Development, implementation, evaluation and validation of a haemophilia nurses’ education program in South Africa

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Chapter 2

Literature Review: Haemophilia

2.1 Introduction

This chapter describes the rare congenital disorder of haemophilia, the devastating effect on the affected person and the preferred management. As an inherited disorder of blood clotting function, if untreated, haemophilia has the ability to inflict significant morbidity and mortality on the individual. Those PWH who have severe haemophilia but no access to treatment usually do not survive beyond adolescence. Although haemophilia has no cure, there is treatment available to effectively manage the disorder. This treatment is dependent upon the PWH being correctly diagnosed, availability of sufficient supplies of treatment being available and access to a haemophilia treatment centre (HTC) or health-care staff knowledgeable about haemophilia management.

A history of haemophilia diagnosis, the mechanism of blood clotting and how haemophilia is defined is now discussed. Also diagnosis procedures, inheritance patterns, treatment options and management, possible complications, and the role of the nurse in haemophilia care are considered. The state of haemophilia care in developing nations and specifically in the South African context will be highlighted.

2.2 Haemophilia defined

Haemophilia is the result of the clotting mechanism not functioning correctly. It is caused by a deficiency of factor VIII in haemophilia A and factor IX in haemophilia B. Haemophilia A is a more common disorder than haemophilia B, occurring in 80-85% of people with haemophilia (World Federation of Hemophilia, 2012). Worldwide, the number
of people affected with haemophilia is estimated at approximately 400,000 (World Federation of Hemophilia, 2012). Haemophilia occurs largely in males, therefore throughout this thesis the PWH is identified as “he”. Furthermore, to eliminate confusion, both haemophilia A and B will be discussed jointly and referred to as haemophilia.

Haemophilia is a rare genetic disorder carried on the X chromosome which occurs in 1:10,000 live births (Mahlangu & Gillham, 2008; World Federation of Hemophilia, 2012). It occurs in all races and ethnic groups. Haemophilia is characterised by prolonged and uncontrollable bleeding unless adequately treated. According to Sohail and Heijnen (2001), diagnosis of haemophilia is a profound encumbrance for the PWH and his family. If the PWH is living in a developing country, haemophilia is “a heavy social and economic burden on society” (p. 14).

Significant morbidity is common. Crippling can occur from bleeding into joints resulting in severe arthritis. Bleeding into muscles can result in muscle atrophy. Serious physical disability is the outcome of these bleeding episodes. The individual is unable undertake normal daily functions and attend school which severely reduces his education level and consequent ability to obtain work (Sohail & Heijnen, 2001). The level of mortality has a direct correlation with untreated bleeding into vital organs and structures such as the brain or neck, resulting in respiratory obstruction. Since such bleeds can have severe consequences, haemophilia is considered a life-threatening genetic disorder.

A complex physiological process is initiated in response to a bleed. Due to a deficiency in the clotting process, the bleeding will not be spontaneously arrested, resulting in blood leaking into joints and tissues causing further injury, severe pain and possible damage. Administration of the missing factor is the ultimate effective treatment for a PWH. However, complications can occur as a result of treatment. The most common
complications are antibodies in the blood, known as inhibitors, and blood-borne viruses, such as hepatitis C and HIV (Haemophilia Foundation of Australia, 2010). The pivotal issue here is that haemophilia can initiate serious and sometimes fatal health consequences. It is for this reason that a PWH must be provided with the appropriate treatment to avert serious health consequences and premature death.

2.3 History of haemophilia

Throughout history, information about haemophilia was gathered by those who witnessed it. The first written descriptions are attributed to the Jewish community in 2C when links were made with circumcision and death from bleeding. Rabbi Judah the Patriarch ruled that a woman who had lost two sons from bleeding after circumcision should not have subsequent male children circumcised (Ingram, 1976). Similarly, another Rabbi forbade the son of a woman to be circumcised because the sons of her older sisters had bled to death following circumcision. Further references to fatal bleeding after minor trauma in sons or cousins who are related through the maternal line are documented in Jewish manuscripts (Ingram, 1976). Moses Maimonides, a Jewish physician, decreed that sons of women whose first and second born sons died of exsanguination after circumcision should not have subsequent sons circumcised, even if the father of the subsequent sons is a second husband. This edict indicates that this ancient people concluded that boys inherit the bleeding tendency from their mother, thus recognising the hereditary nature of haemophilia. Albucasis, an Arabic physician, describes cautery as the best treatment for males with a tendency to excess bleeding, thus providing the first written reference to the treatment of bleeding due to haemophilia.

It was not until the end of the eighteenth century that clinicians began to identify haemophilia as a clinical syndrome or collection of symptoms. Dr John Otto, of the New
York Hospital (USA), published his observations of haemophilia from 1796 to 1817, and it was these observations which added significantly to the understanding of this complex disorder. At this time Otto described a woman who was a haemophilia carrier, noting that while she displayed no symptoms, her sons were afflicted with excessive bleeding. He concluded that the inheritance pattern was sex-linked and that haemophilia was associated with premature death of the person with the disorder (Lee, 2010). These patients were termed “bleeders”, and in 1828 Hopff introduced the word haemophilia, from the Greek haima = of the blood, philia = affection (Ingram, 1976).

By the early nineteenth century, haemophilia had attracted accounts from numerous sources tracing family trees back several generations or describing the damage to joints caused by prolonged bleeding. The rare presentation of haemophilia in the female emerged. A lengthy monograph by Bulloch and Fildes documented 1000 case reports and 200 pedigrees of families with haemophilia (Ingram, 1976; Lee, 2010). This information added to the increasing pool of knowledge about the disorder and in essence developed an accurate account of the devastation that haemophilia can impose on the individual and his family.

2.3.1 History of the management and treatment of haemophilia.

A documented account exists of a boy in 1840 with haemophilia who was administered a blood transfusion which stopped the bleeding. Samuel Lane, a surgeon, was credited with the realisation that a blood transfusion was the only effective treatment for a haemophilia bleed (Schramm, 2014). In 1840 there was no knowledge of blood typing, so the boy was fortunate to survive. While a transfusion of plasma was effective for the treatment of minor bleeds, the volume of whole plasma required to arrest a major bleed risked overloading the circulatory system.
In 1976, Ingram from the Department of Haematology at St Thomas’ Hospital in London published a paper which traced the history of treatment for haemophilia (Ojeda-Thies & Rodriguez-Merchan, 2003). It is remarkable that some of these measures described in the publication are still currently used. The first documented effective treatment was in 1934 when Macfarlane experimented with the topical application of Russell’s viper venom (Ingram, 1976). He found that the venom was effective in rapidly clotting the blood of a PWH. When the venom was added in the laboratory to the blood of a PWH at the dilution of 1:1000 000, the blood sample clotted as quickly. Thus, Viper venom was used regularly for local application.

It was not until 1965 that the particular deficiency was able to be treated with a specific product. Professor Judith Pool reported that by slowly thawing frozen plasma, much of the residue of fibrinogen which was slow to dissolve, was rich in factor VIII (Ingram, 1976). This product became known as cryoprecipitate or “cryo”. Cryo was especially useful for controlling life-threatening bleeds and to provide haemostatic cover for emergency surgery. It was however, only effective to treat people with haemophilia A who were deficient in factor VIII. In 1961, MacMillan in the USA, first used factor VIII and around the same time Edith Bidwell, based in Oxford, England, pioneered much of the work in the use of factor IX (Lee, 2010).

In the early 1970s, pharmaceutical companies began to produce factor concentrates derived from donated pooled plasma in large volumes and in lyophilised (freeze-dried) form which could be reconstituted in small volumes of sterile water. This innovative process meant that the factor could be immediately administered at home by the PWH or family member (Bolton-Maggs, 2006; Lee 2010; Mannucci, 2008). Additionally, during the 1970s Swedish physicians began to treat PWH using primary prophylaxis by administering factor
on a regular basis to prevent bleeds occurring in a response to a bleeding episode (secondary prophylaxis). The use of primary prophylaxis helped to eliminate the worst of the musculo-skeletal damage that resulted from poorly treated bleeds into muscles and joints. The availability of factor meant that life changed dramatically for PWH (Lee, 2010), in developed countries at least.

2.4 Inheritance patterns of haemophilia

As almost all PWH are male, the disorder is passed to all daughters of men with haemophilia as these daughters inherit the defective X chromosome from their fathers (Vidler, 2003). The father of any child has only one X chromosome to transfer to his female off-spring and if defective, the daughter will inherit that faulty X chromosome. Consequently, these daughters have one normal functioning X chromosome and one faulty X chromosome. They will therefore be carriers, with a 50% chance in each pregnancy of passing the affected X chromosome to their children. The carrier mothers may have daughters with the faulty X chromosome who in turn inherit haemophilia carrier status or sons who may have haemophilia. Of note is that the severity of the disorder remains constant from one generation to the next, for example, a man with severe haemophilia will pass on that level of severity to the his carrier daughter who in turn will pass it on to any children who inherit the disorder. Regardless of the transfer of the X chromosome, one third of people born with haemophilia can demonstrate no family history of haemophilia; as did British Queen, Victoria (1819-1901) (DiMichele & Neufeld 1998; World Federation of Hemophilia, 2012). This form of inheritance is known as a spontaneous mutation. The following section has been included in order to show how this congenital condition affected subsequent progeny.
2.4.1 The effect of haemophilia on a particular family.

Although no history of haemophilia had been detected in Victoria’s family, she was nevertheless, a haemophilia carrier. Following her marriage to Prince Albert, they had nine children, three of whom were affected by haemophilia (Figure 2.2). Leopold died as a young man and Beatrice and Alice were both carriers. Beatrice had a daughter Ena, who married into the Spanish royal family. Ena had two sons who were both affected with haemophilia. There was a daughter, a carrier, who went on to have two sons both with haemophilia. Alice’s daughter, Alexandra was a carrier and married into the Russian royal family. Alexandra was the mother of Alexis, the Tsarevitch of Russia, and heir to the throne, who inherited a severe form of haemophilia. Alexis was prone to prolonged and severe haemophilic bleeds which caused his parents great distress. In a desperate bid to cure her son of this disorder, Alexandra became inappropriately influenced by Rasputin, known as the mad monk. It is this association that some historians suggest can be attributed to the downfall and subsequent assassinations of the royal family in Russia in the early 20th century culminating in the end of the Romanov Empire (Ingham, 1976; Lee, 2010).
Figure 2.1 Queen Victoria’s family tree. Source: National Hemophilia Foundation (U.S.).
2.5 Mechanism of blood clotting

In order to comprehend the impact of haemophilia on a person, it is necessary to understand the mechanism of blood clotting and the process of haemostasis. Haemostasis means “the stoppage of bleeding or haemorrhage” (American Heritage Medical Dictionary, 2007). This is a complex process which results in the formation of a blood clot to plug the site of injury in a blood vessel wall. This blood clot prevents unnecessary blood loss, while simultaneously maintaining a clot-free environment in unaffected blood vessels. The clotting response is vitally dependent on normal functioning and sufficient numbers of circulating platelets; and coagulation factors that are functioning normally and in sufficient amounts (Higgins, 2012).

The physiology of coagulation is a delicate and complex mechanism that the body utilises to ensure that blood clots at the site of the blood vessel injury. Immediately after injury, vasoconstriction occurs at the injured blood vessel site and adjacent small arteries with the effect of slowing the flow of blood to the area. This system process allows adhesion of platelets to the injured blood vessel wall, a process partly facilitated by von Willebrand factor (VWF) which is stored in the endothelial cells of the blood vessel walls. Platelets are produced in the bone marrow from stem cells and circulate in the blood. The main function of platelets is to plug holes in injured blood vessel walls. The platelets circulating in the blood stream secrete many substances, some of which allow the platelets to change shape and bond together, a process termed aggregation. The adhesion and aggregation of platelets form a platelet plug. The secretion of substances from the surface of the platelets further activates clotting proteins resulting in the formation of fibrin strands which weave around and between the platelets to stabilise the platelet plug (Ziedins & Mann, 2010).
The proteins required for clotting act sequentially which is known as the clotting cascade or the coagulation pathway (Figure 2.2). This is a collection of proteins, termed factors, which circulate in the blood and are activated when bleeding occurs. As each factor is activated, the next factor in the clotting cascade is stimulated to become activated, with the end product being fibrin. There are thirteen known factors, identified by Roman numerals, although, factor VI is no longer thought to exist. For fibrin to be formed, adequate amounts of clotting factors which function normally are required (Hoffman & Monroe, 2007; Smith, 2009).

Note: The letter “a” beside a numeral indicates that the factor is activated.

Figure 2.2 Coagulation pathway/cascade.
The clotting pathway/cascade is not a complete explanation for the activation of clotting factors. The clotting cascade model can be used to explain laboratory tests that indicate coagulation abnormalities and also demonstrates the relationship between clotting factors. However, the clotting cascade does not fully explain the process of haemostasis in vivo (in the body), where the ultimate outcome is the formation of a robust fibrin clot to stop the bleeding (Hoffman, 2003; Smith, 2009).

The cell-based model of fibrin formation explained by Hoffman (2003) and Smith (2009) may help to explain more fully the coagulation mechanism in a dynamic environment that is, circulating in the blood. In particular, this model may provide possible reasons why some factor deficiencies such as factor VIII and factor IX, the deficiencies that cause haemophilia, are related to significant bleeding while others, such as factor XII deficiency, are not associated with bleeding (Hoffman & Monroe, 2007). The cell-based model highlights the relationship between clotting factors and the surface of specific cells. Studies of the cell-based model indicate that coagulation in vivo takes place in three distinct, overlapping stages and that two different cell types are required: cells containing tissue factor (TF) and platelets (Smith, 2009).

The cell-based model consists of three phases, firstly, the Initiation Phase where TF is activated when exposed to flowing blood following an injury to the blood vessel. A small amount of Factor IXa and thrombin diffuse away from the TF-bearing cell surface to the platelets. The second stage is called the Amplification Phase when the thrombin activates platelets, releases vWF and activates Factor V, Factor VIII and Factor XI. The third and final phase is known as the Propagation Phase where various enzymes gather on the surface of the platelets to form intrinsic tenase and activate Factor X. Prothrombinase forms from this action and a burst of thrombin is generated on the surface of the platelets, resulting in
sufficient fibrin to form an insoluble fibrin matrix (Smith, 2009). In haemophilia this process does not occur since an essential substance (Factor VIII or IX) is absent.

2.5.1 Coagulation inhibition.

If the blood clotting process is allowed to go unchecked, clotting in healthy blood vessels (thrombosis) would occur. It is therefore vital that the effect of the clotting mechanism occurs only at the site of injury. Substances circulating in the blood called inhibitors regulate the process of coagulation inhibition by inactivating the activated clotting factors. Examples of these substances are protein C which inactivates factors V and VIII, and antithrombin which inactivates factors Xa and thrombin. The clot at the site of injury will be broken down once the blood vessel wall is healed. This process is known as fibrinolysis, and occurs when fibrin is degraded by a substance called plasmin. Fibrinolytic activity can be detected in the laboratory by the presence of fibrin degradation products (FDPs). Anti-fibrinolytic medications, such as tranexamic acid, slow down the fibrinolysis process, maintaining the clot in situ longer, giving the injured site more time to heal (Smith, 2004).

Clot formation and fibrinolysis are usually well balanced but sometimes the tissue damage is so severe that large amounts of thromboplastin are released into the circulating plasma, causing widespread clotting throughout the body. This is known as disseminated intravascular coagulation (DIC), which occludes blood vessels and causes ischaemic damage to tissues, which release more thromboplastin. Finally, the circulating platelets dwindle and the clotting factors become exhausted, so that clotting can no longer take place and bleeding occurs. Any organ in the body can be affected and without prompt treatment, death can result (Robertson, Wu & Greer, 2004).
2.6 Diagnosing haemophilia

Accurate diagnosis of haemophilia is essential to enable the correct treatment to be prescribed and administered. In developed countries such as Australia, if a person is suspected of having haemophilia, the initial diagnosis is made through rigorous assessment including clinical presentation, family history and laboratory testing (World Federation of Hemophilia, 2012). This is done to exclude other inherited bleeding disorders which can be similar, such as von Willebrand Disorder (VWD). It is important to observe that the family history and clinical signs of haemophilia A and haemophilia B are identical (World Federation of Hemophilia, 2012) and the differentiation cannot be established until the laboratory assays are performed.

Since haemophilia impairs the coagulation process, it is imperative that early diagnosis is made to reduce the risk of morbidity and mortality. If a PWH has access to quality management and treatment, as is the case in developed countries, the person’s lifespan will reflect that of the non-haemophilia population (World Federation of Hemophilia, 2012).

2.6.1 Clinical presentation.

Symptoms of haemophilia include bleeding which can occur in any part of the body but most commonly into joints, muscles, gums, nose and mouth, and urinary tract. In severe haemophilia, bleeding can be spontaneous with no apparent cause. Trauma or even minor surgery, such as dental extraction, can cause a devastating haemorrhage. A bleed that occurs in the central nervous system, gastrointestinal tract, neck, after surgery and following severe trauma is considered life-threatening and requires prompt and appropriate intervention to arrest the bleeding (World Federation of Hemophilia, 2012).
Uncontrolled bleeding in joints and soft tissues can result in severe pain. Repeated bleeding into the same joint, known as a target joint, can lead to progressive arthritis and eventual crippling due to joint and muscle damage (Sohail & Heijnen, 2001).

It is possible to diagnose a child with haemophilia soon after birth as symptoms of birth trauma such as intracranial haemorrhage, cephalic haematoma and/or bleeding from the umbilical cord are often present (Giangrande, 2003). When toddlers begin to walk it is predictable that they will have falls. However, if the child shows signs such as excessive bruising, or prolonged bleeding from the mouth due to the usual spills experienced at this age, haemophilia should be considered (WFH, 2005). Unfortunately, parents are often suspected of child abuse because of the extensive bruising before a diagnosis is made (Swedish guidelines for the care and treatment of haemophiliacs, 2003), especially when there is no family history of haemophilia.

2.6.2 Family history.

In order to make a definite diagnosis, data are collected in relation to the medical histories of the individual and both male and female family members who might describe similar bleeding episodes. For example, females may report post-partum haemorrhage or menorrhagia (Gringeri, 2005) and other family members may describe lifelong frequent and prolonged epistaxis or easy bruising. Women who are haemophilia carriers may present with bleeding into joints, muscles and mucosa (Lambing, 2007), while others may not have experienced any bleeding symptoms. In developing countries, due to lack of education or health awareness, including haemophilia, relatives often do not know the cause of death in a family member, so it is sometimes difficult to elicit an accurate family history. To further complicate the situation, many clinicians are unaware of the symptoms and clinical presentation of haemophilia, so the disorder can remain unrecognised and undiagnosed.
2.6.3 Laboratory tests to aid diagnosis.

Laboratory tests result in the definitive diagnosis of haemophilia. However, specimens must reach the laboratory within four hours of collection from the patient (World Federation of Hemophilia, 2012) to maintain integrity of the specimen. Initially platelet count, bleeding time, prothrombin time and activated prothrombin time will be performed. If these tests are within normal limits, further tests such as coagulation assays (tests) which measure levels of factor VIII, factor IX and von Willebrand Factor may be required which will provide a more definitive diagnosis (World Federation of Hemophilia, 2012). From these tests a diagnosis of haemophilia A or B will be determined.

Factor assays are required to monitor treatment when a PWH requires management for an acute episode such as surgery or trauma. The laboratory scientists will perform regular factor assays to assess the factor levels. These levels will guide the haematologist about factor dosage, to facilitate haemostasis and minimise the threat of a further bleed (World Federation of Hemophilia, 2012). When a known haemophilia carrier, a mother or a woman with a family history of haemophilia goes into labour, it is recommended that umbilical cord blood be collected at the time of delivery to test for haemophilia. Collecting an umbilical cord blood sample has two advantages. Firstly, the sample can be delivered to the laboratory as soon as the cord is cut; and secondly, attempts to obtain blood samples from a peripheral vein in a newborn is difficult and may result in severe bruising or bleeding, thus requiring factor (Giangrande, 2003).

Expensive laboratory equipment and reagents to perform blood tests are required to establish the level of deficiency of factor as it is this result which determines the severity of haemophilia. Those individuals with less than one percent of factor are considered severe, one to five percent of factor is deemed moderate, and five to 25 percent of factor is
considered mild. Many people with mild haemophilia are not diagnosed until they sustain trauma or undergo surgery when such an experience can trigger excessive bleeding (World Federation of Hemophilia, 2012).

2.7 Complications of haemophilia

There are several complications that may arise with regard to haemophilia such as inhibitors and blood borne viruses. These are discussed in what follows.

2.7.1 Inhibitors.

A complication of haemophilia which can have serious consequences for PWH is the development of antibodies, known as inhibitors, to the factor replacement. When a PWH is given treatment with factor VIII or IX to raise the level of the missing factor, the body perceives the factor as an invading foreign protein and the inhibitor attaches to the factor, impeding its action and rendering it ineffective. The development of an inhibitor makes management of haemophilic bleeding more complex and difficult (Kasper, 2004).

Inhibitors occur more frequently in those people with severe or moderately severe haemophilia A, and are much less common in people with haemophilia B. Inhibitors have been reported to develop most commonly in PWH less than 12 years of age and after they have been exposed to an average of nine to 12 treatments. There is a tendency for the development of inhibitors to occur in families, and ethnic groups; for example, Africans are twice as likely to develop inhibitors as Caucasians (DiMichelle, 2008; Kasper, 2004). This statistic is of significance to this study since the management of haemophilia is being evaluated in SA, where the majority of PWH are of African heritage.

If an inhibitor is present it is usually discovered by either a routine blood test taken at the time of a regular visit to the haemophilia treatment centre (HTC) or when the normal
doses of factor are not arresting bleeding effectively. The presence of inhibitors is confirmed by the Bethesda inhibitor assay, a blood test carried out in the coagulation laboratory. This test indicates the level of inhibitors present, with the level being measured in Bethesda units (BU) or Bethesda titre. The higher the Bethesda titre, the greater the amount of inhibitor present in the blood (Mitchell & Phillott, 2008). A PWH with a Bethesda titre more than five is known as a high responder and those with a Bethesda titre less than five are termed low responders. This level is an important distinction because the treatment differs according to the level of the Bethesda titre. Fortunately, most HTCs in SA have laboratories with the capacity to perform these assays.

Treatment using factor VIII or IX for low-responding inhibitors is frequently effective, although the dosage may need to be higher, given more frequently or as a large bolus dose to overwhelm the inhibitor (DiMichelle, 2008; Kasper, 2004). For most PWH with high responder status, a bypassing agent such as recombinant factor VIIa or Factor Eight Inhibitor Bypassing Activity (FEIBA), prothrombin complex concentrates and activated prothrombin complex concentrates which contain other factors, are used to “bypass” the requirement for factor VIII or IX and therefore do not activate the inhibitor. In developed countries, PWH are fortunate to have access to immune tolerance which can be accomplished by giving frequent doses of factor over a long period of time. The aim is to overwhelm the inhibitor so that it no longer has the ability to produce antibodies to the factor (DiMichelle, 2008; Kasper, 2004). Immune tolerisation and the use of bypassing agents is expensive therapy and therefore rarely available to PWH living in developing countries.
2.7.2 Blood-borne viruses.

Cryoprecipitate and factor VIII and IX are plasma-derived products produced from donated blood. It was not until the 1980s that transfusion scientists and haematologists identified that some donated blood was contaminated by viruses; most notably, HIV. However, this discovery was too late for countless PWH, many of whom developed Acquired Immune Deficiency Syndrome (AIDS). This event was disastrous as many PWH died (Lee, 2010) before effective treatment became available to arrest the debilitating progress of HIV and AIDs. Other viruses, which contaminated the blood supply and its products were the hepatitis viruses. Scientists were able to identify the hepatitis B virus, however the hepatitis C virus (HCV) was not visible under microscope and was referred to as non-A, non-B hepatitis. In the early 1990s, more sophisticated diagnostic techniques became available (Lee, 2010) and the non-A non-B virus was identified and is now referred to as hepatitis C (HCV). Although these are now identified and effective treatment is available, there are still some genotypes of HCV that are resistant to treatment (Hepatitis Australia, 2017).

In developed countries, recombinant factor VIII and IX, which are manufactured in a laboratory and do not contain any human tissue, are now available for the treatment of PWH. These products have a very low risk of contamination by viruses. In contrast, PWH in developing countries continue to be treated with plasma-derived products such as factor VIII, factor IX and cryoprecipitate, as the recombinant products are unavailable.

Countries in the developing world that produce their own plasma-derived product have put in place safeguards to protect the consumers from contamination. These safeguards reflect those that well-resourced nations had developed to protect PWH recipients prior to the introduction of recombinant products (Farrugia, 2017). The
safeguards include strict pre-screening of the donors prior to donation; firstly, to exclude high-risk behaviour, for example, unprotected sexual encounters; and, secondly, serologic screening assays to identify viruses that are transmissible by blood and plasma products; and thirdly, treatment such as pasteurisation and nano-filtration of the plasma to ensure the products are safe (Muller, 2004). Cryoprecipitate is manufactured in some developing countries but the viral reduction techniques used for factor are not easy to apply to cryoprecipitate because the product’s low purity prevents it being decontaminated by heat processes such as pasteurisation (Farrugia, 2008).

2.8 Treatment and management of haemophilia

Joint bleeding, termed haemarthrosis, is the most common presentation in haemophilia. The PWH will present with pain, swelling, restricted range of movement, stiffness and tingling in the affected joint. If the bleeding continues and the joint fills with blood, it becomes hot, more swollen and painful with a significant decrease in articulation. If provided with appropriate treatment, soon after the symptoms appear, the bleeding stops quickly and the symptoms often resolve promptly. Muscle bleeds are also common and managed in the same way as joint bleeds to prevent contractures and nerve compression (Chandy 2005; Shamsi & Chughtai, 2001).

Essentially, the aim of treatment is to arrest the bleed, minimise damage to the joint, muscle or other tissues, stop the pain and restore the affected part to the level of function prior to the bleed. Prompt treatment, using the appropriate product for the deficiency even if only with minimal doses of factor, fresh frozen plasma (FFP) or cryoprecipitate (“cryo”) can provide haemostasis better than delayed application. If the haemophilia diagnosis is known, this treatment should be administered immediately before any further investigations (Mahlangu, 2008). In some cases, particularly in the developing world, there can be delays
of several days before administering treatment after a bleed due to poor transportation, or the PWH needing to travel long distances to access treatment. Conservative measures such as immobilisation, application of ice and gentle compression can be implemented by the PWH or a family member to reduce the pain and swelling until factor can be administered and should be continued until the bleeding stops (World Federation of Hemophilia, 2012). The PWH can be given a personal supply of factor to instigate treatment if a bleed commences. Pain can be managed by using paracetamol or mild opioid preparations. Aspirin and salicylates such as non-steroidal anti-inflammatory drugs are contraindicated since they influence the agglutination of platelets, affecting the body’s ability to achieve haemostasis. Once the bleeding ceases, rehabilitative exercises are commenced to restore strength to the muscles surrounding the affected joint or limb (World Federation of Hemophilia, 2012). The objective is to strengthen the muscles so they can support the joint, restore range of motion and reduce crippling. These exercises can be taught to the PWH so he can continue them at home, helping to reduce frequency of bleeds and damage caused by bleeding into joints (Shamsi & Chughtai, 2001).

Bleeding in the region of the head, neck, chest, abdomen and gastro-intestinal tract are life-threatening bleeds, considered as emergencies and should be treated with factor replacement without delay (Chandy, 2004). Mucous membrane bleeds such as nose bleeds and bleeds from the oral cavity are treated with tranexamic acid, fibrin glue or a single dose of factor. The application of a suture if necessary after dental extraction or skin laceration can be safely carried out and the first aid measures of ice packs and elevation can also be implemented. Bleeding after circumcision can be fatal if not adequately managed. In neonates, a blood transfusion followed by the appropriate factor once the bleeding disorder has been identified should be administered to arrest the bleeding. Fibrin glue has been shown to be effective post-circumcision (Shamsi & Chughtai, 2001). Surgical procedures,
including orthopaedic surgery, require careful management and are ideally performed in establishments that have access to both experienced surgeons and a haemophilia comprehensive care team who can work in tandem to ensure that the PWH receives optimal and appropriate care.

The WFH’s Guidelines for the Management of Hemophilia (2012) recommend that optimal haemophilia care be delivered using the comprehensive care model involving a multidisciplinary health care team approach. This approach, directed by a haematologist, includes a nurse, physiotherapist and social worker as core team members. The team members can access further resources including a coagulation laboratory, appropriate clotting factor concentrates and specialist consultants such as an orthopaedic surgeon, dentist, rheumatologist and geneticist. The Haemophilia Treatment Centre (HTC), which is usually located in the capital city of a province or country, is the specialised care centre for the PWH and has a multi-functional approach. It provides outpatient facilities for those patients not requiring hospital admission as well as education to healthcare staff, education of PWH and their families, instruction and support for home therapy (infusions of factor at home) and psychosocial support (Hoots, 2003). In Australia, there is sufficient factor available for all PWH provided free of charge. Also within Australia and other developed countries, a PWH who receives this level of care will maintain health outcomes enabling a more positive future. In contrast, a PWH living in developing countries, particularly if they live in regional areas may never be diagnosed, and those who are, may not receive this level of care.

2.9 Current treatment protocols

As currently understood, several haemophilia treatment options are available. These are described below.
2.9.1 Plasma-derived treatments.

Optimal treatment of haemophilia requires intravenous replacement of the clotting factor. In haemophilia A the clotting factor is factor VIII and in haemophilia B the clotting factor is IX. The dosage of factor is calculated by the body weight of the PWH, the severity of the individual’s haemophilia and the severity of the bleeding episode (World Federation of Hemophilia, 2012). In developed countries such as Australia, management of children with severe haemophilia is replacement of factor two or three times weekly, known as primary prophylaxis. This process raises the factor levels sufficiently to achieve haemostasis and prevent bleeding (Khair, Lawrence, Butler, O’Shea & Christie, 2008). In contrast, a child with haemophilia in a developing country in the best-case scenario will be treated “on demand” that is, in response to a bleed, known as secondary prophylaxis. If factor is unavailable, the risk of death significantly increases. According to Mahlangu (2009), there were ten deaths per annum from haemophilia causes in the years 2004 to 2007 in SA. In Australia it is rare for a PWH to die of the disease. Sufferers are more likely to die of complications such as hepatic malignancy as a result of hepatitis C infection.

Factor is either plasma-derived from blood donations or recombinant, a synthetic version made in a laboratory, containing no human plasma (DiMichele & Neufeld, 1998), which would be the treatment of choice given the AIDS risk in SA. In plasma-derived product, the clotting factor is separated from the blood plasma and freeze-dried (lyophilised) to a powder to be reconstituted with sterile water when ready to be administered. This procedure however, requires a sophisticated manufacturing process to eliminate blood-borne viruses, such as hepatitis C (DiMichele & Neufeld, 1998). This complicated procedure means that the replacement factor is very expensive (Mahlangu & Gillham, 2008). As the cost is around U$1 per unit, with an average dose for an 80kg male being in the region of
2500 to 3000 units of factor to stop a bleed, the cost per dose would be US$3000, being approximately the same in Australia.

The discovery and introduction of factor replacement therapy significantly changed the way haemophilia was managed (Lee, 2010). Prior to the discovery of this treatment, the life expectancy of a PWH was short and children died of the disorder at a very young age, for example, in Sweden life expectancy was eight to 11 years. From the 1970s to the present time, however, survival rates have extended to around 65 years (Bolton-Maggs, 2006), a significant improvement. Immediate treatment of spontaneous bleeds with factor eliminated the long periods of recovery and rehabilitation following a bleed. Previously, children had to endure prolonged hospital admissions, which resulted in erratic school attendances and educational opportunities. Consequently, employment opportunities were reduced.

2.9.1.2 Cryoprecipitate (Cryo).

Cryo (from the Greek word, kruos, meaning cold) was used widely in the 1960s in the management of haemophilia A and was the forerunner of factor replacement concentrates (Bolton-Maggs, 2006, Hoffbrand & Pettit, 1993). After thawing at one to six degrees Celsius, cryo is separated from fresh frozen plasma (FFP) and is found in the remaining precipitate, which is then refrozen. Factor VIII, Fibrinogen, factor XIII and fibronectin are contained in cryo (PathWest, 2011). Cryo is produced in blood centres in developing countries, such as Thailand and Cuba, providing the main source of treatment product for haemophilia A and can be used without further processing. Approximately 600 units of factor VIII can be supplied from one litre of plasma with the final result a freeze-dried product which can be stored at home by PWH and reconstituted and self-injected when required (Farrugia, 2008).
The use of safe cryo without supplies of factor concentrates is an affordable and viable alternative for treatment of PWH in developing countries. However, Farrugia (2008) explains that techniques used to eliminate viruses from factor concentrates are not suitable for use in cryo. In the blood centre setting, heat treatment cannot exceed 60° C, which is not sufficient to nullify viral contamination. Until technology is available to perform viral inactivation for cryo, other methods need to be implemented to ensure that the product is safe from blood-borne viruses. Consequentially, appropriate selection of low-risk blood and plasma donors is the most important preventative measure available to policy-makers and producers of cryo in developing countries (Farrugia, 2008).

2.9.1.3 Fresh frozen plasma.

Fresh frozen plasma (FFP) contains factor VIII and factor IX, 250 units in 250 millilitres. Given by infusion, care needs to be taken during administration that fluid overload does not occur, particularly with children. Fresh frozen plasma carries similar problems with viral screening as cryo (Shamsi & Chughtai, 2001).

2.9.1.4 Fibrin glue.

Fibrin glue, also known as fibrin sealant, is made using a mixture of fibrinogen and thrombin. It acts as a sealant, and promotes haemostasis and healing. It is used for dental extraction, circumcision and to arrest mucous membrane bleeding. It is available as a commercial product, which is very expensive, but can be made in inexpensively in transfusion laboratories using cryoprecipitate (Chandy, 2005), so is a useful adjunct therapy in developing countries.

Desmopressin Acetate (DDAVP) is a pharmaceutical treatment option which raises the activity of the von Willebrand Factor (VWF). It increases the levels of VWF and factor
VIII in the bloodstream by stimulating the release of VWF from the endothelial cells in blood vessels. It is a synthetic analogue of vasopressin, an anti-diuretic hormone.

Advantages of using DDAVP are that it is inexpensive in comparison to factor replacement and being a pharmaceutical, carries no blood-borne viruses. Its use is indicated in some forms of von Willebrand Disease, mild haemophilia and to carry out DDAVP trials which are implemented to test the effect of DDAVP. Contra-indications for the use of DDAVP include severe haemophilia A, haemophilia B, severe von Willebrand Disease, type 2B von Willebrand Disease, pregnancy and older patients or those with a history of cardiovascular disease and/or hypertension.

The drug DDAVP can be given intravenously, intra-nasally and subcutaneously. It is given as an intravenous infusion diluted in 50 - 100mls of normal saline over 20-30 minutes. Intra-nasal DDAVP is a spray containing 150 micrograms per dose to each nostril. Subcutaneously DDAVP has been found to be effective and is particularly useful if intravenous access is difficult. As DDAVP is an anti-diuretic hormone, it causes fluid retention therefore it is necessary to observe for hyponatremia and over-hydration which can lead to cardiac failure and death. Children and the elderly are particularly susceptible to these problems (Smith, 2004).

Tranexamic acid is an anti-fibrinolytic which acts by delaying the process of fibrinolysis and is especially useful in controlling bleeding of mucous membranes. It can be used as a mouthwash after dental or oral surgery, epistaxis and menorrhagia (Chandy, 2005). However, it is important to note that tranexamic acid is contra-indicated for urinary tract bleeds. The oral dosage is 25 milligrams per kilogram of body weight taken three to four times per day for 10 days to allow wound healing.
2.9.2 Further considerations in developing countries.

In developing countries, the financial burden of factor replacement often results in reluctance of governments to purchase the product (Chuansumrit, 2003; Evatt & Robilliard, 2000) resulting in the PWH being untreated, thus increasing the risk of morbidity and mortality. However, these outcomes can be reduced if the patient, his family and the physician are knowledgeable about the management and treatment of haemophilia, even if factor replacement availability is limited (Chuansumrit, 2003). Chandy, in his WFH Monograph “Treatment Options in the Management of Hemophilia in Developing Countries” (2005), supports this position. The importance of education of the PWH, their families, health care providers and the general public is stressed by Shamsi and Chughtai (2001), Pakistani physicians, who believe that education is the basis of haemophilia care where financial resources are inadequate and factor is unattainable. These physicians state that simple first aid measures such as immobilisation and applying ice to the site of the bleed can help to minimise morbidity. Chandy (2001) maintains that education is not expensive to implement in the developing world and that much of the morbidity associated with haemophilia could be reduced if the PWH, and those involved in his care, have sufficient knowledge about the disorder.

2.10 Recent developments

In 2000 the United Nations Millennium Development Goals (MDGs) were signed by 191 countries. Each signatory member state agreed to strive to accomplish these goals by the year 2015. The goals were aimed at eradicating extreme poverty and hunger; providing equality, empowerment and improved maternal health for women; reducing child mortality; combating diseases; and developing global partnerships for development and environmental sustainability. The eight Millennium Goals came to the end of their tenure and have been
superseded by a new plan. In 2015, the World Health Organisation, (WHO) introduced seventeen Sustainable Development Goals (SDGs) to take the place of the MDGs, building on the successes of the MDGs and broadening the scope to encompass climate change, economic inequality, sustainable consumption and peace and justice.

Although haemophilia is not identified directly in the United Nations MDG and SDG goals, improved care of people with haemophilia would help address goal four by reducing child morbidity and mortality. However, the treatment of haemophilia is expensive, even in developed countries, and the cost burden is considerable. In developed countries, five to ten percent of Gross Domestic Product (GDP) is expended on health, whereas under-developed countries are only able to channel less than two percent of the GDP on health (WHO/WFH] International Society of Thrombosis and Haemostasis, ISTH, 2002). In countries where as little as U$1 per head is spent annually on health care, the cost of haemophilia treatment is unattainable (WHO/WFH/ISTH, 2002). South Africa has haemophilia treatment available for all PWH who require it which reflects expenditure of 8.8 % of the GDP on health (WHO, 2015b).

The United Nations has a variety of programs that assist governments to develop specific plans that will benefit their citizens. One of these programs is the United Nations Development Program (UNDP) which uses the Human Development Index (HDI) and encompasses the following three dimensions: health, education and living standards, to estimate a nation’s living standard. The indicators for the health dimension include life expectancy at birth (in years), public health expenditure expressed in percentage of the GDP and under-five years of age mortality rate per 1,000 live births. For education, the indicators are public expenditure on education as a percentage of the GDP, expected years of schooling of children under 7 years of age, adult literacy rate which includes the percentage
of both sexes over 15 years of age, mean years of schooling of adults over 25 years and the combined gross enrolment in education of both sexes expressed in a percentage. The indicators for living standards are GDP per capita in Purchasing Power Parity which describes whether the cost of goods purchased in two different countries is the same when expressed in US dollars. Also utilised is the Gross National Income (GNI) which is an indicator designed by the World Bank which expresses the average income of a country by dividing the dollar value of the country’s annual income by the population (UNDP Human Development Report, 2011). Using this method, the UNDP is able to differentiate between developed countries and developing countries. On the HDI, SA is rated 123, in contrast to Australia which is rated two. This figure demonstrates that Australia has a much higher standard of living than SA and shows that SA has little expenditure focussed on essential health and education.

However, the UNDP has found that a country’s overall HDI can disguise the fact that different groups within the country can have different levels of development: examples are groups characterised by income, geographical regions, urban or rural habitation, gender or ethnicity. By using disaggregated HDIs, (applying the HDI components to the sub-group of concern and treating them like a separate country), inequalities can be identified which can be used to guide policies and implementation of recommended actions to address gaps. The use of the HDI and disaggregation can help to illustrate more strongly disparities that are already known of in a community. There is evidence to support that the HDI provides assistance to social and regional groups to strengthen their case for more resources. Therefore, if more resources are available in health, there is a greater probability that more resources for haemophilia care are available.
2.11 The nurse’s role in haemophilia care

As Chandy (2005) observed, education is the keystone to improvement in healthcare. Haemophilia nurses play a vital role within the haemophilia comprehensive health care team. These nurses create a link between the PWH and other health providers and serve two functions, firstly, to treat acute bleeding episodes; and secondly, to take on the role of educator. The haemophilia nurse educates patients and their families about haemophilia, the inheritance patterns, treatment options available and when and how to treat a bleed, and at the same time supporting the families so that they can better deal with the challenges of living with haemophilia (Oyesiku & Butler, 2007). Following initial diagnosis, the haemophilia nurse or doctor will administer the factor to the child with haemophilia. Gradually the parents of the child are encouraged to learn how to undertake venepuncture and inject the factor. Through such education, treatment can eventually be provided at home, known as home therapy, thereby eliminating repeated hospital visits and reducing the strain on a fragile haemophilia care system which currently exists in SA. Essentially, teaching patients to administer factor as soon as the bleed occurs means that immediate treatment can reduce the pain and possible damage to joints or organs (Di Michelle & Neufeld, 1998; Evatt, 2006; Vidler, 2000).

Studies have demonstrated that prophylaxis is the most important measure to prevent joint damage in children with haemophilia (Lofqvist, Nilsson, Berntorp & Pettersson, 1997; Panicker, Warrier, Thomas & Lusher, 2003). Prophylaxis is therefore much easier and more convenient if the venepuncture and administration can be delivered at home. Parents are also instructed how to perform immediate care such as applying ice and conservative measures such as resting the affecting area. Educating the family provides the necessary skill to assess and respond immediately to bleeding episodes. Often only one injection of
factor plus the application of conservative measures are required to stem the bleed. It is evident that such treatment and intervention is cost-effective in both human and financial terms (WFH, 2005).

Education of the patient and family is a central component within the role of the haemophilia nurse and pivotal to the efficient management and treatment of haemophilia. Once a treatment plan is formulated, the nurse will ensure that the PWH and his family understand the plan and that it must be evaluated regularly to address any difficulties with implementation. Progress of the PWH is monitored continually, ongoing support is provided and accurate records are observed to document progress and identify any problems. The nurse works with the PWH and family to ensure that the plan is successful and acts as the liaison with other haemophilia comprehensive care team members (WFH, 2007).

The nurse endeavours to educate all people involved with the PWH, such as the wider community, school staff and employers. It is also essential to advocate for the PWH in relation to schools and workplaces. For example, contact sports, which some schools would expect boys to participate in, are not recommended for children with haemophilia (WFH, 2007).

Studies by Khair, Lawrence, Butler, O’Shea, and Christie, (2008) and Miller, Guelcher and Taylor (2009) support and indeed reinforce the importance of education in the care of PWH and the haemophilia nurse is crucial in this endeavour. As the PWH reaches adulthood he must assume responsibility for his health. An independent pilot study conducted by Miller et al., (2009), involving haemophilia nurses in the USA, found that 187 PWH or their caregivers rated health care providers (nursing and medical) as the most important source of information about haemophilia and treatment. This study is supported
by a survey conducted by haemophilia nurses in the US, UK, Sweden and Canada, which found that education similar to that described above, was the most suitable method to conquer difficulties with prophylaxis and home therapy in more than 10,100 patients with severe haemophilia A (Khair et al., 2008).

2.12 Haemophilia care in developing countries

The care and support in developing countries significantly contrasts with a wealthy country such as Australia. Prophylaxis, as practiced in developed countries, requires an annual supply of hundreds to thousands of units of factor for each PWH each year. Factor replacement is a very expensive commodity for the individual to purchase, thus the PWH is reliant on the government to provide this treatment. In developing countries, a government with a low GDP and limited health budget has little chance of purchasing factor for prophylactic purposes, therefore other measures need to be initiated to manage haemophilia (Chuansumit, 2003). Prevention of a bleed is the primary aim and maintenance of good health will assist fulfilment of these aims. It is essential for the PWH to avoid situations which may provoke bleeds, for example, poor dental health. Regular exercise to improve fitness; regular check-ups at the haemophilia clinic, especially of examination of joints and muscles; avoiding contact sports; and obtaining vaccinations against hepatitis will help the PWH to remain well (Chandy, 2005).

Conservative management of a bleeding episode consists of first aid and analgesia. First aid measures recommend rest, for example a sling for a wrist bleed, intermittent application of ice packs for the first 48 hours and gentle compression using an elastic bandage. Analgesia such as paracetamol or codeine are suitable, although aspirin and other salicylates should be avoided. Rehabilitative physiotherapy exercises can commence once the pain and swelling have abated. If a physiotherapist is available, they will carry out the
exercises initially (Battistella, 2001). Once the PWH begins to recover, he is then taught how to perform these exercises. Exercise will help restore muscle and maintain the range of motion in joints, both of which can decrease the frequency and severity of bleeds and avoid permanent damage (Chandy, 2005). In developing countries often a physiotherapist is unavailable, therefore it becomes the responsibility of the haemophilia nurse to initiate the rehabilitation program.

2.13 The South African context

The focus of care in haemophilia in SA generally reflects treatment in Australia and other developed nations but managed with fewer resources. Currently, in SA there are 17 government-funded haemophilia centres (Mahlangu, 2009) and availability of factor is rarely a concern, which demonstrates the commitment to addressing the problem. However, it is the lack of resources and infrastructure in some areas of SA which prevent access to health care and as a consequence increase the risk morbidity and mortality of PWH (Mahlangu, 2009). Furthermore, there is also the issue of access to specific drugs such as FEIBA. Unfortunately, it is the poor black South African who is already disadvantaged and is at an increased risk due to the limited access to healthcare.

As stated earlier, individuals living in rural and remote areas have to overcome substandard infrastructure, such as poor roads, inadequate telecommunication and unreliable power supplies; all of which make it difficult to access health care (Cruickshank, 2009). The photographs (Figures 2.3, 2.4 & 2.5) below show the poor state of roads and inadequate modes of transport in some rural areas.
Figure 2.3 Road in rural area. Source: Researcher’s personal photographs.
In 2001, to help surmount problems related to remoteness and poor infrastructure, consultation with SA Haemophilia Foundation Medical Advisory Committee members such as

\[\text{Figure 2.4 Primitive means of transport. Source: Researcher’s personal photographs.}\]

\[\text{Figure 2.5 A “Settlement”. Source: Researcher’s personal photographs.}\]
as haematologists and provincial government health department coordinators was convened to decide how to transfer haemophilia treatment to the provinces. As a result of discussions, the following guidelines were recommended:

- All PWH would attend the haemophilia treatment centres for assessment and treatment plan;
- PWH would then be referred back to their local health care facility after collaboration with the provincial health care person in charge;
- This action would allow the PWH to be treated close to where they lived, in essence, reducing the risk of non-treatment.

As a consequence of this recommendation, the SA National Department of Health (SANDoH) approved a training program which would involve the education of Registered Nurses (RNs) to recognise, diagnose, manage, and care for people with haemophilia (Cruickshank, 2009). The implementation of this training program was a progressive initiative to address the inequality of care for PWH in rural and regional areas. By educating nurses in a post graduate program, the SANDoH believed that these nurses had the ability and enthusiasm to engage in education and apply this new knowledge to clinical practice. This became the catalyst to develop a dedicated teaching program – the Haemophilia Nurses’ Education Program (HNEP).

Anecdotally, doctors and nurses in HTCs in SA report that since the implementation of the HNEP, outcomes for PWH have improved. Fewer catastrophic bleeding events have occurred, including fatalities, and those which had resulted in serious disability as a result of a bleed, such as brain injury, have been averted. Thus, it is necessary to formally establish whether the HNEP has contributed to this improvement.
2.14 Conclusion

This chapter explained the inherited, incurable bleeding disorder known as haemophilia. The symptoms, diagnosis, inheritance patterns and treatment options have been explored. It has attempted to show the important facts about haemophilia, the history of the diagnosis and treatment of haemophilia, and the management of a PWH in a country with adequate resources to provide best available treatment. The difference between haemophilia treatment in developed countries and developing countries and the consequences of inadequate and delayed treatment have been outlined. The country in which the PWH resides is the determinant of how heavily haemophilia impacts on the wellness, fitness and life expectancy of the individual PWH.

SA has been categorised as a middle-income developing country by the UN and has treatment for all PWH but has difficulty delivering that treatment. These impediments are due to inadequate infrastructure such as transport, telecommunications, poor quality roads and unhealthy water supplies in some areas. Social problems such as unemployment, illiteracy, poverty and high crime rates impact on PWH especially in rural and regional areas, preventing them from receiving the treatment they require. These factors are compounded by healthcare staff in these areas not understanding haemophilia management and therefore the PWH suffering greater morbidity, or in several cases death. After lobbying by stakeholders in haemophilia, the government approved the implementation of an education program for RNs in an attempt to overcome the problem of poor management of PWH.

The next chapter discusses the review of the literature regarding cultural care, adult learning, curriculum development and evaluation in order to describe the development and implementation of the HNEP.
Chapter 2

Literature Review: Haemophilia

2.1 Introduction

This chapter describes the rare congenital disorder of haemophilia, the devastating effect on the affected person and the preferred management. As an inherited disorder of blood clotting function, if untreated, haemophilia has the ability to inflict significant morbidity and mortality on the individual. Those PWH who have severe haemophilia but no access to treatment usually do not survive beyond adolescence. Although haemophilia has no cure, there is treatment available to effectively manage the disorder. This treatment is dependent upon the PWH being correctly diagnosed, availability of sufficient supplies of treatment being available and access to a haemophilia treatment centre (HTC) or health-care staff knowledgeable about haemophilia management.

A history of haemophilia diagnosis, the mechanism of blood clotting and how haemophilia is defined is now discussed. Also diagnosis procedures, inheritance patterns, treatment options and management, possible complications, and the role of the nurse in haemophilia care are considered. The state of haemophilia care in developing nations and specifically in the South African context will be highlighted.

2.2 Haemophilia defined

Haemophilia is the result of the clotting mechanism not functioning correctly. It is caused by a deficiency of factor VIII in haemophilia A and factor IX in haemophilia B. Haemophilia A is a more common disorder than haemophilia B, occurring in 80-85% of people with haemophilia (World Federation of Hemophilia, 2012). Worldwide, the number
of people affected with haemophilia is estimated at approximately 400,000 (World Federation of Hemophilia, 2012). Haemophilia occurs largely in males, therefore throughout this thesis the PWH is identified as “he”. Furthermore, to eliminate confusion, both haemophilia A and B will be discussed jointly and referred to as haemophilia.

Haemophilia is a rare genetic disorder carried on the X chromosome which occurs in 1:10,000 live births (Mahlangu & Gillham, 2008; World Federation of Hemophilia, 2012). It occurs in all races and ethnic groups. Haemophilia is characterised by prolonged and uncontrollable bleeding unless adequately treated. According to Sohail and Heijnen (2001), diagnosis of haemophilia is a profound encumbrance for the PWH and his family. If the PWH is living in a developing country, haemophilia is “a heavy social and economic burden on society” (p. 14).

Significant morbidity is common. Crippling can occur from bleeding into joints resulting in severe arthritis. Bleeding into muscles can result in muscle atrophy. Serious physical disability is the outcome of these bleeding episodes. The individual is unable undertake normal daily functions and attend school which severely reduces his education level and consequent ability to obtain work (Sohail & Heijnen, 2001). The level of mortality has a direct correlation with untreated bleeding into vital organs and structures such as the brain or neck, resulting in respiratory obstruction. Since such bleeds can have severe consequences, haemophilia is considered a life-threatening genetic disorder.

A complex physiological process is initiated in response to a bleed. Due to a deficiency in the clotting process, the bleeding will not be spontaneously arrested, resulting in blood leaking into joints and tissues causing further injury, severe pain and possible damage. Administration of the missing factor is the ultimate effective treatment for a PWH. However, complications can occur as a result of treatment. The most common
complications are antibodies in the blood, known as inhibitors, and blood-borne viruses, such as hepatitis C and HIV (Haemophilia Foundation of Australia, 2010). The pivotal issue here is that haemophilia can initiate serious and sometimes fatal health consequences. It is for this reason that a PWH must be provided with the appropriate treatment to avert serious health consequences and premature death.

2.3 History of haemophilia

Throughout history, information about haemophilia was gathered by those who witnessed it. The first written descriptions are attributed to the Jewish community in 2C when links were made with circumcision and death from bleeding. Rabbi Judah the Patriarch ruled that a woman who had lost two sons from bleeding after circumcision should not have subsequent male children circumcised (Ingram, 1976). Similarly, another Rabbi forbade the son of a woman to be circumcised because the sons of her older sisters had bled to death following circumcision. Further references to fatal bleeding after minor trauma in sons or cousins who are related through the maternal line are documented in Jewish manuscripts (Ingram, 1976). Moses Maimonides, a Jewish physician, decreed that sons of women whose first and second born sons died of exsanguination after circumcision should not have subsequent sons circumcised, even if the father of the subsequent sons is a second husband. This edict indicates that this ancient people concluded that boys inherit the bleeding tendency from their mother, thus recognising the hereditary nature of haemophilia. Albucasis, an Arabic physician, describes cautery as the best treatment for males with a tendency to excess bleeding, thus providing the first written reference to the treatment of bleeding due to haemophilia.

It was not until the end of the eighteenth century that clinicians began to identify haemophilia as a clinical syndrome or collection of symptoms. Dr John Otto, of the New
York Hospital (USA), published his observations of haemophilia from 1796 to 1817, and it was these observations which added significantly to the understanding of this complex disorder. At this time Otto described a woman who was a haemophilia carrier, noting that while she displayed no symptoms, her sons were afflicted with excessive bleeding. He concluded that the inheritance pattern was sex-linked and that haemophilia was associated with premature death of the person with the disorder (Lee, 2010). These patients were termed “bleeders”, and in 1828 Hopff introduced the word haemophilia, from the Greek *haima* = of the blood, *philia* = affection (Ingram, 1976).

By the early nineteenth century, haemophilia had attracted accounts from numerous sources tracing family trees back several generations or describing the damage to joints caused by prolonged bleeding. The rare presentation of haemophilia in the female emerged. A lengthy monograph by Bulloch and Fildes documented 1000 case reports and 200 pedigrees of families with haemophilia (Ingram, 1976; Lee, 2010). This information added to the increasing pool of knowledge about the disorder and in essence developed an accurate account of the devastation that haemophilia can impose on the individual and his family.

### 2.3.1 History of the management and treatment of haemophilia.

A documented account exists of a boy in 1840 with haemophilia who was administered a blood transfusion which stopped the bleeding. Samuel Lane, a surgeon, was credited with the realisation that a blood transfusion was the only effective treatment for a haemophilia bleed (Schramm, 2014). In 1840 there was no knowledge of blood typing, so the boy was fortunate to survive. While a transfusion of plasma was effective for the treatment of minor bleeds, the volume of whole plasma required to arrest a major bleed risked overloading the circulatory system.
In 1976, Ingram from the Department of Haematology at St Thomas’ Hospital in London published a paper which traced the history of treatment for haemophilia (Ojeda-Thies & Rodríguez-Merchan, 2003). It is remarkable that some of these measures described in the publication are still currently used. The first documented effective treatment was in 1934 when Macfarlane experimented with the topical application of Russell’s viper venom (Ingram, 1976). He found that the venom was effective in rapidly clotting the blood of a PWH. When the venom was added in the laboratory to the blood of a PWH at the dilution of 1:1000 000, the blood sample clotted as quickly. Thus, Viper venom was used regularly for local application.

It was not until 1965 that the particular deficiency was able to be treated with a specific product. Professor Judith Pool reported that by slowly thawing frozen plasma, much of the residue of fibrinogen which was slow to dissolve, was rich in factor VIII (Ingram, 1976). This product became known as cryoprecipitate or “cryo”. Cryo was especially useful for controlling life-threatening bleeds and to provide haemostatic cover for emergency surgery. It was however, only effective to treat people with haemophilia A who were deficient in factor VIII. In 1961, MacMillan in the USA, first used factor VIII and around the same time Edith Bidwell, based in Oxford, England, pioneered much of the work in the use of factor IX (Lee, 2010).

In the early 1970s, pharmaceutical companies began to produce factor concentrates derived from donated pooled plasma in large volumes and in lyophilised (freeze-dried) form which could be reconstituted in small volumes of sterile water. This innovative process meant that the factor could be immediately administered at home by the PWH or family member (Bolton-Maggs, 2006; Lee 2010; Mannucci, 2008). Additionally, during the 1970s Swedish physicians began to treat PWH using primary prophylaxis by administering factor
on a regular basis to prevent bleeds occurring in a response to a bleeding episode (secondary prophylaxis). The use of primary prophylaxis helped to eliminate the worst of the musculo-skeletal damage that resulted from poorly treated bleeds into muscles and joints. The availability of factor meant that life changed dramatically for PWH (Lee, 2010), in developed countries at least.

2.4 Inheritance patterns of haemophilia

As almost all PWH are male, the disorder is passed to all daughters of men with haemophilia as these daughters inherit the defective X chromosome from their fathers (Vidler, 2003). The father of any child has only one X chromosome to transfer to his female off-spring and if defective, the daughter will inherit that faulty X chromosome. Consequently, these daughters have one normal functioning X chromosome and one faulty X chromosome. They will therefore be carriers, with a 50% chance in each pregnancy of passing the affected X chromosome to their children. The carrier mothers may have daughters with the faulty X chromosome who in turn inherit haemophilia carrier status or sons who may have haemophilia. Of note is that the severity of the disorder remains constant from one generation to the next, for example, a man with severe haemophilia will pass on that level of severity to the his carrier daughter who in turn will pass it on to any children who inherit the disorder. Regardless of the transfer of the X chromosome, one third of people born with haemophilia can demonstrate no family history of haemophilia; as did British Queen, Victoria (1819-1901) (DiMichele & Neufeld 1998; World Federation of Hemophilia, 2012). This form of inheritance is known as a spontaneous mutation. The following section has been included in order to show how this congenital condition affected subsequent progeny.
2.4.1 The effect of haemophilia on a particular family.

Although no history of haemophilia had been detected in Victoria’s family, she was nevertheless, a haemophilia carrier. Following her marriage to Prince Albert, they had nine children, three of whom were affected by haemophilia (Figure 2.2). Leopold died as a young man and Beatrice and Alice were both carriers. Beatrice had a daughter Ena, who married into the Spanish royal family. Ena had two sons who were both affected with haemophilia. There was a daughter, a carrier, who went on to have two sons both with haemophilia. Alice’s daughter, Alexandra was a carrier and married into the Russian royal family. Alexandra was the mother of Alexis, the Tsarevitch of Russia, and heir to the throne, who inherited a severe form of haemophilia. Alexis was prone to prolonged and severe haemophilic bleeds which caused his parents great distress. In a desperate bid to cure her son of this disorder, Alexandra became inappropriately influenced by Rasputin, known as the mad monk. It is this association that some historians suggest can be attributed to the downfall and subsequent assassinations of the royal family in Russia in the early 20th century culminating in the end of the Romanov Empire (Ingham, 1976; Lee, 2010).
Figure 2.1 Queen Victoria’s family tree. Source: National Hemophilia Foundation (U.S.).
2.5 Mechanism of blood clotting

In order to comprehend the impact of haemophilia on a person, it is necessary to understand the mechanism of blood clotting and the process of haemostasis. Haemostasis means “the stoppage of bleeding or haemorrhage” (American Heritage Medical Dictionary, 2007). This is a complex process which results in the formation of a blood clot to plug the site of injury in a blood vessel wall. This blood clot prevents unnecessary blood loss, while simultaneously maintaining a clot-free environment in unaffected blood vessels. The clotting response is vitally dependent on normal functioning and sufficient numbers of circulating platelets; and coagulation factors that are functioning normally and in sufficient amounts (Higgins, 2012).

The physiology of coagulation is a delicate and complex mechanism that the body utilises to ensure that blood clots at the site of the blood vessel injury. Immediately after injury, vasoconstriction occurs at the injured blood vessel site and adjacent small arteries with the effect of slowing the flow of blood to the area. This system process allows adhesion of platelets to the injured blood vessel wall, a process partly facilitated by von Willebrand factor (VWF) which is stored in the endothelial cells of the blood vessel walls. Platelets are produced in the bone marrow from stem cells and circulate in the blood. The main function of platelets is to plug holes in injured blood vessel walls. The platelets circulating in the blood stream secrete many substances, some of which allow the platelets to change shape and bond together, a process termed aggregation. The adhesion and aggregation of platelets form a platelet plug. The secretion of substances from the surface of the platelets further activates clotting proteins resulting in the formation of fibrin strands which weave around and between the platelets to stabilise the platelet plug (Ziedins & Mann, 2010).
The proteins required for clotting act sequentially which is known as the clotting cascade or the coagulation pathway (Figure 2.2). This is a collection of proteins, termed factors, which circulate in the blood and are activated when bleeding occurs. As each factor is activated, the next factor in the clotting cascade is stimulated to become activated, with the end product being fibrin. There are thirteen known factors, identified by Roman numerals, although, factor VI is no longer thought to exist. For fibrin to be formed, adequate amounts of clotting factors which function normally are required (Hoffman & Monroe, 2007; Smith, 2009).

Note: The letter “a” beside a numeral indicates that the factor is activated.

Figure 2.2 Coagulation pathway/cascade.
The clotting pathway/cascade is not a complete explanation for the activation of clotting factors. The clotting cascade model can be used to explain laboratory tests that indicate coagulation abnormalities and also demonstrates the relationship between clotting factors. However, the clotting cascade does not fully explain the process of haemostasis in vivo (in the body), where the ultimate outcome is the formation of a robust fibrin clot to stop the bleeding (Hoffman, 2003; Smith, 2009).

The cell-based model of fibrin formation explained by Hoffman (2003) and Smith (2009) may help to explain more fully the coagulation mechanism in a dynamic environment that is, circulating in the blood. In particular, this model may provide possible reasons why some factor deficiencies such as factor VIII and factor IX, the deficiencies that cause haemophilia, are related to significant bleeding while others, such as factor XII deficiency, are not associated with bleeding (Hoffman & Monroe, 2007). The cell-based model highlights the relationship between clotting factors and the surface of specific cells. Studies of the cell-based model indicate that coagulation in vivo takes place in three distinct, overlapping stages and that two different cell types are required: cells containing tissue factor (TF) and platelets (Smith, 2009).

The cell-based model consists of three phases, firstly, the Initiation Phase where TF is activated when exposed to flowing blood following an injury to the blood vessel. A small amount of Factor IXa and thrombin diffuse away from the TF-bearing cell surface to the platelets. The second stage is called the Amplification Phase when the thrombin activates platelets, releases vWF and activates Factor V, Factor VIII and Factor XI. The third and final phase is known as the Propagation Phase where various enzymes gather on the surface of the platelets to form intrinsic tenase and activate Factor X. Prothrombinase forms from this action and a burst of thrombin is generated on the surface of the platelets, resulting in
sufficient fibrin to form an insoluble fibrin matrix (Smith, 2009). In haemophilia this process does not occur since an essential substance (Factor VIII or IX) is absent.

### 2.5.1 Coagulation inhibition.

If the blood clotting process is allowed to go unchecked, clotting in healthy blood vessels (thrombosis) would occur. It is therefore vital that the effect of the clotting mechanism occurs only at the site of injury. Substances circulating in the blood called inhibitors regulate the process of coagulation inhibition by inactivating the activated clotting factors. Examples of these substances are protein C which inactivates factors V and VIII, and antithrombin which inactivates factors Xa and thrombin. The clot at the site of injury will be broken down once the blood vessel wall is healed. This process is known as fibrinolysis, and occurs when fibrin is degraded by a substance called plasmin. Fibrinolytic activity can be detected in the laboratory by the presence of fibrin degradation products (FDPs). Anti-fibrinolytic medications, such as tranexamic acid, slow down the fibrinolysis process, maintaining the clot in situ longer, giving the injured site more time to heal (Smith, 2004).

Clot formation and fibrinolysis are usually well balanced but sometimes the tissue damage is so severe that large amounts of thromboplastin are released into the circulating plasma, causing widespread clotting throughout the body. This is known as disseminated intravascular coagulation (DIC), which occludes blood vessels and causes ischaemic damage to tissues, which release more thromboplastin. Finally, the circulating platelets dwindle and the clotting factors become exhausted, so that clotting can no longer take place and bleeding occurs. Any organ in the body can be affected and without prompt treatment, death can result (Robertson, Wu & Greer, 2004).
2.6 Diagnosing haemophilia

Accurate diagnosis of haemophilia is essential to enable the correct treatment to be prescribed and administered. In developed countries such as Australia, if a person is suspected of having haemophilia, the initial diagnosis is made through rigorous assessment including clinical presentation, family history and laboratory testing (World Federation of Hemophilia, 2012). This is done to exclude other inherited bleeding disorders which can be similar, such as von Willebrand Disorder (VWD). It is important to observe that the family history and clinical signs of haemophilia A and haemophilia B are identical (World Federation of Hemophilia, 2012) and the differentiation cannot be established until the laboratory assays are performed.

Since haemophilia impairs the coagulation process, it is imperative that early diagnosis is made to reduce the risk of morbidity and mortality. If a PWH has access to quality management and treatment, as is the case in developed countries, the person’s lifespan will reflect that of the non-haemophilia population (World Federation of Hemophilia, 2012).

2.6.1 Clinical presentation.

Symptoms of haemophilia include bleeding which can occur in any part of the body but most commonly into joints, muscles, gums, nose and mouth, and urinary tract. In severe haemophilia, bleeding can be spontaneous with no apparent cause. Trauma or even minor surgery, such as dental extraction, can cause a devastating haemorrhage. A bleed that occurs in the central nervous system, gastrointestinal tract, neck, after surgery and following severe trauma is considered life-threatening and requires prompt and appropriate intervention to arrest the bleeding (World Federation of Hemophilia, 2012).
Uncontrolled bleeding in joints and soft tissues can result in severe pain. Repeated bleeding into the same joint, known as a target joint, can lead to progressive arthritis and eventual crippling due to joint and muscle damage (Sohail & Heijnen, 2001).

It is possible to diagnose a child with haemophilia soon after birth as symptoms of birth trauma such as intracranial haemorrhage, cephalic haematoma and/or bleeding from the umbilical cord are often present (Giangrande, 2003). When toddlers begin to walk it is predictable that they will have falls. However, if the child shows signs such as excessive bruising, or prolonged bleeding from the mouth due to the usual spills experienced at this age, haemophilia should be considered (WFH, 2005). Unfortunately, parents are often suspected of child abuse because of the extensive bruising before a diagnosis is made (Swedish guidelines for the care and treatment of haemophiliacs, 2003), especially when there is no family history of haemophilia.

2.6.2 Family history.

In order to make a definite diagnosis, data are collected in relation to the medical histories of the individual and both male and female family members who might describe similar bleeding episodes. For example, females may report post-partum haemorrhage or menorrhagia (Gringeri, 2005) and other family members may describe lifelong frequent and prolonged epistaxis or easy bruising. Women who are haemophilia carriers may present with bleeding into joints, muscles and mucosa (Lambing, 2007), while others may not have experienced any bleeding symptoms. In developing countries, due to lack of education or health awareness, including haemophilia, relatives often do not know the cause of death in a family member, so it is sometimes difficult to elicit an accurate family history. To further complicate the situation, many clinicians are unaware of the symptoms and clinical presentation of haemophilia, so the disorder can remain unrecognised and undiagnosed.
2.6.3 Laboratory tests to aid diagnosis.

Laboratory tests result in the definitive diagnosis of haemophilia. However, specimens must reach the laboratory within four hours of collection from the patient (World Federation of Hemophilia, 2012) to maintain integrity of the specimen. Initially platelet count, bleeding time, prothrombin time and activated prothrombin time will be performed. If these tests are within normal limits, further tests such as coagulation assays (tests) which measure levels of factor VIII, factor IX and von Willebrand Factor may be required which will provide a more definitive diagnosis (World Federation of Hemophilia, 2012). From these tests a diagnosis of haemophilia A or B will be determined.

Factor assays are required to monitor treatment when a PWH requires management for an acute episode such as surgery or trauma. The laboratory scientists will perform regular factor assays to assess the factor levels. These levels will guide the haematologist about factor dosage, to facilitate haemostasis and minimise the threat of a further bleed (World Federation of Hemophilia, 2012). When a known haemophilia carrier, a mother or a woman with a family history of haemophilia goes into labour, it is recommended that umbilical cord blood be collected at the time of delivery to test for haemophilia. Collecting an umbilical cord blood sample has two advantages. Firstly, the sample can be delivered to the laboratory as soon as the cord is cut; and secondly, attempts to obtain blood samples from a peripheral vein in a newborn is difficult and may result in severe bruising or bleeding, thus requiring factor (Giangrande, 2003).

Expensive laboratory equipment and reagents to perform blood tests are required to establish the level of deficiency of factor as it is this result which determines the severity of haemophilia. Those individuals with less than one percent of factor are considered severe, one to five percent of factor is deemed moderate, and five to 25 percent of factor is
considered mild. Many people with mild haemophilia are not diagnosed until they sustain trauma or undergo surgery when such an experience can trigger excessive bleeding (World Federation of Hemophilia, 2012).

### 2.7 Complications of haemophilia

There are several complications that may arise with regard to haemophilia such as inhibitors and blood borne viruses. These are discussed in what follows.

#### 2.7.1 Inhibitors.

A complication of haemophilia which can have serious consequences for PWH is the development of antibodies, known as inhibitors, to the factor replacement. When a PWH is given treatment with factor VIII or IX to raise the level of the missing factor, the body perceives the factor as an invading foreign protein and the inhibitor attaches to the factor, impeding its action and rendering it ineffective. The development of an inhibitor makes management of haemophilic bleeding more complex and difficult (Kasper, 2004).

Inhibitors occur more frequently in those people with severe or moderately severe haemophilia A, and are much less common in people with haemophilia B. Inhibitors have been reported to develop most commonly in PWH less than 12 years of age and after they have been exposed to an average of nine to 12 treatments. There is a tendency for the development of inhibitors to occur in families, and ethnic groups; for example, Africans are twice as likely to develop inhibitors as Caucasians (DiMichelle, 2008; Kasper, 2004). This statistic is of significance to this study since the management of haemophilia is being evaluated in SA, where the majority of PWH are of African heritage.

If an inhibitor is present it is usually discovered by either a routine blood test taken at the time of a regular visit to the haemophilia treatment centre (HTC) or when the normal
doses of factor are not arresting bleeding effectively. The presence of inhibitors is confirmed by the Bethesda inhibitor assay, a blood test carried out in the coagulation laboratory. This test indicates the level of inhibitors present, with the level being measured in Bethesda units (BU) or Bethesda titre. The higher the Bethesda titre, the greater the amount of inhibitor present in the blood (Mitchell & Phillott, 2008). A PWH with a Bethesda titre more than five is known as a high responder and those with a Bethesda titre less than five are termed low responders. This level is an important distinction because the treatment differs according to the level of the Bethesda titre. Fortunately, most HTCs in SA have laboratories with the capacity to perform these assays.

Treatment using factor VIII or IX for low-responding inhibitors is frequently effective, although the dosage may need to be higher, given more frequently or as a large bolus dose to overwhelm the inhibitor (DiMichelle, 2008; Kasper, 2004). For most PWH with high responder status, a bypassing agent such as recombinate factor VIIa or Factor Eight Inhibitor Bypassing Activity (FEIBA), prothrombin complex concentrates and activated prothrombin complex concentrates which contain other factors, are used to “bypass” the requirement for factor VIII or IX and therefore do not activate the inhibitor. In developed countries, PWH are fortunate to have access to immune tolerance which can be accomplished by giving frequent doses of factor over a long period of time. The aim is to overwhelm the inhibitor so that it no longer has the ability to produce antibodies to the factor (DiMichelle, 2008; Kasper, 2004). Immune tolerisation and the use of bypassing agents is expensive therapy and therefore rarely available to PWH living in developing countries.
2.7.2 Blood-borne viruses.

Cryoprecipitate and factor VIII and IX are plasma-derived products produced from donated blood. It was not until the 1980s that transfusion scientists and haematologists identified that some donated blood was contaminated by viruses; most notably, HIV. However, this discovery was too late for countless PWH, many of whom developed Acquired Immune Deficiency Syndrome (AIDS). This event was disastrous as many PWH died (Lee, 2010) before effective treatment became available to arrest the debilitating progress of HIV and AIDS. Other viruses, which contaminated the blood supply and its products were the hepatitis viruses. Scientists were able to identify the hepatitis B virus, however the hepatitis C virus (HCV) was not visible under microscope and was referred to as non-A, non-B hepatitis. In the early 1990s, more sophisticated diagnostic techniques became available (Lee, 2010) and the non-A non-B virus was identified and is now referred to as hepatitis C (HCV). Although these are now identified and effective treatment is available, there are still some genotypes of HCV that are resistant to treatment (Hepatitis Australia, 2017).

In developed countries, recombinant factor VIII and IX, which are manufactured in a laboratory and do not contain any human tissue, are now available for the treatment of PWH. These products have a very low risk of contamination by viruses. In contrast, PWH in developing countries continue to be treated with plasma-derived products such as factor VIII, factor IX and cryoprecipitate, as the recombinant products are unavailable.

Countries in the developing world that produce their own plasma-derived product have put in place safeguards to protect the consumers from contamination. These safeguards reflect those that well-resourced nations had developed to protect PWH recipients prior to the introduction of recombinant products (Farrugia, 2017). The
safeguards include strict pre-screening of the donors prior to donation; firstly, to exclude high-risk behaviour, for example, unprotected sexual encounters; and, secondly, serologic screening assays to identify viruses that are transmissible by blood and plasma products; and thirdly, treatment such as pasteurisation and nano-filtration of the plasma to ensure the products are safe (Muller, 2004). Cryoprecipitate is manufactured in some developing countries but the viral reduction techniques used for factor are not easy to apply to cryoprecipitate because the product’s low purity prevents it being decontaminated by heat processes such as pasteurisation (Farrugia, 2008).

**2.8 Treatment and management of haemophilia**

Joint bleeding, termed haemarthrosis, is the most common presentation in haemophilia. The PWH will present with pain, swelling, restricted range of movement, stiffness and tingling in the affected joint. If the bleeding continues and the joint fills with blood, it becomes hot, more swollen and painful with a significant decrease in articulation. If provided with appropriate treatment, soon after the symptoms appear, the bleeding stops quickly and the symptoms often resolve promptly. Muscle bleeds are also common and managed in the same way as joint bleeds to prevent contractures and nerve compression (Chandy 2005; Shamsi & Chughtai, 2001).

Essentially, the aim of treatment is to arrest the bleed, minimise damage to the joint, muscle or other tissues, stop the pain and restore the affected part to the level of function prior to the bleed. Prompt treatment, using the appropriate product for the deficiency even if only with minimal doses of factor, fresh frozen plasma (FFP) or cryoprecipitate (“cryo”) can provide haemostasis better than delayed application. If the haemophilia diagnosis is known, this treatment should be administered immediately before any further investigations (Mahlangu, 2008). In some cases, particularly in the developing world, there can be delays.
of several days before administering treatment after a bleed due to poor transportation, or the PWH needing to travel long distances to access treatment. Conservative measures such as immobilisation, application of ice and gentle compression can be implemented by the PWH or a family member to reduce the pain and swelling until factor can be administered and should be continued until the bleeding stops (World Federation of Hemophilia, 2012). The PWH can be given a personal supply of factor to instigate treatment if a bleed commences. Pain can be managed by using paracetamol or mild opioid preparations. Aspirin and salicylates such as non-steroidal anti-inflammatory drugs are contraindicated since they influence the agglutination of platelets, affecting the body’s ability to achieve haemostasis. Once the bleeding ceases, rehabilitative exercises are commenced to restore strength to the muscles surrounding the affected joint or limb (World Federation of Hemophilia, 2012). The objective is to strengthen the muscles so they can support the joint, restore range of motion and reduce crippling. These exercises can be taught to the PWH so he can continue them at home, helping to reduce frequency of bleeds and damage caused by bleeding into joints (Shamsi & Chughtai, 2001).

Bleeding in the region of the head, neck, chest, abdomen and gastro-intestinal tract are life-threatening bleeds, considered as emergencies and should be treated with factor replacement without delay (Chandy, 2004). Mucous membrane bleeds such as nose bleeds and bleeds from the oral cavity are treated with tranexamic acid, fibrin glue or a single dose of factor. The application of a suture if necessary after dental extraction or skin laceration can be safely carried out and the first aid measures of ice packs and elevation can also be implemented. Bleeding after circumcision can be fatal if not adequately managed. In neonates, a blood transfusion followed by the appropriate factor once the bleeding disorder has been identified should be administered to arrest the bleeding. Fibrin glue has been shown to be effective post-circumcision (Shamsi & Chughtai, 2001). Surgical procedures,
including orthopaedic surgery, require careful management and are ideally performed in establishments that have access to both experienced surgeons and a haemophilia comprehensive care team who can work in tandem to ensure that the PWH receives optimal and appropriate care.

The WFH’s Guidelines for the Management of Hemophilia (2012) recommend that optimal haemophilia care be delivered using the comprehensive care model involving a multidisciplinary health care team approach. This approach, directed by a haematologist, includes a nurse, physiotherapist and social worker as core team members. The team members can access further resources including a coagulation laboratory, appropriate clotting factor concentrates and specialist consultants such as an orthopaedic surgeon, dentist, rheumatologist and geneticist. The Haemophilia Treatment Centre (HTC), which is usually located in the capital city of a province or country, is the specialised care centre for the PWH and has a multi-functional approach. It provides outpatient facilities for those patients not requiring hospital admission as well as education to healthcare staff, education of PWH and their families, instruction and support for home therapy (infusions of factor at home) and psychosocial support (Hoots, 2003). In Australia, there is sufficient factor available for all PWH provided free of charge. Also within Australia and other developed countries, a PWH who receives this level of care will maintain health outcomes enabling a more positive future. In contrast, a PWH living in developing countries, particularly if they live in regional areas may never be diagnosed, and those who are, may not receive this level of care.

2.9 Current treatment protocols

As currently understood, several haemophilia treatment options are available. These are described below.
2.9.1 Plasma-derived treatments.

Optimal treatment of haemophilia requires intravenous replacement of the clotting factor. In haemophilia A the clotting factor is factor VIII and in haemophilia B the clotting factor is IX. The dosage of factor is calculated by the body weight of the PWH, the severity of the individual’s haemophilia and the severity of the bleeding episode (World Federation of Hemophilia, 2012). In developed countries such as Australia, management of children with severe haemophilia is replacement of factor two or three times weekly, known as primary prophylaxis. This process raises the factor levels sufficiently to achieve haemostasis and prevent bleeding (Khair, Lawrence, Butler, O’Shea & Christie, 2008). In contrast, a child with haemophilia in a developing country in the best-case scenario will be treated “on demand” that is, in response to a bleed, known as secondary prophylaxis. If factor is unavailable, the risk of death significantly increases. According to Mahlangu (2009), there were ten deaths per annum from haemophilia causes in the years 2004 to 2007 in SA. In Australia it is rare for a PWH to die of the disease. Sufferers are more likely to die of complications such as hepatic malignancy as a result of hepatitis C infection.

Factor is either plasma-derived from blood donations or recombinant, a synthetic version made in a laboratory, containing no human plasma (DiMichele & Neufeld, 1998), which would be the treatment of choice given the AIDS risk in SA. In plasma-derived product, the clotting factor is separated from the blood plasma and freeze-dried (lyophilised) to a powder to be reconstituted with sterile water when ready to be administered. This procedure however, requires a sophisticated manufacturing process to eliminate blood-borne viruses, such as hepatitis C (DiMichele & Neufeld, 1998). This complicated procedure means that the replacement factor is very expensive (Mahlangu & Gillham, 2008). As the cost is around U$1 per unit, with an average dose for an 80kg male being in the region of
2500 to 3000 units of factor to stop a bleed, the cost per dose would be US$3000, being approximately the same in Australia.

The discovery and introduction of factor replacement therapy significantly changed the way haemophilia was managed (Lee, 2010). Prior to the discovery of this treatment, the life expectancy of a PWH was short and children died of the disorder at a very young age, for example, in Sweden life expectancy was eight to 11 years. From the 1970s to the present time, however, survival rates have extended to around 65 years (Bolton-Maggs, 2006), a significant improvement. Immediate treatment of spontaneous bleeds with factor eliminated the long periods of recovery and rehabilitation following a bleed. Previously, children had to endure prolonged hospital admissions, which resulted in erratic school attendances and educational opportunities. Consequently, employment opportunities were reduced.

2.9.1.2 Cryoprecipitate (Cryo).

Cryo (from the Greek word, kruos, meaning cold) was used widely in the 1960s in the management of haemophilia A and was the forerunner of factor replacement concentrates (Bolton-Maggs, 2006, Hoffbrand & Pettit, 1993). After thawing at one to six degrees Celsius, cryo is separated from fresh frozen plasma (FFP) and is found in the remaining precipitate, which is then refrozen. Factor VIII, Fibrinogen, factor XIII and fibronectin are contained in cryo (PathWest, 2011). Cryo is produced in blood centres in developing countries, such as Thailand and Cuba, providing the main source of treatment product for haemophilia A and can be used without further processing. Approximately 600 units of factor VIII can be supplied from one litre of plasma with the final result a freeze-dried product which can be stored at home by PWH and reconstituted and self-injected when required (Farrugia, 2008).
The use of safe cryo without supplies of factor concentrates is an affordable and viable alternative for treatment of PWH in developing countries. However, Farrugia (2008) explains that techniques used to eliminate viruses from factor concentrates are not suitable for use in cryo. In the blood centre setting, heat treatment cannot exceed 60° C, which is not sufficient to nullify viral contamination. Until technology is available to perform viral inactivation for cryo, other methods need to be implemented to ensure that the product is safe from blood-borne viruses. Consequentially, appropriate selection of low-risk blood and plasma donors is the most important preventative measure available to policy-makers and producers of cryo in developing countries (Farrugia, 2008).

2.9.1.3 Fresh frozen plasma.

Fresh frozen plasma (FFP) contains factor VIII and factor IX, 250 units in 250 millilitres. Given by infusion, care needs to be taken during administration that fluid overload does not occur, particularly with children. Fresh frozen plasma carries similar problems with viral screening as cryo (Shamsi & Chughtai, 2001).

2.9.1.4 Fibrin glue.

Fibrin glue, also known as fibrin sealant, is made using a mixture of fibrinogen and thrombin. It acts as a sealant, and promotes haemostasis and healing. It is used for dental extraction, circumcision and to arrest mucous membrane bleeding. It is available as a commercial product, which is very expensive, but can be made in inexpensively in transfusion laboratories using cryoprecipitate (Chandy, 2005), so is a useful adjunct therapy in developing countries.

Desmopressin Acetate (DDAVP) is a pharmaceutical treatment option which raises the activity of the von Willebrand Factor (VWF). It increases the levels of VWF and factor
VIII in the bloodstream by stimulating the release of VWF from the endothelial cells in blood vessels. It is a synthetic analogue of vasopressin, an anti-diuretic hormone.

Advantages of using DDAVP are that it is inexpensive in comparison to factor replacement and being a pharmaceutical, carries no blood-borne viruses. Its use is indicated in some forms of von Willebrand Disease, mild haemophilia and to carry out DDAVP trials which are implemented to test the effect of DDAVP. Contra-indications for the use of DDAVP include severe haemophilia A, haemophilia B, severe von Willebrand Disease, type 2B von Willebrand Disease, pregnancy and older patients or those with a history of cardiovascular disease and/or hypertension.

The drug DDAVP can be given intravenously, intra-nasally and subcutaneously. It is given as an intravenous infusion diluted in 50 - 100mls of normal saline over 20-30 minutes. Intra-nasal DDAVP is a spray containing 150 micrograms per dose to each nostril. Subcutaneously DDAVP has been found to be effective and is particularly useful if intravenous access is difficult. As DDAVP is an anti-diuretic hormone, it causes fluid retention therefore it is necessary to observe for hyponatremia and over-hydration which can lead to cardiac failure and death. Children and the elderly are particularly susceptible to these problems (Smith, 2004).

Tranexamic acid is an anti-fibrinolytic which acts by delaying the process of fibrinolysis and is especially useful in controlling bleeding of mucous membranes. It can be used as a mouthwash after dental or oral surgery, epistaxis and menorrhagia (Chandy, 2005). However, it is important to note that tranexamic acid is contra-indicated for urinary tract bleeds. The oral dosage is 25 milligrams per kilogram of body weight taken three to four times per day for 10 days to allow wound healing.
2.9.2 Further considerations in developing countries.

In developing countries, the financial burden of factor replacement often results in reluctance of governments to purchase the product (Chuansumrit, 2003; Evatt & Robilliard, 2000) resulting in the PWH being untreated, thus increasing the risk of morbidity and mortality. However, these outcomes can be reduced if the patient, his family and the physician are knowledgeable about the management and treatment of haemophilia, even if factor replacement availability is limited (Chuansumrit, 2003). Chandy, in his WFH Monograph “Treatment Options in the Management of Hemophilia in Developing Countries” (2005), supports this position. The importance of education of the PWH, their families, health care providers and the general public is stressed by Shamsi and Chughtai (2001), Pakistani physicians, who believe that education is the basis of haemophilia care where financial resources are inadequate and factor is unattainable. These physicians state that simple first aid measures such as immobilisation and applying ice to the site of the bleed can help to minimise morbidity. Chandy (2001) maintains that education is not expensive to implement in the developing world and that much of the morbidity associated with haemophilia could be reduced if the PWH, and those involved in his care, have sufficient knowledge about the disorder.

2.10 Recent developments

In 2000 the United Nations Millennium Development Goals (MDGs) were signed by 191 countries. Each signatory member state agreed to strive to accomplish these goals by the year 2015. The goals were aimed at eradicating extreme poverty and hunger; providing equality, empowerment and improved maternal health for women; reducing child mortality; combating diseases; and developing global partnerships for development and environmental sustainability. The eight Millennium Goals came to the end of their tenure and have been
superseded by a new plan. In 2015, the World Health Organisation, (WHO) introduced seventeen Sustainable Development Goals (SDGs) to take the place of the MDGs, building on the successes of the MDGs and broadening the scope to encompass climate change, economic inequality, sustainable consumption and peace and justice.

Although haemophilia is not identified directly in the United Nations MDG and SDG goals, improved care of people with haemophilia would help address goal four by reducing child morbidity and mortality. However, the treatment of haemophilia is expensive, even in developed countries, and the cost burden is considerable. In developed countries, five to ten percent of Gross Domestic Product (GDP) is expended on health, whereas under-developed countries are only able to channel less than two percent of the GDP on health (WHO/WFH] International Society of Thrombosis and Haemostasis, ISTH, 2002). In countries where as little as U$1 per head is spent annually on health care, the cost of haemophilia treatment is unattainable (WHO/WFH/ISTH, 2002). South Africa has haemophilia treatment available for all PWH who require it which reflects expenditure of 8.8 % of the GDP on health (WHO, 2015b).

The United Nations has a variety of programs that assist governments to develop specific plans that will benefit their citizens. One of these programs is the United Nations Development Program (UNDP) which uses the Human Development Index (HDI) and encompasses the following three dimensions: health, education and living standards, to estimate a nation’s living standard. The indicators for the health dimension include life expectancy at birth (in years), public health expenditure expressed in percentage of the GDP and under-five years of age mortality rate per 1,000 live births. For education, the indicators are public expenditure on education as a percentage of the GDP, expected years of schooling of children under 7 years of age, adult literacy rate which includes the percentage
of both sexes over 15 years of age, mean years of schooling of adults over 25 years and the
combined gross enrolment in education of both sexes expressed in a percentage. The
indicators for living standards are GDP per capita in Purchasing Power Parity which
describes whether the cost of goods purchased in two different countries is the same when
expressed in US dollars. Also utilised is the Gross National Income (GNI) which is an
indicator designed by the World Bank which expresses the average income of a country by
dividing the dollar value of the country’s annual income by the population (UNDP Human
Development Report, 2011). Using this method, the UNDP is able to differentiate between
developed countries and developing countries. On the HDI, SA is rated 123, in contrast to
Australia which is rated two. This figure demonstrates that Australia has a much higher
standard of living than SA and shows that SA has little expenditure focussed on essential
health and education.

However, the UNDP has found that a country’s overall HDI can disguise the fact
that different groups within the country can have different levels of development: examples
are groups characterised by income, geographical regions, urban or rural habitation, gender
or ethnicity. By using disaggregated HDIs, (applying the HDI components to the sub-group
of concern and treating them like a separate country), inequalities can be identified which
can be used to guide policies and implementation of recommended actions to address gaps.
The use of the HDI and disaggregation can help to illustrate more strongly disparities that
are already known of in a community. There is evidence to support that the HDI provides
assistance to social and regional groups to strengthen their case for more resources.
Therefore, if more resources are available in health, there is a greater probability that more
resources for haemophilia care are available.
2.11 The nurse’s role in haemophilia care

As Chandy (2005) observed, education is the keystone to improvement in healthcare. Haemophilia nurses play a vital role within the haemophilia comprehensive health care team. These nurses create a link between the PWH and other health providers and serve two functions, firstly, to treat acute bleeding episodes; and secondly, to take on the role of educator. The haemophilia nurse educates patients and their families about haemophilia, the inheritance patterns, treatment options available and when and how to treat a bleed, and at the same time supporting the families so that they can better deal with the challenges of living with haemophilia (Oyesiku & Butler, 2007). Following initial diagnosis, the haemophilia nurse or doctor will administer the factor to the child with haemophilia. Gradually the parents of the child are encouraged to learn how to undertake venepuncture and inject the factor. Through such education, treatment can eventually be provided at home, known as home therapy, thereby eliminating repeated hospital visits and reducing the strain on a fragile haemophilia care system which currently exists in SA. Essentially, teaching patients to administer factor as soon as the bleed occurs means that immediate treatment can reduce the pain and possible damage to joints or organs (Di Michelle & Neufeld, 1998; Evatt, 2006; Vidler, 2000).

Studies have demonstrated that prophylaxis is the most important measure to prevent joint damage in children with haemophilia (Lofqvist, Nilsson, Berntorp & Pettersson, 1997; Panicker, Warrier, Thomas & Lusher, 2003). Prophylaxis is therefore much easier and more convenient if the venepuncture and administration can be delivered at home. Parents are also instructed how to perform immediate care such as applying ice and conservative measures such as resting the affecting area. Educating the family provides the necessary skill to assess and respond immediately to bleeding episodes. Often only one injection of
factor plus the application of conservative measures are required to stem the bleed. It is
evident that such treatment and intervention is cost-effective in both human and financial
terms (WFH, 2005).

Education of the patient and family is a central component within the role of the
haemophilia nurse and pivotal to the efficient management and treatment of haemophilia.
Once a treatment plan is formulated, the nurse will ensure that the PWH and his family
understand the plan and that it must be evaluated regularly to address any difficulties with
implementation. Progress of the PWH is monitored continually, ongoing support is
provided and accurate records are observed to document progress and identify any
problems. The nurse works with the PWH and family to ensure that the plan is successful
and acts as the liaison with other haemophilia comprehensive care team members (WFH,
2007).

The nurse endeavours to educate all people involved with the PWH, such as the
wider community, school staff and employers. It is also essential to advocate for the PWH
in relation to schools and workplaces. For example, contact sports, which some schools
would expect boys to participate in, are not recommended for children with haemophilia
(WFH, 2007).

Studies by Khair, Lawrence, Butler, O’Shea, and Christie, (2008) and Miller,
Guelcher and Taylor (2009) support and indeed reinforce the importance of education in the
care of PWH and the haemophilia nurse is crucial in this endeavour. As the PWH reaches
adulthood he must assume responsibility for his health. An independent pilot study
conducted by Miller et al., (2009), involving haemophilia nurses in the USA, found that 187
PWH or their caregivers rated health care providers (nursing and medical) as the most
important source of information about haemophilia and treatment. This study is supported
by a survey conducted by haemophilia nurses in the US, UK, Sweden and Canada, which found that education similar to that described above, was the most suitable method to conquer difficulties with prophylaxis and home therapy in more than 10,100 patients with severe haemophilia A (Khair et al., 2008).

2.12 Haemophilia care in developing countries

The care and support in developing countries significantly contrasts with a wealthy country such as Australia. Prophylaxis, as practiced in developed countries, requires an annual supply of hundreds to thousands of units of factor for each PWH each year. Factor replacement is a very expensive commodity for the individual to purchase, thus the PWH is reliant on the government to provide this treatment. In developing countries, a government with a low GDP and limited health budget has little chance of purchasing factor for prophylactic purposes, therefore other measures need to be initiated to manage haemophilia (Chuansumit, 2003). Prevention of a bleed is the primary aim and maintenance of good health will assist fulfilment of these aims. It is essential for the PWH to avoid situations which may provoke bleeds, for example, poor dental health. Regular exercise to improve fitness; regular check-ups at the haemophilia clinic, especially of examination of joints and muscles; avoiding contact sports; and obtaining vaccinations against hepatitis will help the PWH to remain well (Chandy, 2005).

Conservative management of a bleeding episode consists of first aid and analgesia. First aid measures recommend rest, for example a sling for a wrist bleed, intermittent application of ice packs for the first 48 hours and gentle compression using an elastic bandage. Analgesia such as paracetamol or codeine are suitable, although aspirin and other salicylates should be avoided. Rehabilitative physiotherapy exercises can commence once the pain and swelling have abated. If a physiotherapist is available, they will carry out the
exercises initially (Battistella, 2001). Once the PWH begins to recover, he is then taught how to perform these exercises. Exercise will help restore muscle and maintain the range of motion in joints, both of which can decrease the frequency and severity of bleeds and avoid permanent damage (Chandy, 2005). In developing countries often a physiotherapist is unavailable, therefore it becomes the responsibility of the haemophilia nurse to initiate the rehabilitation program.

2.13 The South African context

The focus of care in haemophilia in SA generally reflects treatment in Australia and other developed nations but managed with fewer resources. Currently, in SA there are 17 government-funded haemophilia centres (Mahlangu, 2009) and availability of factor is rarely a concern, which demonstrates the commitment to addressing the problem. However, it is the lack of resources and infrastructure in some areas of SA which prevent access to health care and as a consequence increase the risk morbidity and mortality of PWH (Mahlangu, 2009). Furthermore, there is also the issue of access to specific drugs such as FEIBA. Unfortunately, it is the poor black South African who is already disadvantaged and is at an increased risk due to the limited access to healthcare.

As stated earlier, individuals living in rural and remote areas have to overcome substandard infrastructure, such as poor roads, inadequate telecommunication and unreliable power supplies; all of which make it difficult to access health care (Cruickshank, 2009). The photographs (Figures 2.3, 2.4 & 2.5) below show the poor state of roads and inadequate modes of transport in some rural areas.
Figure 2.3 Road in rural area. Source: Researcher’s personal photographs.
In 2001, to help surmount problems related to remoteness and poor infrastructure, consultation with SA Haemophilia Foundation Medical Advisory Committee members such
as haematologists and provincial government health department coordinators was convened to decide how to transfer haemophilia treatment to the provinces. As a result of discussions, the following guidelines were recommended:

- All PWH would attend the haemophilia treatment centres for assessment and treatment plan;
- PWH would then be referred back to their local health care facility after collaboration with the provincial health care person in charge;
- This action would allow the PWH to be treated close to where they lived, in essence, reducing the risk of non-treatment.

As a consequence of this recommendation, the SA National Department of Health (SANDoH) approved a training program which would involve the education of Registered Nurses (RNs) to recognise, diagnose, manage, and care for people with haemophilia (Cruickshank, 2009). The implementation of this training program was a progressive initiative to address the inequality of care for PWH in rural and regional areas. By educating nurses in a post graduate program, the SANDoH believed that these nurses had the ability and enthusiasm to engage in education and apply this new knowledge to clinical practice. This became the catalyst to develop a dedicated teaching program – the Haemophilia Nurses’ Education Program (HNEP).

Anecdotally, doctors and nurses in HTCs in SA report that since the implementation of the HNEP, outcomes for PWH have improved. Fewer catastrophic bleeding events have occurred, including fatalities, and those which had resulted in serious disability as a result of a bleed, such as brain injury, have been averted. Thus, it is necessary to formally establish whether the HNEP has contributed to this improvement.
2.14 Conclusion

This chapter explained the inherited, incurable bleeding disorder known as haemophilia. The symptoms, diagnosis, inheritance patterns and treatment options have been explored. It has attempted to show the important facts about haemophilia, the history of the diagnosis and treatment of haemophilia, and the management of a PWH in a country with adequate resources to provide best available treatment. The difference between haemophilia treatment in developed countries and developing countries and the consequences of inadequate and delayed treatment have been outlined. The country in which the PWH resides is the determinant of how heavily haemophilia impacts on the wellness, fitness and life expectancy of the individual PWH.

SA has been categorised as a middle-income developing country by the UN and has treatment for all PWH but has difficulty delivering that treatment. These impediments are due to inadequate infrastructure such as transport, telecommunications, poor quality roads and unhealthy water supplies in some areas. Social problems such as unemployment, illiteracy, poverty and high crime rates impact on PWH especially in rural and regional areas, preventing them from receiving the treatment they require. These factors are compounded by healthcare staff in these areas not understanding haemophilia management and therefore the PWH suffering greater morbidity, or in several cases death. After lobbying by stakeholders in haemophilia, the government approved the implementation of an education program for RNs in an attempt to overcome the problem of poor management of PWH.

The next chapter discusses the review of the literature regarding cultural care, adult learning, curriculum development and evaluation in order to describe the development and implementation of the HNEP.