# ADHERENCE, BLEEDING OUTCOMES AND SAFETY PROFILE OF EMICIZUMAB PROPHYLAXIS AMONG HAEMOPHILIA A PATIENTS ATTENDING MUHIMBILI NATIONAL HOSPITAL, DAR-ES-SALAAM, TANZANIA

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**By**

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**A Dissertation Submitted in Partial Fulfillment of Requirements for the Degree of Master of Medicine in Haematology and Blood Transfusion at Muhimbili University of Health and Allied Sciences**

**October, 2024**

## CERTIFICATION

The undersigned certify that they have read and hereby recommend for the acceptance this dissertation entitled ***'Adherence, bleeding outcomes and safety profile of Emicizumab prophylaxis among Haemophilia A patients attending Muhimbili National Hospital, Dar es Salaam'*** in partial fulfilment of the requirements for the degree of Master of Medicine in Haematology and Blood Transfusion of the Muhimbili University of Health and Allied Sciences.

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## DECLARATION

## AND

## COPYRIGHT

I, **Rebbecca Wughanga Mwakichako**, declare that this **dissertation** is my own original work and that it has not been presented and will not be presented to any other University for similar or any other degree award.

Signature ……Date ……

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## DEDICATION

I dedicate this dissertation to all Haemophilia patients in Tanzania, with the hope that this work will significantly assist in advocating for the initiation of a stable and dependable prophylaxis program, while we strive to achieve zero bleeds, disabilities, and fatalities among patients. I also dedicate it to their caregivers for their compassionate and unwavering support towards this group of patients, who, despite their special needs, have a promising future regarding treatment and research. Additionally, I dedicate this to the Haemophilia Society of Tanzania, an organization that persistently promotes quality lives not only for Haemophilia patients and their families but also for individuals with other rare inherited bleeding disorders. Volunteering with this association while working on my master's was a privilege and truly one of the most fulfilling experiences of my life.

I dedicate it to my department and particularly to the first-year residents, in hopes that they too will develop an interest in Haemophilia and advance in this area of research. Lastly, I dedicate this to my nephew Leiyan and my nieces Resian and Zuri, who continually inspire me to strive for excellence**.** I hope that reflecting on this work will motivate them to volunteer in initiatives that will ultimately enhance the lives of patients with Haemophilia.

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## LIST OF ABBREVIATIONS

| | |
|---|---|
| ABR | Annual Bleeding Rate |
| aPCC | Activated Prothrombin Complex Concentrate |
| APTT | Activated Partial Thromboplastin Time |
| BPA | By Passing Agent |
| CFCs | Clotting Factor Concentrates |
| EMA | European Medical Association |
| EUHASS | European Haemophilia Safety Surveillance System |
| FDA | Food and Drug Administration |
| FVIII | Factor 8 |
| FIX | Factor 9 |
| FX | Factor 10 |
| GIT | Gastrointestinal tract |
| GUT | Genitourinary tract |
| HA | Haemophilia A |
| HTC | Haemophilia Treatment Center |
| ITI | Immune Tolerance Induction |
| **MNH** | Muhimbili National Hospital |
| PwHA | People with Haemophilia A |
| rFVIIa | Recombinant Activated Factor 7 |
| TMAs | Thrombotic Microangiopathies |
| TTI | Transfusion Transmitted Infections |
| USA | United States of America |
| VWD | Von Willebrand Disease |
| WFH | World Federation of Haemophilia (WFH) |
| WFHHAP | World Federation of Haemophilia Humanitarian Aid Program |

## DEFINITIONS OF KEY TERMS

**Annual Bleeding Rate –** a standardized method of determining the number of bleeding episodes. It is calculated by dividing the number of bleeding events by the cumulative period in which they occurred (in months) and multiplying it by 12.

**Bypassing agents -** agents used in the management of Haemophilia patients with high titer inhibitors. They do not replace the missing factor but rather employ an alternative mechanism of action that uses different factors to produce thrombin and, hence, "bypass" pathways that would be affected by the inhibitor or bypass the need for the need for clotting factor treatment.

**Haemophilia A carrier -** a female who inherits a defective X chromosome that has the haemophilia gene but produces factor levels similar to the healthy population.

**Immune tolerance induction**- elimination of inhibitors through regular administration of factor concentrates to induce tolerance by the immune system.

**Inhibitor** -IgG alloantibodies to exogenous FVIII or FIX that develop in patients exposed to infused factor concentrates, hence neutralizing their function

**Symptomatic carrier** – a haemophilia A carrier who shows symptoms because of low production of factor VIII.

**Prophylaxis therapy –** administration of clotting factor concentrates (CFCs) or bypassing agents before a bleeding episode to protect a person from bleeding.

**On-demand therapy-** administration of CFCs or bypassing agents after bleeding has occurred as part of acute management.

**Overt bleeding-** bleeding that is easily visible to the patient or clinician**.**

**Target joint –** a joint that has more than three spontaneous bleeds over a period of six consecutive month**s.**

**Thrombotic Microangiopathies-** a group of disorders characterized by haemolytic anaemia, thrombocytopenia and formation of micro thrombi in small vessels mainly capillaries and arterioles.

## ABSTRACT

**Background:** Prophylaxis is the global standard of care for people with Haemophilia (PWH). Despite being recommended, only a handful of countries in Sub-Saharan Africa have embraced prophylaxis due to limited access to factor concentrates and an excessive dependence on donor assistance. Tanzania initiated the first prophylaxis program, supported by the World Federation of Haemophilia (WFH) by donating Emicizumab to a select group of patients with Haemophilia A. Emicizumab is a monoclonal antibody that restores haemostasis by cross-linking FIXa and X, resulting in thrombin production. Although this agent has been available for the past three years, no studies had examined adherence patterns, bleeding outcomes, and its safety profile in Tanzania.

**Aim of the study:** To evaluate adherence patterns, bleeding outcomes, and the safety profile of Emicizumab prophylaxis among HA patients attending MNH.

**Methodology:** We undertook a cross-sectional analysis involving HA patients receiving Emicizumab prophylaxis, gathering information on their adherence patterns, self-reported adverse events, and bleeding results, which included an annual bleeding rate (ABR) and the resolution of target joints. Factors linked to breakthrough bleeding were assessed using a comprehensive poison method.

**Results:** Among the 55 individuals who participated in the study, the median age was 8 years, and half of the patients (50%) had severe haemophilia. The median ABR for spontaneous bleeding was 8 prior to treatment and decreased to zero after 12 months of prophylaxis. During the study period, a majority of the patients (78%) exhibited adherence. Bleeding was noted in 63% of the patients, predominantly (61%) due to trauma. Of the 19 (34.6%) patients with target joints, 79% saw resolution during Emicizumab prophylaxis. Age was the sole factor linked to breakthrough bleeding, with those over 18 years being the most at risk. Regarding safety, only 5% of the patients reported adverse events, with injection site reactions being the most frequent.

**Conclusions:** The majority of patients adhered to Emicizumab prophylaxis. Emicizumab prophylaxis proves effective in averting spontaneous bleeding and exhibits a favorable safety profile. Older age was the only significant factor associated with spontaneous bleeding during prophylaxis. Ongoing monitoring and pharmacovigilance are crucial for evaluating long-term outcomes and enhancing patient management strategies.

# 1.0 INTRODUCTION

## 1.1 Background

Genetic coagulation disorders are uncommon but can pose serious risks, especially in low- and middle-income nations where sophisticated treatment options are scarce (1). Among these disorders, Haemophilia A (HA) ranks second after Von Willebrand's disease and is nearly four times more prevalent than Haemophilia B (Christmas disease). Presently, the worldwide incidence of HA is approximated at 1 in 5000 males (2). This incidence varies across different populations, influenced by the existence of diagnostic facilities, updated patient registries, and available treatment options. For example, the prevalence of HA per 100,000 males is documented as 12.8 in affluent countries compared to 6.6 in other regions (3). In Tanzania, with an estimated population of 60 million, there are only 300 reported cases of hereditary bleeding disorders, with most being HA, which is significantly lower than anticipated for this demographic. HA is a rare inherited bleeding disorder caused by a deficiency or total absence of Factor 8 (FVIII), a vital protein in the intrinsic coagulation pathway (2, 4). Individuals with this disorder typically exhibit unusual bleeding tendencies, leading to various complications that greatly impact their health and overall quality of life. Due to its X-linked inheritance, HA predominantly affects males, whereas females are generally carriers. However, there are instances where females have been affected, particularly those born to HA fathers and carrier mothers, as well as carriers with skewed lyonization that inactivates the normal X gene (5, 6). HA arises from a range of genetic mutations in the FVIII gene, found at the distal end of the long arm of the X chromosome (Xq28) (7). Among the identified mutations, inversion mutations involving intron 22 and intron 1 are the most prevalent, accounting for nearly 40-50% and 5-7% of severe HA mutations, respectively. In other cases, point mutations or small rearrangements have been noted. While it is understood that most cases result from inheriting the defective gene from one's parents, approximately one-third occur due to spontaneous mutations, which means these patients often do not have a notable family history of HA at the time of diagnosis (8, 9).

## Clinical Presentation of HA

The primary feature of HA is atypical bleeding tendencies. Based on remaining FVIII levels, individuals with HA are categorized as having mild (6-40%), moderate (1-5%), or severe disease (<1%) ((9)). The degree of FVIII deficiency not only indicates the severity of the disease but also affects the age of diagnosis. Individuals with severe disease are usually diagnosed early in life due to conditions such as cephalohematomas at birth or extended umbilical cord bleeding. Other incidents include bleeding following vaccination, circumcision, venous puncture, and easy bruising during early movement ((6, 9, 10)). Those with moderate disease often display prolonged bleeding after significant trauma or surgery, but they too face risks of spontaneous bleeding (9). Individuals with mild disease frequently remain undiagnosed until late adolescence or adulthood, often revealed by surgery or significant injuries (11). The most commonly affected areas are musculoskeletal, particularly the joints ((9, 12). Muscle bleeds occasionally lead to complications like compartment syndrome, hypovolemic shock, and severe cases can even result in mortality (6). Life-threatening bleeding episodes can occur in the central nervous and gastrointestinal systems, as well as in the head and neck, posing risks of airway obstruction (6, 13). Joint arthropathies resulting from repeated bleeding into joints and subsequent damage to articular cartilage have been identified as a leading cause of disability (14). Intracranial hemorrhages and cancers, particularly hepatocellular carcinoma in patients with Hepatitis B and C histories, rank among the highest causes of mortality in this group (15).

## Diagnosis of HA

Diagnosis typically occurs after clinical presentations of extended bleeding either spontaneously or due to injury (2). About two-thirds of patients report a positive family history of abnormal bleeding among relatives (11). Diagnosis should **still be considered** in patients with similar presentations but without significant family histories, as about one-third of cases arise from de-novo mutations (8). Prolonged activated partial thromboplastin time (APTT) alongside a normal prothrombin time (PT) and platelet count should prompt a mixing study to see if APTT corrects when patient plasma is combined with FVIII-

containing plasma (1). A definitive diagnosis is established through factor assays and mutation analyses. Besides confirming the diagnosis, mutation analyses give insights into the risk of inhibitor development. Large deletions and nonsense mutations are associated with the highest inhibitor risks, while missense and splicing mutations correlate with lower risks (16).

**Management of HA**

HA management should be provided by a well-coordinated, multidisciplinary team (13). The main objectives of management include preventing bleeding, (17)psychosocial support . Definitive treatment consists of factor replacement therapies using plasma-derived or recombinant clotting factor concentrates (CFCs). The introduction of recombinant factors has improved safety for patients who were previously vulnerable to transfusion-transmitted infections (TTIs), including HIV/AIDS and Hepatitis B and C, which were leading causes of mortality in this population when using plasma products (18, 19). Nonetheless, CFC use is complicated by the development of alloantibodies (inhibitors) against exogenous FVIII. This rendering some patients resistant to factor replacement therapy (20, 21). These patients are treated with bypassing agents (BPA) like activated prothrombin complex concentrates (aPCC) and recombinant activated FVII (rFVIIa). However, for low responders with an inhibitor titre below 5 Bethesda units, immune tolerance induction (ITI) remains appropriate (17). Recent innovations have led to the approval of gene therapy (22)treatment involves the introduction of a functional gene via a vector, resulting in continuous FVIII production and restoring normal coagulation (23). Although promising, this treatment is highly costly and is currently available in only a limited number of countries.

**Emicizumab prophylaxis**

Emicizumab (Hemlibra) is a novel agent recommended for individuals with HA(24). It is a recombinant bispecific monoclonal antibody that functions by linking activated FIX and FX, thereby mimicking the function of natural FVIII(22). This connection stimulates Factor X, resulting in the production of thrombin and the restoration of normal coagulation. Although

its mechanism is akin to that of endogenous FVIII, its entirely different structure provides a notable therapeutic benefit by preventing interference from inhibitors, making it suitable for use in patients with inhibitors (25). It received its initial approval in 2018 from both the European Medicines Agency (EMA) and the Food and Drug Administration (FDA) primarily for HA patients with inhibitors, but it is now recognized as the standard prophylactic measure against bleeding for all HA patients, irrespective of their age, disease severity, or inhibitor status (26). It is administered as a subcutaneous injection, beginning with a loading dose of 3 mg/kg once a week for one month, followed by maintenance doses given either weekly at 1.5 mg/kg, biweekly at 3 mg/kg, or monthly at 6 mg/kg (22). The selection of the maintenance regimen depends on the preferences of both the patient and the doctor, thus ensuring adherence. Its administration method, which involves both loading and maintenance doses combined with a long half-life of approximately 5 weeks, overcomes the pharmacokinetic challenges noted in patients using factor concentrates for prophylaxis. These patients often experience fluctuating peaks and troughs of plasma factor levels that can lead to breakthrough bleeding during troughs (27). Emicizumab has demonstrated efficacy in both clinical trials (HAVEN studies) and real-world analyses reported from various centers. Advantages of Emicizumab prophylaxis include a decrease in bleeding rates, improvement of joint health and enhancement of overall quality of life ((28-30)). Productivity has also seen improvement, indicated by increased attendance and performance in work and school. Some patients have resumed sports and other vigorous activities that were previously avoided to prevent excessive bleeding due to trauma (26). Starting newly diagnosed patients on Emicizumab is cost-effective over time. Particularly because the immune tolerance induction (ITI) done for patients with inhibitors to CFCs is costly due to the larger quantities of factor needed (26). Evidence from both clinical trials and real-world experiences indicates that Emicizumab has a favorable safety profile across various populations and age groups (26, 29). The most frequently reported side effects are reactions at the injection site, generally classified as mild to moderate (26, 31). A few instances of microangiopathies and thromboses have been documented, although further investigations determined that these were linked to the concurrent use of aPCC while on Emicizumab

prophylaxis . Rates of thromboses and mortality did not increase with Emicizumab in comparison with other hemostatic agents . A small number of cases involving antibody development against Emicizumab have been recorded with suboptimal bleeding outcomes; nevertheless, the immunogenicity remains lower than that associated with factor usage (22). Other reported adverse events include headache, arthralgia, diarrhea, and fever (26).

**Emicizumab prophylaxis in Tanzania**

Emicizumab prophylaxis was first launched in Tanzania in April 2021, marking the commencement of prophylaxis for patients with Hemophilia in the country. Prior to the introduction of Emicizumab, the absence of a prophylaxis program was primarily due to insufficient availability of adequate CFCs and BA. The establishment of the prophylaxis program has been facilitated through a donation initiative by the World Federation of Hemophilia Humanitarian Aid Program (WFHHAP), thereby providing the therapy free of charge to a select group of patients. As it is new, the initiation and monitoring of patients on Emicizumab occurs exclusively at Muhimbili National Hospital.

## 1.2 Problem Statement

Estimates from the World Federation of Haemophilia (WFH) indicate that there are roughly 815,100 instances of Haemophilia worldwide. Out of these, only 347,026 have received a diagnosis (32). It is now understood that 90% of all undiagnosed cases are found in developing nations, including Sub-Saharan Africa {Diallo YL, June 2020 #79}. With nearly 18% of the global population living in Africa, the continent represents less than 3% of the total reported Haemophilia cases globally (33), with under 2% of these patients having access to clotting factor concentrates (CFCs) (34). The World Federation of Haemophilia Humanitarian Aid program (WFHHAP) has enhanced access to treatment by donating almost 24 million units of CFC annually to member nations, Tanzania included (26). Although it offers support and enhances the care of individuals with Haemophilia, most African nations, including Tanzania, still provide factor concentrates on demand instead of prophylactically as advised. While on demand factor use addresses acute bleeding events quickly, it fails to prevent long-term complications like joint arthropathies (35). Although Emicizumab is now globally recognized as the standard treatment for patients with Hemophilia A (HA), its high price and the limited number of doses available through donations have restricted access for those living with Haemophilia in Tanzania. Following discussions with the Haemophilia Treatment Center (HTC) in MNH, WFH suggested criteria for the use of Emicizumab. It is allocated for patients with inhibitors, severe disease, those with moderate disease who have experienced a significant bleed, individuals with poor venous access, and patients under the age of five. Despite its utilization in Tanzania for the past three years, no research had been conducted to assess the actual experience of HA patients receiving Emicizumab prophylaxis.

### 1.3 Conceptual framework

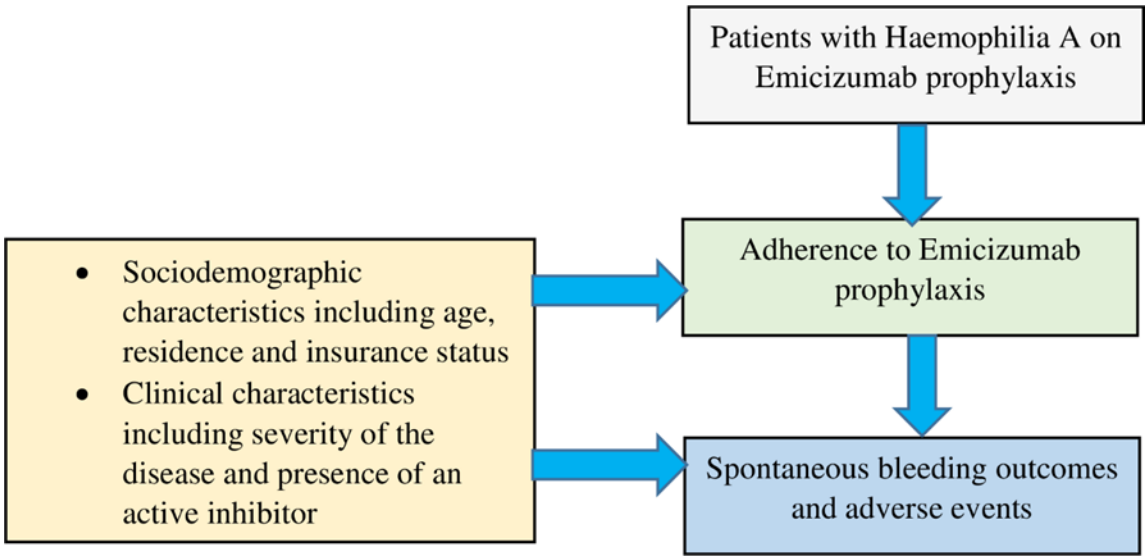



**Figure 1: Conceptual framework showing the different factors which may influence bleeding outcome while on Emicizumab prophylaxis**

**Description of the conceptual Framework**

Although bleeding events are significantly reduced in patients on Emicizumab prophylaxis, the risk of bleeding is not eliminated altogether(36). The paediatric age group as well as the adolescents have been noted to have lower bleeding rates as opposed to adults with most of their events bleeding being traumatic(29, 37). The presence of inhibitors prior to treatment has been associated in certain studies with a higher likelihood of breakthrough bleeding(37) . Adherence to treatment is associated with better bleeding outcomes(36). Patients with no insurance cover in places where Emicizumab is purchased by patients have poor adherence patterns(38, 39).Although not stipulated from literature, distance to the HTCs where prophylaxis was seen to affect adherence and bleeding outcomes in our setting given that all patients received their treatment from MNH.

**1. 4 Rationale of the study**

Although about 29 African countries now have access to Emicizumab through the support of WFHHAP (26)very few have published the outcomes of their patients. Since this represents the only group of patients in Tanzania on prophylaxis, it was paramount to document their experience with special consideration to their adherence patterns, bleeding outcomes, factors associated with spontaneous bleeding and adverse events experienced while on Emicizumab. Unlike clinical trials and longitudinal prospective studies that have been done with strict follow up of the patients involved, our study provided an opportunity for a pragmatic review and the interplay of socio-demographic and economic characteristics on their experience of Emicizumab prophylaxis. Results from this study enabled us to compare the experience of our patients with those from clinical trials and other real-world studies. It provided information to health care workers on the benefits of prophylaxis therapy and better follow up for patients on Emicizumab. Lastly, we hope that it will also help guide the government and other stakeholders on the importance of supporting the ongoing initiative of prophylaxis therapy in Tanzania.

## 1.5 Research questions

1. What are the adherence patterns of HA patients on Emicizumab prophylaxis attending Muhimbili National Hospital?
2. What are the bleeding outcomes of HA patients on Emicizumab prophylaxis attending Muhimbili National Hospital?
3. What are the factors associated with spontaneous bleeding among HA patients on Emicizumab prophylaxis?
4. What are the adverse events experienced by HA patients on Emicizumab prophylaxis attending Muhimbili National Hospital?

## 1.6 Study hypothesis

We hypothesize that patients on Emicizumab prophylaxis have lesser episodes of spontaneous bleeding events compared to when they are on factor concentrate on demand.

## 1.7 Study objectives

### 1.7. 1 Broad objective

To assess adherence patterns, bleeding outcomes and safety profile of Emicizumab prophylaxis among Haemophilia A patients attending Muhimbili National Hospital from January-March 2024.

### 1.7. 2 Specific Objectives

1. To describe the adherence patterns of HA patients on Emicizumab prophylaxis attending
   Muhimbili National Hospital from January-March 2024.
2. To determine the bleeding outcomes of HA patients on Emicizumab prophylaxis attending Muhimbili National Hospital from January-March 2024.
3. To determine factors associated with spontaneous bleeding among Haemophilia A patients on Emicizumab prophylaxis from January-March 2024.

4.To describe the adverse events experienced by HA patients on Emicizumab prophylaxis attending Muhimbili National Hospital from January-March 2024.

## 1.8 Literature review

### 1.8.1 Clinical characteristics of Haemophilia A patients on Emicizumab prophylaxis

Globally, the estimated number of Emicizumab users is over 12,500 individuals(26). Initially its use was mainly by patients with inhibitors (40). With Emicizumab now gaining acceptance as the new standard of care for individuals with HA with or without inhibitors, other patients have gained access to its use(31). The WFHHAP that provides Emicizumab to member organizations of the WFH has also advocated for its use by paediatric patients under the age of 12. The reason for this being joint protection by preventing or delaying joint bleeds thus reducing the rates of disability in the future (10, 14).The National Haemophilia Foundation now advises health care providers taking care of all HA patients to discuss Emicizumab as an option for routine prophylaxis regardless their ages, inhibitor status, severity or history of previous treatment (41). Data from clinical trials have shown that patients previously on prophylaxis by CFCs or BA still enjoy the benefits of Emicizumab evidenced by the significant reduction in annual bleeding rate (ABR)(25, 42). Caution is only provided when there is concurrent aPCC use (24).

### 1.8.2 Adherence to Emicizumab Prophylaxis

Unlike CFCs or BA that are administered as intravenous injections, Emicizumab given subcutaneously allows for a slow and consistent absorption (26, 27). Its flexible mode of administration has gone on to make Emicizumab use preferable for most HA patients reducing the previous burden of several weekly injections of CFCs as prophylaxis (28). While one would argue that clinical trials are controlled environments and hence adherence influenced by strict follow up by investigators, adherence patterns as seen in real world studies have been equally good (43). Various factors have however been shown to influence adherence patterns. These include age, modality of treatment prior to Emicizumab prophylaxis and the presence of inhibitors (44). Children and adolescents for example, have been shown to be more adherent than young adults and adults, while patients previously

non- adherent to factor concentrates and those with active inhibitors seen to adhere less to Emicizumab (44). A study looking at the influence of adverse events experienced by certain patients has also suggested they could result in discontinuation of Emicizumab despite favorable bleeding outcomes (37).A survey conducted on Haematologist taking care of HA patients however showed that patients on Emicizumab were likely to have a better adherence rate than HA patients on other treatments. To encourage better adherence, they emphasized to patients the need for proper use of the drug on every clinic visit. They however cited lack of insurance cover, high treatment costs, personal choice and tolerability to subcutaneous injections as the other reasons for discontinuation of the Emicizumab(45). Although a study done in Ivory coast showed excellent adherence and acceptance of Emicizumab, data from other African countries is still lacking(43).

**1.8.3 Bleeding outcomes of HA patients on Emicizumab prophylaxis – HAVEN studies**

HAVEN studies are a series of pivotal Phase III open label clinical trials investigating the outcome of Emicizumab prophylaxis among HA individuals in different circumstances. These studies have formed the basis of our knowledge on the pharmacokinetics, dosing, adverse events and the efficacy of Emicizumab use (31, 42). HAVEN 1 was a multicenter clinical trial, that looked at the outcome of Emicizumab prophylaxis among adolescents and adult (>12 years old) HA patients with high titer inhibitor who were on either routine prophylaxis or on demand treatment using BPA. After a mean exposure time of about 21.38 weeks, the ABR for treated bleeds in patients on Emicizumab prophylaxis reduced dramatically to 2.9 compared to 23.3 in patients not receiving Emicizumab. It was also noted that there was a reduction in ABR for treated bleeds for the patients who were previously on prophylaxis with BPA after switching to Emicizumab (25). HAVEN 2 looked at the efficacy, pharmacokinetics and safety of Emicizumab in the paediatric age group with inhibitors on different maintenance doses including 1.5mg/kg weekly ,3mg/kg biweekly and 6mg/kg monthly. The ABR for treated bleeds reduced to 0.3, 0.2 and 2.2 respectively across the three groups. HAVEN 3 aimed to look at the use of Emicizumab among adolescents and adult HA individuals without inhibitors. There was a significant reduction in the ABR for treated bleeds among participants. An intraindividual variation of 48 patients on previous

Factor VIII prophylaxis showing a 68% reduction in ABR when Emicizumab was initiated (29). Finally, HAVEN 4, a single arm study was done with the aim of investigating the efficacy of Emicizumab use given as a once monthly maintenance dose at 6mg/kg. The ABR for treated bleeds in the individuals on the once monthly dosing after the initial loading period was determined at 2.4. While the study showed that once monthly dosing was equally effective in managing bleeds with convenient dosing pattern eliminating treatment burden and improving adherence (27). The above clinical trials sufficiently provided evidence concerning the efficacy of Emicizumab prophylaxis in reducing bleeding events among HA patients regardless of their inhibitor status or age groups. Due to these outcomes FDA granted Emicizumab priority review and recognized it as a breakthrough therapy. Still ongoing are other HAVEN studies looking at its efficacy in patients with mild and moderate disease (HAVEN 6) as well as in the younger paediatric groups (HAVEN 7). Interim data from both studies show similar results as seen in the earlier studies confirming that Emicizumab prophylaxis is suitable for all HA patients regardless their disease severity, inhibitor status or age group.

### 1.8.4 Bleeding outcomes of patients on Emicizumab prophylaxis in real world studies

Although studies investigating the efficacy of Emicizumab prophylaxis among HA patients are scarce, documented experiences from both single and multicenter studies show almost similar outcomes as those noted in clinical trials. A single center study done in Milan involving both adult and paediatric patients with and without inhibitors switched to Emicizumab showed a marked reduction of ABR in the entire cohort. Specific analyses showed a reduction in ABR of 70% in adults versus 100% in the paediatric group. Of the patients with significant breakthrough bleeding, one was noted to have developed antibodies against Emicizumab. Target joint bleeding was also noted to have significantly improved by 73% (29). The University of Colorado Haemophilia and Thrombosis center that conducted a study of their HA patients on Emicizumab found a median ABR of 1.12 for patients who had been on prophylaxis for more than 6 months and of these, majority were traumatic(46). Few studies have focused specifically on Emicizumab use in the paediatric population.

Beijing Children's Hospital in China that enrolled HA paediatric patients with moderate to severe disease regardless their inhibitor status, found a significant improvement in bleeding outcomes with a reduction of ABR from 5 to 0.4 after the initiation of Emicizumab prophylaxis (47).One of the largest real world studies done on the efficacy and safety of Emicizumab prophylaxis among HA patients was on a cohort in the Israeli National Haemophilia Center. Of 53 patients, 24 being adults experienced 0 bleeding episodes after 53 weeks of follow up with the rest of the study participants experiencing at least one bleeding episode during the study period. Traumatic bleeds were more common in the paediatric age group as compared to spontaneous bleeds seen in the adults. Noted however in this cohort was a history of major bleeding in 4 participants with a fatal outcome in one who developed retroperitoneal bleeding. Although 50% of the individuals had at least an episode of breakthrough bleeding while on prophylaxis, this study still demonstrated good efficacy (37). To our best knowledge, outside clinical trials, Ivory coast is the only African country that has published their experience on Emicizumab prophylaxis. After 12 months of Emicizumab use, the results of this study showed a 99% reduction in bleeding rates with a raise in patients with no spontaneous bleeds from 18% to 100%. Only 3 boys with traumatic bleeding needed treatment with CFCs (43). As currently the one documented real-world studies on non-replacement therapy with Emicizumab in Africa, this study also brought out the crucial role of expanding care with novel therapies to low-income countries and the role of strategic partnerships between various stakeholders in improving the care of patients with haemophilia.

### 1.8.5 Factors associated with breakthrough bleeding among patients on Emicizumab prophylaxis

While Emicizumab prophylaxis confers protection against bleeding, the risk of breakthrough bleeding is not eliminated(29, 37, 43, 47). Spontaneous bleeding is however significantly reduced with majority of bleeding seen in both clinical trials and real-world studies being traumatic(26, 46). These observations have led to the hypothesis that HA individuals on Emicizumab prophylaxis are probably converted to a milder phenotype hence experiencing bleeding mostly in the face of trauma (46). While factors associated with

breakthrough bleeding are still under investigation, a few have been suggested from the single and multi-center real world experiences documented. Age, for example, has been noted to influence the rate of breakthrough bleeding, with studies showing that the paediatric age group has lower bleeding rates as opposed to adults. A study done in Israel, looking at the bleeding rates in patients at different points during their prophylaxis therapy showed the odds of bleeding increased by about 1.029 with every 1-year increase in age (48). In addition, spontaneous bleeding was mostly seen in adults as compared to the paediatric group whose bleeding was majorly traumatic (37, 48, 49). While the risk of developing antibodies against Emicizumab is much less compared to when factor concentrates are administered, the presence of anti-drug antibodies has also been associated with increased risk of breakthrough bleeding in certain patients (50). In the Milan cohort for example a total of 11 bleeding events were reported ,5 of which were reported in a single patient who had developed anti-drug antibodies while on treatment (29).Whether the presence of active inhibitors developed because of previous CFC exposure increases the risk of bleeding while on Emicizumab prophylaxis is still debatable. A few real-world studies have showed in their cohorts that the presence of inhibitors did not significantly impact the risk of breakthrough bleeding when compared to patients who had not developed inhibitors (29, 37). A study in New York, however, found higher risks of breakthrough bleeding in those with inhibitors. Possible explanation for this as described by the authors was that confidence to participate in high impact sports or previously prohibited activities after the initiation of Emicizumab prophylaxis led to reduction in their previous protective behaviors hence increasing the risk of bleeding while on prophylaxis (50). Low Emicizumab plasma levels linked to poor compliance has also been associated with increase in bleeding rates (36). African countries using Emicizumab are yet to publish their data and as such information on factors associated with breakthrough bleeding unique to our setting is still lacking.

### 1.8.6 Adverse events associated with Emicizumab prophylaxis

The safety profile of Emicizumab has been consistent from the clinical trials to real world documented studies. Of the adverse events noted in the first four HAVEN studies

(HAVEN1-HAVEN4) that included a total of about 391 patients, injection site reactions were the commonest (22). These accounted for about 22% of all the adverse events and were described as either site bruising, discomfort, induration, pain, pruritus, rash, site reaction, swelling or urticarial formation most of which were of mild to moderate severity (26). Other adverse reactions included headaches (15%), arthralgia (15%) diarrhea (6%) and fever (6%) (22, 25, 26). The most serious adverse events documented were three thrombotic microangiopathies (TMAs) all noted in HAVEN1 and four thrombotic events, two observed in HAVEN1 and one each in HAVEN 2 and 3. Thrombotic events included both venous and arterial thromboses ,with venous sites involving the cavernous sinus and saphenous vein being described (51). These events however, on further evaluation, were noted to have occurred in patients who had concomitant aPCC use at a cumulative dose of 100units per kilogram (100 U/kg) or more in 24 hours (25, 26). Patients who had multiple doses of aPCC were also at risk. Discontinuation of Emicizumab in patients with thrombotic events or TMAs was noted to lead to resolution of symptoms as reported by the investigators (26). This has gone on to inform the black box warning that comes with Emicizumab where caution is to be observed when aPCC is used in patients on Emicizumab prophylaxis and recommendation is given to discontinue or suspend Emicizumab use when symptoms occur (22). While it was noted that one of the patients who developed a TMA had a fatal outcome, the death was unlikely Emicizumab related as the investigator reported that the TMA symptoms were resolving at the time of death (22, 26). Real world studies done after the roll out of Emicizumab continue to ascertain its safety and tolerability among patients who use it with no unusual findings outside those seen from the clinical trials (29, 37).

Larger studies including a survey by The European Haemophilia Safety Surveillance (EUHASS) looking at adverse events in over 900 patients on Emicizumab prophylaxis from 2017-2020 showed a total of four thrombotic and four allergic events as well as one FVIII inhibitor recurrence (52). In addition to this, a study looking at the adoption of Emicizumab in Europe with participation from about 21 countries found its use to be safe and efficacious (53).Back in Africa, Ivory Coast which is one of the only African country that has

documented and published their patient experience while on Emicizumab outside clinical trials, reported excellent tolerability with no adverse effects noted (43).

# CHAPTER TWO

## 2.0 METHODOLOGY

### 2.1 Study Design

This was a hospital based analytical cross-sectional study

### 2.2 Study Area

The research was carried out at Muhimbili National Hospital (MNH) in the department of Haematology and Blood Transfusion, specifically at the HTC situated at the Upanga branch. MNH serves as a teaching institution, research facility, and is currently the sole national referral hospital in the United Republic of Tanzania. The HTC was inaugurated in November 2020 and stands as the largest comprehensive treatment facility in the country, providing consultative, therapeutic, and rehabilitative care for individuals with Haemophilia and other inherited bleeding disorders. This center caters to both adult and pediatric patients**.** It is supported by the central pathology laboratory (CPL) where most diagnostic and follow-up investigations are conducted. The clinic operates Monday through Friday (excluding public holidays) and is staffed by a consultant hematologist, a medical officer, two nurses, one pharmacist, and two physiotherapists. There is a fully equipped in-house pharmacy where CFCs, BA, and Emicizumab vials are meticulously stored, all of which are received as donations from the WFH. Over the past three years, in collaboration with the Tanzanian government and other partners, the center has facilitated the establishment of satellite HTCs in Morogoro Regional Referral Hospital, Bugando Medical Center, Kilimanjaro Christian Medical Center, and Mbeya Zonal Referral Hospital to enhance access to care for all individuals with Haemophilia in Tanzania. Notwithstanding the presence of these treatment facilities, Emicizumab, being a controlled substance, can only be initiated at the MNH HTC. Prescription refills are also exclusively done at MNH. The interval between appointments varies from weekly to three months based on the patient's condition. Despite this limitation, regional HTCs and other peripheral facilities are permitted to administer weekly or monthly subcutaneous injections until the next appointment at MNH. Regional HTCs can likewise

offer specialized laboratory tests and physiotherapy services tailored for Haemophilia patients.

### 2.3 Study population

This study enrolled patients with classical Haemophilia on Emicizumab prophylaxis who had completed the loading dose.

### 2.3 Sample size estimation

A formula for calculating sample size for finite population was used to estimate the sample size in this study (54) . Based on a previous study by Warren BB *et al*., 2021, out of 68 patients on Emicizumab prophylaxis 63.2% experienced bleeding (46). Currently, the entire country has a total of 65 patients on Emicizumab prophylaxis since the launch of the Emicizumab program by WFH in Tanzania in April 2021. Using 63.2% as the proportion of patients who experienced bleeding and other assumptions including a confidence interval of 95%, using Open Epi info software (version 3.01) the minimum sample size to estimate effectiveness of Emicizumab prophylaxis was found to be 56 patients. The sample size calculation is based on the formula below.

$$n = deff \times \frac{N\hat{p}\hat{q}}{\frac{d^2}{1.96^2}(N-1) + \hat{p}\hat{q}}$$

where

$n$ = sample size
$deff$ = design effect
$N$ = population size
$\hat{p}$ = the estimated proportion
$\hat{q} = 1 - \hat{p}$
$d$ = desired absolute precision or absolute level of precision

### 2.4 Inclusion and exclusion criteria

#### 2.4.1 Inclusion criteria

- All patients who were confirmed with HA bleeding on Emicizumab prophylaxis.

- Patients and caregivers who consented to participate in the study.

### 2.4.2 Exclusion criteria

- HA patients on Emicizumab prophylaxis who had not completed the loading dose (the first 4 weeks of prophylaxis)

## 2.5. Sampling Technique

A convenient sampling technique was used to recruit patients into the study. Therefore, patients were consecutively enrolled until the required sample size was reached.

## 2.6 Recruitment of study subjects

Recruitment of study participants was done daily at the comprehensive Haemophilia treatment center at MNH from Monday to Friday excluding public holidays. The diagnosis was confirmed from the hospital database (JEEVA) and only those with HA on Emicizumab prophylaxis who had met the inclusion criteria were enrolled. In addition, the invitation to participate in the study was done through phone calls for patients who were eligible but did not attend the clinic.

## 2.7 Data collection tool and procedures

### 2.7.1 Data collecting tool

A structured questionnaire with six sections was used to collect data from the participants. The sections captured participants identification, patient's socio-demographic characteristics, clinical characteristics prior to Emicizumab prophylaxis, initiation, maintenance and adherence, bleeding outcomes and adverse events experienced while on Emicizumab prophylaxis.

### 2.7.2 Data collection procedures

The principal investigator together with a trained research assistant administered the questionnaire to patients and parents or caregivers where the patient was under 18. Information on clinical characteristics and laboratory investigations relevant to the study including severity and inhibitor status prior to the start of Emicizumab prophylaxis were collected from patients' booklets and verified from the hospital patient electronic database (JEEVA).

### 2.7.3 Assessment of adherence to Emicizumab prophylaxis

Adherence was evaluated by gathering patient-reported information regarding the vials of Emicizumab that were prescribed and used in the three months leading up to the interview. This was validated by reviewing the Emicizumab dispensing ledger at the clinic alongside pharmacy records. As Emicizumab is provided as a donation, every vial is tracked by the clinic through the retention of stickers from the vials that include the barcode, which are subsequently affixed to the patients' records in the register for each clinic visit where Emicizumab was administered and dispensed. A formula was applied to determine adherence by dividing the vials utilized as indicated by patients and verified from clinic documentation by the vials dispensed and transforming this into a percentage. This was performed cumulatively over the three-month period and also individually for each month. Patients were subsequently categorized as adherent, sub-optimal, or non-adherent depending on whether they had missed less than 15%, 15-25%, or more than 25% of the recommended dosage, respectively.(55). Individuals who had skipped any dose during these three months were requested to explain the reasons for not receiving their prescribed treatment.

### 2.7.4 Assessment of bleeding outcome and its determinants

In this research, bleeding was characterized as visible bleeding from mucocutaneous areas, bleeding validated by imaging reports for individuals with CNS bleeding, and as pain or swelling managed with CFCs or supportive methods (rest, ice, compression) for patients with musculoskeletal bleeds. Collected bleeding variables included the frequency of

bleeding episodes, the nature of the bleed (spontaneous versus traumatic), the location of the bleed, and whether there was a resolution of a target joint after Emicizumab for patients with a noted history of a target joint before prophylaxis. The resolution of the target joint was defined as a decrease in the number of spontaneous bleeds to fewer than three or more in a six-month span, accompanied by an improvement in joint movement and activity as reported by the patient. An assessment of the ABR was conducted to objectively measure and standardize bleeding rates among patients, regardless of the length of prophylaxis.(46). This was determined for every patient by taking the total count of bleeding incidents (whether spontaneous, traumatic, or a combination of both) by the annualized time from initiation of treatment to the day of the interview.

$$ABR = (X/Y) \times 12$$

Where X is the total number of bleeding episodes the patient had while on Emicizumab prophylaxis. Y being the duration of time in months that the patient was on Emicizumab and 12 being the total number of months in a year. Associations of bleeding outcomes and age, inhibitor status, severity of disease, insurance status and residence were made.

### 2.7.5 Assessment of adverse events.

An adverse event was defined as any negative or unintended sign or symptom that arose or intensified from baseline following the commencement of Emicizumab prophylaxis. A compilation of adverse events was presented based on reports from HAVEN studies and other real-world investigations, including thrombotic incidents, headaches, diarrhea, reactions at the injection site (such as bruising, discomfort, induration, pain, pruritus, rash, site reactions, swelling, or urticarial formations), arthralgia, myalgia, and fever. Participants were permitted to report any additional new symptoms outside those listed that they would associate with the use of Emicizumab. Occurrence of any of these symptoms at least once after the start of Emicizumab was recorded as a potential side effect.

## 2.8 Study variables

### Primary Outcome

- Bleeding outcomes among HA patients on Emicizumab prophylaxis

### Secondary outcomes

- Adherence patterns
- Factors associated with spontaneous bleeding.
- Adverse events following Emicizumab prophylaxis.

### 2.8.1 Dependent Variables

- Spontaneous bleeding while on Emicizumab prophylaxis

### 2.8.2 Independent Variables

- Sociodemographic information including age, means of payment for medical treatment, area of residence.
- Clinical data including HA severity (based on baseline FVIII level prior to Emicizumab prophylaxis).

## 2.9 Data Management and Analysis

Data gathered from the questionnaire was entered into the Open Data Kit (ODK) database and subsequently migrated into a Microsoft Excel sheet, where it was cleaned and analyzed utilizing Stata version 17. Descriptive statistics were applied for the evaluation of both socio-demographic and clinical information. The Chi-square or Fisher's Exact test, as applicable, was employed to evaluate the correlation among age, disease severity, adherence patterns, mode of payment, residence, and spontaneous bleeding. A Robust Poisson regression model was utilized to pinpoint the predictors of spontaneous bleeding. The Mann Whitney U test was carried out to compare the median occurrences of ABR for spontaneous bleeding before and after. Emicizumab prophylaxis. A p-value below 0.05 was regarded as statistically significant.

### 2.10 Ethical considerations

Ethical approval to conduct this research was obtained from the MUHAS Institutional Review Board (IRB) (Ref No. DA.282/298/01.C/2006) (Appendix III). Additionally, authorization to gather patient information was provided by the MNH Directorate of Research and Publications (MNH/CRTCU/Perm/2024/080) (Appendix III). A permission letter from MNH was subsequently submitted to the head of the MNH HTC. Both written and verbal informed consent were acquired from every eligible patient who took part in the study in person. Verbal consent was collected from participants who were involved through telephone interviews. Consent and assent from parents/caregivers and patients were sought for those below 18 years of age. Data from this research was handled anonymously to ensure confidentiality, and the research outcomes were and will continue to be utilized solely for the aims of this study.

# CHAPTER THREE

# 3.0 RESULTS

## 3.1 Socio-demographic characteristics of the patients

A total of 55 male participants, both pediatric and adult, with classical HA were included in this research. The median age (IQR) of the group was 8 years (4, 14), with most individuals falling within the 5 to 18-year range (61.0%). The majority of the patients were students (61.8%), while 10.1% had reached employment age, 5.5% were unemployed. To manage hospital expenses, most of them were insured (54.0%), and only one patient was part of an exemption scheme. Even though the HTC is located in Dar-es-salaam, approximately 49.0% of the patients lived outside the area. Table 1 provides an overview of the sociodemographic characteristics.

**Table 1: Socio-demographic characteristics of patients**

| Variable | Frequency | Percentage |
|---|---|---|
| **Age group** | | |
| Below 5 | 14 | 25.5 |
| 5-18 | 34 | 61.8 |
| Above 18 | 7 | 12.7 |
| **Median (IQR)** | 8 (4,14) | |
| **Respondent** | | |
| Patient | 7 | 12.7 |
| Mother | 35 | 63.6 |
| Father | 9 | 16.4 |
| Guardian | 4 | 7.3 |
| **Level of education of patient** | | |
| Primary education | 23 | 41.8 |
| Secondary education | 12 | 21.8 |
| University/College | 4 | 7.8 |
| Not started formal education | 16 | 29.1 |
| **Means of payment** | | |
| Insurance | 30 | 54.6 |
| Public (cost sharing) | 16 | 29.1 |
| Private | 8 | 14.5 |
| Exemption | 1 | 1.8 |
| **Area of residence** | | |
| Dar es Salaam | 28 | 50.9 |
| Outside Dar es Salaam | 27 | 49.1 |

### 3.2 Clinical characteristics of patients prior to Emicizumab prophylaxis

The vast majority of participants exhibited moderate (40.0%) to severe (50.9%) disease. Although none were found to have active inhibitors quantified at diagnosis via Bethesda assay, 23.0% had an inhibitor identified through a mixing study and had a positive history of CFC exposure. None of the individuals were on a prophylaxis program before starting Emicizumab prophylaxis; however, most had received on-demand treatment with CFCs (83.6%) and fresh frozen plasma (72.7%). Approximately 10.0% of the patients had not been treated with any product. Before initiating Emicizumab prophylaxis, the median annualized bleed rate (ABR) for spontaneous bleeds was 8 episodes, with 34.6% of participants indicating the presence of a target joint. Additionally, only 10.9% of patients experienced

permanent joint damage in at least one joint due to recurrent joint bleeding (Table 2). Regarding bleeding locations prior to prophylaxis, most participants had encountered musculoskeletal bleeds (Joints 78.2% and muscle 69.1%) (Figure 2).

**Table 2: Clinical characteristics of the patients pre-Emicizumab prophylaxis**

| Variable | Frequency (n) | Percentage (%) |
|---|---|---|
| **Disease severity (based on baseline Factor VIII level)** | | |
| Severe (<1%) | 28 | 50.9 |
| Moderate (1-5%) | 22 | 40.0 |
| Mild (6-40%) | 4 | 7.3 |
| Unknown | 1 | 1.8 |
| **Presence of FVIII Inhibitor after Factor concentrates exposure** | | |
| Present | 13 | 23.6 |
| Absent | 42 | 76.4 |
| **Factor replacement therapies prior to Emicizumab** | | |
| Factor concentrates | 46 | 83.6 |
| Use of bypassing agents (FEIBA) | 6 | 10.9 |
| Fresh frozen plasma | 40 | 72.7 |
| None | 6 | 10.9 |
| **Reported ABR for spontaneous bleeds prior to Emicizumab prophylaxis** | | |
| Median and IQR | 8 | 5,16 |
| **Target Joint** | | |
| Present | 19 | 34.6 |
| Absent | 36 | 65.4 |
| **Joint Arthropathy** | | |
| Present | 6 | 10.9 |
| Absent | 49 | 89.1 |

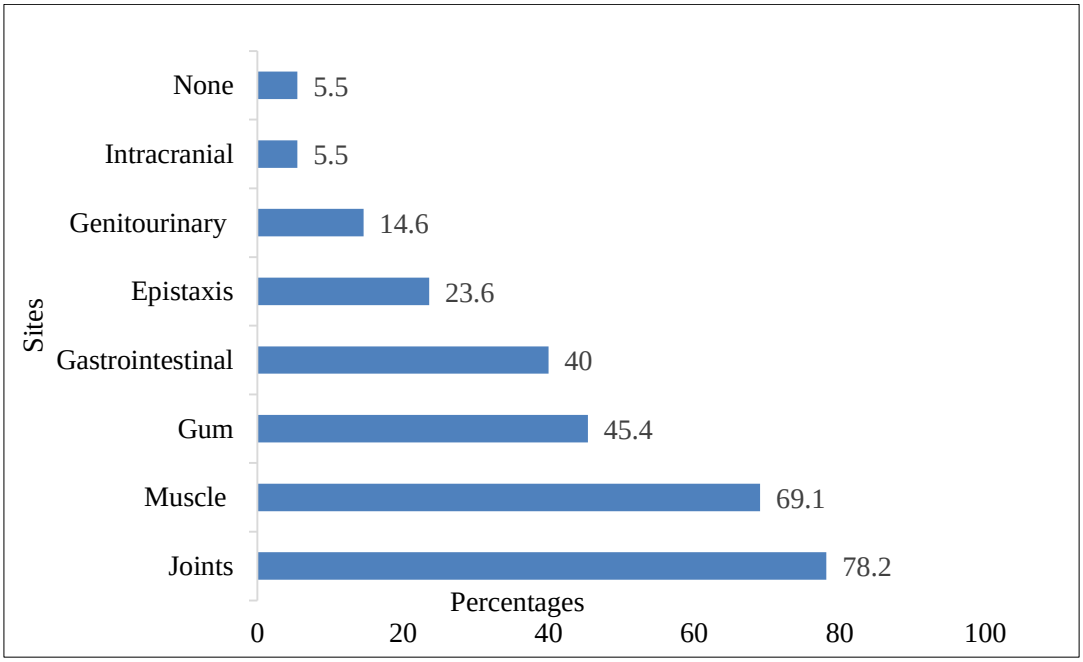



**Figure 2: Bleeding sites reported prior to Emicizumab prophylaxis**

Being under 5 (32.7%) was the most prevalent reason for starting Emicizumab prophylaxis. Since the clinic does not typically employ ITI due to a shortage of CFCs, all patients with inhibitors (23.6%) began Emicizumab prophylaxis. With the benefit of subcutaneous delivery, three patients (5.5%) were started on the treatment due to inadequate venous access. The median duration of Emicizumab prophylaxis among the study participants was 12 months (7, 32), with the longest duration being 32 months for our population. For maintenance, the majority of patients preferred monthly treatments (67.3%), with most (38.2%) receiving their maintenance doses at nearby facilities. Although it is a subcutaneous injection allowing for flexible maintenance, only 30.0% of the patients were injecting themselves at home. Among those not self-injecting, a lack of self-efficacy (57.9%) was the primary reason (Figure 3). Notably, two patients attending boarding school received their injections from their school nurse (Table 3).

**Table 3: Emicizumab prophylaxis initiation and maintenance**

| Variable | Frequency (n) | Percentage (%) |
|---|---|---|
| **Indication for Emicizumab Prophylaxis** | | |
| Under 5 years | 18 | 32.7 |
| Presence of inhibitors | 13 | 23.6 |
| Severe disease | 11 | 20.0 |
| Moderate disease with a history of major bleed | 7 | 12.7 |
| Poor intravenous access | 3 | 5.5 |
| Others | 3 | 5.5 |
| **Place of administration of maintenance dose** | | |
| MNH | 12 | 21.8 |
| Peripheral facility near me | 21 | 38.2 |
| Self-administered at home. | 17 | 30.9 |
| Either MNH or peripheral based on convenience | 11 | 20.0 |
| Others. | 2 | 3.6 |
| **Frequency of maintenance dose administered** | | |
| Weekly | 0 | 0.0 |
| Twice monthly | 18 | 32.7 |
| Monthly | 37 | 67.3 |
| **Duration of Emicizumab prophylaxis (in months)** | | |
| **Median and IQR** | **12 (7,32)** | |

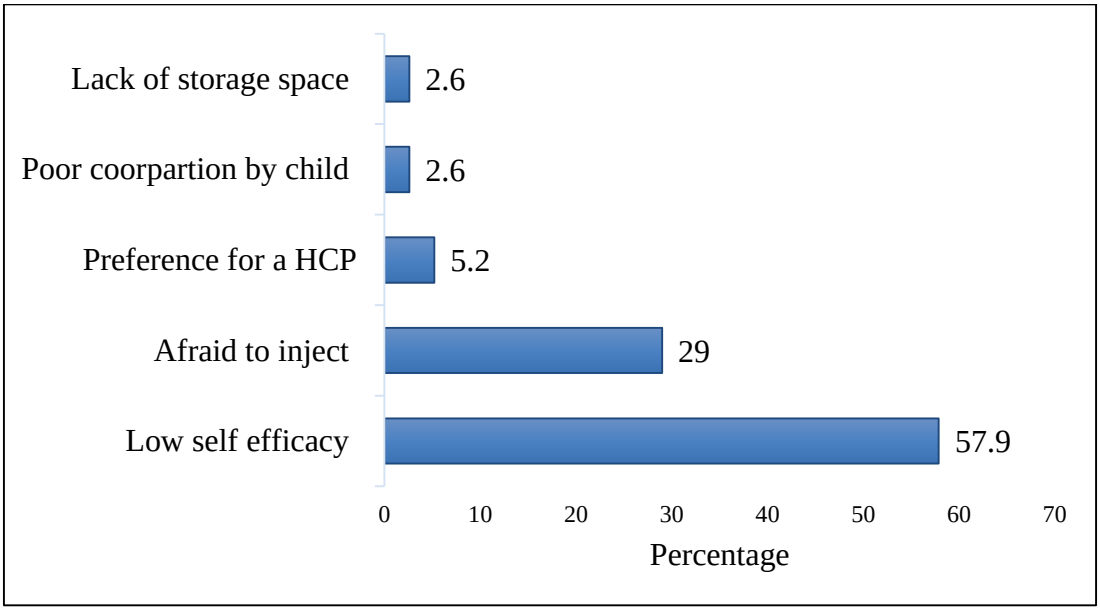



**Figure 3: Reasons for low self-administration rate**

### 3.4 Adherence patters to Emicizumab prophylaxis

Although almost half of the participants (49.1%) admitted to having missed at least one dose, overall, the vast majority of those involved in the study adhered to Emicizumab prophylaxis (78.2%) over the last 3 months leading to the date of their interview. A downward trend in the adherence pattern was noted, with only 56.4% of patients remaining adherent in the most recent month, compared to (72.7%) in the initial month (Figure 4). A significant number of study participants cited distance from the HTC (44.4%), absence of a consultation fee (33.3%), and transition to CFC due to a shortage of Emicizumab (25.9%) as the primary reasons for missed doses (Table 4).

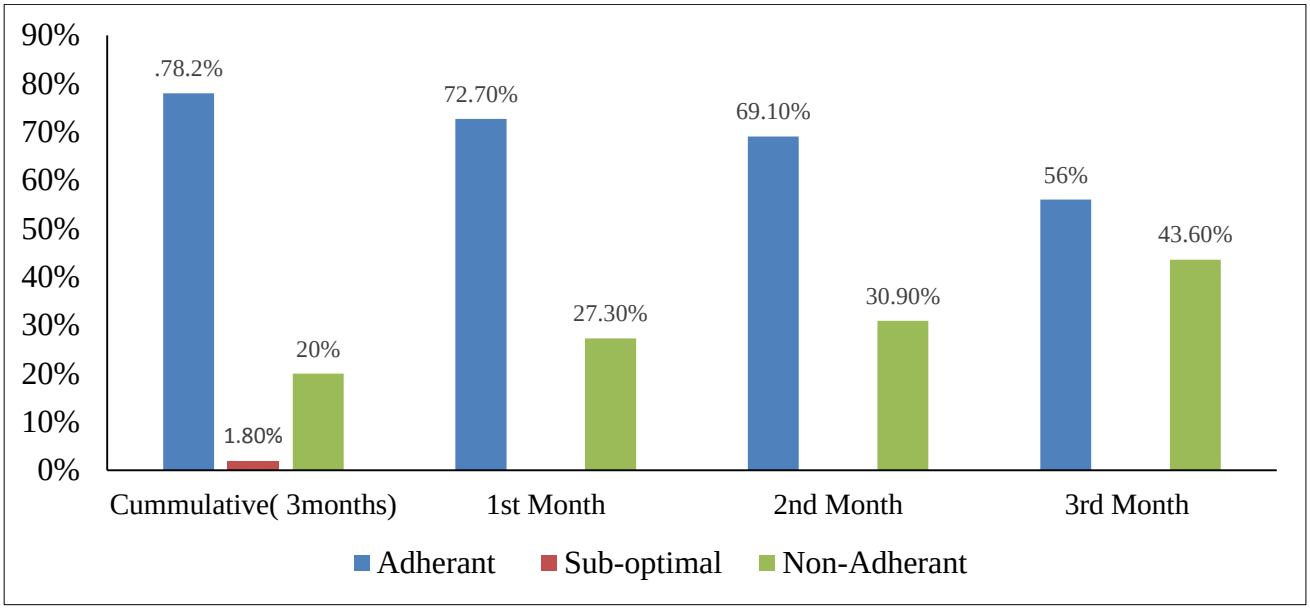



**Figure 4: Adherence Patterns on Emicizumab Prophylaxis**

**Table 4: Reasons for missed doses**

| Variable | Freq | Percentage |
|---|---|---|
| The clinic was too far | 12 | 44.4 |
| I couldn't afford consultation fees | 9 | 33.3 |
| Changed to prophylaxis with CFC due to drug shortage | 7 | 25.9 |
| I couldn't raise my transport | 3 | 11.1 |
| I didn't bleed for a while, I decided to take a break | 2 | 7.4 |
| I was overwhelmed by the numerous injections | 1 | 3.7 |
| **The caregiver was unwell during** | 1 | 3.7 |

### 3.5 Bleeding outcomes while on Emicizumab prophylaxis

A total of 35 (63.6%) patients experienced at least one episode of bleeding during the Emicizumab prophylaxis period. Among these, 62.9% had traumatic bleeds, 17.1% had spontaneous bleeding, and 20.0% experienced both types. The total reported bleeds were 77, with the majority being traumatic (61%, 41/77). The overall median Annualized Bleeding Rate (ABR) (IQR) for both spontaneous and traumatic bleeds was 0.75 (0, 1.7). In contrast, the median for spontaneous bleeding alone was significantly lowered to 0 (IQR 0, 0) (Table 5). The reduction in ABR for spontaneous bleeds before and after Emicizumab prophylaxis was statistically significant ($p < 0.001$) (Table 6).

**Table 5: Bleeding outcomes while on Emicizumab prophylaxis**

| Variable | Frequency (n) | Percentage (%) |
|---|---|---|
| **Proportion of patients with a history of bleeding** | | |
| Present | 35 | 63.6 |
| Absent | 20 | 36.4 |
| **Types of bleeds as experienced by the patients** | | |
| Traumatic | 22 | 62.9 |
| Spontaneous | 6 | 20.0 |
| Both spontaneous and traumatic | 7 | 17.1 |
| **Overall ABR** | | |
| Median and IQR | 0.75 (0, 1.7) | |
| Min and Max | 0.12 | |
| **ABR for Unprovoked Bleeds** | | |
| Median and IQR | 0 (0, 0) | |
| Min and Max | 0,12 | |
| **ABR for Traumatic** | | |
| Median and IQR | 0.38 (0, 1) | |
| Min and Max | 0 ,5 | |

**Table 6: Comparison of the median ABR for spontaneous bleeding pre and post Emicizumab prophylaxis**

| Variable | Median and IQR | Min | Max | *p*-value |
|---|---|---|---|---|
| **Spontaneous bleeds before Emicizumab prophylaxis** | 8 (5, 16) | 0 | 60 | <0.001 |
| **Spontaneous bleeds after Emicizumab prophylaxis** | 0(0,0) | 0 | 5 | |

The majority of the bleeding events involved the musculoskeletal system, as illustrated in Figure 5. One individual experienced two instances of gastrointestinal bleeding, while another had a case of intracranial bleeding. After initiating Emicizumab prophylaxis, out of the 19 patients who indicated a target joint before starting Emicizumab prophylaxis, (15/19) 79.0% reported resolution of the target joint during the prophylaxis period (Figure 6).

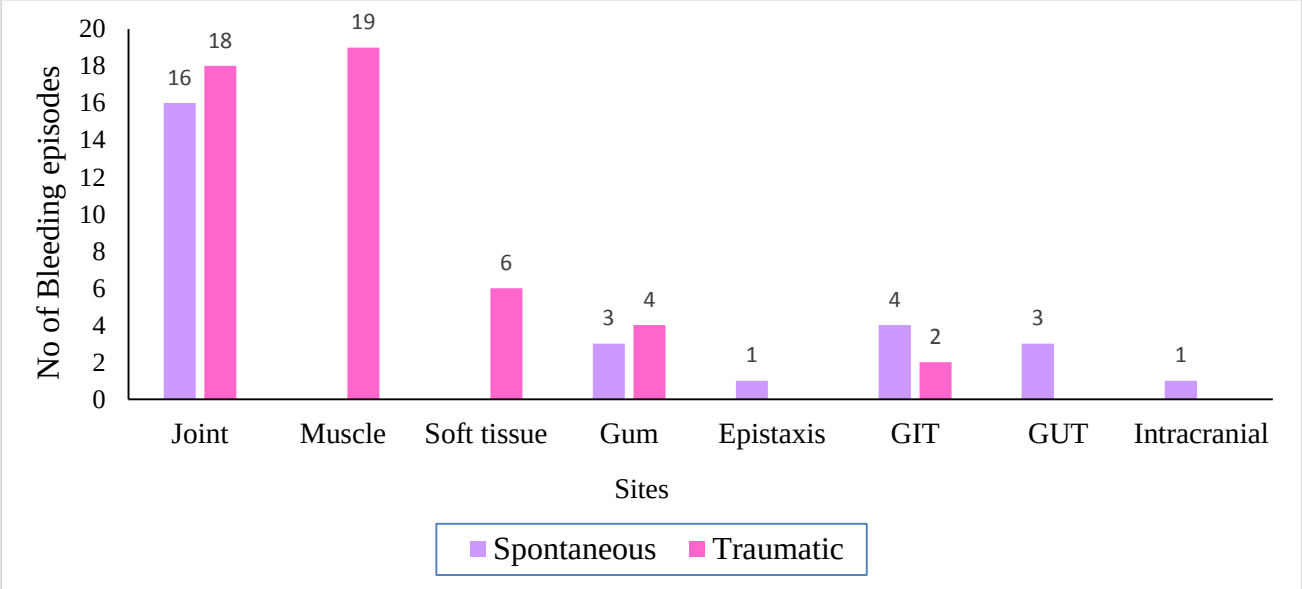



**Figure 5: Bleeding sites while on Emicizumab prophylaxis**

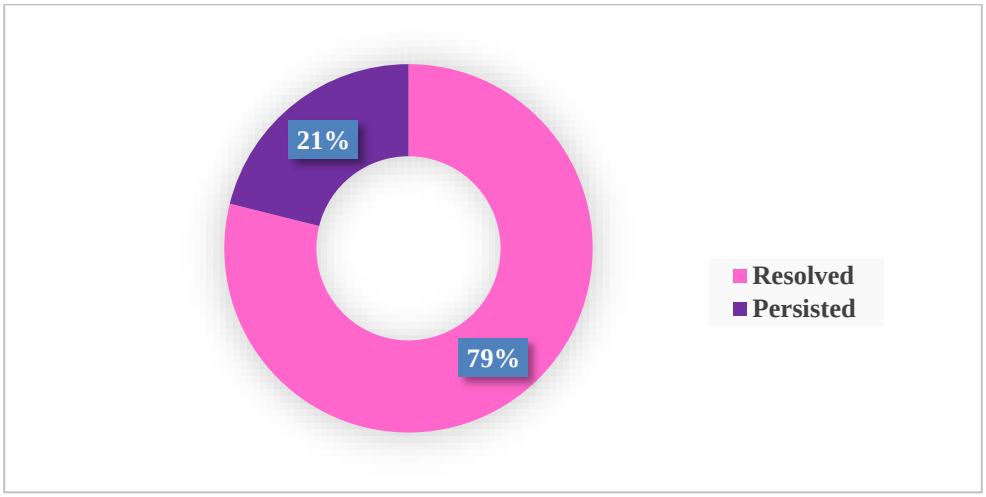



**Figure 6: Proportion of participants with resolution of target joints**

### 3.6 Association between sociodemographic, clinical characteristics and spontaneous bleeding

On cross-tabulation analysis, only age had a significant correlation with spontaneous bleeding, with individuals over 18 years exhibiting the highest rate of spontaneous bleeding in comparison to other age categories ($p < 0.001$) (Table 7). The adherence patterns did not show a significant difference between the group aged ≤ 18 years (79.2%) and the group aged >18 years (71.4%) ($p = 0.64$)

**Table 7: Association between sociodemographic, clinical characteristics and spontaneous bleeding**

| | Spontaneous bleeding | | |
|---|---|---|---|
| **Variable** | **Yes (%)** | **No (%)** | **p – value** |
| **Age group (years)** | | | |
| < 5 | 1 (7.1) | 13 (92.9) | < 0.0001 |
| 5 – 18 | 5 (15.2) | 28 (84.8) | |
| >18 | 5 (83.3) | 1 (16.7) | |
| **Severity of disease** | | | |
| Mild | 1 (25.0) | 3 (75.0) | 0.885 |
| Moderate | 4 (18.2) | 18 (81.8) | |
| Severe | 6 (23.1) | 20 (76.9) | |
| **Cumulative adherence** | | | |
| Adherence | 6 (14.6) | 35 (85.4) | 0.098 |
| Non-adherence | 5 (41.7) | 7 (58.3) | |
| **Residence** | | | |
| Dar-es-Salaam | 5 (19.2) | 21 (80.8) | 1.000 |
| Outside Dar-es-Salaam | 6 (22.2) | 21 (77.8) | |
| **Mode of payment** | | | |
| Exemption | 0 (0.0) | 1 (100.0) | |
| Insured | 7 (23.3) | 23 (76.7) | 1.000 |
| Private | 2 (25.0) | 6 (75.0) | |
| Public (cost sharing) | 4 (25.0) | 12 (75.0) | |

### 3.7 Factors associated with spontaneous bleeding while on Emicizumab prophylaxis

Based on literature, the following variables were included in the regression. Only, age was a significant predictor of spontaneous bleeding (aPR-11.67% $p < 0.012$) (Table 8).

**Table 8: Univariable analysis of the factors associated with bleeding**

| | | Univariable analysis | | |
|---|---|---|---|---|
| **Variable** | **Category** | **aPR** | **95% CI** | **p –value** |
| Age (years) | >18 | 11.67 | 1.71 – 79.76 | **0.012** |
| | 5 – 18 | 2.12 | 0.27 – 16.54 | 0.473 |
| | < 5 | Ref | | |
| Severity of disease | Severe | 0.92 | 0.15 – 5.79 | 0.932 |
| | Moderate | 0.73 | 0.11 – 4.94 | 0.744 |
| | Mild | Ref | | |
| Residence | Outside Dar-es Salaam | 1.16 | 0.40 - 3.33 | 0.789 |
| | Dar-es Salaam | Ref | | |
| Mode of payment | Exemption | 0.80 | 0.68 - 0.95 | 0.010 |
| | Insured | 0.99 | 0.80 - 1.22 | 0.900 |
| | Private | 1.00 | 0.75 - 1.34 | 1.000 |
| | Public (cost sharing) | Ref | | |
| Adherence | Adherence | 0.35 | 0.13 – 0.95 | 0.040 |
| | Non-adherence | Ref | | |

### 3.8: Adverse events experienced while on Emicizumab prophylaxis

Only 5 out of 55 patients (9.1%) reported to have experienced at least one adverse event while on Emicizumab prophylaxis. Injection site reactions were the most reported adverse events (5.5%) followed by headache (3.6%) (Figure 7). All observed adverse events were mild and transient as none of these patients' needed treatment.

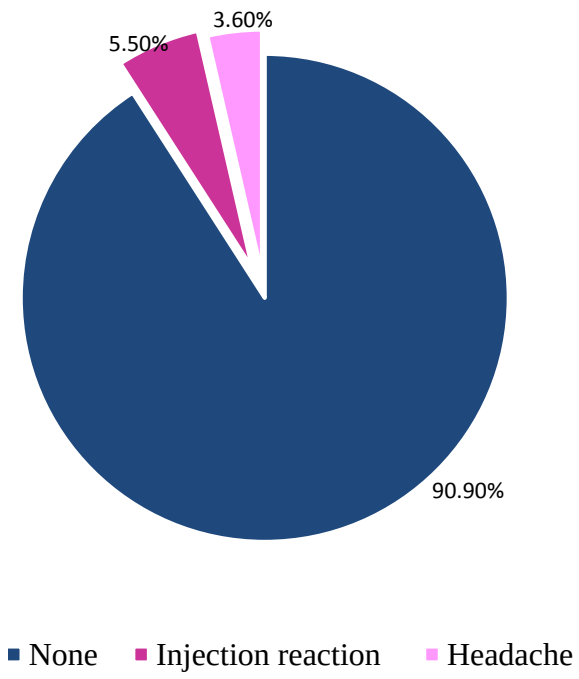



**Figure 7: Types of adverse events reported post Emicizumab prophylaxis**

# CHAPTER FOUR

## 4.0 DISCUSSION

This research examined the patterns of adherence, bleeding outcomes, and safety profile of Emicizumab prophylaxis among patients with hemophilia A in Tanzania. Our key findings reveal that (i) while almost half of the participants reported missing at least one dose, a significant portion of the study group adhered to Emicizumab prophylaxis (78.2%), (ii) around 63.6% of patients at least one bleeding incident during Emicizumab prophylaxis, with only 37.1% suffering spontaneous bleeds. The annualized bleeding rate (ABR) for spontaneous bleeds saw a notable decline following Emicizumab prophylaxis. After initiating Emicizumab, 79.0% of those with a previous history of target joints reported resolution, (iii) older age (>18 years) emerged as the sole significant predictor of spontaneous bleeding, and (iv) fewer than 10% of participants indicated they had faced adverse events after starting Emicizumab prophylaxis.

This study revealed that over three-quarters of patients adhered to Emicizumab prophylaxis. A much greater adherence rate was noted in a study by Li et al. (2019), which explored the patterns and predictors of adherence to Emicizumab prophylaxis. In their research, patients transitioning from on-demand to Emicizumab prophylaxis achieved an adherence rate of 89%, while those moving from routine prophylaxis with CFCs or BA reached an even higher rate of 98% (44). The adherence rate observed in our study was also lower than that reported from a study in West Africa, which noted a 100% adherence rate. However, their study exclusively included individuals who had previously adhered to factor prophylaxis. This disparity may stem from selection bias(43) . Unlike in many real-world studies, our cohort had no prior exposure to prophylaxis, making the concept of maintenance dosing of Emicizumab, despite the absence of bleeding, a new one. This highlights that a lack of previous prophylactic experience may have influenced our patients' adherence to Emicizumab. Nonetheless, a majority of study participants remained adherent. We attribute the high adherence rate to the supportive presence of caregivers, which may have positively impacted their compliance. Disease severity and a history of major bleeding may have

further incentivized adherence. The decreasing pattern in adherence noted from the initial to the final months can be accounted for by the short-term unavailability of Emicizumab in the HTC since they had not yet been given their donation. This resulted in the transition of certain patients to prophylactic treatment with CFCs, while keeping Emicizumab solely for those with severe disease inhibitors, and inadequate venous access reserving Emicizumab for those with severe conditions, inhibitors, and challenging venous access. This underscores the challenges of excessive dependence on donor support. Conversely, the conversion of some patients to CFC prophylaxis creates an opportunity to initiate a prophylactic program with CFCs for at-risk populations. This allows Emicizumab, which is pricier, to be reserved for those with no alternative treatment options. Although provided at no cost, it was unfortunate to find that some patients were unable to adhere to treatment due to the inability to pay consultation fees. Patients living outside of Dar-es-Salaam also mentioned distance as a significant barrier. With only a small number of individuals able to self-administer Emicizumab, empowering and educating patients to achieve self-efficacy in their management is essential. Indeed, training patients and caregivers has been shown to enhance patients' autonomy for self-administration, enabling home prophylaxis (44).

Our study also found that over half of the patients experienced at least one bleeding incident during Emicizumab prophylaxis, with most instances triggered by trauma. These findings align with results from a study in Colorado, where 63.2% of their cohort had bleeding while on prophylaxis, and 70% of the total bleeds were traumatic(46). The ABR for spontaneous bleeds significantly reduced in a majority of our patients, supporting the hypothesis that although the risk of bleeding during Emicizumab prophylaxis is not entirely eliminated, patients transitioned to milder phenotypes who primarily bleed due to trauma. This substantial reduction in ABR corresponds with findings from the HAVEN studies and also from a study in Ivory Coast, which reported an ABR of zero for spontaneous bleeds over 12 months of prophylaxis (43). Despite the absence of antibody testing against Emicizumab in this study, none of our patients experienced recurrent bleeding while on prophylaxis, except one individual who faced two gastrointestinal bleeding incidents. This required hospitalization and treatment with CFCs for acute bleed management. Further assessment

indicated he was positive for H. pylori and an esophagogastroduodenoscopy revealed active bleeding gastric ulcers. Our results also showed that a significant share of patients with target joints found resolution due to prophylaxis. This finding parallels a study conducted in Taiwan on the efficacy, safety, and cost of Emicizumab prophylaxis, which indicated that only 17.9% of the 69.2% of patients with target joints at the beginning of the study continued to have them after prophylaxis(56).

Regarding factors linked to bleeding while on prophylaxis, older age (> 18 years) was identified as a significant predictor of spontaneous bleeding. Similar conclusions were drawn by Mendelovich et al. from the Israeli National Hemophilia Center, which found a correlation between age and bleeding risk, noting that those over 18 were more significantly affected (48). We speculate that older patients faced challenges with adherence potentially due to a lack of caregiver supervision, which would facilitate strict follow-up. In this investigation, while disease severity, location of residence, insurance coverage, and adherence status were not significant indicators of bleeding, adherence to Emicizumab prophylaxis appeared to have some protective effect. We also recognize that the small sample size of our study may affect the findings, suggesting that studies with larger samples could yield different results.

Our research demonstrated that Emicizumab prophylaxis is safe, with fewer than 10% of patients reporting adverse events. Injection site reactions were the most frequently observed adverse events, consistent with findings from the first four HAVEN studies and other prior research. This is expected, as Emicizumab is a biologic administered via subcutaneous injection. The lower occurrence of adverse events following Emicizumab prophylaxis has also been reported in West African studies (43). Like other studies, our findings indicated that the adverse events were generally mild and temporary, with no patients discontinuing treatment due to intolerable adverse events. In contrast to the HAVEN studies, our cohort did not experience any thrombotic events, possibly due to the limited exposure to aPCC among participants, who reported using it for less than three days during circumcision, with none exceeding 100 IU/kg per day. Although we did not test for antibodies against

Emicizumab, the absence of recurrent bleeding among those adhering to treatment further indicates that the immunogenicity of Emicizumab is lower than that associated with CFCs.

This study has certain limitations: while we acknowledge the availability of contemporary methods to evaluate adherence for patients on Emicizumab prophylaxis, such as the "VERITAS – Nextgen," which incorporates elements of planning, drug administration, timing, dosing, and patient autonomy in managing bleeds during prophylaxis, this option was not utilized as only 30.0% of participants self-administered. Being a cross-sectional study that assessed patient characteristics before treatment, it might have encountered an element of recall bias from participants. Nevertheless, to the best of our knowledge, this study stands as one of the few studies conducted in the Sub-Saharan population to thoroughly evaluate adherence, treatment outcomes, and the safety profile of Emicizumab prophylaxis. These distinctive results are critical in highlighting the disparities between patients from low and middle-income countries and those from developed nations, an essential consideration when designing humanitarian programs for these regions. The study encompassed approximately 80% of all patients with hemophilia A in the country on prophylaxis, providing valuable insights into the actual circumstances for patients receiving Emicizumab prophylaxis in Tanzania.

# CHAPTER FIVE

## 5.0 CONCLUSIONS AND RECOMMENDATIONS

### 5.1 Conclusions

This study revealed that the majority of the HA patients were adherent to Emicizumab prophylaxis. Emicizumab prophylaxis is efficacious in preventing spontaneous bleeding and has demonstrated a good safety profile. Older age was the only significant factor associated with spontaneous bleeding while on prophylaxis. Continued monitoring and pharmacovigilance are essential to assess long term outcomes and optimize patient management strategies.

### 5.2 Recommendations

It is our hope that this study will pave way for the discussion on the need for a robust prophylaxis program in Tanzania and other sub-Saharan countries. The following are recommended:

- The roll out of Emicizumab to regional HTCs to allow initiation and follow up of patients. While administration of Emicizimab is allowed at other facilities including the regional HTCs, initiation and refill of the prescriptions can only be done at MNH.Capacity building for healthcare providers working on the regional HTCs is warranted to cut down the need for travel for patients living outside Dar es Salaam.
- The government should make considerations for waiver for consultation fees for patients on this novel agent given that it is expensive yet provided on donation by WFH. This will go a long way in improving adherence, treatment outcomes and quality of life of HA patients.
- Patient education on the role of prophylaxis and self-administration of Emicizumab would further improve accessibility. The flexibility of drug administration was unfortunately not realized by the majority of our participants
- Donations to include 105mg or 150mg vials to cater to patients of higher body weights therefore prophylaxis burden.

- Future research should focus on evaluating the quality of life of patients and caregivers on Emicizumab prophylaxis and also factors affecting adherence in different age groups.
- Incorporation of Emicizumab, BA and CFCs in the Haemophilia treatment guidelines and its addition to the essential drug list will further buttress the importance government support in making treatment and prophylaxis available for patients with HA.
- Finally, the incorporation of health economists would be crucial in following up the long-term advantage of prophylaxis by Emicizumab in especially bringing down the cost of CFCs utilized by patients with severe disease and those with inhibitors when treated on demand. Even more would be the long-term impact of their contribution to the country's economy as we expect a significant reduction in disability in the future after aversion of joint arthropathy through prophylaxis therapy.

# CHAPTER SIX

## 6.0 DISSEMINATION PLAN AND PUBLICATION

The results of this publication have already been presented in departmental presentations and will be published in peer reviewed journals and presented in scientific conferences. It shall also be shared with the HTC in MNH where the patients are followed up,WFH and Novo Nordisk Haemophilia Foundation who provided the funding.

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# APPENDICES

## Appendix 1: informed consent form (English version)

**CONSENT TO PARTICIPATE IN THE STUDY ON ADHERENCE, BLEEDING OUTCOMES AND SAFETY PROFILE OF EMICIZUMAB PROPHYLAXIS AMONG HAEMOPHILIA A PATIENTS ATTENDING MUHIMBILI NATIONAL HOSPITAL, DAR ES SALAAM, TANZANIA**

Principal investigator **: Dr Rebbecca Wughanga Mwakichako**

Address: Muhimbili University of Health and Allied Sciences

P.O Box 65001,Dar es Salaam.

Name of the patient_____

Name of the parent/ guardian (if the patient is a dependent) _____

MR/Number _____

Dear Sir/Madam,

My name is Rebbecca Wughanga Mwakichako, a resident doctor at the department of Haematology and Blood Transfusion at the Muhimbili University of Health and Allied Sciences. I am conducting research on adherence, bleeding outcomes and the safety profile of Emicizumab prophylaxis among Haemophilia A patients attending Muhimbili National Hospital Dar-es -salaam, Tanzania. Being among the patients who qualify for this study I hereby request your participation.

**Purpose of the study :** The purpose of this study is to evaluate the adherence patterns, bleeding outcomes and safety profile of patients on Emicizumab prophylaxis. This will be explored in the following sections.

(i)Adherence

Questions on the adherence patterns will evaluate how you use your medication. We will look at whether you took your loading dose, the dosage that was given and whether you managed to complete it. We will also evaluate your maintenance dose and especially the frequency you chose (weekly, twice weekly or monthly) and whether this is followed. Finally, we will explore a few challenges if any that might have influenced your adherence patterns.

(ii)Bleeding outcomes

As you are aware, you are on prophylaxis treatment while on Emicizumab. Meaning that this drug is administered to prevent bleeding and not to treat active bleeding. Questions in this section will be aimed at exploring whether you have had any bleeding while you have been on prophylaxis and the type and severity of these bleeding.

(iii)Safety profile

Like any drug Emicizumab users experience unwanted effects of the drug. This section will explore whether you have experienced such effects and whether you ever needed treatment for the same.

(iv)Others

For completeness we will also explore a few questions on your social-demographic characteristics including your marital, educational, occupational status and area of residence. Finally, we shall look at your previous history prior to Emicizumab prophylaxis including your disease characteristics including the severity of disease, bleeding characteristics and treatment history.

**How to participate:** Once you agree to take part in this study, you will sign this consent form after the purpose of this study is well explained and understood by you. Patients under the age of 18 will give their assent but their guardians will have to provide their consent in writing. You will participate by answering questions on a questionnaire. It will also involve reviewing your previous medical records both electronic and a physical file for previously done laboratory test. There will be no drawing of blood in this study or administration of any new drug.

**Risk:** We do not anticipate that your participation in this study will be associated with any health risks.

**Benefits:** Being among the few patients on Emicizumab prophylaxis in Tanzania, your participation will go a long way in providing firsthand information on the actual impact of Emicizumab. The information will help to guide clinicians on how to better manage patients on this treatment based on the unique experiences you describe.

It will help lobby for better partnerships between the government and other stakeholders to expand this program to cover many more patients should the benefits be obvious from these results. Feedback to the manufacturer will also be given should there be results that are unique for this population and hence trigger more research in this area.

More important is that you will be educated on this drug and will be free to ask any question about your treatment and haemophilia in general. Should there be discrepancies in your dosing (over or under dosing) your treatment team will be advised.

To be noted however is that this study carries no monetary benefit to the participant.

**Right to withdraw and alternatives:** Your participation in this study is purely on a voluntary basis. Though receiving care at the clinic, you are under no obligations to participate. At any point, you are free to withdraw from this study and this will not in any way negatively affect your care and treatment at the clinic.

**Confidentiality:** The information obtained in this study will be used only for the purposes research and your treatment. It will not be absolutely not shared to anyone outside this study without your consent.

**Who to contact.:** For any questions and clarifications about this study and your rights to participate kindly contact/ call

1. Dr Rebbecca Wughanga Mwakichako
   E-mail: beckymwakichako@gmail.com
   Tel: +255769835750
   +254713138330
   For more information, contact

2. **Director of research, publications and innovations (DRPI)**
   Muhimbili University of Health and Allied Sciences (MUHAS)
   P.O Box 65001, Dar es Salaam, Tanzania
   Tel: +255222152489 Email drp@muhas.ac.tz

**Appendix 2: Fomu ya kuomba ridhaa.**

**RIDHAA YA KUSHIRIKI KATIKA UTAFITI KUHUSU UZINGATIAJI, MATOKEO YA UVUJAJI DAMU NA MADHARA YA KINGA YA EMICIZUMAB KWA WAGONJWA WA HIMOFILIA A WANAOHUDHURIA HOSPITALI YA TAIFA YA MUHIMBILI, DAR ES SALAAM, TANZANIA**

Mtafiti Mkuu: **Dkt Rebbecca Wughanga Mwakichako**

Anuani: Chuo Kikuu cha Afya na Sayansi ya Tiba cha Muhimbili

Sanduku la Posta 65001, Dar-es-Salaam

Jina La magonjwa_____

Jina la mzazi au mlezi (ikiwa magonjwa yuko chini ya miaka 18) _____

Namba ya Hospitali_____

Kwa Bibi/ Bwana,

Jina langu ni Rebbecca Wughanga Mwakichako, daktari na mwanafuzi wa shahada ya uzamili katikaChuo Kikuu chaAfya naSayansishirikishi cha Muhimbili kwenye idara ya magonjwa ya damu.Nanuia kufanya utafiti unaoangalia uzingatiaji, matokeo ya uvujaji wa damuna athari mbaya za utumiaji wa kinga ya Emicizumab kwa wagonjwa wa Himofilia A wanaopokea matibabu katika hospitali ya taifa ya Muhimbili jijini Dar-es-salaam Tanzania.Ukiwa mmoja wa wagojwa wanaotumia dawa hii ili kukinga uvujaji wa damu ninaomba ushiriki wako.

**Nia ya Utafiti**

Utafiti huu utaangali uzingatiaji wa utumaiaji , matokeo ya uvujaji damu ana athari mbaya za kwa wagonjwa wa Himofilia A wanaotumiakinga ya  Emicizumab. Utafiti huu zingatia maswala yafuatayo.

(i)Uzingatiaji wa utumiaji wa Emicizumab:

Maswali haya yataangalia jinsi unavyotumia dawa hii. Tutaangali ulivyotumia dozi za kwanza zinazochomwa kila wiki kwa mwezi na dozi zinazofuata. Tutaangalia mtindo uliochagua iwapo unaendela kuchomwa dawa hii kila wiki, kila baada ya wiki mbili au mara moja kwa mwezi. Tutaangalia ikiwa unazingatia kikamilifu dozi zako na changamoto unazokumbana nazo unapotumia dawa hii.

(ii)Matokeo ya uvujaji damu

Kwa kuwa unatumia dawa ilihii kukinga uvujaji damu, tutaangalia iwapo umevuja damu wakati wowote ukiwa kwenye kingahii. Tutaangali ulipovija damu ( sehemu za mwili), umevujadamu mara ngapi na ukali wa uvujaji damu.

(iii) Athari za Kinga ya Emicizumab

Kama dawa zingine, utumiaji wa Emicizumab unaweza kuleta athari mbaya. Sehemu hii itaangalia iwapoumekutana na athari hizi na kama ulihitaji matibabu kwa ajili hio.

(iv) Maswali Mengine

Tutuila maswali kuhusu ndoa, elimu, kazi naunapoishi.Mwisho tutaangalia historia ya ugonjwa huu tukizingatia ukali wa Himofilia, tiba ulizopokea na uvujaji damu kabla ya kuanza kutumia kinga ya Emicizumab.

**Jinsi ya Kushiriki:** Utakapokubali kuendelea na kuelewa vyema lengo la utafiti huu, utatia sahihi kwenye fomu hii ya ridhaa kama ishara ya kwamba umetupa ruhusa. Watoto wenye chini ya miaka kumi na minane watashiriki pale ambapo mzazi au mlezi atatupa ruhusa kwa

ishara ya kutia sahihi fomu hii. Kushiriki kutakuwa kwa njia ya kujibu maswali yatakayohusu tulioyataja hapo mbeleni. Pia tutaangalia rekodi zako za hospitali kwenye mtandao wa JEEVA au faili yako ya hospitali ili kuangalia majibu ya maabara. Utafiti huu hautatoa damu kwa ajili ya upimaji wala kukupa dawa mpya pasi na unayotomia sasa hivi.

**Hatari za kushiriki:** Hatutarajii matatizo yoyote ya kiafya kutokea kwa sababu ya kushiriki katika utafiti huu

**Faida ya kushiriki :** Hivi vyote vitatusaidia kuelewa hali yako unapotumia kinga ya Emicizumab. Ikiwa utafiti wa kwanza hapa Tanzania na moja wapo wa tafiti chache barani Africa , utafiti huu utatoa mwanga kuhusu hali yenu halisi kama wagonjwa wanaotumia dawa hii kwetu sisi madktari ,serikali, wanaotengeneza dawa hii na washika dao wengine .Na tunatumai majibu tutakayoyapata yatatusaidia kujua jinsi ya kuboresha matibabu na kuhamasisha serikali kujiunga na mradi wa kutoa dawa hii ili na wagonjwa wengine wajiunge kwenye kinga hii.

Zaidi ya haya utapata maelezo zaidi huhusu kinga ya Emicizumab na ugonjwa wa Himofilia.Ikiwa utapatikana kwenye dozi isiyosahihi ( zaidi au iliyopungua) madktari wako watajulishwa ili wafanye marekebisho.

Ni muhimu kuelewa kuwa utafiti huu hautakuwa na faida ya kifedha kwa watakaoshiriki .

**Uhuru wa kujiuzulu:** Kujiunga na kuendela katika utafiti huu ni kwa hali ya kujitolea. Endapo utahitaji kujiondoa kwenye utafiti huu unao uhuru wakuondoka wakati wowote. Kujiunga au kujiuzulu hautaathiri kwa njia yoyote wala matibabu yako kuathirika.

**Usiri:** Maelezo yoyote yatakayotolewa yatatumika kwa faida ya utafiti huu pekee na wahayatatumika popote bila ruhusa yako.

**Wahusika:** Kwa maswali yoyote kuhusu utafiti huu na kushiriki, tafadhali wasiliana;

1. Dr Rebbecca Wughanga Mwakichako

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2.Mkurugenzi wa tafiti na uchapishaji

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**Appendix 3: Respondent Data Collection Tool**

**SECTION A**

| No | QUESTION | OPTIONS | ANSWER |
|---|---|---|---|
| **1** | Research unique ID | | |
| **2** | File number | | |
| **3** | Date of interview | | |
| **4** | Who is the respondent? | 1. Patient<br>2. Mother<br>3. Father<br>4. Guardian | |
| **5** | Contact Telephone number of the respondent | | |
| **6** | Alternative Telephone number the respondent | | |
| **7** | What is the relationship with the patient? | | |

**SECTION B: SOCIAL DEMOGRAPHIC CHARACTERISTICS OF PATIENT**

| No | QUESTION | OPTIONS | ANSWER |
|---|---|---|---|
| **8** | Respondent's date of birth (MM/DD/ YYYY) | | |
| **9** | Sex | 1. Male<br>2. Female | |
| **10** | Education level | 1. Informal/none<br>2. Primary education<br>3. Secondary education<br>4. High school<br>5. University/ college<br>6. Not school going age | |
| **11** | Employment history | 1. Unemployed<br>2. Employed (Private/Public)<br>3. Farmer<br>4. Business<br>5. Fishing<br>6. NA-Students<br>7. Others | |
| **12** | Means of payment for medical treatment | 1. Insurance. Specify<br>2. Public (cost sharing)<br>3. Private<br>4. Exemption | |
| **13** | If Qn 12 is Insurance, please give the name of your insurance | | |
| **14** | Respondents' region of residence | | |
| **15** | Respondents' district of residence | | |

**SECTION C: CLINICAL HISTORY PRIOR TO EMICIZUMAB PROPHYLAXIS**

**Responses in this section should be cross-checked with the patient's hospital records and Haemophilia ID**

| No | QUESTION | OPTIONS | ANSWER |
|---|---|---|---|
| **16** | What is your disease severity according to baseline factor assay | 1. Severe (<1%)<br>2. Moderate (1-5%)<br>3. Mild (6-40%)<br>4. Missing | |
| **17** | Do you have a history of FVIII Inhibitor after Factor concentrates exposure? | 1. Yes<br>2. No<br>3. Unknown | |
| **18** | What factor replacement therapies have you ever been exposed to prior to Emicizumab use? (***Multiple responses***) | 1. Factor concentrates.<br>2. Use of bypassing agents (FEIBA)<br>3. Fresh frozen plasma/ cryoprecipitate<br>4. None | |
| **19** | What is the estimated average number of spontaneous bleeding episodes you experienced in a year before Emicizumab use? (***Hint: Average number of times you had spontaneous bleeding in a month, infusion of CFCs, hospital admission, conservative management, absenteeism at work or school all unrelated to trauma -every month)*** | | |
| **20** | What types of serious bleeds have you ever experienced in your lifetime? ***(Multiple responses)*** | 1. Joints<br>2. Muscles<br>3. Gum<br>4. Epistaxis<br>5. Haematuria<br>6. None | |

| | | | |
|---|---|---|---|
| **21** | Have you ever experienced any of the following life-threatening bleeds in your lifetime?<br>**Hint {*intracranial, Neck/throat Gastrointestinal (vomiting blood, passing black stools, passing frank blood in stool)}*** | 1.Yes<br>2.No | |
| **22** | If yes in Qn 25 above, select where appropriate (***Multiple responses***) | 1. Intracranial,<br>2. Neck/throat<br>3. Gastrointestinal (vomiting blood, passing melena stools, passing frank blood in stool | |
| **23** | Have you ever experienced 3 or more episodes of unprovoked bleeding on the same joint for 6 consecutive months? before Emicizumab use (***Target joint)*** | 1.Yes<br>2.No | |
| **24** | Do you any joint permanently destroyed because of recurrent bleeding before Emicizumab use? (joint arthropathy)<br>**Hint** {**Probe for permanent disability**} | 1.Yes<br>2.No | |

**SECTION D: EMICIZUMAB INITIATION, MAINTANCE AND ADHERENCE**

| No | QUESTION | OPTIONS | ANSWER |
|---|---|---|---|
| **29** | What was the main reason for initiation of Emicizumab prophylaxis? ***(Confirm this response from clinical records)*** | 1. Under 5 years<br>2. Presence of inhibitors<br>3. Severe disease<br>4. Moderate disease with a history of major bleed<br>5. Poor intravenous access<br>6. Others, specify | |
| **30** | For how long have you been on Emicizumab prophylaxis? (***Duration in months)*** | | |
| **31** | Where was the first injection of your loading dose administered? | 1. MNH Haemophilia Clinic<br>2. Peripheral Facility near me<br>3. Other. Specify | |
| **32** | From where do you receive your weekly, biweekly, or monthly maintenance dose of Emicizumab? **(*Multiple response*)** | 1. MNH<br>2. Peripheral facility near me<br>3. Self-administered at home.<br>4. Either hospital or home whichever is convenient at the time<br>5. Others. Specify | |
| **33** | How frequently is your maintenance dose administered? | 1. Weekly<br>2. Twice monthly<br>3. Monthly<br>4. I just completed the induction<br>5. I don't have a fixed frequency. | |
| **34** | Have you ever missed any of the recommended doses of Emicizumab in the last three months? | 1.Yes<br>2.No | |

**SECTION E: ADHERENCE (CHECK IN THE IN THE PATIENT RECORDS)**

| No | | QUESTION | ANSWER |
|---|---|---|---|
| **35** | **WEIGHT** | Average Weight (kg) in the last 3 months | |
| **36** | | Weight (kg) in Month one | |
| **37** | | Weight (kg) in Month two | |
| **38** | | Weight (kg) in Month three | |
| **39** | **VIALS** | The cumulative dose of Emicizumab (Vials) prescribed in the last 3 months | |
| **40** | | How many vials of Emicizumab were prescribed to you in month one | |
| **41** | | How many vials of Emicizumab were prescribed to you in month two | |
| **42** | | How many vials of Emicizumab were prescribed to you in month three | |
| **43** | **CONSUMED** | The cumulative dose of Emicizumab (Vials) consumed in the last three months | |
| **44** | | Emicizumab (mg) consumed in month one | |
| **45** | | Emicizumab (mg) consumed in month two | |
| **46** | | Emicizumab (mg) consumed in month three | |

**SECTION F: REASONS FOR MISSING EMICIZUMAB IN THE LAST THREE MONTHS**

| No | QUESTION | Hints | ANSWER |
|---|---|---|---|
| **47** | If you answered Yes to Qn 36, what would you attribute your missed doses to? (***Multiple responses*****)** | 1. I could not afford consultation fees<br>2. The clinic was far<br>3. I could not raise transportation<br>4. I had not experienced bleeding for a while therefore I did not need treatment<br>5. The medication was out of stock in the country<br>6. I was overwhelmed by the number of injections<br>7. I experienced an unusual /side effect of the drug, so I opted not to continue<br>8. Other. Specify | |

**SECTION G: BLEEDING OUTCOMES WHILE ON EMICIZUMAB PROPHYLAXIS**

| No | QUESTION | OPTION | ANSWER |
|---|---|---|---|
| **48** | Have you ever experienced bleeding at any time in the period of Emicizumab prophylaxis? | 1.Yes<br>2.No | |
| **49** | If yes in Qn 48, What kind of bleeding episode was it /were they? (**Multiple**) | 1. Unprovoked (spontaneous)<br>2. Traumatic | |
| **50** | Kindly specify the number for Unprovoked **{put zero if Qn 49 is Traumatic}** | | |
| **51** | Kindly specify the number of traumatic **{put zero if Qn 49 is Unprovoked}** | | |
| **52** | Kindly specify the location of unprovoked site (s) | 1. Joints<br>2. Muscles<br>3. Gum<br>4. Epistaxis<br>5. Gastrointestinal<br>6. Genitourinary<br>7. Intracranial<br>8. Other. Specify | |
| **53** | Kindly specify location of traumatic site (s) | 1. Joints<br>2. Muscles<br>3. Gum<br>4. Epistaxis<br>5. Gastrointestinal<br>6. Genitourinary<br>7. Intracranial<br>8. Other. Specify | |
| **54** | If Qn 48 is Yes, did you receive treatment for the bleed? | 1.Yes<br>2.No | |
| **55** | If the answer in Qn 54 is Yes, how was it treated? Hint{PRICE-Protection Rest Ice Compression Elevation} | 1. Conservatively (PRICE)<br>2. Factor viii concentrates.<br>3. By Passing agent Activated vii (NOVO 7) /Activated prothrombin complex (FEIBA)<br>4. Surgical intervention-suturing | |

| | | | |
|---|---|---|---|
| | | 5. Others (specify) | |
| **56** | If yes in Qn 27, For patients who answered to a history of a target joint(s) before Emicizumab, did it resolve while on Emicizumab prophylaxis***?(HINT: You did not experience more than 3 episodes of bleeding on the joint consecutively over a period of six months )*** | 1.Yes<br>2.No | |
| **57** | Have you ever had surgery while on Emicizumab *(including tooth extraction and circumcision)* | 1.Yes<br>2.No | |
| **58** | If Yes in Qn 60 Specify the surgery | | |
| **59** | If yes in Qn 60, Kindly answer the following questions related to the events after your surgery (**Multiple choice qn**) | 1. Did you need treatment with factor concentrate to control bleeding?<br>2. Did you return to the facility for re-dressing due to excessive bleeding?<br>3. Did you receive a blood transfusion?<br>4. Did you think you experienced excessive bleeding because of the procedure | |

**SECTION H: ADVERSE EFFECTS EXPERIENCED WHILE ON EMICIZUMAB.**

| No | QUESTION | OPTION | ANSWER |
|---|---|---|---|
| **60** | Have you experienced any unwanted symptoms or an increase from normal an existing symptom since the initiation of Emicizumab? **Hint** (you previously did not have these symptoms, or they have worsened throughout drug use) | 1. Inject site reaction (Redness, rash, irritation, pain)<br>2. Joint pain<br>3. Headache<br>4. Fever<br>5. Diarrhoea<br>6. Thrombotic event (formation of clot)<br>7. Other. Specify<br>8. I never experienced any unwanted events | |
| **61** | If Qn 63 above is less than 8, then have you ever required treatment for the symptoms mentioned above? | 1.Yes<br>2.No | |
| **62** | If Qn 64 is Yes specify which one | | |

**Thank you for your cooperation**

**Appendix 4: Dodoso**

**SEHEMU YA: A**

| **Na** | **SWALI** | **DOKEZO** | **JIBU** |
|---|---|---|---|
| **1** | Kitambulisho cha pekee cha utafiti | | |
| **2** | Namba ya faili | | |
| **3** | Tarehe ya mahojiano | | |
| **4** | Mhojiwa ni nani? | 1. Mgonjwa<br>2. Mama<br>3. Baba<br>4. Mlezi | |
| **5** | Namba ya simu ya mhojiwa | | |
| **6** | Namba mbadala ya mhojiwa | | |
| **7** | Mahusiano kati ya mhojiwa na mgonjwa | | |

**SEHEMU B: MAELEZO YA KIJAMII YA MGONJWA**

| Na | SWALI | DOKEZO | JIBU |
|---|---|---|---|
| **8** | Tarehe ya kuzaliwa ya mgonjwa (MM/SS/ MMMM) | | |
| **9** | Jinsia | 1. Mwanamme<br>2. Mwanamke | |
| **10** | Kiwango cha elimu | 1. Sijasoma<br>2. Msingi<br>3. Sekondari<br>4. Chuo kikuu<br>5. Sijatimiza miaka ya kuanza shule | |
| 11 | Historia ya kuajiriwa | 1. Sina ajira<br>2. Nimeajiriwa (binafsi/uma)<br>3. Mkulima<br>4. Mwanabiashara<br>5. Mvuvi<br>6. Mwanafunzi<br>7. Nyingine | |
| **12** | Njia za malipo kwa matibabu | 1. Bima<br>2. Umma (kugawana gharama)<br>3. Malipo binafsi<br>4. Msamaha<br>5. Nyingine | |
| **13** | Ikiwa 12 ni bima, taja jina la bima | | |
| **14** | Eneo la makazi | | |
| **15** | Wilaya ya makazi | | |

**SEHEMU C: HISTORIA YA UGONJWA KABLA YA KUTUMIA EMICIZUMAB**

**Majibu katika sehemu hii yanapaswa kukaguliwa na rekodi za hospitali ya mgonjwa na Kitambulisho cha Himophilia**

| Na | SWALI | DODEZO | JIBU |
|---|---|---|---|
| **16** | Aina ya Himophilia A | 1. Kali zaidi(<1%)<br>2. Wastani (1-5%)<br>3. Kiasi (6-40%)<br>4. Haijulikani | |
| **17** | Una historia ya kutengeneza usugu dhidi ya fakta | 1. Ndio<br>2. Hapana<br>3. Haijulikani | |
| **18** | Kabla ya kutumia Emicizumab, je umetumia matibabu gani mengine? (***majibu zaidi ya moja yanakubalika)*** | 1. Fakta<br>2. Matumizi ya dawa zinazomudu Usugu wa factor<br>3. Plasma safi iliyogandishwa / cryoprecipitate<br>4. Sijawahi kutumia tiba yoyote | |
| **19** | Ni wastani gani wa idadi ya matukio ya kutokwa na damu bila kujeruhiwa uliyopata katika mwaka kabla ya matumizi ya Emicizumab? (***dokezo: mara ambazo ulikuwa na damu ya hiari kwa mwezi, matumizi ya fakta uandikishaji wa hospitali, usimamizi wa kihafidhina, ukosefu wa kazi au shule zote zisizohusiana na kiwewe - kila mwezi)*** | | |
| **20** | Umewahi kuvuja damu kwa sehemu zipi?***(jibu zaidi la moja linakubaliaka)*** | 1. Magoti<br>2. Misuli<br>3. Fizi<br>4. Pua<br>5. Kwenye mkojo<br>6. Hamna | |

| | | | |
|---|---|---|---|
| **21** | Umewa kuvuja dama kwenye sehemu hatarishi?<br>(***Ubongo , kooni na Utumbo***) | 1.Ndio<br>2.Hapana | |
| **22** | Kama jibu ni ndio kwa swali 21, ni sehemu gani hio ***?(Jibu zaidi ya moja linakubaliaka)*** | 1. Ubongo<br>2. Kooni<br>3. Utumbo | |
| **23** | Umewahi kupata vipindi 3 au zaidi vya kutokwa kwa damu bila jeraha kwenye kiungo hicho hicho kwa miezi 6 mfululizo kabla ya matumizi ya Emicizumab? **(goti sugu*)*** | 1.Ndio<br>2.Hapana | |
| **24** | Je una kiungo chochote kilichopata ulemavu kwa sababu ya kutokwa na damu mara kwa mara kabla ya matumizi ya Emicizumab | 1.Ndio<br>2.Hapana | |

**SEHEMU D: KUANZISHWA KWA EMICIZUMABNA UZINGATIAJI**

| Na | SWALI | DOKEZO | JIBU |
|---|---|---|---|
| **29** | Ni Kwa nini ulianzishiwa kinga ya Emicizumab***? (thibitisha jibu hili kutoka kwa rekodi za kliniki)*** | 1. Chini ya miaka 5<br>2. Uwepo wa inhibitors/usugu<br>3. Ugonjwa mkali<br>4. Ugonjwa wa wastani na historia ya kutokwa na damu kwa sehemu hatari<br>5. Mishipa isioopatikana kwa urahisi<br>6. Nyingine, taja _ | |
| **30** | Kwa muda gani umekuwa kwenye kinga ya Emicizumab? (Muda kwa miezi) | | |
| **31** | Ulianzishiwa kinga ya Emicizumab wapi? | 1. MNH HTC<br>2. Hospitali iliyo karibu na mimi<br>3. Nyingine | |
| **32** | Unapokea dozi endelezi ya Emicizumab wapi ? ***(jibu zaidi ya moja)*** | 1. MNH<br>2. Hospitali iliyo karibu na mimi<br>3. Najichoma nyumbani<br>4. Hospitali au nyumbani kulingana na iliyokaribu<br>5. Sehemu nyingine | |
| **33** | Unapata dozi yako endelezi baada ya muda gani? | 1. Kila wiki<br>2. Mara mbili kwa mwezi<br>3. Kila mwezi<br>4. Nimekamilisha dozi za kwanza<br>5. Sina muda maalum | |
| **34** | Umewahi kukosa dozi yoyote iliyopendekezwa ya Emicizumab katika miezi mitatu iliyopita? | 1.Ndio<br>2.Hapana | |

**SEHEMU E: UZINGATIAJI WA DOZI NA MATUMIZI YA EMICIZUMAB**

| Na | | SWALI | JIBU |
|---|---|---|---|
| **35** | **KILO** | Uzito wa wastani katika miezi mitatu iliyopita | |
| **36** | | Uzito kwa mwezi wa kwanza | |
| **37** | | Uzito kwa mwezi wa pili | |
| **38** | | Uzito kwa mwezi wa tatu | |
| **39** | **CHUPA** | Kiwango cha jumla cha Emicizumab (chupa) kilichoagizwa katika miezi 3 iliyopita | |
| **40** | | Kiwango cha Emicizumab (chupa) kilichoagizwa katika mwezi wa kwanza | |
| **41** | | Kiwango cha Emicizumab (chupa) kilichoagizwa katika mwezi wa pili | |
| **42** | | Kiwango cha Emicizumab (chupa) kilichoagizwa katika mwezi wa tatu | |
| **43** | **CHUPA** | Kiwango cha jumla cha Emicizumab (Vials) zilizochukuliwa na mgonjwa katika miezi mitatu iliyopita | |
| **44** | | Emicizumab (mg) zilizotumiwa katika mwezi mmoja | |
| **45** | | Emicizumab (mg) zilizotumiwa katika mwezi wa pili | |
| **46** | | Emicizumab (mg) zilizotumiwa katika mwezi wa tatu | |

**SEHEMU F: SABABU ZA KUKOSA EMICIZUMAB KATIKA MIEZI MITATU ILIYOPITA**

| Na | SWALI | DOKEZO | JIBU |
|---|---|---|---|
| **47** | Kama jibu ni ndio kwa swali la 36, je ni kwa nini ulikuwa? ***(jibu zaidi ya moja linakubaliaka)*** | 1. Sikuweza kumudu ada ya mashauriano<br>2. Kliniki ulikuwa mbali<br>3. Sikuweza kuongeza usafiri<br>4. Sikuwa nimepatwa na kutokwa na damu kwa muda kwa hivyo sikuhitaji matibabu<br>5. Dawa ilikuwa nje ya hisa nchini<br>6. Nilizidiwa na idadi ya sindano<br>7. Nilipata athari isiyo ya kawaida / ya kando ya dawa hiyo kwa hivyo niliamua kutoendelea<br>8. Nyingine. Bainisha | |

**SECTION G: KUTOKWA KWA DAMU WAKATI WA UTUMIAJI WA EMICIZUMAB**

| No | SWALI | DOKEZO | JIBU |
|---|---|---|---|
| **48** | Je, umewahi kutokwa na damu wakati wowote katika kipindi cha kinga ya Emicizumab ? | 1.Ndio<br>2.Hapana | |
| **49** | Ikiwa ndio katika Qn 48, Ni aina gani ya kipindi cha kutokwa na damu<br>**(*jibu zaidi ya moja linakubaliaka )*** | 1. Bila kujeruhiwa<br>2. Baada ya jeraha | |
| **50** | Ainisha idadi ya uvujaji damu bila jeraha **{weka sifuri kama Swali la 49 is baada ya jeraha}** | | |
| **51** | Ainisha idadi za uvujaji damu baada ya kujeruhiwa **{weka sifuri ikiwa swali la 49 ni bila jeraha}** | | |
| **52** | Taja eneo/maeneo la uvujaji damu bila jeraha | 1. Viungo<br>2. Misuli<br>3. Fizi<br>4. Puani<br>5. Utumbo wa tumbo<br>6. Mkojo<br>7. Ubongo<br>8. Nyingine. Bainisha | |
| **53** | Kindly specify location of traumatic site (s) | 1.Viungo<br>2. Misuli<br>3. Fizi<br>4. Puani<br>5. Utumbo wa tumbo<br>6. Mkojo<br>7. Ubongo<br>8. Nyingine. Bainisha | |
| **54** | Je ulihitaji matibabu? | 1.Ndio<br>2.Hapa | |
| **55** | Ikiwa jibu ni ndio kwenye swali la 48 Ulipata matibabu? | 1. Kupumzisha, kuinua goti, na barafu<br>2. Fakta | |

| | | | |
|---|---|---|---|
| | | 3. (NOVO 7) /Activated prothrombin complex (FEIBA)<br>4. Kushonwa kwa nyuzi<br>5. Nyingine | |
| **56** | Ikiwa jibu lilikuwa ndio kwa swali 27,je ulipata unafuu kwenye goti hilo baada ya kinga ya Emicizumab | 1.Ndio<br>2.Hapana | |
| **57** | Umewahi kufanyiwa upasuaji ukiwa kwenye Emicizumab (ikiwa ni pamoja na uchimbaji wa jino na tohara) | 1.Ndio<br>2.Hapana | |
| **58** | Ikiwa Ndio katika Qn 60 Bainisha upasuaji | | |
| **59** | Ikiwa ndio katika Qn 60, Jibu maswali yafuatayo yanayohusiana na matukio baada ya upasuaji wako ***(jibu zaidi ya moja linakubalika)*** | 1. Je, utahitaji matibabu kwa kuzingatia sababu ya kudhibiti kutokwa na damu<br>2. Je, ulirudi kituoni kwa ajili ya kuvalia tena kutokana na kutokwa na damu nyingi<br>3. Je, ulipokea kuongezewa damu<br>4. Je, ulidhani kuwa umetokwa na damu nyingi kwa sababu ya utaratibu | |

**SEHEMU H: ATHARI MBAYA ZILIZOPATIKANA WAKATI WA EMICIZUMAB.**

| Na | SWALI | DOKEZO | JIBU |
|---|---|---|---|
| **60** | Je, umepata dalili zozote zisizohitajika au ongezeko kutoka kwa dalili ya kawaida iliyopo tangu kuanzishwa kwa Emicizumab? dokezo (***hapo awali haukuwa na dalili hizi, au zimezidi kuwa mbaya wakati wa matumizi ya madawa ya kulevya)*** | 1. Madhara kwenye sehemu ya kuchomwa sindano (Nyekundu, upele, kuwasha, maumivu)<br>2. Maumivu ya viungo<br>3. Maumivu ya kichwa<br>4. Homa<br>5. Kuharisha<br>6. Kuganda kwa damu<br>7. Nyingine. Bainisha<br>8. Sijawahi kupata matukio yoyote yasiyotakikana | |
| **61** | Ikiwa swali 63 hapo juu ni chini ya 8, basi umewahi kuhitaji matibabu kwa dalili zilizotajwa hapo juu? | 1.Ndio<br>2.Hapana | |
| **62** | Ikiwa swali 64 ni ndio fananu zaidi kuhusu madhara na matibabu iliyohitajika | | |

**Asante kwa ushirikiano wako**

## Appendix 5: Ethical clearance certificate

**UNITED REPUBLIC OF TANZANIA**

MINISTRY OF EDUCATION, SCIENCE AND TECHNOLOGY

MUHIMBILI UNIVERSITY OF HEALTH AND ALLIED SCIENCES

**OFFICE OF THE DIRECTOR – RESEARCH, PUBLICATIONS AND INNOVATION**

Ref. No.DA.282/298/01.C/2006 Date: 15/01/2024

MUHAS-REC-01-2024-2006
REBBECCA WUGHANGA MWAKICHAKO
MUHAS

**RE: APPROVAL FOR ETHICAL CLEARANCE FOR A STUDY TITLED: ADHERENCE, BLEEDING OUTCOMES AND SAFETY PROFILE OF EMICIZUMAB PROPHYLAXIS AMONG HAEMOPHILIA A PATIENTS ATTENDING MUHIMBILI NATIONAL HOSPITAL, DAR ES SALAAM, TANZANIA**

Reference is made to the above heading,

I am pleased to inform you that the Chairman has on behalf of the University Senate, approved ethical clearance of the above-mentioned study, on recommendations of the Senate Research and Publications Committee meeting accordance with MUHAS research policy and Tanzania regulations governing human and animal subjects research.

APPROVAL DATE: 15/01/2024
EXPIRATION DATE OF APPROVAL: 15/01/2025

**STUDY DESCRIPTION:**
**Purpose:**

The purpose of this cross-sectional study is to look at the adherence patterns, bleeding outcomes and the safety profile of Emicizumab prophylaxis among HA patients at MNH.

The approved protocol and procedures for this study is attached and stamped with this letter, and can be found in the link provided:

https://irb.muhas.ac.tz/storage/Certificates/Certificate%20-%2015058.pdf and in the MUHAS archives.

**The PI is required to:**

1. Submit bi-annual progress reports and final report upon completion of the study.
2. Report to the IRB any unanticipated problem involving risks to subjects or others including adverse events where applicable.
3. Apply for renewal of approval of ethical clearance one (1) month prior its expiration if the study is not completed at the end of this ethical approval. You may not continue with any research activity beyond the expiration date without the approval of the IRB. Failure to receive approval for continuation before the expiration date will result in automatic termination of the approval for this study on the expiration date.
4. Obtain IRB amendment (s) approval for any changes to any aspect of this study before they can be implemented.
5. Data security is ultimately the responsibility of the investigator.
6. Apply for and obtain Data Transfer Agreement (DTA) from NIMR if data will be transferred to a foreign country.
7. Apply for and obtain Material Transfer Agreement (MTA) from NIMR, if research materials (samples) will be shipped to a foreign country.
8. Apply for and obtain permission to publish the results from National Institute for Medical Research. The application should be before submitting to a publisher and not concurrently through the email publications@nimr.or.tz.
9. Any researcher, who contravenes or fail to comply with these conditions, shall be guilty of an offence and shall be liable on conviction to a fine as per NIMR Act No. 23 of 1979, PART III section 10 (2)
10. The PI is required to ensure that the findings of the study are disseminated to relevant stake holders.
11. PI is required to be versed with necessary laws and regulatory policies that govern research in Tanzania. Some guidance is available on our website https://drp.muhas.ac.tz/.




Dr. Kasusu Nyamuryekung'e
**Ag. Chairperson, MUHAS Research and Ethics Committee**

## Appendix 6: Permission Letter from MNH

THE UNITED REPUBLIC OF TANZANIA

MINISTRY OF HEALTH

**MUHIMBILI NATIONAL HOSPITAL**

*In reply please quote:*

Ref. No.: MNH/CRTCU/Perm/2024/080 Date: 12th February, 2024

Head of Department,
Internal Midicine
**Muhimbili National Hospital**

**RE: PERMISSION TO COLLECT DATA AT MNH**

| | |
|---|---|
| Name of Student | Rebbecca W. Mwakichako |
| Title | "**Adherence, Bleeding Outcomes and Safety Profile of Emicizumab Prophylaxis Among Haemophilia a Patients Attending MNH, Dar es Salaam Tanzania.**" |
| Institution | Muhimbili University of Health and Allied Sciences |
| Supervisor | Dr. Rajab Hussein (MUHAS)<br>Dr. William Mawala |
| Co – supervisor | Dr. Stella Rwezahula (MNH) |
| Period | 12th February 2024 to 30th May, 2024 |

Approval has been granted to the above principal investigators to collect data at MNH. Dissemination of study findings at MNH shall be overseen by **Dr. Stella Rwezahula** (MNH) supervisor.

Kindly ensure the named principal investigator abide to the ethical principles and other conditions of the research approval.

Sincerely

**Dr. Charles K. Pallangyo**
**For: Head of Clinical Research, Training and Consultancy Unit**

c.c DMS
c.c Dr. Stella Rwezahula
c.c Rebbecca Waghanga

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