President Brand Street
Bloemfontein 9301
South Africa/Suid-Afrika

PO Box/Posbus 339 (G66)
Bloemfontein 9300
South Africa/Suid-Afrika
www.ufs.ac.za

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

APPENDIX E2

LETTER OF APPROVAL: HEAD OF CLINICAL MANAGEMENT: ROBERT MANGALISO SOBUKWE HOSPITAL: MEDICAL

DEPARTMENT OF HEALTH
LEFAPHA LA BOPHELO BO BOTLE
DEPARTEMENT VAN GESONDHEID
ISEBE LENKONZO ZENTLALONTLE

Robert Mangaliso
Sobukwe Hospital

Head Clinical Management: Medical

Du Toitspan Road
Private Bag X5021
Kimberley

Tel: 053 802 2147
Fax: 053 832 9435 /
086 617 4089

Reference : Tshupelo : Verwysings : Isalathiso :

Date : Leshupelo : Datum : Umhla : 9th November 2018 Dr H Saeed

TO: Mr H Koekemoer

RE: Permission to do research

Permission is hereby granted to conduct a medical research project at Kimberley Hospital complex, title proposed: "Prevalence of comorbid psychiatric illness and quality of life of adults with bleeding disorders at the Bloemfontein Haemophilia Treatment Centre, South Africa"

Please submit proof of ethics clearance, before commencing with the research.
Kindly submit research protocol to the Northern Cape Provincial Health Research and Ethics Committee for approval.

Contact Details:
Dr E Worku
Email address: eworku@ncpg.gov.za
Tel: (053) 8302134

Dr H Saeed
MBBS,H.Dip.Int.Med.(CMSA),M.Fam.Med.(UFS),
Specialist Family Physician
Acting Head Clinical Management: Medical

Date: 09/11/18

APPENDIX E3

LETTER OF APPROVAL: DEPARTMENT OF BIOSTATISTICS

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

UFS·UV
HEALTH SCIENCES
GESONDHEIDSWETENSKAPPE

17 November 2017

Health Sciences Research Ethics Committee, UFS

Title of project:
Prevalence of comorbid psychiatric illness and quality of life in adults with bleeding disorders at the Bloemfontein Haemophilia Treatment Centre, South Africa.

Researcher:
Dr HT Koekemoer, Dept of Psychiatry

I hereby confirm that I provided inputs on the protocol and approve the study design, sampling, measurement and measuring instruments, as well as statistical analysis.

Best regards

Gina Joubert

Departement Biostatistiek
Department of Biostatistics
T: +27(0)51 401 3114/5/6/7, F: +27(0)51 401 3641
205 Nelson Mandela Drive/Rylaan, Park West/Parkwes, Bloemfontein 9301, South Africa/Suid-Afrika
P.O. Box/Posbus 339 (G31), Bloemfontein 9300, South Africa/Suid-Afrika, www.ufs.ac.za

APPENDIX F

COPY OF THE RESEARCH PROTOCOL APPROVED BY THE HSREC

PROTOCOL

PREVALENCE OF COMORBID PSYCHIATRIC ILLNESS AND QUALITY OF LIFE IN ADULTS WITH INHERITED BLEEDING DISORDERS IN CENTRAL SOUTH AFRICA

Researchers:

Heinrich T. Koekemoer (Principal investigator)
University of the Free State
Department of Psychiatry
Free State Psychiatric Complex
Bloemfontein
9300

Richard J. Nichol
University of the Free State
Department of Psychiatry
Free State Psychiatric Complex
Bloemfontein
9300

Marius J. Coetzee
University of the Free State
Department of Haematology & Cell Biology
Universitas Academic Hospital
Bloemfontein
9300

Jaco Joubert
University of the Free State
Department of Haematology & Cell Biology
Universitas Academic Hospital
Bloemfontein
9300

Biostatistician:

Gina Joubert
University of the Free State
Department of Biostatistics
Bloemfontein
9300

TABLE OF CONTENTS

SUMMARY

The purpose of this study is to sensitise health workers to the psychiatric comorbidities of patients with bleeding disorders and to promote holistic care to better patients' quality of life. Therefore, the researchers aim to establish the prevalence of psychiatric comorbidities in patients with bleeding disorders, as well as their quality of life. If numbers permit, risk factors associated with psychiatric illness will be assessed.

A quantitative, cross-sectional analytical study will be conducted using the information gained from patient interviews, questionnaires and clinical records. There are 57 adult patients on the record at the Bloemfontein Haemophilia Treatment Centre and we plan to sample 40 adult participants consecutively to participate in our study at the clinic.

The data will be published in a scientific journal and a presentation will be made at the annual Medical and Scientific Advisory Council meeting of the South African Haemophilia Foundation.

1. INTRODUCTION

Although inherited bleeding disorders are rather uncommon, the patients with these conditions are often faced with unique health related problems and treatment challenges. Congenital bleeding disorders encompass a group of disorders with multiple different aetiologies that lead to a tendency to bleed abnormally. The causes range from insufficient levels of coagulation factors (such as haemophilia A, haemophilia B and Von Willebrand disease abbreviated as VWD) to vessel wall abnormalities (such as hereditary haemorrhagic telangiectasia) and platelet functional disorders (such as Bernard-Soulier syndrome). Haemophilia A is the most common congenital coagulation factor disorder and affects 1 in 10 000 males worldwide. It is caused by insufficient levels of factor VIII as a result of many different defects in the X-linked factor VIII gene. Haemophilia B results from insufficient levels of factor IX as result of mutations in the X-linked factor IX gene and VWD results from insufficient levels of or functional defects of Von Willebrand factor (VWF) due to defects of the VWF-gene on chromosome 12. Haemophilia severity can range from mild through moderate to severe depending on the circulating level of procoagulant factor with mild disease correlating with 5 - 40%, moderate with 1 - 5% and severe < 1% of normal circulating factor. Coagulation disorders are characterised by soft tissue bleeds as well as haemarthroses affecting knee, elbow, ankle and hip joints most commonly. Bleeding into joints is painful and repeated bleeding leads to secondary osteoarthrosis, often resulting in limitation of movements. Before 1985 many patients in South Africa contracted treatment related viral infections such as hepatitis B virus (HBV), hepatitis C virus (HCV) and human immunodeficiency virus (HIV), (1,2) but this transmission risk was virtually eliminated after the introduction of newer therapies. Current treatment involves, amongst others, raising the deficient factor levels with intravenous infusion of recombinant or plasma-derived factor. This can be done as home therapy, provided the family is capable. (1)

Perhaps the most feared treatment-related complication of haemophilia is the development of inhibitors - antibodies that develop in response to infused factor concentrates, rendering them ineffective. It occurs in approximately 10 - 15% of patients with haemophilia A and 1 - 3% of haemophilia B patients. (3)

In 2009 there were 11 haemophilia treatment centres (HTCs) in South Africa that cared for 2200 patients with bleeding disorders. (4) Studies investigating the psychological aspects influencing quality of life in patients with bleeding disorders have demonstrated an overall negative impact on psychological well-being (5) and have been associated with high levels of distress (6) and lower self-esteem than controls. (7) Patients also report feeling that others do not understand their illness, reluctance to disclose health status, especially when they are HIV positive, and difficulty in managing drug and alcohol problems. (8) Furthermore, patients' quality of life significantly declines with increasing age (9,10) and patients tend to retire earlier than controls do. (11) While one study in 2003 (2) reported no increased risk for depression, other studies investigating psychiatric comorbidities in patients with bleeding disorders have demonstrated significant levels of depression and anxiety. (7,9,12) In addition, increased severity of disease, (9) lack of social support and unemployment (12) were significant risk factors for developing depression. Likewise, the presence of comorbid depression can have a negative impact on the quality of life of patients with severe haemophilia. (13)

When compared to bleeding disorders, far more research has been done on the negative impact of common chronic illnesses such as diabetes, arthritis and asthma and their impact on psychological health. Diabetes mellitus has been associated with psychiatric problems such as depression, anxiety (14-17) and distress. (18) Rheumatoid arthritis has also been strongly associated with the development of depression. (19) In addition, studies showed that comorbid psychiatric illness can affect the control, adherence and the general health of patients suffering from chronic illnesses such as diabetes, rheumatoid arthritis and asthma (18,20-24) and that early treatment of psychiatric disorders can greatly impact the course of chronic illnesses. (20)

According to our knowledge there are no published data available on the psychiatric comorbidities of patients with bleeding disorders in South Africa. An unpublished study, conducted in 2011 at the Bloemfontein Haemophilia Treatment Centre (BHTC) and the Kimberley Haemophilia Treatment Centre, measured health related quality of life in adults with haemophilia with the aid of the A36 Haemophilia-QoL® questionnaire. (25) This study demonstrated an overall good quality of life, but that 'emotional functioning' and 'mental health' were the main factors affecting quality of life in those scoring lower. 'Physical health' and 'daily activities' were the other important domains affecting quality of life in study participants. Another unpublished study, similar to our intended study, was

done at the BHTC in 2005. (26) It included 30 adult patients suffering from haemophilia. At the time 80% were mentally healthy and 10% had major depression, with 73% not regarding haemophilia as a health stressor. Twenty-two (73%) of the respondents had had a major depressive episode (MDE), of which 12 had one and 9 had more than 5 MDEs. Thirteen had contemplated suicide, but with no attempts. Seven had previously used antidepressants. Seventy percent indicated that they would have liked psychological intervention. Despite having haemophilia, 83% had adequate levels of functioning. In the intervening 12 years the profile of patients and delivery of care has changed.

2. AIM

Our aim is to assess the prevalence of comorbid psychiatric conditions and the quality of life in patients with bleeding disorders visiting the BHTC, South Africa from 5 February 2018 to 26 October 2018. Associations will be investigated if numbers permit.

3. METHODOLOGY

Study design

This is a cross-sectional study using data collected from three questionnaires, a functional assessment, as well as the patients' clinical notes. Potential participants will be interviewed, and information collected with the aid of the Mini International Neuropsychiatric Interview (M.I.N.I.), as well as a face-to-face questionnaire about their clinical condition. They will then undergo a functional assessment, and after this, participants will be asked to complete the EQ-5D-5L questionnaire while the rest of the clinical data will be gained from patient clinical notes. The principal researcher will be assisted in this by one of the other researchers, Dr Jaco Joubert - consultant at the Department Haematology and Cell Biology. Each questionnaire will receive a unique participant number. The entire session is expected to last about 60 minutes.

Sample selection

There are 208 patients on record at the BHTC, of which 57 attend the clinic regularly (at least twice a year) and the majority are at least 18 years old. Consecutive sampling will be used by inviting patients attending the BHTC on their follow up date. A text message will be sent to patients registered with the BHTC on the telephone numbers that are allocated in their files at the start of the study to make them aware of the study and to invite them to participate. Data will be collected during Haemophilia Clinics on the first and last Thursday of each month. The study will be advertised at the Clinic on three A4 posters in the BHTC waiting area in order to obtain participants and should it happen that we are unable to evaluate the target number of participants for our study, we will call them and invited them for participation. The study will commence on the 5th of February 2018 and data collection will continue until 28 February 2019 or until data from a total of 40 participants have been collected successfully by the researcher, whichever occur last.

Inclusion criteria:
- Adult patients (18 years of age or older) receiving treatment for a bleeding disorder at the BHTC who give informed consent.

Exclusion criteria:
- Age < 18 years of age.
- Acquired bleeding disorders.
- Patients who are not willing to give consent.

Measurement

Psychiatric comorbidities:

The M.I.N.I. interview is a brief structured diagnostic tool validated for research surveys. (27-29) The standard version screens for the 17 most common psychiatric conditions and consists of 'yes' or 'no' questions that the interviewer marks while interviewing the participant. It is estimated to take about 15 minutes to complete. If it transpires during the interview that the participant has cognitive symptoms such as memory deficit, the lead researcher will do a screening Montreal Cognitive Assessment (MoCA) questionnaire on the participant. The MoCA has been validated as a screening

tool for cognitive impairment in psychiatry (30). An English or Afrikaans version will be used. The MoCA have not been validated for the Sotho population as of yet, therefore the MoCA test will be performed with the aid of a translator - the BHTC nurse - whom is well versed in Sesotho. She will briefly be trained in the use of the MoCA by the principal researcher to enhance the screening process for Sesotho speaking participants. The subsets of the tests where words need to be remembered, words will be translated from the English version into a Sesotho word that falls in the same category (e.g. verb to a verb, noun to a noun, etc.). Where a sentence needs to be translated it will have the same structure as the English sentence. The same Sesotho versions will be used for different Sesotho speaking participants.

Quality of life:

The EQ-5D-5L questionnaire will be used to assess the quality of life of the participants. It is a self-rated questionnaire that assesses five domains of functioning: mobility, self-care, usual activities, pain and psychological status. The participant ticks one of five answers for each domain, correlating with severity where the first box correlates with no impairment and the 5th box to severe level of impairment. The responses describe the health profile of the participant numerically from 11111 to 55555 and the results can be presented as frequencies for reported problems for each dimension and compared across other variables such as age and comorbidities. Health profiles can also be converted into index values which are presented in country specific value sets, and this can be used to facilitate calculations of quality-adjusted life years (QALYs). Value sets are not available for South Africa yet and, thus, value sets from the country that resembles South Africa closest can be used to interpret results. It is a standardized tool that provides a measure of health for clinical, as well as economic appraisal. (31-34) The questionnaire is made available in English, Afrikaans and Sesotho by the EuroQol Group and should take about 5 minutes to complete.

Functional assessment:

We intend to assess potential participants' level of disability with the aid of the FISH (Functional Independence Score in Hemophilia). It is a performance-based tool validated to assess the functional ability of patients with haemophilia. (35,36) It assesses the level of self-care (dressing, bathing, grooming and eating), ability to transfer (squatting and chair transfer), as well as locomotion (walking, running and climbing stairs), by observing potential participants performing these activities in an outpatient setting and then scoring them from 1 through 4. The worst level of functioning correlating with a score of 1 and the best level of functioning with a score of 4. We decided to assess joint health with the use of a clinical measure like the FISH, as opposed to using radiological assessments, as the latter often correlate poorly with clinical functioning, as is the case with osteoarthritis. (10,36-38) Non-haemophilia patients will be analysed as a separate subgroup as this tool is only validated for haemophilia. The assessment is estimated to last about 15 minutes.

Haemophilia questionnaire:

A face-to-face questionnaire will be used to gather demographic data: age, gender, place of residence, self-reported ethnicity, employment status, highest level of education, marital status and whether or not the participant receives a disability grant. It will also include clinical questions to ascertain information about the frequency of bleeds, appointments missed, use of home therapy, perceived social support, use of a MedicAlert bracelet and other medical conditions. Questions will be read out by the interviewer in English or Afrikaans and should the patient prefer, the questions will be read out in Sesotho by a translator from the standardized questionnaire. It is expected to take about 5 minutes to complete.

Clinical data:

Clinical data concerning the diagnosis, severity, HIV, HBV and HCV infections will be gained from patient clinical files. Current and previous inhibitor status (positive or negative), and current and previous inhibitor quantities in positive patients (Bethesda Unit level), will also be recorded from patient clinical records.

Methodological and measurement errors:

The use of consecutive sampling renders the study susceptible to bias. Outcomes may be hampered by non-responder bias as we will only be assessing the patients that follow up regularly and will miss valuable data on patients who do not regularly attend or default appointments. It is possible that patients not attending clinics may have economic or personal motives for missing appointments. These reasons are potential risk factors for the development of comorbid psychiatric illnesses. Reliability of results may be hampered by a small sample size.

Systematic bias is limited by using validated questionnaires for each participant. Inclusion and exclusion criteria are used to limit the errors in bias.

Pilot study

A pilot study is planned to start on the 29th of January 2018 where 5 participants with a bleeding disorder at the BHTC will be interviewed. It will continue until the 1st of February 2018. Should the pilot study show no need for change to the research protocol, data from participants who do fulfil the sample criteria of the main study may be included in the final analysis.

4. ANALYSIS OF DATA

The study will determine the prevalence rates of psychiatric illness and level of quality of life. The data will be provided to the Department of Biostatistics in Excel format. Results will be summarised by frequencies and percentages (categorical variables) and means and standard deviations or percentiles (numerical variables). Associations will be assessed using contingency tables with relative risks, 95% confidence intervals and appropriate hypothesis testing. Data analysis will be done by Prof. Gina Joubert, biostatistician from the Department of Biostatistics at the University of the Free State (UFS).

5. IMPLEMENTATION OF FINDINGS

The results will be made available to the BHTC. We plan to publish the results in a scientific journal to stimulate awareness among health care workers. We also plan to present the results at the annual Medical and Scientific Advisory Council (MASAC) meeting of the South African Haemophilia Foundation.

6. TIME SCHEDULE

Literature review	August, September 2017
Planning and writing of research protocol	October, November 2017
Application for Ethics Committee approval	November 2017
Pilot study	January 2018
Data collection	February - October 2018
Checking data	February - October 2018
Typing and verifying data	February - October2018
Data analysis	October, November 2018
Writing research report and article	February 2019
Present results	November 2019

7. BUDGET

Paper	60 pages x 40 participants	50c/page	R1200
Fuel	70 km	R14/l	R100
Telecommunication			R200
M.I.N.I questionnaire			No cost
EQ-5D-5L			No cost
FISH tool			No cost
Bulk SMSs	300	R0.32/SMS	R96
Reimbursement for transport expenses	+/- 20 participants x +/- R120		R2400
Total			R3996

The project will be funded by the principal researcher.

8. ETHICAL CONSIDERATIONS

Approval will be obtained from the Health Sciences Research Ethics Committee (HSREC), Faculty of Health Sciences, UFS.

The value of the intended study is that it will increase awareness of common conditions which should lead to more comprehensive interventions and, thus promoting individual health.

The study will be conducted at Universitas Academic Hospital in a consultation room in the Haemophilia Clinic on the 2nd floor. Neither the room nor the flight of stairs pose any obvious hazards to participants. The regular clinic activities and psychiatric assessments will not increase the bleeding risk. Participants will not be randomly exercised - FISH assessments of all subjects will be performed strictly according to the published FISH instructions (Attachment K). Regular FISH assessments can be viewed as part of routine haemophilia care. The risk of bleeding when using the FISH score is negligible, as it was specifically designed to be administered in a clinic setting. Activities that can lead to bleeding such as carrying heavy objects, jumping and throwing, are not included in the assessment. One of the limitations of the FISH score is that activities such as these (which may be encountered in certain occupations or as activities of daily living) are omitted. (35)

The FISH score, already published in 2005, was originally developed using patients with a high bleeding risk (patients with severe haemophilia A or B, who had proven severe bleeding phenotypes; i.e. at least three major bleeds per year) in which it was found to be safe and useful. It was subsequently evaluated and found to be safe and useful in children with mild and moderate disease as well. (39). In a psychometric analysis of the FISH tool in 63 patients, no bleeds were encountered (36) again confirming its safety for clinical use.

The FISH tool is also designed to be used in such a way that should a patient not feel comfortable attempting a certain activity or know that he is definitely not able to perform a certain activity (e.g. running) then that activity is not assessed. This further minimizes the risk of bleeding, pain and discomfort. The instructions for performing the FISH assessment specifically state the following regarding stair climbing: “As this is a provocative test, ask the patient first if he is able to climb the flight of 14 steps. If he says it is not possible, ask him to try to do so with aid from the railings; but if he still says it is not possible, score 1. Do not force the subject to do the activity”. It states the following regarding running: “As this is a provocative test, ask the patient firs if he feels able to perform the activity. If he says it is not possible for him to run, assess his ability to walk briskly, by asking him to walk the same distance as fast as he can. If at any point the subject complains of pain, or is reluctant to proceed, the test should be stopped, and the subject scored appropriately. Do not force the subject to do the activity.” FISH assessments of all subjects will be performed strictly according to these instructions. The Physiotherapy Department at the Universitas Academic Hospital will assist in the functional assessment. Participants, that are indeed still able to run, will be assessed on a treadmill in the Gymnasium.

Should a participant start bleeding during the functional assessment, medical help will be provided by the health care workers at the BHTC. The main researcher will accompany participants during the assessment (for example, while walking up the flight of stairs) to ensure safety and should it happen that an injury occurs, it will be attended to by the researcher if it is mild (such as a soft tissue injury), or the participant will be referred to the appropriate level of care should there be suspicion of a more serious injury. Participants that are diagnosed with a psychiatric illness will be referred by the researcher to the appropriate psychiatric services, should they so desire.

Most potential participants will be interviewed when visiting the clinic for regular follow up appointments; others may be invited to participate in the study via telephone call. Patients residing inside Bloemfontein usually arrange and pay for their own transport to the BHTC. Patients residing outside Bloemfontein usually use the Free State Department of Health (FSDoH) patient commuter service to get to the clinic. A place on this service needs to be booked in advance. Sometimes the patient commuter service is full, or ambulances are not available. The NovoGo® project runs under the auspices of the South African Haemophilia Foundation (http://ipasa.cp.za/innovation-boosts-access-to-medicines/), which is funded by the pharmaceutical company Novo Nordisk. Indigent patients can register with it in order to be reimbursed for transport to the hospital or clinic for treatment if government transport is not available. The BHTC authorizes the use of the NovoGo® service every

time a patient requests assistance; and gets a monthly summary as well. NovoGo® determines what a reasonable reimbursement is for each patient depending on where that patient lives. If the patient comes to the BHTC specifically for this research study, we will reimburse the patient according to rates NovoGo® advises for transport to the clinic and back home if the patient cannot be booked on the FSDoH commuter service. Patients will not be reimbursed for money spent on other expenditures such as meals or accommodation on the same day. The table below provides examples of the NovoGo® transport rates for patients attending the BHTC:

Place (Suburb of Bloemfontein, or Town)	Tariff (One-way)	Tariff (Return)
Khayelisha, Bloemfontein	R 40-00	R 80-00
Rocklands, Bloemfontein	R 40-00	R 80-00
Phahameng, Bloemfontein	R 80-00	R 160-00
Bloemfonein Central	R 40-00	R 80-00
Heidedal, Bloemfontein	R 40-00	R 80-00
QwaQwa	R 360-00	R 720-00
Excelsior	R 145-00	R 290-00
Springfontein	R 145-00	R 290-00
Kroonstad	R 200-00	R 400-00
Welkom	R 280-00	R 560-00
Navalsig, Bloemfontein	R 160-00	R 320-00
Rammulotsi, Viljoenskroon	R 260-00	R 520-00
Sasolburg	R 350-00	R 700-00
Ventersburg	R 300-00	R 600-00
Witsieshoek	R 380-00	R 760-00

Participants will only be paid at the end of the visit and will sign a notebook to confirm payment.

Potential participants will need to give informed consent, voluntarily and personally, to participate in the study. Should the patient decline to consent, he/she will still be managed at the clinic as usual and without penalty. Consent forms will be available in English, Afrikaans and Sesotho, and where necessary, a translator will be used to communicate information. Dr Heinrich Koekemoer will inform potential participants of the intended aim, duration, potential benefit and possible harms of the study. They will be given an information leaflet to take home containing all the information of the intended study, as well as the contact details of the researcher in their language of preference.

A text message will be sent to all participants that fit inclusion criteria at the start of the study that will contain information on the study and on how to volunteer for participation. The clinic keeps a current list of cell phone numbers of all patients and frequently communicates with patients by bulk SMS. Three A4 posters will be visible during the time of the study in the BHTC waiting area with information on the study, as well as, how to volunteer for participation.

Participants may request a hard copy of the study results from the health care workers at the BHTC or directly from Dr Koekemoer whose cell phone number appears on the information leaflet, should they wish to receive it.

Potential participants will be interviewed privately. All questionnaires, as well as the data form will only contain a unique participant number and no participant name. The researcher will have access to a list of participant names linked to their participation number for the purpose of tracing participants who have been diagnosed with a psychiatric disorder and require further management. All data will be de-identified and no data that can lead to identification of an individual patient or health care worker will be included in Excel spread sheet used by the Department of Statistics or in the final report.

Although haemophilia affects individuals from all races, data will be collected on patient self-reported ethnicity as there are distinct ethnic differences especially regarding the most feared complication of haemophilia – inhibitor development. Persistent inhibitors (antibodies that develop in response to infused factor concentrates, rendering them ineffective) occur in approximately 10 - 15% of patients with haemophilia A and 1 - 3% of haemophilia B patients, and are more common in African patients. (3) This higher risk in African populations has been found to be independent of genotype. (40) In South Africa, it is recommended that all patients be monitored every 3 - 6 months for the development of inhibitors, and that this should be done more frequently in newly diagnosed African patients with

severe haemophilia A, who are at greatest risk. (3) This higher rate of laboratory testing for inhibitors in African patients may impact adversely on their quality of life, and the higher risk of inhibitor development in African patients can conceivably lead to levels of anxiety about their disease, which is greater than that experienced by their Caucasian counterparts. The recent SIPPET study (41) did not document any relationship between ethnicity and inhibitor development. However, a recent small South African study appears to support the ethnic differences in inhibitor development. (42)

No blood or tissue specimens will be collected from patients for the purposes of this study and patients will not be subjected to any therapeutic interventions for the purposes of this study.

9. CONCLUSION

Very little is known about the prevalence of psychiatric disorders and quality of life of patients suffering from bleeding disorders in South Africa. Analysis of the results of the study will facilitate a more realistic approach to caring for patients with bleeding disorders.

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M.I.N.I.

MINI INTERNATIONAL NEUROPSYCHIATRIC INTERVIEW

English Version 7.0.2

For

DSM-5

DISCLAIMER

Our aim is to assist in the assessment and tracking of patients with greater efficiency and accuracy. Before action is taken on any data collected and processed by this program, it should be reviewed and interpreted by a licensed clinician.

This program is not designed or intended to be used in the place of a full medical and psychiatric evaluation by a qualified licensed physician – psychiatrist. It is intended only as a tool to facilitate accurate data collection and processing of symptoms elicited by trained personnel. It is not a diagnostic test.

M.I.N.I. 7.0.2 (August 8, 2016) (8/8/16)

Patient Name:		***Patient Number:***	
Date of Birth:		***Time Interview Began:***	
Interviewer's Name:		***Time Interview Ended:***	
Date of Interview:		***Total Time:***	

	MODULES	TIME FRAME	MEETS CRITERIA	ICD-10-CM	PRIMARY DIAGNOSIS
A	MAJOR DEPRESSIVE EPISODE	Current (2 weeks)	☐		
		Past	☐		
		Recurrent	☐		
	MAJOR DEPRESSIVE DISORDER	Current (2 weeks)	☐	F32.x	☐
		Past	☐	F32.x	☐
		Recurrent	☐	F33.x	☐
B	SUICIDALITY	Current (Past Month)	☐		☐
		Lifetime attempt	☐	☐ Low ☐ Moderate ☐ High	☐
	SUICIDE BEHAVIOR DISORDER	Current	☐	(In Past Year)	☐
		In early remission	☐	(1 - 2 Years Ago)	☐
C	MANIC EPISODE	Current	☐		
		Past	☐		
	HYPOMANIC EPISODE	Current	☐		
		Past	☐	☐ Not Explored	
	BIPOLAR I DISORDER	Current	☐	F31.0 - F31.76	☐
		Past	☐	F31.0 - F31.76	☐
	BIPOLAR II DISORDER	Current	☐	F31.81	☐
		Past	☐	F31.81	☐
	OTHER SPECIFIED BIPOLAR AND RELATED DISORDER	Current	☐	F31.89	☐
		Past	☐	F31.89	☐
D	PANIC DISORDER	Current (Past Month)	☐	F41.0	☐
		Lifetime	☐	F40.0	☐
E	AGORAPHOBIA	Current	☐	F40.00	☐
F	SOCIAL ANXIETY DISORDER (Social Phobia)	Current (Past Month)	☐	F40.10	☐
G	OBSESSIVE-COMPULSIVE DISORDER	Current (Past Month)	☐	F42.2	☐
H	POSTTRAUMATIC STRESS DISORDER	Current (Past Month)	☐	F43.10	☐
I	ALCOHOL USE DISORDER	Past 12 Months	☐	F10.10 - F10.21	☐
J	SUBSTANCE USE DISORDER (Non-alcohol)	Past 12 Months	☐	F11.10 - F19.21	☐
K	ANY PSYCHOTIC DISORDER	Current	☐	F20.81-F29	☐
		Lifetime	☐	F20.81-F29	☐
	MAJOR DEPRESSIVE DISORDER WITH PSYCHOTIC FEATURES	Current	☐	F32.3/F33.3	☐
		Past	☐	F32.3/F33.3	☐
	BIPOLAR I DISORDER WITH PSYCHOTIC FEATURES	Current	☐	F31.2/F31.5/F31.64	☐
		Past	☐	F31.2/F31.5/F31.64	☐

L	ANOREXIA NERVOSA	Current (Past 3 Months)	☐	F50.01/F50.02	☐
M	BULIMIA NERVOSA	Current (Past 3 Months)	☐	F50.2	☐
MB	BINGE-EATING DISORDER	Current (Past 3 Months)	☐	F50.81	☐
N	GENERALIZED ANXIETY DISORDER	Current (Past 6 Months)	☐	F41.1	☐
O	MEDICAL, ORGANIC, DRUG CAUSE RULED OUT			☐ No ☐ Yes ☐ Uncertain	
P	ANTISOCIAL PERSONALITY DISORDER	Lifetime	☐	F60.2	☐

IDENTIFY THE PRIMARY DIAGNOSIS BY CHECKING THE APPROPRIATE CHECK BOX.
(Which problem troubles you the most or dominates the others or came first in the natural history?)

GENERAL INSTRUCTIONS

The M.I.N.I. was designed as a brief structured interview for the major psychiatric disorders in DSM-5 and ICD-10. Validation and reliability studies have been done comparing the M.I.N.I. to the SCID-P for DSM-III-R and the CIDI (a structured interview developed by the World Health Organization). The results of these studies show that the M.I.N.I. has similar reliability and validity properties, but can be administered in a much shorter period of time (mean 18.7 ± 11.6 minutes, median 15 minutes) than the above referenced instruments. Clinicians can use it, after a brief training session. Lay interviewers require more extensive training.

INTERVIEW:

In order to keep the interview as brief as possible, inform the patient that you will conduct a clinical interview that is more structured than usual, with very precise questions about psychological problems which require a yes or no answer.

GENERAL FORMAT:

The M.I.N.I. is divided into **modules** identified by letters, each corresponding to a diagnostic category.
•At the beginning of each diagnostic module (except for psychotic disorders module), screening question(s) corresponding to the main criteria of the disorder are presented in a **gray box**.
•At the end of each module, diagnostic box(es) permit the clinician to indicate whether diagnostic criteria are met.

CONVENTIONS:

Sentences written in « normal font » should be read exactly as written to the patient in order to standardize the assessment of diagnostic criteria.

Sentences written in « CAPITALS » should not be read to the patient. They are instructions for the interviewer to assist in the scoring of the diagnostic algorithms.

Sentences written in « **bold** » indicate the time frame being investigated. The interviewer should read them as often as necessary. Only symptoms occurring during the time frame indicated should be considered in scoring the responses.

Answers with an arrow above them (➡) indicate that one of the criteria necessary for the diagnosis or diagnoses is not met. In this case, the interviewer should go to the end of the module, circle « **NO** » in all the diagnostic boxes and move to the next module.

When terms are separated by a *slash* (/) the interviewer should read only those symptoms known to be present in the patient (for example, questions J2b or K6b).

Phrases in (parentheses) are clinical examples of the symptom. These may be read to the patient to clarify the question.

RATING INSTRUCTIONS:

All questions must be rated. The rating is done at the right of each question by circling either YES or NO. Clinical judgment by the rater should be used in coding the responses. Interviewers need to be sensitive to the diversity of cultural beliefs in their administration of questions and rating of responses. The rater should ask for examples when necessary, to ensure accurate coding. The patient should be encouraged to ask for clarification on any question that is not absolutely clear.

The clinician should be sure that each dimension of the question is taken into account by the patient (for example, time frame, frequency, severity, and/or alternatives).

Symptoms better accounted for by an organic cause or by the use of alcohol or drugs should not be coded positive in the M.I.N.I. The M.I.N.I. has questions that investigate these issues.

For any questions, suggestions, need for a training session or information about updates of the M.I.N.I, please contact:
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e-mail : dsheehan@health.usf.edu
For licensing, permissions, or questions, contact: davidvsheehan@gmail.com

APPENDIX H1

EQ-5D-5L QUESTIONNAIRE (ENGLISH)

Under each heading, please tick the ONE box that best describes your health TODAY.

MOBILITY

I have no problems in walking about ❑
I have slight problems in walking about ❑
I have moderate problems in walking about ❑
I have severe problems in walking about ❑
I am unable to walk about ❑

SELF-CARE

I have no problems washing or dressing myself ❑
I have slight problems washing or dressing myself ❑
I have moderate problems washing or dressing myself ❑
I have severe problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ❑
I have slight problems doing my usual activities ❑
I have moderate problems doing my usual activities ❑
I have severe problems doing my usual activities ❑
I am unable to do my usual activities ❑

PAIN / DISCOMFORT

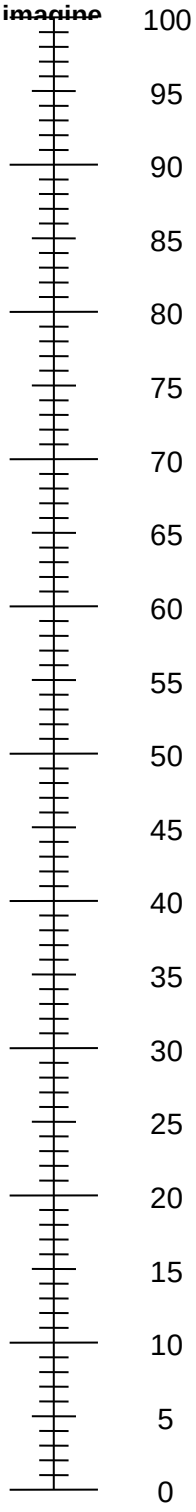
I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

I am not anxious or depressed ❑
I am slightly anxious or depressed ❑
I am moderately anxious or depressed ❑
I am severely anxious or depressed ❑
I am extremely anxious or depressed ❑

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



APPENDIX H2

EQ-5D-5L QUESTIONNAIRE (SESOTHO)

Tlasa sehlooho ka seng, ka kopo tshwaya lebokose LE LE LENG le hlalosang bophelo ba hao KAJENO hantle ka ho fetisisa.

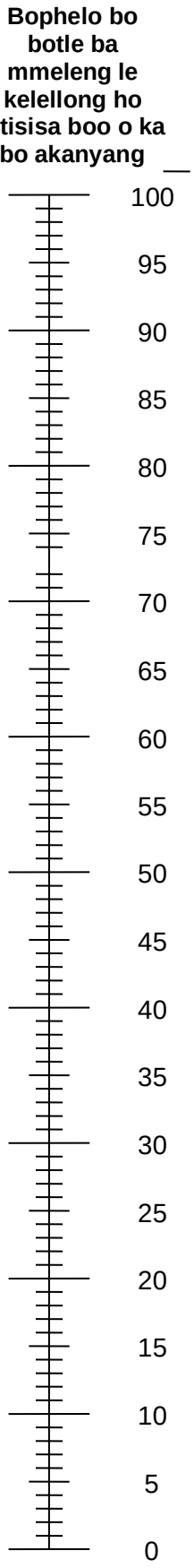
HO TSAMAYA
Ha ke na bothata ba ho tsamaya ❑
Ke na le bothata bo bonyane ba ho tsamaya ❑
Ha ke na bothata bo bokaalo ba ho tsamaya ❑
Ke na le bothata bo mahlonoko ba ho tsamaya ❑
Ha ke kgone ho tsamaya ❑

HO ITLHOKOMELA
Ha ke na bothata ba ho itlhatswa kapa ho ikapesa ❑
Ke na le bothata bo bonyane ba ho itlhatswa kapa ho ikapesa ❑
Ha ke na bothata bo bokaalo ba ho itlhwatswa kapa ho ikapesa ❑
Ke na le bothata bo mahlonoko ba ho itlhatswa kapa ho ikapesa ❑
Ha ke kgone ho itlhatswa kapa ho ikapesa ❑

MESEBETSI YA SETLWAEDI *(mohlala: mosebetsi, ho ithuta, mosebetsi wa ka tlung, mesebetsi ya lelapa, kapa ya ho iketla)*
Ha ke na bothata ba ho etsa mesebetsi ya ka ya setlwaedi ❑
Ke na le bothata bo bonyane ba ho etsa mesebetsi ya ka ya setlwaedi ❑
Ha ke na bothata bo bokaalo ba ho etsa mesebetsi ya ka ya setlwaedi ❑
Ke na le bothata bo mahlonoko ba ho etsa mesebetsi ya ka ya setlwaedi ❑
Ha ke kgone ho etsa mesebetsi ya ka ya setlwaedi ❑

HO OPELWA / MAKUKUNO
Ha ke na ho opelwa kapa makukuno ❑
Ke na le ho opelwa ho honyane kapa makukuno ❑
Ke na le ho opelwa ho seng hokaalo kapa makukuno ❑
Ke na le ho opelwa ho mahlonoko kapa makukuno ❑
Ke na le ho opelwa ho hobe ho fetisisa kapa makukuno ❑

HO TSHWENYEHA KAPA HO WA HA MAIKUTLO
Ha ke a tshwenyeha kapa ho wa maikutlo ❑
Ke tshwenyehile hanyane kapa ho wa maikutlo ❑
Ha ke a tshwenyeha hakaalo kapa ho wa maikutlo ❑
Ke tshwenyehile ho mahlonoko kapa ho wa maikutlo ❑
Ke tshwenyehile hampempe kapa ho wa maikutlo haholoholo ❑



- Re lakatsa ho tseba hore na bophelo ba hao ba mmeleng le kelellong bo botle kapa bo bobe hakae KAJENO.
- Sekala se nomorilwe ho tloha ho 0 ho isa ho 100.
- 100 e bolela bophelo bo botle ba mmeleng le kelellong ho fetisisa ka moo o ka akanyang.
  0 e bolela bophelo bo bobe ba mmeleng le kelellong ho fetisisa ka moo o ka akanyang.
- Tshwaya ka X sekaleng ho bontsha hore na bophelo ba hao ba mmeleng le kelellong bo jwang KAJENO.
- Jwale, ngola nomoro eo o e tshwaileng sekaleng ka lebokoseng le ka tlase ka kopo.

BOPHELO BA HAO BA MMELLENG LE KELELLONG KAJENO = ☐

APPENDIX H3

EQ-5D-5L QUESTIONNAIRE (AFRIKAANS)

Merk asseblief onder elk van die opskrifte die EEN blokkie wat u gesondheid VANDAG die beste beskryf.

BEWEEGLIKHEID

Ek het geen probleme om rond te loop nie ❑
Ek het effens probleme om rond te loop ❑
Ek het taamlik probleme om rond te loop ❑
Ek het erge probleme om rond te loop ❑
Ek is nie in staat om rond te loop nie ❑

SELFVERSORGING

Ek het geen probleme om myself te was of aan te trek nie ❑
Ek het effens probleme om myself te was of aan te trek ❑
Ek het taamlik probleme om myself te was of aan te trek ❑
Ek het erge probleme om myself te was of aan te trek ❑
Ek is nie in staat om myself te was of aan te trek nie ❑

GEWONE AKTIWITEITE *(bv. werk, studeer, huiswerk, familie- of ontspanningsaktiwiteite)*

Ek het geen probleme om my gewone aktiwiteite uit te voer nie ❑
Ek het effens probleme om my gewone aktiwiteite uit te voer ❑
Ek het taamlik probleme om my gewone aktiwiteite uit te voer ❑
Ek het erge probleme om my gewone aktiwiteite uit te voer ❑
Ek is nie in staat om my gewone aktiwiteite uit te voer nie ❑

PYN / ONGEMAK

Ek het geen pyn of ongemak nie ❑
Ek het effense pyn of ongemak ❑
Ek het matige pyn of ongemak ❑
Ek het erge pyn of ongemak ❑
Ek het uiterste pyn of ongemak ❑

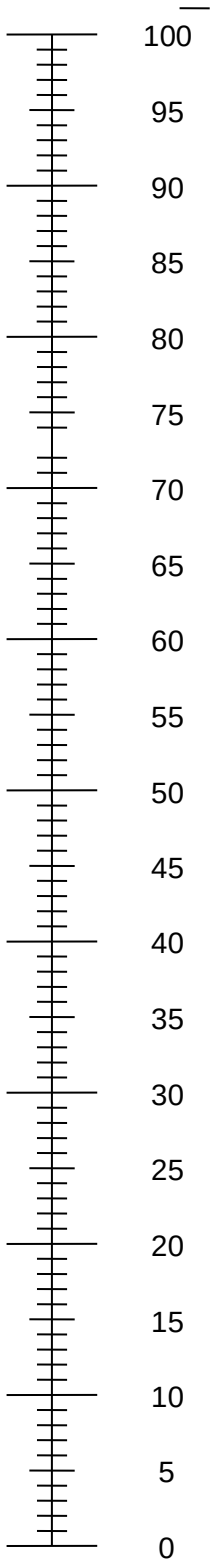
ANGSTIGHEID / NEERSLAGTIGHEID

Ek is nie angstig of neerslagtig nie ❑
Ek is effens angstig of neerslagtig ❑
Ek is taamlik angstig of neerslagtig ❑
Ek is erg angstig of neerslagtig ❑
Ek is uiters angstig of neerslagtig ❑

- Ons wil graag weet hoe goed of sleg u gesondheid VANDAG is.
- Hierdie skaal is van 0 tot 100 genommer.
- 100 beteken die beste gesondheid wat u u kan indink.
  0 beteken die slegste gesondheid wat u u kan indink.
- Merk met ’n kruisie op die skaal om aan te dui hoe u gesondheid VANDAG is.
- Skryf nou die nommer wat u op die skaal gemerk het in die blokkie hier onder.

U GESONDHEID VANDAG = ☐

Die beste gesondheid wat u u kan indink



Die slegste gesondheid wat u u kan

FUNCTIONAL INDEPENDENCE SCORE IN HEMOPHILIA (FISH)

Performance based instrument

Patient Name:	**Patient Code:**
	Today (dd/mm/yyyy):___/___/___.
A.Self Care	
1. Eating and grooming	◯ 1 ◯ 2 ◯ 3 ◯ 4
2. Bathing	◯ 1 ◯ 2 ◯ 3 ◯ 4
3. Dressing	◯ 1 ◯ 2 ◯ 3 ◯ 4
B. Transfers	
4. Chair	◯ 1 ◯ 2 ◯ 3 ◯ 4
5. Squatting	◯ 1 ◯ 2 ◯ 3 ◯ 4
C. Locomotion	
6. Walking	◯ 1 ◯ 2 ◯ 3 ◯ 4
7. Stairs (12 - 14 steps)	◯ 1 ◯ 2 ◯ 3 ◯ 4
8. Running	◯ 1 ◯ 2 ◯ 3 ◯ 4
Total Score	

Scores range from 1 - 4 depending on the degree of independence (see scoring key)

Comments:

CLINICAL QUESTIONNAIRE (ENGLISH)

1-2

3-8

1. Date of interview:
   (DD/MM/YY) _____ D D M M Y Y

2. What is your age?_____ 9-10

3. What is your gender? 11

1	Male
2	Female

4. What Ethnic group do you consider yourself part of? 12

1	Black
2	White
3	Coloured
4	Other (Specify)_____

5. Where is your place of residence? 13

1	Inside Bloemfontein/Mangaung
2	Not inside Bloemfontein/Mangaung, but inside Free State
3	Outside Free State borders (specify)_____

6. Are you currently working? 14

1	Yes
2	No

For official use

7. What is your highest level of education?

1	No formal education	15
2	Special education	
3	General education (Gr. R - Gr.9)	
4	Further education (Gr. 10 - Gr. 12)	
5	Higher education (Certificate - Doctorate)	

8. What is your marital status?

1	Never married	16
2	Married/Traditional marriage	
3	Divorced/Separated	
4	Widow/Widower	
5	Co-habiting	

9. Do you receiving a disability grant?

1	Yes	17
2	No	

10. How many times do you bleed in a month due to your disorder?

1	< 1	18
2	1-3	
3	4 or >	

For official use

11. How often do you miss appointments at the Haemophilia clinic?

1	< 1 a year	19
2	1-2 a year	
3	3 or > times a year	

12. What are the most common reasons for missing appointments?

_____ 20-21

_____ 22-23

_____ 24-25

_____ 26-27

_____ 28-29

13. Do you use prophylactic treatment for your bleeds?

1	Yes	30
2	No	

14. If yes, as home therapy or at a clinic?

1	Home therapy	31
2	Clinic	
3	N/A	

15. Are you currently wearing a MedicAlert bracelet?

1	Yes
2	No

For official use

32

16. Do you have other family members with bleeding disorders?

1	No
2	Yes, 1
3	Yes, more than 1

33

17. Do your friends and family help and support you?

1	Yes
2	No

34

18. Do you feel that family and friends understand your bleeding illness?

1	Yes
2	No

35

19. Do you have any other physical or mental conditions?

_____

_____

_____

_____

_____

36-37

38-39

40-41

42-43

44-45

CLINICAL QUESTIONNAIRE (SESOTHO)

1-2

3-8

1. Letsatsi la Puisano:
   (DD/MM/YY) _____

D D M M Y Y

2. O dilemo tse kae?_____ 9-10

3. O mong? 11

1	Ntate
2	Mme

4. Morabe wa hao ke o fe? 12

1	Motho ea motsho
2	Motho ea mosoeu (lekgowa)
3	Wa mmala
4	O mong (Hlalosa)_____

5. O dula kae? 13

1	Ka hara Bloemfontein/Mangaung
2	Kantle ho Bloemfontein/Mangaung empa ka hara Foreisitata
3	Kantle ho Foreisitata_____

6. O a sebetsa na? 14

1	Eya
2	Tjee

Tshebediso ya Semmuso

7. Maemo a hao a thuto ke a fe?

1	Letho	15
2	Thuto e Ikgethileng	
3	Gr R– Gr 9	
4	Gr 10– Gr 12	
5	Thuto e Phahameng	

8. O nyetse/nyetswe?

1	Ha kea nyala/nyalwa	16
2	Nyetswe/Nyetswe ka setso	
3	Re Hlalane	
4	Ke Mohlolohadi	
5	Re Dula Mmoho	

9. O thola grant na (SASSA)?

1	Eya	17
2	Tjee	

10. O tswa madi ha kae kgweding?

1	< 1	18
2	1-3	
3	4 kaapa >	

Tshebediso ya Semmuso

11. O ke o fetwe ke matsatsi a kliniki ha kae?

1	< 1 selemong	19
2	ha 1-2 selemong	
3	ha 3 kaapa ho feta selemong	

12. Ke mabaka a feng ka sehlohong a etsang o fetwe ke matsatsi a kliniki?

_____ 20-21

_____ 22-23

_____ 24-25

_____ 26-27

_____ 28-29

13. O sebedisa meriana e thibelang ho tswa madi na?

1	Eye	30
2	Tjee	

14. Ha karabo e le "Eya", o e sebedisetsa hae kaapa kliniking?

1	Hae	31
2	Kliniking	
3	N/A	

Tshebediso ya Semmuso

15. O kentse tjheini ya letsoho e tsebisang ka lefu la hao ha jwale?

1	Eya
2	Tjee

32

16. Ho na le batho ba bang lelokong ba amehileng ke mafu a madi?

1	Tjee
2	Eya, 1
3	Eya, > 1

33

17. Metswalle le ba leloko ba o tshusa mme ba o tshehetsa?

1	Eya
2	Tjee

34

18. O dumela hore metswalle ya hao le ba leloko ba utlwisisa lefu le na la hao?

1	Eya
2	Tjee

35

19. O na le mahloko a mang a mmele kaapa a kelello?

_____

_____

_____

_____

_____

36-37

38-39

40-41

42-43

44-45

CLINICAL QUESTIONNAIRE (AFRIKAANS)

1. Datum van onderhoud:
   (DD/MM/JJ) _____ 1-2 | 3-8 (D D M M J J)

2. Wat is u ouderdom (In jare)?_____ 9-10

3. Wat is u geslag? 11

1	Manlik
2	Vroulik

4. Aan watter etniese groep behoort u? 12

1	Swart
2	Blank
3	Kleurling
4	Ander (Spesifiseer)_____

5. Waar woon u? 13

1	In Bloemfontein/Mangaung
2	Nie in Bloemfontein/Mangaung nie, maar in Vrystaat
3	Buite Vrystaat se grens (spesifiseer)_____

6. Werk u huidiglik? 14

1	Ja
2	Nee

Vir kantoor gebruik

7. Wat is u hoogste vlak van opleiding?

1	Geen formele opleiding	15
2	Spesiale opleiding	
3	Algemene opleiding (Gr. R - Gr.9)	
4	Verdere opleiding (Gr. 10 - Gr. 12)	
5	Hoër opleiding (Sertifikaat - Doktoraal)	

8. Wat is u huwelik status?

1	Nooit getroud	16
2	Getroud/Tradisionele huwelik	
3	Amptelik geskei/Nie-amptelik geskei	
4	Weduwee/Wewenaar	
5	Woon saam	

9. Ontvang u ń ongeskiktheidstoelaag?

1	Ja	17
2	Nee	

10. Hoeveel keer in ń maand bloei u as gevolg van u bloedingsiekte?

1	< 1	18
2	1-3	
3	4 of >	

Vir kantoor gebruik

11. Hoe gereeld mis u ń afspraak by die hemofilie kliniek?

1	< 1 keer per jaar	19
2	1-2 keer per jaar	
3	3 of > keer per jaar	

12. Wat is die algemeenste redes hiervoor?

_____ 20-21

_____ 22-23

_____ 24-25

_____ 26-27

_____ 28-29

13. Maak u gebruik van profilaktiese behandeling (voorkoming)?

1	Ja	30
2	Nee	

14. Indien Ja, gebruik u dit as tuis behandeling of kry u dit by ń kliniek?

1	Tuis behandeling	31
2	Ek gaan na ń kliniek	
3	Nie van toepassing	

15. Dra u huidiglik ń MedicAlert armband?

Vir kantoor gebruik

1	Ja
2	Nee

32

16. Is daar enigiemand in u familie wat ook ń bloedingsiekte het?

33

1	Nee
2	Ja, 1 familielid
3	Ja, meer as 1 familielid

17. Ondersteun en help u familie u?

34

1	Ja
2	Nee

18. Voel u dat familie en vriende u bloedingsiekte verstaan?

35

1	Ja
2	Nee

19. Het u enige ander siektes (fisies of psigies)?

_____

_____

_____

_____

_____

36-37

38-39

40-41

42-43

44-45

DATA COLLECTION FORM

[ ][ ] 1-2

Completed by: _____

Date: _____ [ ][ ][ ][ ][ ][ ] 46-51 (D D M M Y Y)

1. Type of bleeding disorder:

1	Haemophilia A
2	Haemophilia B
3	VWBD (Von Willebrand Disease)
4	HHT (Hereditary Haemorrhagic Telangiectasia)
5	Other_____

[ ] 52

2. Severity of bleeding disorder (If haemophilia)

1	Mild
2	Moderate
3	Severe
4	Unknown

[ ] 53

3. HCV infection

1	Never
2	Previous
3	Chronic
4	Unknown

[ ] 54

For official use

4. HBV infection

1	Never	55
2	Previous	
3	Chronic	
4	Unknown	

5. HIV status

1	Reactive	56
2	Non-reactive	
3	Unknown	

6. History of inhibitors:

1	Yes	57
2	No	

7. Highest previous Bethesda Unit level (BU):

_____BU 58-60

8. Inhibitors currently:

1	Yes	61
2	No	

9. Current Bethesda Unit level (BU):

_____BU 62-64

Result of M.I.N.I:

10. DSM5 diagnosis:

1	Yes
2	No

11. If yes, DSM5 diagnosis?

_____

_____

_____

12. If yes, referred for treatment?

1	Yes
2	No

13. If no; reason

_____

_____

_____

EQ-5D-5L (Questionnaire)

14. EQ5D health score: (example 11245).

_____

15. EQ VAS (0-100)

_____


65


66-67

68-69

70-71


72


73-74

75-76

77-78


79

80

81

82

83


84-86

APPENDIX L1

EXAMPLE: TEXT MESSAGE ADVERTISEMENT (ENGLISH)

Good day. You are invited to take part in a research study, conducted at the Haemophilia Clinic, from February to October 2018. If you agree to participate you will be interviewed, asked to fill in a form about your health and undergo a physical examination, lasting about 60 minutes in total. We are looking at the mental health and quality-of-life of patients with bleeding disorders. If you come in on another day than your clinic day, we will pay the transport costs (this does not include other costs like meals, etc.). Participation is voluntary.

Just ask the clinic doctors about the study next time you visit the clinic or phone Dr Koekemoer on 0726520075 for more information.

Thank you.

APPENDIX L2

EXAMPLE: TEXT MESSAGE ADVERTISEMENT (SESOTHO)

Kgotsong. Ba Kliniki ya Haemophilia ba labalabela ho ntlafatsa ditshebeletso tsa bona ho wena le bakudi ba bang, ka ho le memela ho nka karolo diphuputsong tse tlo etsahalang ho tloha ka la 5 Hlakola ho fihlela 26 Mphalane 2018. Re le kopa hore nakong e tlang ha le etela BHTC le arabe tse ding tsa dipotso tsa rona mme le re dumelle ho etsa hlahlobo ya mmele ho lona. Re lekola maemo a bophelo le ho ameha ha kelello ho batho ba amehileng ke mafu a madi. Hona ho tla nka metsotso e mashome a tsheletseng a nako ya lona. Ha ho ka etsahala hore o tle ka letsatsi leo e seng la hao la kliniki, re tla lefella ditjeho tsa leeto leo.

Bakeng sa tlhahiso leseding e fetang mona, le ka botsa e mong wa basebeletsi ba tsa bophelo bo botle ha le tla ho re etela; kaapa le ka letsetsa Dr Koekemoer ho 0766520075.

Rea leboha.

APPENDIX L3

EXAMPLE: TEXT MESSAGE ADVERTISEMENT (AFRIKAANS)

Goeie dag. U word uitgenooi na ń navorsingstudie wat plaas vind vanaf Februarie tot Oktober 2018 by die Hemofilie kliniek. Ons wil geestesgesondheids-probleme en kwaliteit van lewe bepaal in pasiënte met bloedingsiektes. Ons vra u om ń paar vrae te beantwoord, ń vraelys in te vul en om ń fisiese ondersoek te ondergaan die volgende keer dat u die kliniek bywoon. Dit sal omtrent 60 minute duur. As u in kom op ń ander dag as u geréelde afspraak datum sal ons u vervoer onkostes dek (dit sluit nie ander onkostes soos maaltye, ens. in nie). Deelname is vrywillig.

Vra u gesondheidswerker oor die studie die volgende keer as u by die kliniek is of kontak Dr Koekemoer by 0726520075 vir meer inligting.

Dankie.

EXAMPLE: POSTER AT CLINIC ADVERTISEMENT (ENGLISH)

WERE YOU BORN WITH A BLEEDING DISORDER?

IF YOU ARE 18 YEARS OR OLDER ASK THE CLINIC HOW TO GET INVOLVED IN OUR RESEARCH STUDY

Help us improve the care of patients with bleeding disorders by answering questions and filling in a form about your mental health and having a physical examination lasting about 60 minutes.

If you spend any costs to participate we will pay you back

Participation is voluntary

From 5 February till 26 October 2018, Haemophilia clinic, Universitas

FOR MORE INFORMATION PHONE DR KOEKEMOER AT 0726520075

EXAMPLE: POSTER AT CLINIC ADVERTISEMENT (SESOTHO)

A NA O TSWETSWE O ENA LE BOHLOKO BA MADI?

Ha eba o na le dilemo tse leshame le metso e robedi (18), kaapa kahadimo ho moo o ka botsa mosebeletsi wa hao wa tsa bophelo bo botle hore na o ka bapala karolo jwang diphuputsang tsa rona tsa mahlale

Re thuse ho ntlafatsa tlhokomelo ya bakudi ba amehileng ke mafu a madi, ka ho araba dipotso le ho tlatsa foromo mabapi le boemo ba hao ba kelello mme o re dumelle ho etsa hlahlobo ya mmele e tla nkang mashome a tsheletseng a nako ya hao

O tla lefuwa ditshenyehelo tse sebedisitsweng bakeng sa dipalangwang ha o nka karolo

---

Ho nka kanoto ho boithaopong

---

5 Hlakola - 26 Mphalane 2018
Haemophilia clinic, Universitas

BAKENG SA TLHAHISO LESEDING E FETANG MONA, O KA LETSETSA DR KOEKEMOER: 0726520075

EXAMPLE: POSTER AT CLINIC ADVERTISEMENT (AFRIKAANS)

IS U GEBORE MET N BLOEDING SIEKTE?

INDIEN U 18 JAAR OF OUR IS, VRA DIE KLINIEK HOE OM BETROKKE TE RAAK BY ONS NAVORSING-STUDIE

Help ons om dienslewering aan pasiente met

bloedingsiektes te verbeter deur vra te beantwoord en n vraelys in te vul oor u geestesgesondheid, sowel as n fisiese ondersoek te ondergaan wat u om en by 60 minute gaan neem

Ekstra vervoer kostes om deel te neem sal deur ons gedek word

Deelname is vrywillig

Van 5 February tot 26 Oktober 2018, Hemofilie kliniek, Universitas

VIR MEER INLIGTING SKAKEL DR KOEKEMOER AT 0726520075

SUPPLEMENTARY TABLES

Table 8: Associations between variables and HR-QoL outcomes in the haemophilia subgroup

Table 7. Associations between variables and psychiatric illness in the haemophilia population

	DSM-5 diagnosis			MDE			Substance use		
	n	(%)	*P*	n	(%)	*P*	n	(%)	*P*
Severity									
Mild/mod	3	(43)	1	1	(14)	0,65	3	(43)	0,07
Severe	9	(41)		6	(27)		2	(9)	
Comorbidities									
Yes	9	(45)	0,69	3	(33)	0,64	5	(25)	0,15
No	3	(33)		4	(20)		0	-	
Treatment setting									
Home	11	(42)	1	7	(27)	0,56	5	(19)	1
Clinic	1	(33)		0	-		0	-	
Inhibitors									
Yes	3	(43)	1	2	(29)	1	0	-	0,3
No	9	(41)		5	(23)		5	(23)	
Bleeding frequency									
<1	7	(50)	0,08	2	(14)	0,08	2	(14)	0,54
1 to 3	3	(23)		4	(31)		2	(15)	
>3/ month	2	(100)		1	(50)		1	(50)	
Family history									
No	2	(67)	0,55	2	(67)	0,14	1	(33)	0,45
Yes	10	(39)		5	(19)		4	(15)	
Regimen									
On demand	9	(50)	0,27	5	(28)	0,68	3	(17)	1
Prophylaxis	3	(27)		2	(18)		2	(18)	
Support									
Yes	11	(42)	1	7	(27)	0,56	4	(15)	0,45
No	1	(33)		0	-		1	(33)	
Feel understood									
Yes	11	(41)	1	6	(22)	0,43	5	(19)	1
No	1	(50)		1	(50)		0	-	
HIV status									
Reactive	1	(100)	0,42	0	-	0,23	0	-	1
Non-reactive	10	(40)		6	(24)		5	(20)	
Age (years)									
18-34	10	(48)	0,8	6	(29)	0,73	4	(19)	1
35-64	2	(29)		1	(14)		1	(14)	
>64	0	-		0	-		0	-	
Ethnicity									
Black	11	(52)	0,15	6	(29)	1	4	(19)	1
White	0	-		0	-		0	-	
Coloured	1	(17)		1	(17)		1	(17)	
Employment									
Yes	3	(33)	0,69	3	(33)	0,64	1	(11)	1
No	9	(45)		4	(20)		4	(20)	
Education									
General	2	(33)	0,1	1	(17)	0,41	1	(17)	0,79
Further	10	(56)		6	(33)		4	(22)	
Higher	0	-		0	-		0	-	
Marital status									
Not married	11	(52)	0,02	6	(29)	0,1	5	(24)	0,41
Married	0	-		0	-		0	-	
Widowed	1	(100)		1	(100)		0	-	
DG									
Yes	7	(50)	0,46	5	(36)	0,21	4	(29)	0,17
No	5	(33)		2	(13)		1	(7)	

MDE, Major Depressive Episode; n, number; mod, moderate; DG, Disability Grant;

	MO		SC		UA		PD		AD	
	%	*P*	%	*P*	%	*P*	%	*P*	%	*P*
Age (years)										
18-34	71%	0,3	14%	1	33%	1	71%	0,7	43%	0,52
35-64	86%		14%		29%		86%		57%	
>64	0%		0%		0%		100%		100%	
Ethnicity										
Black	76%	0,5	14%	1	19%	0,05	71%	1	43%	0,48
White	50%		0%		50%		100%		100%	
Coloured	67%		16%		67%		83%		50%	
Work										
Yes	78%	1	11%	1	44%	0,4	78%	1	44%	1
No	70%		15%		25%		75%		50%	
Education										
None	0%	0,5	0%	0,04	0%	1	0%	1	0%	0,38
Special	0%		0%		0%		0%		0%	
General	50%		50%		33%		83%		67%	
Further	78%		6%		33%		72%		50%	
Higher	80%		0%		20%		80%		20%	
Marital status										
Not married	71%	1	14%	1	29%	0,76	76%	0,4	43%	0,52
Married	71%		14%		43%		85%		57%	
Widowed	100%		0%		0%		0%		100%	
DG										
Yes	79%	0,7	14%	1	29%	1	71%	0,7	57%	0,47
No	67%		13%		33%		80%		40%	
Regimen										
On demand	61%	0,1	22%	0,27	39%	0,41	72%	0,7	61%	0,13
Prophylactic	91%		0%		18%		82%		27%	
Treatment setting										
Home	73%	1	11%	0,37	31%	1	77%	1	46%	0,6
Clinic	67%		33%		33%		67%		67%	
Inhibitors										
Yes	86%	0,6	28%	0,24	57%	0,19	57%	0,3	57%	0,68
No	68%		9%		23%		82%		45%	
Bleeding frequency										
< 1	71%	1	0%	0,07	14%	0,18	71%	1	50%	0,34
1 to 3	69%		31%		46%		77%		38%	
> 3/month	100%		0%		50%		100%		100%	
Family history										
Yes	73%	1	15%	1	35%	0,53	77%	1	50%	1
No	67%		0%		0%		67%		33%	

Support										
Yes	74%	1	12%	0,37	27%	0,22	73%	0,6	42%	0,1
No	40%		33%		67%		100%		100%	
HIV										
Reactive	100%	1	0%	1	0%	1	0%	0,2	100%	1
N/R	68%		16%		32%		80%		48%	
Comorbidities										
Yes	89%	0,4	22%	0,57	44%	0,4	78%	1	67%	0,25
No	65%		10%		25%		75%		40%	

MO, Mobility; SC, Self-care; UA, Usual activities; PD, Pain/Discomfort; AD, Anxiety/Depression; DG, Disability Grant; N/R, Non-Reactive; HIV, Human Immunodeficiency virus Infection

AUTHOR GUIDELINES (HAEMOPHILIA)

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PREVALENCE OF COMORBID PSYCHIATRIC ILLNESS AND QUALITY OF LIFE IN ADULTS WITH INHERITED BLEEDING DISORDERS IN CENTRAL SOUTH AFRICA v3

by Heinrich Koekemoer

Submission date: 21-Oct-2019 11:00AM (UTC+0200)
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ABSTRACT

Introduction: Inherited bleeding disorders (IBDs) appear to be relatively uncommon, but they pose unique health-related challenges. IBDs are acquired through inheritance of mutations that cause abnormal bleeding. Due to their chronic nature, one would expect similar psychosocial problems as seen in other chronic diseases. The purpose of this study was to obtain information about the psychiatric comorbidities of patients with inherited bleeding disorders in order to be able to sensitize health workers and to promote holistic care in order to better patients' health-related quality of life (HR-QoL).

Aim: To achieve this, the researchers aimed to establish the prevalence of psychiatric comorbidities in patients with IBDs, as well as their QoL. Furthermore, risk factors associated with psychiatric comorbidity and HR-QoL were evaluated.

Methods: A quantitative, cross-sectional, observational study was conducted using a questionnaire, the EQ-5D assessment tool, the Mini International Neuropsychiatric Interview - M.I.N.I. 7.0.2 (B/B16 version), a functional assessment with the aid of the Functional Independence Score in Hemophilia (FISH) tool and also from patients' clinical records. At the Bloemfontein and the Kimberley Haemophilia Treatment Centres respectively there were 57 and 12 adult patients who attended regularly. Forty adult patients were consecutively sampled from these two sites.

Results: The median age of the sample was 29.5 years (range 18 to 65). The majority were male (83%), unemployed (75%), receiving a disability grant (53%) and had never been married (65%). The majority of patients had haemophilia (73%), followed by hereditary haemorrhagic telangiectasia (HHT) (23%), Von Willebrand Disease (VWD) (2.5%) and Bernard-Soulier syndrome (BSS) (2.5%). The prevalence of both hepatitis C virus (HCV) and human immunodeficiency virus (HIV) was 10%. Twenty-three percent of patients reported bleeding more than three times per month. The lifetime prevalence of comorbid psychiatric illness in patients with IBDs was high - 43% had one or more psychiatric comorbidity. Major depressive disorder (MDD) was particularly common, with a lifetime prevalence of 30%. The prevalence of anxiety disorders and substance use disorders were both 15%, followed by post-traumatic stress disorder (PTSD), schizophrenia and suicidality, all present in 2.5% of the sample. The group of patients with severe haemophilia carried most of the burden of psychiatric illness (53%) when compared to mild/moderate haemophilia, HHT and the other IBDs. The total sample had greater impairment in HR-QoL

1

PREVALENCE OF COMORBID PSYCHIATRIC ILLNESS AND QUALITY OF LIFE IN ADULTS WITH INHERITED BLEEDING DISORDERS IN CENTRAL SOUTH AFRICA v3

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2019-10-21

To whom it may concern

TurnItIn report from Dr Heinrich Koekemoer's MMed mini-dissertation "Prevalence of comorbid psychiatric illness and quality of life in adults with inherited bleeding disorders in central South Africa"

I went systematically through the report. It highlighted many generic ways of expressing scientific facts. Phrases which also occurred in other sources were not plagiarized. They were just similar.

I consider that Dr Koekemoer has done original work. His mini-dissertation is ready for examination.

Regards,

Marius J Coetzee
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Associate Professor and Head: Haematology and Cell Biology
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