Cape Peninsula
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COMPRESSION AND DOPPLER ULTRASOUND OF DEEP VEIN THROMBOSIS IN PATIENTS ON TUBERCULOSIS TREATMENT.

By:

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Thesis submitted in fulfilment of the requirements for the degree of Doctor of Technology: Radiography in the Faculty of Health and Wellness Sciences at the Cape Peninsula University of Technology

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DECLARATION

I, Sheila Anne Brock, declare that the contents of this thesis represent my own unaided work, and that the thesis has not previously been submitted for academic examination towards any qualification. Furthermore, it represents my own opinions and not necessarily those of the Cape Peninsula University of Technology.

Signed **Date**

ABSTRACT

Background. Ultrasound has until recently been regarded as a sophisticated examination reserved for tertiary health care. In reality it is well suited to the district or primary health-care situation. A DVT (deep vein thrombosis) is an important complication of the treatment of TB and this can lead to more devastating sequelae such as a pulmonary embolus. Many DVTs are clinically silent, making the diagnosis difficult.

Method. This study was a prospective, longitudinal observational study. The study documented the incidence of DVTs and their onset, assessed certain aspects in an attempt to identify some risk factors, and noted the most common position of the DVT in a TB population. The feasibility of a sonographer-led ultrasound clinic for the diagnosis of DVTs was also assessed.

This was achieved by screening the in-patient population at a district TB hospital. The participants received up to four routine duplex Doppler compression ultrasound examinations of the venous system of the lower extremities on week 0, week 4, week 8 and week 14. In addition a single abdominal ultrasound was performed at week 0.

Results The incidence of DVTs in this TB population was 15.3%. A median of day 10 from commencing TB treatment was identified as the most common day to develop a DVT. The popliteal vein was the most frequent position for a DVT.

Several statistically significant factors were identified, including a decreased ambulatory status, TB regimen and the use of anticoagulants. Only 52% of the DVTs were clinically symptomatic. The clinical evaluation for a DVT diagnosis in this study population had a sensitivity of 52.4% and a specificity of 65.3%. The positive predictive value (PPV) was 21.7%.

Of the abdominal ultrasound reports there were 75.5% (281) abnormal reports, 22.5% (n = 90) normal reports and 4.5% (n = 18) with no report.

Conclusion This body of work has shown how an effective ultrasound service can be provided at a district level TB hospital successfully administered by a trained ultrasonographer. This also facilitated a screening service to diagnose both symptomatic and asymptomatic deep vein thromboses in newly diagnosed tuberculosis patients. This study

confirmed a higher rate of DVT in newly diagnosed TB patients than has been previously seen. It also provided detail on additional risk factors. The study illustrates the poor performance of clinical signs and symptoms as a trigger for further investigation for the confirmation of a DVT. Given the frequency and impact of the embolic complications of DVT, this study provides a strong justification for further research into routine serial ultrasonic screening and/or prophylactic antithrombolytics in newly diagnosed TB patients.

As well as the DVT ultrasound scans there was the ancillary service offered by the research sonographers. This included an abdominal scan that detected abdominal pathology in 75% of the scans performed. An ultrasound scan is not pathognomonic but it does provide significant insight into the extent of some of the abdominal pathologies seen in TB patients.

The information provided from this study gives a good indication of the problem that DVTs present in this population and the complexities of the disease TB. It is hoped that the results from this study will better equip the medical team in the non-tertiary situation to be vigilant for the presence of a DVT and educate them on the usefulness of the ultrasound scan.

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GLOSSARY

AIDS	Acquired immunodeficiency syndrome
APB	Aspirate positive for TB bacilli
ART	Antiretroviral therapy
ATV	Anterior tibial vein
BMI	Body mass index
CFV	Common femoral vein
CNS	Central nervous system
CUS	Compression ultrasound
CVH	Chronic lower limb venous hypertension
DTHC	Desmond Tutu HIV Centre
DOTS	Directly observed treatment short course
DVT	Deep vein thrombosis
HIT	Heparin-induced thrombocytopaenia
HIV	Human immuno-deficiency virus
HPCSA	Health Professional Council of South Africa
IPC	Infection Prevention Control
IPT	Isoniazid preventative therapy
IRIS	Immune reconstitution inflammatory syndrome
LMWH	Low-molecular-weight heparin
MOU	Midwife obstetric unit
NGO	Non-governmental organisation
PE	Pulmonary embolus
PHC	Primary health care
POP	Popliteal vein
PTB	Pulmonary tuberculosis
PTV	Posterior tibial vein
PV	Peroneal vein
SOB	Short of breath
SFV	Superficial femoral vein
TB	Tuberculosis
UFH	Unfractionated heparin
VTD	Venous thromboembolic disease
WHO	World Health Organization

CHAPTER 1

TB, HIV, Deep Vein Thrombosis and Ultrasound

1. Introduction

It is accepted that respiratory infections raise the risk of deep vein thrombosis (DVT) and therefore increase susceptibility to a pulmonary embolism (PE) (Ambosetti et al., 2006:396). While clinicians have also been aware of DVTs in the lower extremities of patients on tuberculosis (TB) treatment (White, 1989:434), their actual incidence is considered underestimated. Clinical symptoms of a DVT are often subtle or absent, suggesting that an active screening approach to seeking confirmation of a DVT diagnosis be employed. This thesis describes the role of ultrasound as a screening tool for TB associated DVTs at a district TB hospital in the Western Cape, South Africa.

1.1.1 Epidemiology of tuberculosis

Tuberculosis (TB) is an infectious disease that is a global public-health challenge (Badri et al., 2002:2059-2064). The World Health Organization (WHO) reports that in 2011, 1.4 million people worldwide died from TB (WHO, 2012). South Africa has reported a fivefold increase in TB notification rates from 1988 to 2008 (figure 1.1) and about 1% of the South African population will develop TB each year (Bekker & Maartens, 2011:397). Worldwide South Africa has the third highest TB burden (Wood et al., 2011:111).

South Africa has the largest number of HIV-positive patients in the world (Bekker & Maartens, 2011:397) and TB is the leading cause of death in this population group (Peter & Theron, 2011:404-408). HIV-positive individuals have a 20 times higher risk of developing TB compared with HIV-negative persons (Kranzer, 2011:418). In 2009, of the total TB case load in Cape Town, the HIV positive-associated TB accounted for 44% (Wood et al., 2011:111).

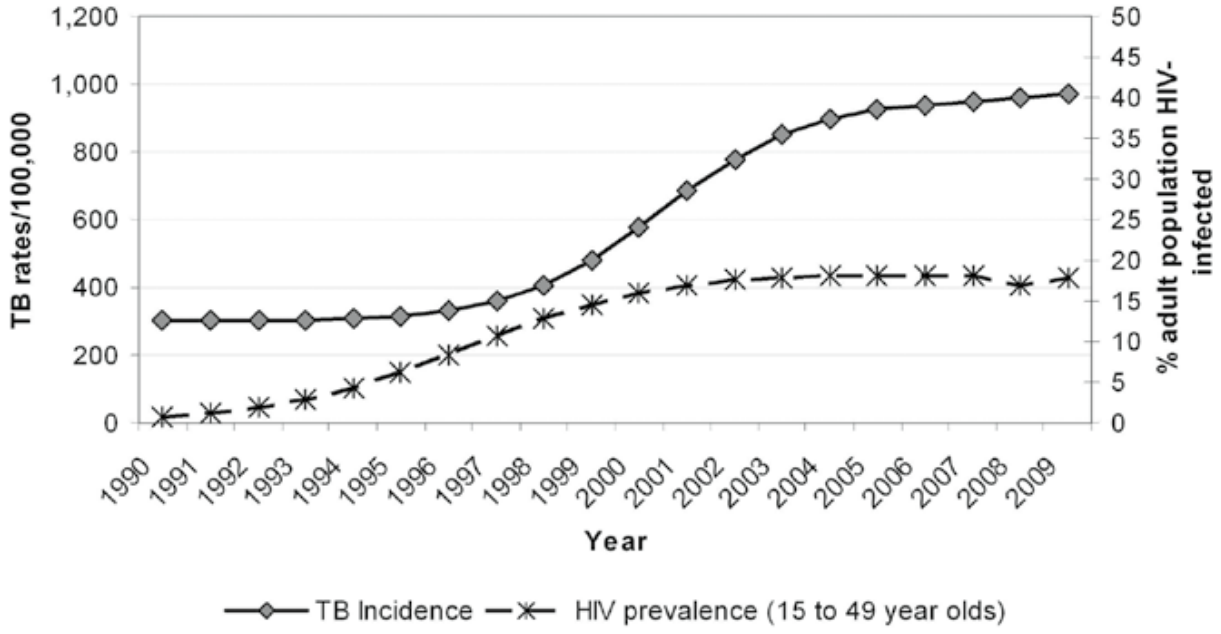


Figure 1.1 TB incidence rates and HIV prevalence in South Africa (Middelkoop, 2011:428)

1.1.2 Pathogenesis

TB or *Mycobacterium* TB (M.tb) is a droplet infection (Sasindran & Torrelles, 2011). TB is transmitted through the inhalation of infected respiratory droplets in the air. The disease is caused by the resulting infection and host response. Thus an infected individual must engage in close proximity in social interactions with an uninfected individual for transmission to occur. There are several risk factors that predispose the patient to infection. These include:

1. The degree of infectiousness of the primary infected patient.
2. The competency of the antimicrobial defence of the exposed individual.
3. The frequency of contact between the two.
4. The environment in which the contact takes place.

Approximately 10% of immune competent individuals who are infected with TB will go on to develop TB in a lifetime. The possibility of developing TB remains with the patient, but the highest risk will be in the first two years. The disease may manifest either by progression of the primary focus of infection, or by reactivation of an endogenous focus many years later. The reasons why or when the infection develops into the clinical manifestation of the disease are not clear, and are likely to be due to multiple causes. HIV-positive co-infection is a major factor in the progression and increased risk of the disease (Fraser et al., 1998: 249, 250, 251).

1.1.3 Primary and post-primary (secondary) TB infections

The progression of the disease within the host largely depends on the efficiency of the response of the host's immune system (Smith, 2003:463). When M.tb infects the respiratory tract, it encounters alveolar macrophages and is transported into the lung parenchyma where the innate and adaptive immune responses organise to create a granuloma. This is composed of macrophages, lymphocytes, dendritic cells, neutrophils and occasionally fibroblasts. There may be a necrotic centre. The granuloma acts as an immune microenviroment that limits the replication of M.tb. These granulomata are dormant and can exist over time. When active TB disease occurs, multiple granulomata in the lungs and in other systems result in the spread of tissue inflammation and necrosis. Cavitation then occurs (Diedrich & Flynn, 2011:1407-1414). Within these cavities, multiple new M.TB organisms are produced. This leads to the ongoing transmission of TB (Hunter et al., 2006:371). Early in the infection, M.tb may further spread to regional lymph nodes and haematogenous spread to other organs, resulting in extra- pulmonary TB (figure 1.2) (Fraser et al., 1998:252).

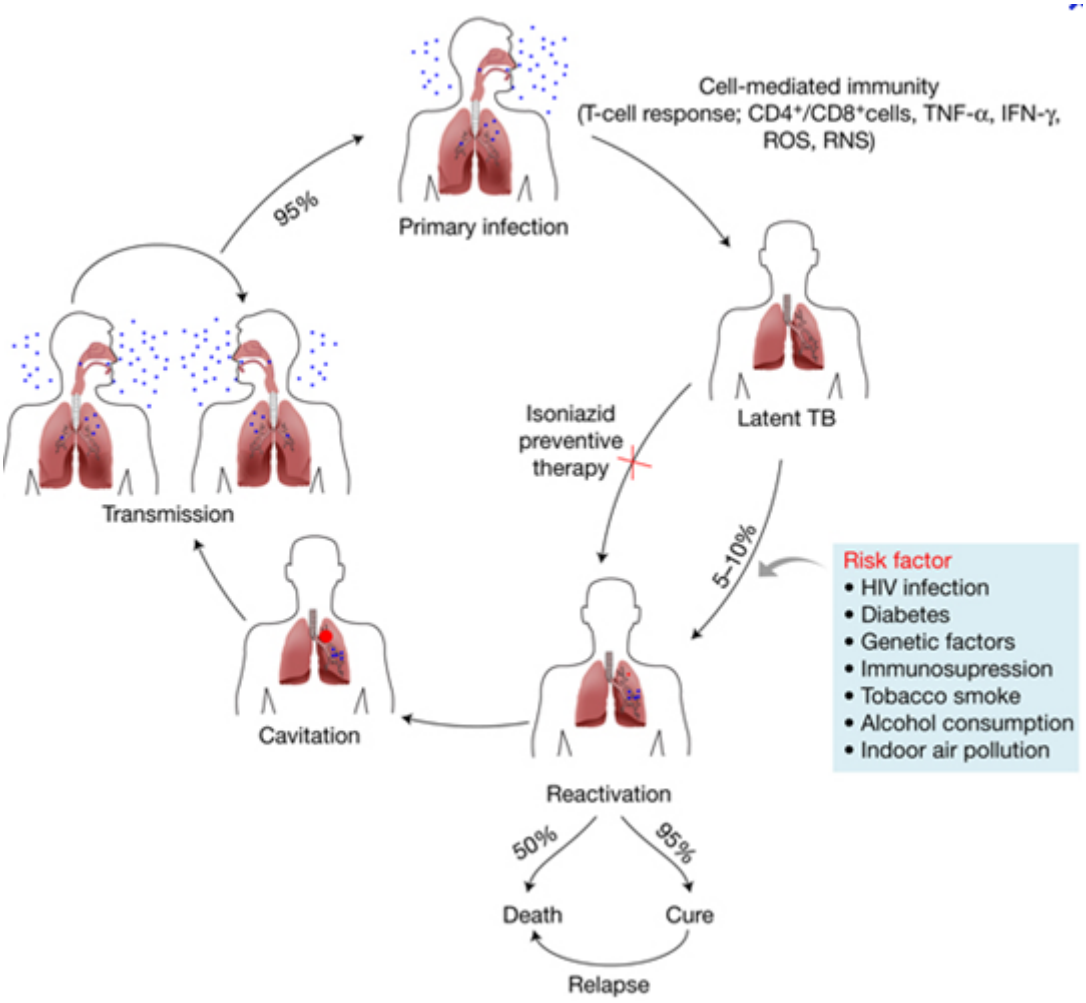


Figure 1.2 Diagram showing the life cycle and progression of tuberculosis. TB is transmitted by air and a primary infection is established. Recovery can occur by a surge of cell-mediated immunity or it can be contained inside the granuloma (latent TB). There may be no symptoms of the disease but the bacilli remain dormant within the host. Treatment at this stage can halt the progress of TB. If not treated, the M.tb bacilli may remain dormant or develop into active TB. Immune-compromising factors, for example, HIV-AIDS, diabetes, indoor air pollution and tobacco smoke can aggravate the risk of the disease's progression. Reactivation TB can be cured with drug therapy. Untreated TB or non-compliance with drug therapy can lead to the formation of TB lung lesions. The bacilli in these cavities are transmitted (via coughing) to other individuals to establish another primary infection and so the cyclical transmission continues (Kumar et al., 2011)

1.1.4 TB control

In 2005 the WHO Regional Committee for Africa declared TB an emergency in Africa. This TB emergency was considered fuelled by the dual epidemic of HIV in this region (WHO, 2005).

In South Africa the leading cause of death in HIV-positive patients is TB (Wood, 2007:S497-S499). Antiretroviral therapy (ART) plays an important role in reducing mortality and by reducing the risk of TB in these individuals. In co-infected people without ART, the fatality rates are as high as 50% (Kranzer, 2011:418). Too often the patient presents late in HIV infection with established TB disease. Effective treatment of HIV-positive patients with ART remains an important aspect of TB control (Wood, 2007:S497-S499).

1.1.5 TB Treatment therapies

Since the advent of antibiotics in 1950, a standard management of TB has evolved called Directly Observed Treatment Short course (DOTS). At the time of this study the treatment began with six months of daily treatments with rifampicin and isoniazid, supplemented with pyrazinamide and ethambutol and +/- streptomycin (depending on whether the patient was on regimen 1 or regimen 2) for the first two months. This is also known as the six-month, four-drug regimen and is the standard 'short' course treatment for TB. This drug regimen has indicated a cure and completion rate of >95% and a relapse rate of 0 – 3% in both clinical trials and routine clinic use. Most of these studies, however, have been with HIV-negative patients, and did not include children (NICE, 2011). About 5% of patients do not respond to treatment, and the primary reason for this is non-adherence to the drug therapy. The successful treatment of TB rests with the continuity (mostly self-administered) of the drugs for six months and sometimes longer (Kumar & Clark, 2009:866).

At the time of this study, the DP Marais hospital used two TB drug regimens. Regimen 1 was used for first-time TB sufferers and patients with known repeat TB infections were given regimen 2. Regimen 1 consisted of four oral drugs: ethambutol, Isoniazid, rifampicin and pyrazinamide**.** Regimen 2 included the above four drugs as well as an intramuscular injection of streptomycin.

1.1.6 TB and PHC in the Western Cape.

In the Western Cape TB is a serious problem. In Cape Town, among the HIV-negative population, there is a one in five chance of developing TB before the age of 60 and this increases in the HIV-positive population (Wood et al., 2011:100).

The TB control programme's main focus has been on the treatment and management of passively presenting TB cases. It aims to identify at least 80% of people infected with M.tb and to cure them at the first diagnosis (Wood et al., 2011:100). Mostly patients will be diagnosed at PHC and treatment can often begin at this level. Depending on the severity of the disease, they may be referred to TB specialist clinics and treated as in-patients. In the

Western Cape, there are 100 reporting units where TB can be registered. These are divided into 96 local authority clinics, two TB hospitals (The Brooklyn Chest Hospital and the DP Marais Hospital) and two correctional service facilities (Pollsmoor and Goodwood prisons). Treatment is accessed through 121 treatment points, as well as a community-based DOTS programme. This DOTS support programme is managed by three non-governmental organisations (NGOs) (Provincial Administration of the Western Cape, 2004:2). At the time this research project was undertaken (April 2010 – December 2011), access to ultrasound imaging for the identification of a DVT was not available at either the local authority clinics or the TB hospitals. Ultrasound imaging was reserved mostly for tertiary and some secondary hospitals.

1.2.1 HIV

HIV is incurable but treatable. The virus replicates in the CD4 T cells and effectively weakens cell-mediated immunity that is critical for the host's response to TB (Diedrich & Flynn, 2011:1407-1417) and resulting in increasing morbidity and mortality in HIV-infected patients (Peter & Theron, 2011:404-408).

1.2.2 Anti-retroviral therapy (ART)

Since 1995, highly active ART usage has radically reduced the mortality of HIV-positive patients (WHO, 2009). Standard therapy consists of at least three antiretroviral (ART) drugs to maximally suppress the HIV virus and allow the immune system to recover. In 2011 there were 1.79 million people receiving ART in South Africa (Johnson, 2012).

1.3 HIV and TB

South Africa is experiencing the dual epidemics of both TB and HIV. There has been a steady increase (five times) in TB since the 1980s owing to the enhanced susceptibility to TB of the large population of HIV-positive individuals (figure 1) (Peter & Theron, 2011:404). South African miners who were HIV positive were shown to be 2 – 3 times more likely to contract TB within two years of seroconversions than the HIV-negative miners (Sonnenberg, et al., 2005:150-158). In areas where TB is endemic, such as South Africa, HIV-positive patients are most likely to develop new infections, rather than a latent infection being reactivated. This has been shown in DNA fingerprinting studies (Diedrich & Flynn, 2011:1407-1417).

The clinical presentation of TB in an HIV-positive patient may be atypical, making the diagnosis difficult (Venkatesh et al., 2011:1133-1152). These patients often present when the TB infection is advanced, because an early TB diagnosis has been missed: they are often

less symptomatic than the HIV negative patient, the smear microscopy is less sensitive and the chest x-rays can show either a normal lung pattern or an atypical TB appearance, despite the presence of TB (Kranzer, 2011:418-419).

In advanced HIV it is not always possible to begin both ART and anti-TB therapy simultaneously evan though this can radically improve the survival rates (Venkatesh et al., 2011:1133-1152). Simultaneous therapies come at a cost, including drug interactions, shared drug toxicities and M.tb immune reconstitution inflammatory syndrome (IRIS) (Venkatesh et al., 2011:1133-1152).

It has recently become apparent that DOTS is insufficient to control the TB epidemic in HIV-burdened countries (Wood et al., 2011:113), and the WHO 'Stop TB' programme has evolved to help counter this. The WHO 'Stop TB' programme supports four strategies for TB control:

1. Aggressive identification of new infections and observation (active case finding).
2. Isoniazid preventative therapy (IPT).
3. Infection control measures.
4. Instituting ART (Habib, 2009:147-155).

The integration of HIV and TB services has also been strongly recommended. Successful integration of TB, HIV services and the initiation of ART is possible; however, there are a number of challenges (Howard & El-Sadr, 2010:S238-S244). There is a need at all health services for the speedy diagnosis of TB and HIV, the availability of ART, and the management of both diseases and their complications, for example, IRIS (Bekker & Wood, 2011:420-426).

1.4 Clinical consequences of TB

While most infections are pulmonary, extra-pulmonary TB is also common, especially in HIV co-infections. Extrapulmonary TB affects all the systems of the body. There are many different modes of infection, but primarily it is by haematogenous spread of pathogens from the lungs to other organs. Other forms of infection include via lymphatics from an infected lymph node, ingestion of the bacilli or by direct spread from an adjacent organ (Lazarus & Thilagar, 2007:32). Extrapulmonary TB can affect the gastrointestinal tract, urogenital tract, central nervous system (CNS), lymph nodes, and skeleton. This extra pulmonary organ involvement results in a variety of clinical presentations (Kumar & Clark, 2009:864).

Abdominal TB infections involve the entire gastro-intestinal tract, the peritoneum and the pancreatobilary system. Ultrasound, when compared to other imaging modalities e.g. CT or MRI, is considered the more economical (table1.3) and available method of assessing abdominal morbidity (Chakraborty & Brandyopadhyay, 2009:10 and Kawooya et al., 2008:62). Typical ultrasound findings include organ enlargement, multiple or focal masses, altered echogenicity or echotexture, fluid collections and abscesses. Lymph node enlargement, bowel wall thickening, free fluid and thrombosis in the retroperitoneal or intraperitoneal vessels can also be visualised. While an ultrasound scan is not pathognomonic of either TB or HIV, it is highly suggestive and provides insight into the extent of the abdominal involvement (Kawooya et al., 2008:62).

In active TB the vascular system can also respond to the acute inflammatory state manifesting as vascular thromboembolic disease (VTE) and deep vein thrombosis (DVT) (Hoffmann et al., 2010). Vascular disease is common in post-primary TB, and is often present in the pulmonary arteries and veins in the vicinity of the active M.tb infection. Symptoms of vascular disease include vasculitis and thrombosis. Rasmussen's aneurysms may also develop in the small- to medium-sized vessels adjacent to the fibrous capsule of a cavity wall. Localised dilatation occurs and if ruptured, haemoptysis and occasionally death can follow (Fraser et al., 1998: 255, 256).

1.5 Deep vein thrombosis

1.5.1 Epidemiology

Deep vein thrombosis (DVT) and pulmonary emboli (PE) fall into the group of diseases known as venous thromboembolic (VTE) disease (Veller & Pillai, 2009:306). The true incidence of venous thromboembolic disease is unknown (Lewis, 2005:946). However Veller and Pillai (2009) cite the following incidences of VTE:

- Any DVT: ~ 2/1000 person-years.
- Symptomatic non-fatal PE: ~ 0.2/1 000 person-years.
- Fatal autopsy-detected PE: ~ 0.5/1 000 person-years (Veller & Pillai, 2009:306).

Venous ulceration rate is 3/1000 and 25% of these were thought to be due to complications of a DVT. The incidence of VTE increases with age, and is more common in men than women. It is thought that at least half the VTE incidents are secondary to one or more primary condition. Most frequently these conditions are malignancy, immobilisation, surgery or major trauma, and in South Africa there is a strong relationship with HIV/AIDS (Veller &

Pillai, 2009:306). Post thrombotic syndrome (PTS) is a chronic complication of of a DVT. One year after the first DVT the incidence of PTS was 25% with 7% with severe complications (Tick et al, 2008: 2075-81), after 44 months it was as much as 43% but the severe complications were much lower 1.4%. Increased risk of PTS includes proximal DVT and recurrent ipsilateral DVTs (Stain et al,2005:2671-6)

Arguably the most serious complication of a DVT is a PE. A PE can be fatal or have serious sequelae for the surviving patient. Some PE may be asymptomatic: in the USA, 630 000 people are diagnosed each year with PE and 400 000 of these patients have a delayed or missed diagnosis for PE (Dähnert, 2007:396). This is of concern, as 10% of PEs are fatal (Kumar & Clark, 2009:784), and therefore all DVTs have the potential to be lethal. PEs are more common in women than men and more women die from PE complications yearly in the USA than die annually from breast cancer (De Azevedo Prazeres, 2009). The number of deaths from pulmonary embolism in South Africa is not widely reported, but the Medical Research Council (MRC) states that PE was the fifth cause of death from cardiovascular disease. This accounted for 2% of the deaths from cardiovascular disease in 2000 (Norman et al., 2000).

1.5.2 Pathogenesis of DVT

A thrombosis can form anywhere in the cardiovascular system, but owing to the different haemodynamics of the arterial and venous systems, the thrombi that are formed differ accordingly. Thrombi are made up of fibrin and blood cells. Arterial thrombi consist mainly of platelet aggregates joined together by strands of fibrin, and are formed where there is high blood flow. Conversely, venous thrombi form where there is slow- to- moderate blood flow, and consist of mixed platelet–fibrin thrombi. These are a combination of red cells, platelets and fibrin (Hirsh et al., 2001:2994).

A DVT can occur in any vein but is most common in the deep veins of the calf. DVT is frequently asymptomatic and because of this it is often not diagnosed until it becomes an embolus, which can have fatal consequences (Meetoo, 2010:1021-1027).

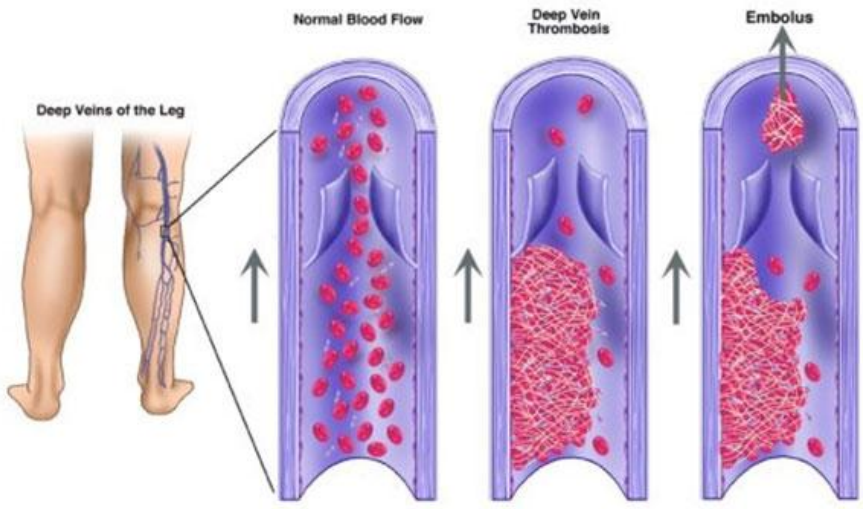


Figure 1.3 Diagram showing the formation of deep vein thrombosis (CLOTS, 2009).

A German pathologist, Rudolf Virchow (1821 – 1902), first explained the triad of risk factors for abnormal thrombus formation in the 1800s and this is still used today (Krafts, 2009). Virchow's triad describes three broad categories of risk factors that contribute to VTE disease:

1. Hypercoagulability
2. Changes in normal blood flow, for example, stasis, or turbulence
3. Damage to the vascular internal wall

This triad favours the formation of thrombus by upsetting the balance of the opposing coagulative and fibrinolytic systems (Line, 2001:90-101). The inflammation induced by M.tb infection encourages the hypercoagulable state seen in patients with PTB (Mark et al., 2009:49-51). One hypothesis on the aetiology of VTE is that patients who suffer from idiopathic VTE have a genetic predisposition that remains silent until an additional insult occurs such as immobilisation for long periods as can occur with an illness such as TB (De Azevedo Prazeres, 2009).

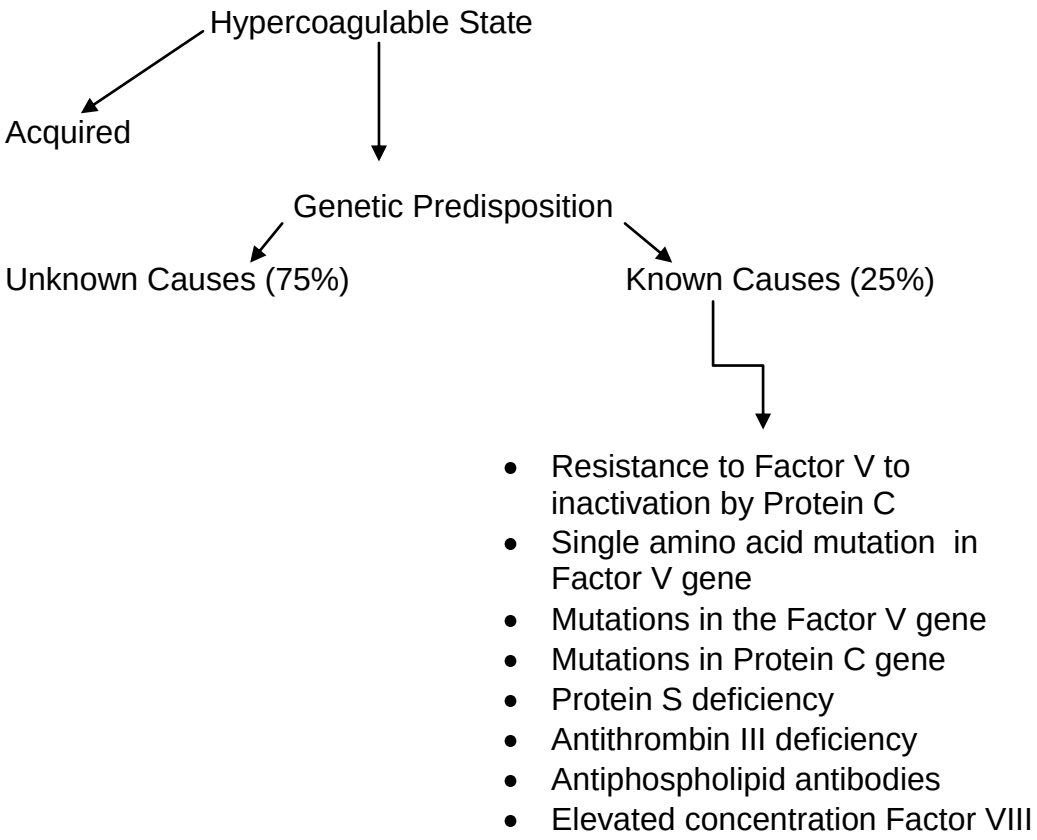


Figure 1.4 Diagram showing the causes of a Hypercoagulable state.

Currently, only 25% of these underlying inherited hypercoagulable states are known. The most common of these is the resistance of Factor V to inactivation by Protein C. Individuals with a single amino acid mutation in the Factor V gene (a mutation known as Factor V Leiden) are unable to control the clotting process correctly, and have an increased tendency to form abnormal blood thrombus (De Azevedo Prazeres, 2009). Other hypercoagulable states associated with venous thrombosis include other mutations in the Factor V gene, mutations in the Protein C gene, Protein S deficiency, antithrombin III deficiency, antiphospholipid antibodies, and an elevated concentration of Factor VIII (De Azevedo Prazeres, 2009). If the TB patient also suffered from one of these underlying inherited hypercoagulable states, it would increase the chances of VTE.

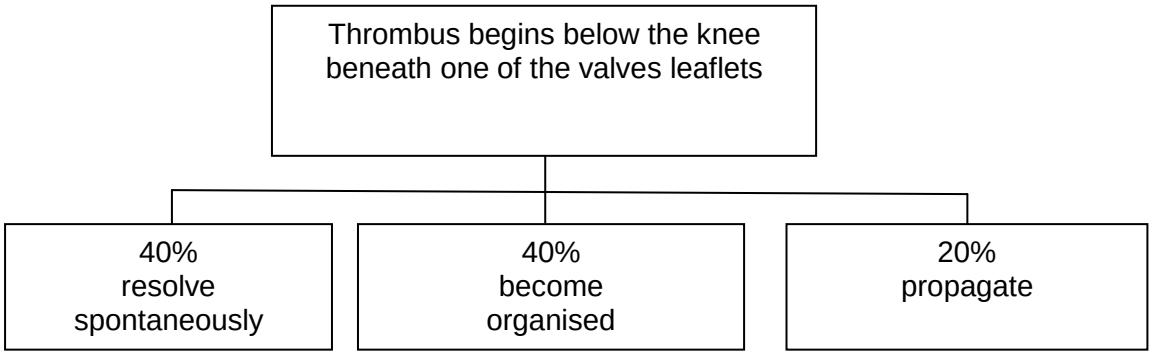


Figure 1.5 The formation of thrombus below the knee and how it develops (Andrews & Fleischer, 2005:213-225)

1.5.3 Risk factors for DVT

1.5.3.1 TB and DVT

DVTs have been described as a complication of the treatment of TB. This is thought to be due to the inflammation caused by infection, and the haemostatic changes that produce a hypercoagulable state (Ahuja et al., 2007:38). While rifampicin is effective in killing the M.tb infection, it enhances the inflammatory effect, probably increasing the thromboembolic complications (White, 1989:434). This occurs because the elevated fibrinogen with damaged fibrinolysis, together with a reduced level of antithrombin III and reactive thrombocytosis, creates a situation that encourages the development of a DVT in PTB. However, it was found that while the fibrinogen levels in all patients rose within the first fortnight of treatment, all the levels corrected within 12 weeks (Robson et al., 1996:943-49). Added to this, TB patients may reduce their activity owing to the state of their disease (Ahuja et al., 2007:38).

Table 1.1 Studies showing the VTE incidence in a TB population

STUDY	YEAR	Place	Pro/Retrospective	Sample Size	VTE INCIDENCE IN TB POPULATION	Ref
WHITE	1989	Cape Town	Retrospective	7542	3.40%	*Lancet*, 344(8660):454-455
PETERSEN et al.	2001	Cape Town	Retrospective	Not available	8%	Poster at the SA ID Conference, Cape Town. December 2001
AMBROSETTI et al.	2006	Italy	Prospective	1237	0.60%	Respiration: 73(3):396

Table 1.1 shows the studies that looked at VTE incidences in TB populations. Both White and Petersen et al. were retrospective studies conducted at a TB hospital in Cape Town. These studies reviewed hospital folders for the DVT incidence that was confirmed with a venogram or a compression ultrasound examination (CUS) (White, 1989:434-435; Petersen et al., 2001). Ambrosetti's study was based in Italy and the data were prospectively collected from 46 TB units throughout the country. The sample group was determined by the willingness of the units to objectively document the VTE events (Ambrosetti et al., 2006:396). All three of these studies were based on clinical symptoms of a DVT before confirmation was obtained with imaging.

1.5.3.2 HIV and DVT

There is evidence to suggest patients infected with HIV may also more commonly experience a hypercoagulable state (Malek et al., 2011:278-282). HIV also causes increased inflammation, leading to abnormalities in the blood-clotting process. One study in the USA assessed the blood samples of 94 women as part of the Women's Interagency HIV study. Of the 94 women, 34 had a history of clinical AIDS, 11 had CD4 <200 but no AIDS symptoms, and the remaining 49 were HIV positive but asymptomatic. A group of 50 HIV-negative women were used as a comparison group. By comparing protein S and factor VIII levels in these patients, the researchers demonstrated a connection between the changes in the blood clotting factors and advancing HIV disease and placing the HIV-positive patient at risk of a DVT and thromboembolic sequelae (Legge, 2006). Over a nine-year period (after age adjustment), the HIV-positive patient had an increase in the odds ratio of 43% for developing a PE, a 10% increase of developing a DVT and a 40% increase of developing both a DVT and a PE (Malek et al., 2011:278-282). Clinically detected VTE is more likely to be observed in HIV-positive patients than in the HIV-negative population (Malek et al., 2011:278-282).

Clotting factor abnormalities are seen in HIV positive infections. Protein S and factor VIII are two components associated with clotting. Protein S levels were found to be highest in the HIV-negative patients, less in asymptomatic HIV-positive patients, even lower in the HIV-positive patients (but with no AIDS symptoms) and the lowest in the patients with clinical AIDS. The opposite association was seen with factor VIII. This demonstrates a connection between the changes in the blood-clotting factors and advancing HIV disease (Legge, 2006).

1.5.3.3 Other risk factors for DVT

There are a number of other risk factors for the development of a DVT, including active malignancy, recent trauma or surgery, pregnancy, hormone therapy, and a history of thrombophilia (Pennell et al., 2008). Immobilisation and an older age group are also factors thought to contribute to DVT development (Binder et al., 2009). A study reported that in elderly patients (aged greater than 65 years) bed rest was the most common risk factor for a DVT and was diagnosed in 15 – 50% of the patients (Masotti et al., 2008). Smoking (Goldhaber & Morrison, 2002:1437) and obesity are also regarded as risk factors for a VTE (obese is when the body mass index (BMI) is greater than 30) (Severinsen et al., 2009: 1297-1303).

In 1992 THRIFT (thromboembolic risk factors) divided patients into different risk groups depending on their illness. This was done to help manage the diseases and risk for developing a thrombosis. Each risk category had a recommended prophylaxis regimen to help reduce the risk of thrombosis formation. The moderate risk group included patients with

major medical illness such as lung disease, where the extent of the disease had caused a reduction in their mobility. Patients with advanced TB fall into this group. Patients in this moderate risk group have a 10 – 40% chance of developing a DVT and a 0.1 – 1% chance of a fatal PE (THRIFT,1992:567-74).

1.6 DVT signs and symptoms

While VTE disease is thought to be fairly common, the clinical signs and symptoms are often unclear and this makes the diagnosis difficult.

The symptoms of a DVT include pain in the calf, swelling, redness, and engorged superficial veins. The calf may be warm with ankle oedema. Pain in the calf on dorsi-flexion – known as Homan's sign – can also be present (Kumar & Clark, 2009:810). The initial pain in the calf persists and can be described as a 'pulling sensation' at the insertion of the inferior calf muscles into the posterior portion of the lower leg (De Azevedo Prazeres, 2009). With a DVT, the thrombosis will form in the vein and the inflammation of the vein wall is secondary to this. Thrombosis that is present in the iliofemoral region can cause severe pain, but with few other physical signs apart from some swelling of the thigh and or ankle oedema (Kumar & Clark, 2009:810).The signs and symptoms of a DVT are due to venous outflow obstruction, vascular inflammation or pulmonary embolisation (Line, 2001:90-101). The severity of symptoms of local obstruction depends on the importance of the vessel that is obstructed (Hirsh et al., 2001:2994).

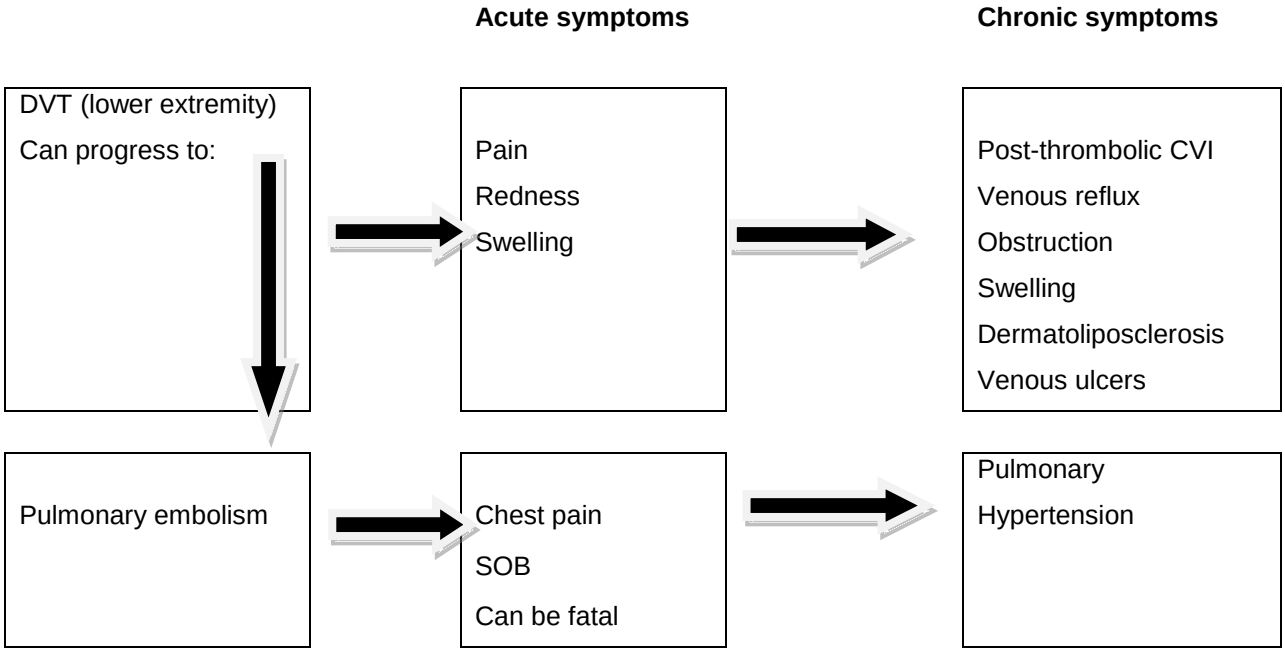
The different symptoms of a DVT however, may not all be present or can be completely absent. Thus, the clinical diagnosis is unreliable and other diagnostics are used to confirm the presence of a DVT (Fraser & Anderson, 2004:279). Furthermore, approximately 70% of patients referred for a clinically suspected DVT are not confirmed with objective tests such as an ultrasound scan. Of the 30% with a confirmed DVT, about 85% have proximal thrombosis and in the rest, the thrombosis is confined to the calf (Line, 2001:90-101). A palpable thrombosed vein is usually due to superficial thrombophlebitis, which is not typically linked with VTE disease (Lewis, 2005:946).

1.7 Treatment of a DVT

There are a number of choices for both the prevention and treatment of DVTs. These include anticoagulation therapies such as low-molecular-weight heparin (LMWH) (both short- and long-term) and oral anticoagulants (both short- and long-term), thrombolysis, vena cava filters, compression stockings, and warfarin (McManus et al., 2011:ii).

The main aim of the treatment of a DVT is to prevent the formation of a pulmonary embolism. There is the possibility that as many as 5 – 15% of patients with untreated DVT can die from a PE (McManus et al., 2011:ii). It is therefore imperative and can be life saving for patients with an identified thrombus above the knee to begin anticoagulation therapy immediately. Anticoagulation is recommended for at least six weeks to prevent proximal extension of the thrombosis (Kumar & Clark, 2009:810). Heparin is the most common choice of drug for the treatment of a DVT (Algahtani:165-8). Heparin can inactivate thrombin and by doing so, not only prevents the formation of fibrin, but reduces the thrombin-induced activation of factor V and factor VIII (Hirsh et al., 2001:2994). LMWH is a safe and effective choice of drug for the acute treatment of DVT and can be used in an outpatient setting (Bellosta et al., 2007:316).

PE and DVT are responsible for significant morbidity and mortality. In the acute setting a PE may be fatal; however the secondary outcomes can result in long-term pulmonary hypertension. The secondary changes from a DVT can be post-thrombotic chronic venous insufficiency also known as post-phlebitic chronic lower-limb venous hypertension (CVH). This occurs because the DVT causes deep vein reflux and/or impedance to the venous flow. The result of this is limb swelling, skin changes (dermatoliposclerosis) and venous ulceration. These chronic sequelae can be debilitating. With quick, appropriate therapy, both the primary and secondary conditions can be minimised (Veller & Pillai, 2009:306).



SOB – short of breath CVI – chronic venous incompetence

Figure 1.6 Flow chart showing the acute and chronic symptoms of a DVT and PE

1.8 Prevention of a DVT

1.8.1 Use of prophylaxis

VTE prophylaxis is underutilised in medical patients in spite of the frequent occurrence of DVT and the availability of guidelines. One reason for prophylaxis is that early detection of a DVT is difficult because it is often silent and has few or no apparent clinical symptoms. Another reason is that the embolic sequelae are serious (Nutescu, 2007:S5).

It is accepted internationally that the prevention of venous thromboembolism in patients who are admitted to hospital is a priority in order to improve patient safety (Wilbur et al., 2011) and reduce the high cost associated with the treatment of thromboembolic disease (Pineo & Hull, 2009:289-500). Low-dose subcutaneous unfractionated heparin (UFH) and low-molecular-weight heparins (LMWH) are successful at reducing the risk of a DVT (Själander et al., 2008:52-56) and reduce the risk of a fatal pulmonary embolism by 60 – 70%. Seriously ill medical patients who are at risk of venous thrombosis can benefit from low-dose heparin, and it has been shown to reduce in-hospital mortality by 31% in patients over the age of 40 (Hirsh et al., 2001:2994). At the time of this study there were no guidelines for TB-related DVT prophylaxis. The DP Marais Hospital, the site of this study, has an in-house policy regarding the use of anticoagulants as a prophylaxis to prevent DVTs. This evolved because of the clinical burden and is an ad hoc application used at the discretion of the resident clinician as the disease worsens and mobility decreases. Prophylaxis is begun when the patient's mobility reduces so that at least 50% of the day time is spent in bed.

1.8.2 Risks related to treatment with anticoagulants and heparin in particular

Although heparin therapies are generally considered to be safe and effective, adverse reactions to treatment such as heparin-induced thrombocytopaenia (HIT) can occur. HIT is an antibody-mediated adverse reaction to heparin (Hirsh et al., 2001:2994). It is caused by the appearance of antibodies that trigger platelets in the presence of heparin (Ahmed et al., 2007:575). HIT is a serious complication of heparin therapy and has a high rate of morbidity and mortality. Approximately 8% of heparinised patients will develop the antibody associated with HIT, and 1 – 5% will develop HIT with thrombocytopaenia. Approximately one-third will have an associated thrombus (Franchini, 2005). The resulting thrombus may be either arterial or venous, and can be diagnosed clinically based on serological features (Hirsh et al., 2001:2994). HIT is more common in surgical patients than in medical patients. It is also more common in patients who are administered UFH rather than LMWH (Franchini, 2005).

Despite the possibility of thrombocytopaenia, bleeding problems are rare. However, the risk of haemorrhage must be considered against the significant risk of a PE. The choice of anticoagulant treatment revolves around inhibiting thrombin formation or direct thrombin inhibition. Once the platelet count has returned to normal range, then warfarin can be used (Ahmed et al., 2007:575). Suitable non-heparin options for anticoagulation include danaparoid, lepirudin and argatroban (Franchini, 2005). Anticoagulants must therefore be used with care and insight (Cundiff et al., 2010:31).

While the bleeding problems are rare, patients with PTB are at risk of haemoptysis. In South African hospitals where there is a high incidence of PTB, life-threatening haemoptysis is a common clinical problem (Corr, 2003). The standard treatment for these patients is bronchial artery embolisation. Repeat episodes of haemoptysis are, however, common and are associated with high mortality (Van der Heuvel et al., 2007).

A study in Hong Kong looked at all the admissions for haemoptysis over a six-year period. About one-tenth (251 patients) of the admissions were considered life threatening. All of them were due to PTB or bronchiectasis and were treated with bronchial artery embolisation (Chan et al., 2009:1167-1173).

1.9 The importance of diagnosis

If undetected, a DVT can progress to a potentially life-threatening PE. For this reason it is very important that diagnosis of a DVT is made so that management can begin as soon as possible. Anticoagulation therapy is the standard treatment for this condition, but this, too, can have fatal complications. Consequently it is of great importance to accurately diagnose or rule out the presence of a DVT in patients presenting with any of the DVT symptoms (Madhusudhana et al., 2009). Patients who have a proximal thrombosis who are ineffectively treated run the risk of a 47% recurrence in the three months following treatment. It is also very difficult to diagnose a recurrent DVT, as only 20 – 30% of these patients will actually have the disease. For the rest the symptoms are due to chronic venous insufficiency or one of the many other causes of lower leg pain. However, with the correct diagnosis and treatment for the DVT there will be a less than 2% clinical detectable recurrence (Line, 2001: 90-101). Recurrent DVTs can mimic other conditions, making diagnosis difficult. Clinically, the differential diagnosis could include ruptured popliteal synovial cyst (Baker's cyst), injured calf muscle or tendon, muscle cramps, referred pain from a lower back injury, or joint disease (De Azevedo Prazeres, 2009).

The risk-benefit ratio will help decide whether the benefit of the ultrasound will outweigh the risk of prophylactic use of anticoagulants. This was not investigated in this study but would

involve the use of anticoagulants as prophylaxis with the risk of haemorrhage on one side versus the use of ultrasound with correct diagnosis on the other. A missed diagnosis (with no ultrasound examination) may increase the risk of a PE, therefore increasing morbidity and mortality.

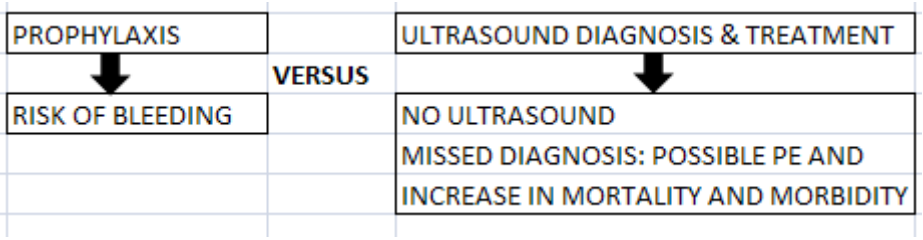


Figure 1.7 The risk benefit ratio

1.10 Diagnosis of a DVT

Imaging plays an important role in the diagnosis of a DVT. The clinical symptoms of a DVT are unreliable and while the D-dimer blood test and the Wells Score are helpful, they are not definitive. The D-dimer also has the potential for false negative results. The sensitivity and specificity of the D-dimer is 82.6% and 70% respectively (Anderson et al., 2003:645-651).

The Wells score (table 1.2) estimates the probability of a DVT. Used in isolation, it cannot rule out a DVT in situations of a low probability score or confirm a DVT when the probability score is high.

Table 1.2 Example of a Wells Score Chart (Wells et al., 2003)

WELLS SCORE **1 POINT EACH FOR:**	
Active cancer	
Paralysis, paresis, recent plaster immobilisation of lower limb	
Recently bedridden for >3 days or major surgery in past 4 weeks	
Localised tenderness along distribution of deep venous system	
Entire leg swollen	
Calf swelling >3 cm compared to asymptomatic leg	
Pitting oedema	
Collateral superficial veins	
–2 POINTS FOR:	
Alternative diagnosis as likely or more likely than that of DV T	
PROBABILITY:	
High	>3 points
Intermediate	1 or 2 points
Low	<0 points

In primary or secondary health care settings when the D-dimer is negative (i.e. <500ng/ml), the Wells score is low or moderate, and the patients are considered very low risk, then these two tests can safely rule out a DVT. However, in high-risk patients this efficiency is a lot lower (Toll et al., 2006:3-8). Today it is commonly agreed that compression ultrasound (CUS) is the modality of choice for detecting a DVT. In the past contrast venography, which has 89% sensitivity and 97% specificity for diagnosing DVTs, has been regarded as the gold standard for DVT diagnosis. However, general opinion has changed owing to the invasive nature of this test and the associated risk factors, including postvenography phlebitis, contrast media adverse reaction, contrast material-induced skin slough, and contrast-induced nephropathy (Dähnert, 2007:396). The exposure to ionising radiation presents an additional risk to the patient (table 1.3). CUS has none of the above risk factors, and with a similar sensitivity and specificity it is now accepted as the primary imaging of choice for DVT diagnosis.

Computer tomography (CT) is currently considered the gold standard for PE diagnosis and there is a limited role for magnetic resonance imaging (MRI) in this regard (Krüger et al., 2008). It is important to note that ultrasound has no role to play in the detection of a PE.

1.11 Ultrasound

The ultrasound examination is a non-invasive useful diagnostic tool. There have been many studies that have provided reassuring evidence that ultrasound imaging is not harmful to adults, children, the human foetus or embryo. The British Medical Ultrasound Society considers ultrasound imaging to be safe when performed carefully, for a clear medical reason, by properly trained professionals using well-maintained equipment. Like other types of medical imaging, all unnecessary exposure to the human body should be avoided (British Medical Ultrasound Society, 2011).

There are different methods of imaging the peripheral veins, and cost and accuracy are key considerations. The following comparisons of costs are based on the recommendations of the Radiology Society of South Africa (RSSA) and the Department of Health (table 1.3). Costs do fluctuate slightly owing to the changing price of the consumables; however, this base price usually remains stable.

Table 1.3 Comparison between ultrasound, venogram, CT and MRA

Imaging modality	Cost per examination[1]	Sensitivity for DVT diagnosis*	Specificity for DVT diagnosis*	Ionising radiation	Contrast media (risk of adverse reactions)	Equipment portability
Ultrasound DVT Exam	R 1,292.20	88-100%[2]	92-100%[2]	NO	NO	YES
Venogram	R 6,100.00	89%[2]	97%[2]	YES	YES	NO
CT angiogram (with delay for venous phase)	R 8,500.00	71-100%[3]	93-100%[3]	YES	YES	NO
MRA	R 9,000.00	91%[4]	94%[4]	NO	YES	NO

*(*Figures may vary depending on the study.)*

[1] *Current suggested pricing for imaging the peripheral veins quoted in South African ra mmnnds.*

[2] *Sensitivity and specificity from Dähnert (2007).*

[3] *Sensitivity and specificity fromThomas et al. (2008).*

[4] *Sensitivity and specificity from Sampson et al. (2007).*

Ultrasound is the most cost effective when compared to other medical imaging modalities (table 1.3). This, coupled with very similar comparatives between sensitivity and specificity, the lack of ionising radiation, and the need for contrast media together with the usefulness of portability, makes the DVT ultrasound examination the modality of choice. What should also be considered is the large radiation dose needed for CT examinations and the risk of an adverse contrast reaction to the use of contrast media. Contrast media are not used with a DVT CUS examination.

With asymptomatic patients the performance of all the radiological tests are not as good as when the patient has symptoms. The ultrasound examination does not replace the clinical examination, but should be seen as an important adjunct in the diagnosis (Goodacre et al., 2006,iii -iv).

1.12 Ultrasound diagnosis of DVT

Compression ultrasound with duplex and colour sonography is at present the modality of choice for the diagnosis of a DVT, particularly with proximal DVTs. Isolated calf vein thrombosis does not have a significant adverse outcome in the short term, and so recommendations are the calf should only be done in patients with localised signs or symptoms. However, high-risk population groups who may be asymptomatic may benefit from duplex and colour sonography screening that includes the calf area (Gaitini, 2006:289-297). Commonly a symptomatic patient will present with unilateral symptoms of a DVT. In hospitalised patients there is a high incidence of asymptomatic contra-lateral DVTs, suggesting that these patients should always have a bilateral study. However, outpatients with unilateral symptoms and no risk factors (especially active malignancy) can safely have a unilateral DVT examination performed (Pennell et al., 2008: 413-16).

With B-mode ultrasound scanning, the distended, non-compressible vein with echogenic thrombus within the lumen is clearly visualised (Grimm & Manson, 2011), making the diagnosis of a DVT easy (figure 1.7). With the addition of colour Doppler, the absence of the dynamic movement of the blood is well seen in the image (Figure 1.8). Acute thrombus may appear hypoechoic, however the vein will also be distended and non-compressible.

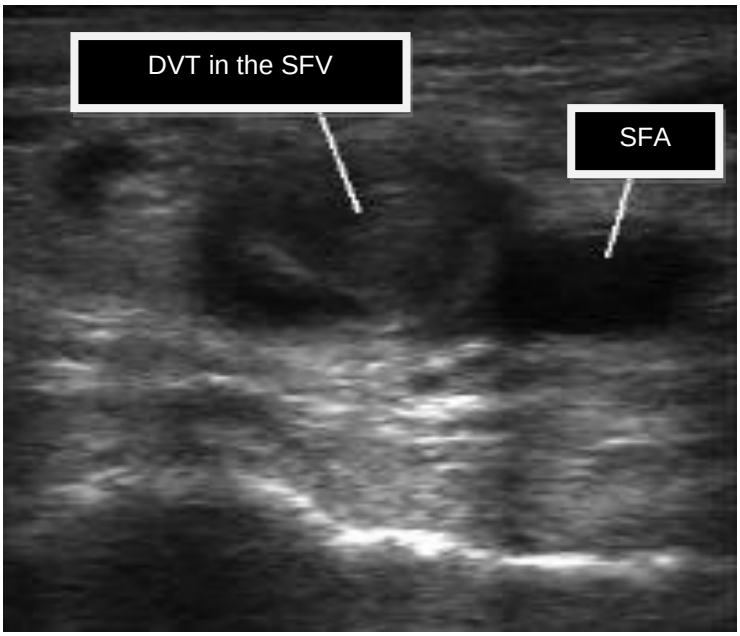


Figure 1.8 A B-mode ultrasound Image of a DVT in the transverse plane of the superficial femoral vein (SFV) (Grimm & Manson, 2011). The SFV is distended, non-compressible and filled with echogenic thrombus that appears grey on the ultrasound image. The superficial femoral artery SFA on the right of the image appears anechoic (black) on the ultrasound image.

Figure 1.9 A colour Doppler ultrasound, transverse plane image of the popliteal vessels. A DVT is visualsised in the left popliteal vein with absent colour flow (see the right side of the above figure 1.8). The right popliteal vessels (on the left side of the above figure) show normal colour Doppler flow in both the popliteal vein and artery. (Ultrasound Image Gallery, 2012)

The modality of choice to diagnose a PE is a CT pulmonary embolism study, and ultrasound does not have a role to play in this diagnosis.

1.13 Rationale for the study

Ultrasound has until recently been regarded as a sophisticated examination reserved for tertiary health care; however, with its low cost, portability and lack of ionising radiation, it may be ideally suited to primary health care (table 1.3). In the past, the performing and reporting of ultrasound examinations fell within the domain of the specialist radiologist, making it an expensive procedure and unlikely to occur at primary health care (PHC) where most TB is diagnosed and managed. Currently a Health Professional Council of South Africa (HPCSA) registered sonographer is qualified to offer an ultrasound service that would benefit the TB and HIV-positive patient with both vascular and abdominal complications.

In South Africa, the present training of sonographers to perform and report on ultrasound examinations increases accessibility to this imaging resource, allowing ultrasound imaging to be considered as an appropriate modality for PHC. This task shifting (for aiding with pregnancy management) from doctor to sonographer and from tertiary to PHC has proved successful in antenatal clinics. At present there are sonographers who competently provide

an ultrasound service to PHC within the midwifery obstetric units (MOU) in the Western Cape.

1.14. This study

A DVT is a relatively common complication of the treatment of TB and an ultrasound scan is the modality of choice to make the DVT diagnosis. This study explored a sonographer-run ultrasound service to screen for the presence of DVTs at a busy TB district hospital in the Western Cape, South Africa, in order to assess both the feasibility and usefulness of this service.

Two previous studies detected a DVT incidence in this population of 3.4% (White, 1989:434) and 8% (Petersen et al., 2001). Both these studies relied on clinical symptoms to alert the clinician to the presence of a DVT. This study, however, actively searched for thrombosis with routine ultrasound imaging to ascertain the DVT incidence prior to the onset of clinical symptoms.

By instituting four routine DVT CUS of the lower extremities over a 15-week period, the typical onset of the DVT could be established. This study attempted to identify risk factors for DVT by recoding the occurrence of smoking, HIV status, mobility and BMI among the participants. The location of the DVT within the lower leg was documented to assist with the suggestion of an ultrasound protocol for future DVT scans when assessing TB patients.

CHAPTER 2

Methodology and Research Design

2.1 Aim, hypotheses and objectives

The aim was to assess the feasibility of an ultrasound diagnosis of deep vein thrombosis (DVT) by sonographers in tuberculous (TB) patients in a TB hospital.

It was hypothesised that: 'Doppler and compression ultrasound can detect deep vein thrombosis in the lower limbs of the participants on TB treatment before clinical symptoms present in patients in a district health care, TB hospital'.

The objectives were:

1. To establish the incidence of DVTs in the study population.
2. To identify the onset of DVTs in participants on TB medication from time of beginning treatment.
3. To establish the risk factors for DVT such as smoking, human immune virus (HIV) status, mobility and body mass index (BMI).
4. To determine the most common locations of the DVTs within the lower extremity.
5. To suggest a DVT ultrasound scanning protocol for TB patients.

An additional objective was to assess the utility of an ultrasound service operated by sonographers to detect an abnormal abdominal ultrasound scan in TB patients.

This study was a prospective, longitudinal observational study. The accrual target comprised 400 participants over a 20-month period from March 2010 to September 2011. The participants all received an initial DVT ultrasound that included Doppler and compression ultrasound (CUS) and thereafter received regular DVT ultrasound examinations over a period of time for up to 14 weeks.

2.2 Setting

The setting of this study was the DP Marais Hospital, a dedicated, district TB hospital in the southern suburbs of Cape Town. Most TB medication in the Western Cape is managed in outpatient settings, largely by nurses at primary health care (PHC) level within the national TB programme which embraces a community-based, directly observed treatment short course (DOTS) approach (PAWC, 2004:2). This study was conducted among in-patients of

the DP Marais Hospital; this hospital is one of two long-term TB treatment facilities in Cape Town. Patients are referred from either PHC, secondary health care or tertiary heath care to this hospital for care if they are considered inappropriate for ambulatory treatment, for example: if they are too ill to manage as an outpatient, do not ahere to the TB medication, suffer from drug toxicities or TB complications, have social problems such as alcohol or drug abuse which may interfere with treatment, or have HIV-related complications. Patients with multidrug resistance TB are also hospitalised and treated at this hospital, although these patients were not included in this study.

2.2.1 Study site

DP Marais Hospital is a 250-bed, dedicated, district TB hospital, which admits approximately 1000 adult TB cases annually. Patients are commonly referred for longer-term care when TB medication has already commenced. Any other co-morbid conditions are assessed and treated. The patients admitted to DP Marais hospital may complete the required 6 – 8 months of treatment with a cure discharge, or their admission may only be from a few days to several months. In these cases they would be considered 'down', referring to ambulatory care if the medical or social admission reason has been resolved, or 'up', referring to more specialised care if indicated. In keeping with the DP Marais' status, prior to this study, this hospital had no onsite imaging service. Ultrasound scans needed to confirm a diagnosis of a DVT were only available about 7km from this hospital at a regional hospital. This meant that patients who were thought to be clinically symptomatic for a DVT had to be transported, often with a medically trained escort, to a radiological department several kilometres away, with inherent human resources implications and risk to the patient. As many of these patients were infectious adequate infection prevention control (IPC) measures have to be in place to minimise the danger of infecting a wider population.

For the purpose of this study an ultrasound machine was obtained and set up in a room with a wash basin within the clinic area of the hospital. IPC in the ultrasound room included the wearing of I 95 face masks, the use of disposable non-sterile latex gloves, open windows, an electric fan (positioned in front of the window and directed to the internal door) and access to the disinfectant spray. This was in keeping with the DP Marais IPC policy. Each week the ultrasound machine and cables were cleaned with a disinfectant spray (provided by D P Marais hospital). The ultrasound probes were wiped between patients and a special cleaning spray used (T-spray). The sonographer changed gloves, washed and sprayed hands between patients. A new I 95-face masked was used each week. The face masks, gloves and disinfectant spary were used by all the staff involed in the study.

The ultrasound service was provided by the principal researcher (a trained sonographer), assisted by a second trained sonographer. This study was supported by a study nurse and the service of an additional porter.

2.3 Study population

The sample size calculation took into consideration the estimated incidence of 3.4% (White, 1989:434), an acceptable margin of error of 5% (standard value of 0.05) and a confidence level of 95% (standard value of 1.96).

The sample size was calculated using the formula:

$n = [z^2 p (1-p)] / e^2$

P(z) = 97.5%

p = 0.6

z = 1.9600

e = 0.05

n = sample size

p =incidence/prevalence estimate

z = degree of confidence

e = maximum tolerable error for the prevalence estimate

A DVT incidence of 3.4% (White.1989:434) was used, and in order to achieve an 80% power, a sample size of 400 was calculated.

The desired sample size of 400 participants was recruited.

Each day the study nurse assessed the hospital's database to identify the new admissions of TB patients. Data documentation at this point included:

- Reference number
- Age
- Sex
- Ward
- The date of the start of TB medication

For this study the participants had to have started TB medication but had had no more than three weeks or 21 days of treatment. This was chosen as earlier studies have shown the

common day for the onset of the DVT to be day 17 – 20 from starting TB medication (Petersen et al., 2001; Ambrosetti, 2006). The multidrug-resistant (MDR) TB patients were excluded by the nurse since MDR TB is resistant to rifampicin and isoniazid, so these are not generally used in the treatment; instead a variety of drugs and drug combinations are used. In order to reduce the confounders, the MDR TB patients were excluded. Secondly, MDR TB patients were excluded to limit the exposure of the research sonographers and study staff to this infectious disease.

Each consecutive patient was then visited by the nurse in the ward and information regarding the inclusion and exclusion criteria (see below) was gained verbally from the patient and from the patient's medical notes within the bedside folder. The eligible patients were invited to participate in the study and informed consent was obtained. This was continued until the calculated sample size of 400 participants was reached.

2.3.1 Inclusion and exclusion criteria

Inclusion criteria included the following patients:

- Those who were part of the in-patient population of this hospital.
- Those aged 18 – 90 years.
- Those who had a definitive diagnosis of TB – by smear, culture, aspirate or biopsy that was positive for TB bacilli (APB) and/or a chest x-ray that was suspicious for TB. (Suspicion of extra-pulmonary TB was usually confirmed with an abnormal result from an abdominal ultrasound or CT scan report.)
- Those who had started TB medication but had had no more than 3 weeks or 21 days of treatment.

Exclusion criteria included patients who:

- failed to give or were incapable of giving informed consent for the study;
- had not been tested for HIV or had refused HIV testing;
- had already had a DVT or PE diagnosed;
- were participating in another simultaneous trial that might have influenced this study in some way;
- had been receiving TB medication for longer than three weeks;
- had been diagnosed with MDR TB; and
- had been admitted with a plan of a short stay at the hospital, that is, less than the 15 weeks of this study.

2.3.2 Recruitment

Recruitment included all admitted to the DP Marais Hospital over the study period. Some patients were eligible, but did not participate in the study owing to their transfer to another hospital, absconding, refusing to sign consent, or death. If the patient was then readmitted, they were not screened again to avoid duplication. The rest of the admissions were screened, deemed eligible, invited to participate, and signed informed consent.

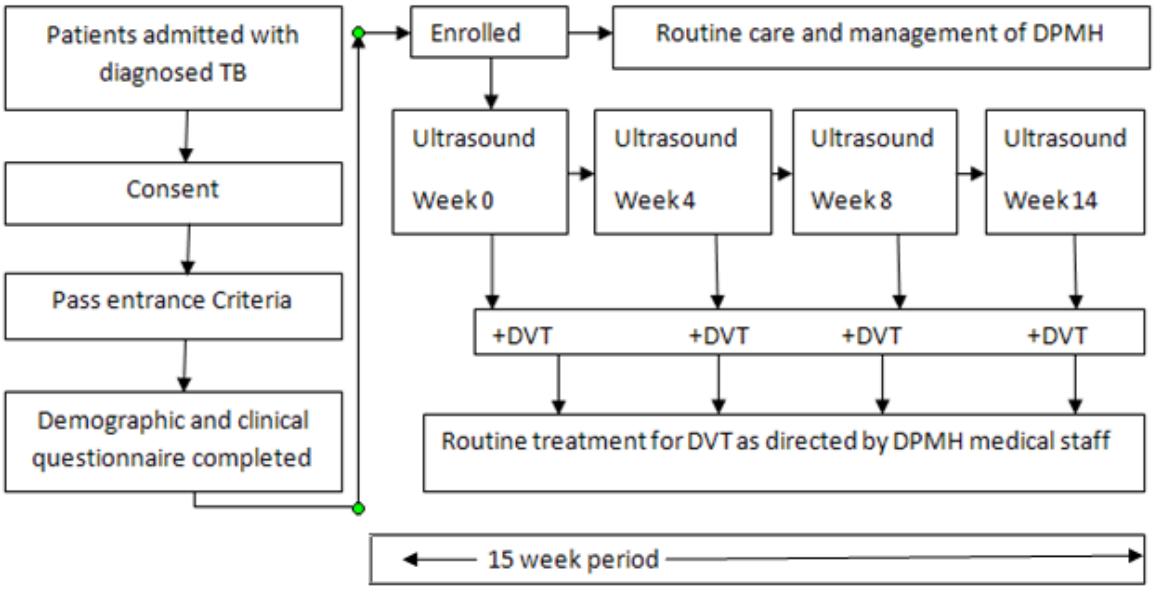


Figure 2.1 Study schematic. The above schematic shows, on the left, how the patients entered the study. Once enrolled, the initial DVT examinations (which included CUS, Doppler and an abdominal ultrasound) were performed at week 0; the regular CUS (DVT examinations) were performed at weeks 4, 8 and 14. These are shown with the routine hospital care of the participant, either with or without the diagnosis of a DVT, running parallel to the 15-week study.

2.4 Study procedures

2.4.1 Enrolment visit: – week 0 and first ultrasound examination

The patient's eligibility was determined from the patient's medical notes by the study nurse. If the patient met the inclusion criteria, the patient would then be approached and the study nurse would obtain informed consent in the appropriate language (Appendix A: Informed Consent). The medical team were notified of the patient's participation in the study. Copies of the signed consent form were kept in a locked cupboard with other confidential study documentation.

The participant was then interviewed by the study nurse, and the following demographic information was collected.

1. Age was recorded in years.
2. Race was divided into one of the black ethnic groups, mixed race or Caucasian.
3. Smoking Status had four categories
    - Current smoker
    - Ex-smoker
    - Never smoked
    - Unknown

   The smoking status of the current smokers was then further divided into
    - Fewer than 5 cigarettes per day
    - 5 – 10 cigarettes per day
    - 11 – 20 cigarettesper day
    - More than 20 cigarettes per day

4. The imbibing of alcohol was divided into:
    - None
    - Social
    - Daily
    - Binge
    - Unknown

The alcohol intake was not measured in units but recorded from the participant's opinion of how much alcohol had been imbibed. Social drinking of alcohol was noted as not needing to consume alcohol every day and the drinking was in moderation. Daily consumption of alcohol was to partake of alcohol every day while binge drinking consisted of heavy episodes of drinking.

5. The use of recreational drugs was recorded as 'yes', 'no' or 'unknown'.

Some information was collected from the participant's medical folder:

- TB drug regimens
- Immune status
- Laboratory results
- Use of anti-coagulants and ART
- CD4 T-cell count.

A limited medical examination was also performed, including both a visual assessment of the participants' legs for swelling and redness, and an assessment of generalised leg pain and pain in the calf with dorsi-flexion (Homan's sign).

The ambulatory status of the participant at the time of the interview was documented and categorised this was divided into five groups:

1. Only in bed to sleep at night.
2. Up most of the day but may rest in bed morning or afternoon.
3. Up for some of the day but with long rests.
4. Only out of bed for meals or bathroom trips.
5. Does not get out of bed during the day and receives meals, medication, etc., at the bedside.

The participant's height in metres was measured and the body mass in kilograms was recorded. The formula for calculating the body mass index (BMI) is weight in kilograms divided by the square of the height in metres. Normal is regarded as between 18 – 25, a BMI <18 is considered underweight, and a BMI >25 overweight. In order to be classified as obese, the BMI must be more than 30 (Severinsen, 2009) (Appendix B the CRF).

2.4.2.1 Follow-up clinical visits – weekly

Once a week the study nurse interviewed each patient and a record was kept. This included asking about calf pain and a targeted clinical evaluation was done to assess for swelling and redness of the legs. Any change in the ambulatory status was documented. Any further signs and symptoms of bleeding, cerebral vascular accident (CVA) or PE were recorded. If either the study nurse or the medical team caring for the participant felt there were clinical symptoms of a DVT, the participant was referred for an additional ultrasound scan at the earliest opportunity.

2.4.2.2 Ultrasound screening

A routine weekly ultrasound clinic was held at the TB hospital where qualified sonographers performed and reported all the ultrasound examinations. The first ultrasound examination was performed at week 0 and follow-up ultrasound examinations were performed at weeks 4, 8 and 14 (figure 2.1).

2.4.3 Ultrasound protocol for the DVT examination with compression ultrasound (CUS) and Doppler

An ultrasound examination of the venous system of the lower extremities to diagnose or rule out a DVT included compression ultrasound used in conjunction with Doppler examinations.

Distally at the level of the ankle there are three main deep veins that are important for the ultrasound scan. The anterior tibial vein (ATV) ascends laterally, the posterior tibial vein (PTV) medially, and the peroneal vein (PV) posteriorly. These three veins join together at the level of the distal popliteal fossa and form the popliteal vein (POP). The POP vein transverses the popliteal fossa and becomes the superficial femoral vein (SFV) as it ascends through the adductor hiatus. The SFV is on the medial aspect of the thigh and at the level of the groin joins the profunda femoral vein to form the common femoral vein (CFV). This is the level at which the DVT ultrasound scan begins. Proximal to this, the CFV becomes the external iliac vein (EIV) and is joined by the internal iliac vein to form the common iliac vein (CIV). At about the level of the umbilicus, the left and right CIVs join together to form the inferior vena cava (IVC). The IVC traverses the abdomen and enters the right atrium of the heart where the blood will enter the pulmonary circulation.

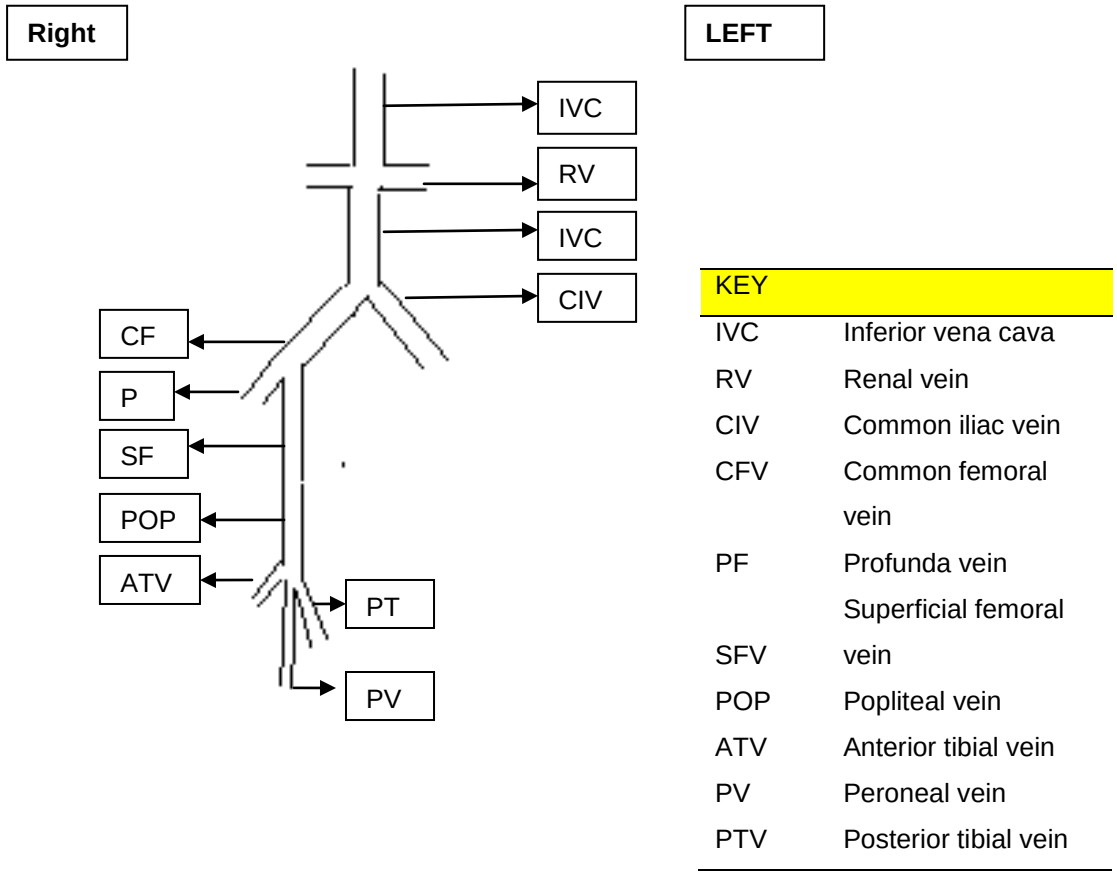
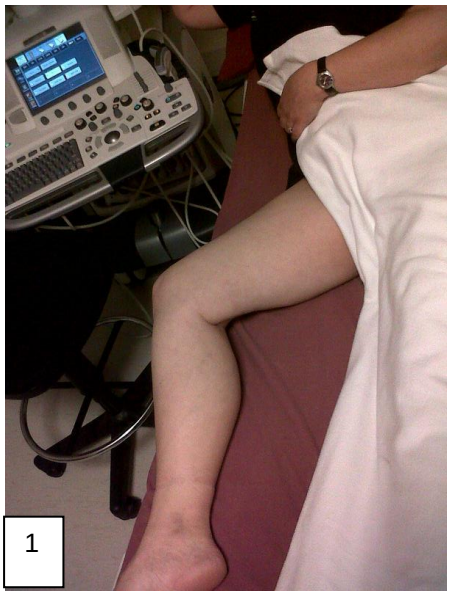


Figure 2.2 Line diagram showing the anatomical position of the deep veins of the lower extremity and the inferior vena cava. The key on the left explains the anatomical abbreviations.

The participants for this study were asked to undress and climb onto the examination couch. If they were too ill to move, a modified version of this protocol was performed at the patient's bedside as per accepted ultrasound practice for such patients. At the patient's bedside, the

sonographer had to stand, and often enlisted help from the nursing staff to position the participant's limb. Although less efficient, the information collected in these cases was still considered to be of adequate standard. In normal circumstances the head of the couch was elevated about 30^0 to help distend the veins of the lower limb. The participant lay comfortably; the knee was flexed and the hip externally rotated (figure 2.3). This allowed easy access to the superficial and deep femoral veins, the popliteal fossa and the medial aspect of the calf.



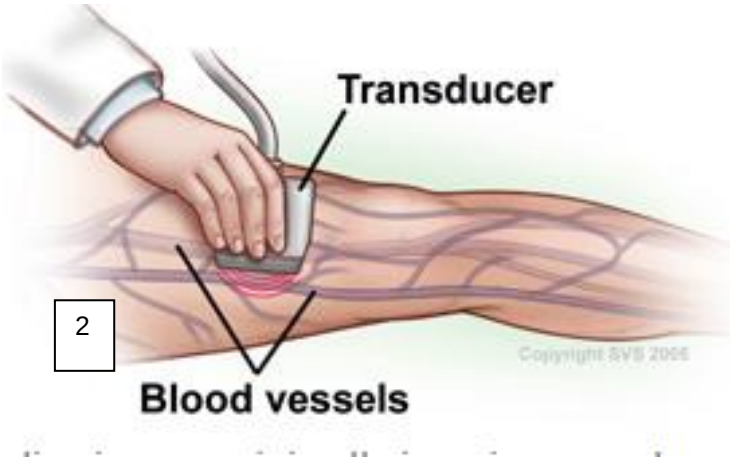


Figure 2.3 Position of the leg for a DVT examination (illustration 1), and below (illustration 2), diagram showing the relationship of the transducer in longitudinal view to the vessels in the thigh (image reproduced with permission from the Society for Vascular Surgery, 2012).

A Toshiba Echocee ultrasound machine was used together with a 7 – 10mHz linear transducer with the appropriate software for a vascular venous programme. The 7 – 10mHz linear transducer that was used had a wide footprint that was helpful when applying compression to the vessel. The 7 – 10mHz transducer is a high-resolution transducer, and was chosen as the vascular structures are superficial and this would maximise the resolution

of these superficial structures. A suitable amount of coupling gel was applied. The scan began with the transducer in a transverse position (i.e. perpendicular to the vessels being imaged) at the level of the inguinal ligament. The common femoral artery and vein appeared as hypoechoic, round structures (figure 2.4.a). On applying firm pressure, a normal vein will collapse, while the artery maintains its shape (figure 2.4.b). This was due to the artery's being a high-pressure system while the venous composition is low pressure.

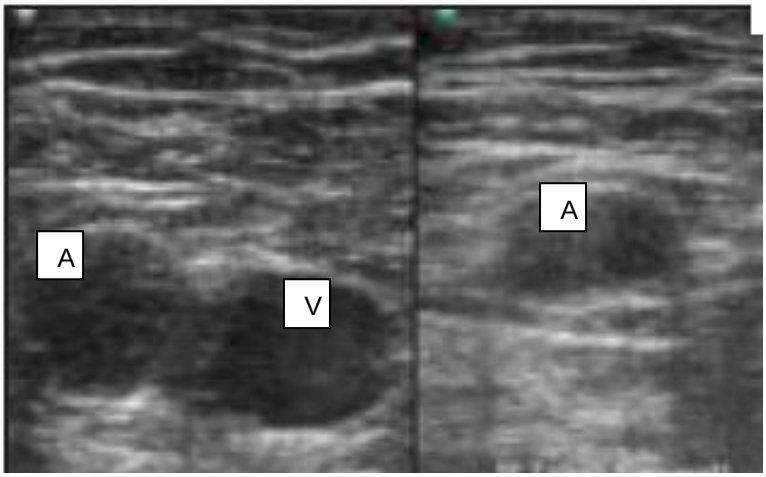


Figure 2.4a **Figure 2.4b**

Figure 2.4 B-mode, grey-scale, transverse image of the femoral artery and vein. The normal artery (A) and vein (V) are seen side by side in the image on the left. The image on the right shows only the artery, as the vein has collapsed and disappears when vertical pressure is applied. Note how the artery (A) maintains its shape (Del Rios et al., 2009).

The transducer was then rotated 90^0 into a longitudinal position (i.e. parallel with the vessels being imaged) and the colour Doppler was activated. Colour should homogeneously fill the vessel in a normal vein (figure 2.5a). When the pulsed wave sample was applied, the spectral waveform showed the undulations associated with normal flow. The calf was squeezed to show augmented flow on the spectral waveform (figure 2.5b). This also indicated there was probably not complete obstruction between the level of the calf compression and the transducer.

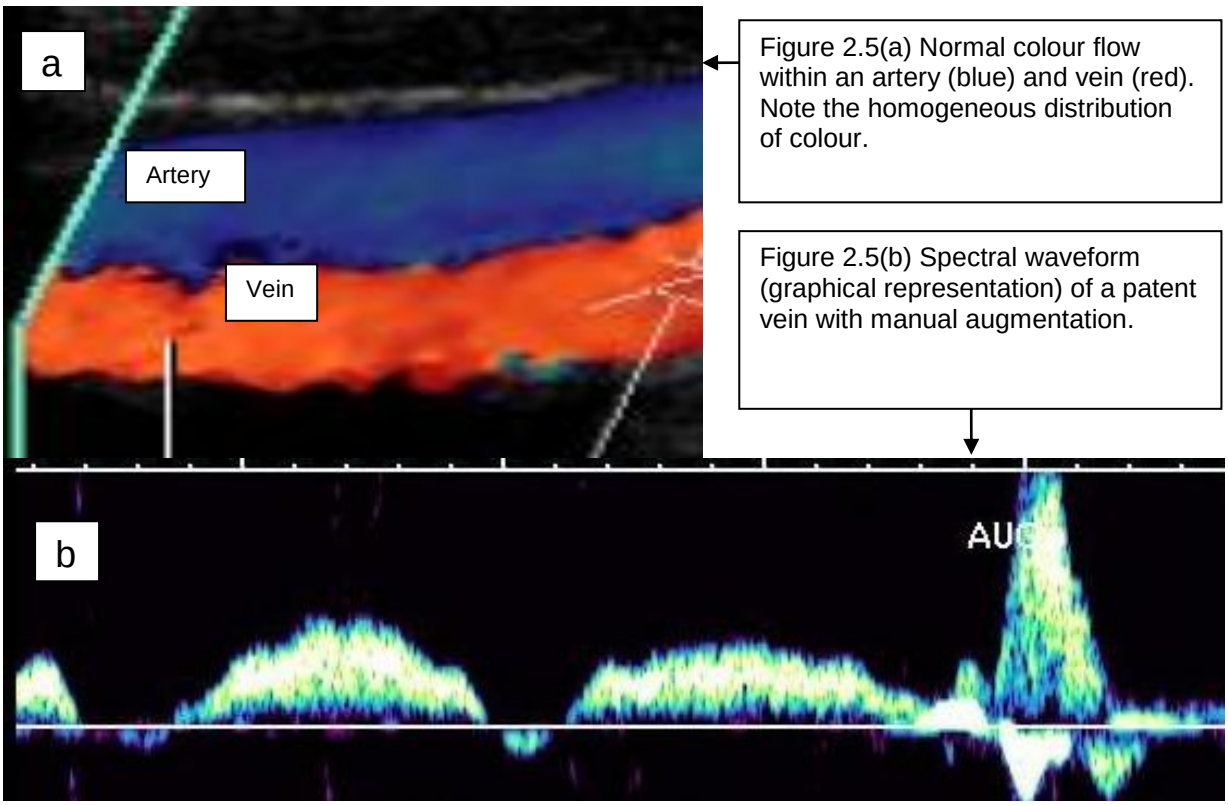


Figure 2.5a Colour Doppler longitudinal image showing normal colour flow in both the artery and the vein. Figure 2.5b Spectral waveform of a normal vein with augmentation.

The transducer was then rotated 90^0 and the vessels once again imaged in transverse. The transducer was then moved distally maintaining the vessels in the middle of the image. Compression was applied between each small increment of movement. It was important to identify the long saphenous vein as it joins the common femoral vein. Once the common femoral vein divided into the superficial and the deep (profunda) veins, the superficial femoral vein was followed distally to the level of the adductor canal. At this point the scan was more of a coronal image, as the vessel became the proximal popliteal vein. This was followed until the vessel could not be seen; the transducer was then repositioned in the popliteal fossa, still in a transverse position. Once in the popliteal fossa, the vein appeared anterior to the artery on the ultrasound but was still easy to compress if it was normal. The popliteal vein was followed distally to the junction of the posterior tibial vein (PTV) and the peroneal vein (PV). Occasionally the junction of the anterior tibial vein (ATV) was seen. Both the PTV and PV were followed with intermittent compression as far distally as possible. The PTV could usually be seen to the level of the ankle, while the PV could be seen to the distal third of the calf. At this point the participant's leg would be straightened and rotated medially. With the transducer transverse, the proximal ATV was identified between the tibia and the head of the fibula. Again this was followed as far distally as possible. Colour Doppler with augmentation was helpful for identifying and confirming patency of the calf vessels. Intermittently during the

leg examination, the transducer would be rotated for a longitudinal image and Doppler applied to that level of the vessel to help verify patency. This DVT examination with CUS and Doppler was performed on both legs. The ultrasound findings were documented on an ultrasound report form (Appendix C.1).

The participants all had a Doppler and CUS (DVT scan) of their lower limbs at week 0 (1st ultrasound examination) which was within three weeks (21 days) of beginning TB medication. This was followed with another DVT ultrasound at week 4, week 8 and week 14. The number of scans received depended on the participant's length of hospital stay. However, if the participant was to have an earlier discharge or transfer to another hospital, then, if it were logistically possible, an extra DVT scan was performed prior to discharge/transfer. Furthermore, if there was a clinical suggestion of a DVT, then an additional DVT scan was performed at the earliest opportunity. The ultrasound report noted whether a DVT was present, if it were bilateral or unilateral (left or right), and which particular vessels were involved (CFV, SFV, POP, PTV, PV or ATV). A copy of the ultrasound report was placed in the participant's hospital folder and a record kept in the study folder. When a DVT was identified, the managing clinician was informed and the participant's name censored from the routine ultrasound scan lists. The participant would receive the standard hospital care and management for a DVT.

2.4.4 Abdominal ultrasound

Together with the DVT scan, all the participants had one routine abdominal ultrasound scan at week 0. This included an ultrasound assessment of the pancreas, liver, gall bladder and biliary system, spleen, kidneys and urinary bladder. The relevant sizes, architecture and echogenicity were recorded. Abnormal lymph adenopathy was looked for in the epigastrium, mesentery and pelvis. Free fluid was noted within the abdomen, as well as around the heart and in the pleural spaces. The presence of any intra-abdominal mass or collection was measured and documented. Doppler ultrasound was used to assess patency of the main vessels of the abdomen (aorta, IVC, CIV and CFV) and the aorta was measured to rule out an incidental abdominal aortic aneurysm (AAA). An abdominal ultrasound report (Appendix C.2) was used.

An abnormal abdominal ultrasound was reported if the following were detected:

- An abnormal size or echogenicity of an abdominal organ.
- The presence of a mass, collection, free fluid or abnormal lymph nodes.

Repeat abdominal ultrasounds were only performed if requested by the clinician.

2.5 Data collection

All the ultrasound scans were performed by the principal researcher and one research assistant. Both the scanners are qualified sonographers with several years of experience in vascular and abdominal ultrasound imaging.

Participants were assigned a study number and all demographic, clinical and ultrasound data were entered into customised clinical research files (CRF). Data were extracted from the CRFs and entered into a specially constructed access database using MS Access 2007.

2.6 Statistical methods

The statistical analysis was performed using IBM SPSS statistical software, version 19, and a Microsoft Exel 2007 package.

2.6.1 Univariate calculations

For the univariate calculations of the demographics, risk factors and clinical factors, the p-value was calculated to test the variables' relationships as to whether they were a statistically significant risk factor for a DVT or not.

The demographics of the study population included age (in years), sex, race, education and employment. The risk factors were smoking, smoking frequency, use of alcohol and recreational drugs, and ambulatory status. The clinical characteristics included the use of prophylactic anticoagulants, BMI, TB regimen, HIV status and the CD4 T cell count.

For the numerical variable age an independent samples median test was used and for BMI and CD4 T cell counts the student t-test. The differences between average /means/medians/inter-quartile range (IQR) and p-values were calculated. The IQR is the difference between the upper and lower quartiles. The IQR and both the upper and lower quartiles were recorded. For the categorical variables (sex, race, smoking, smoking frequency, alcohol, recreational drugs, ambulatory status, prophylactic anticoagulants, TB regimen, HIV status and the use of ART), the chi-squared test was used to calculate the value of p. A p value of less than 0.05 was regarded as a statistically significant risk factor.

These were compared between the positive DVT and the negative DVT group. The overall risk factors between the different variables were compared.

In order to analyse and express the significance of the categorical variables regarding TB history and clinical symptoms, the variable comparisons between the proportions were

calculated using the chi-squared test and expressed a p-value. It was considered significant if $p < 0.05$. The position of the DVT was expressed using descriptive statistics.

The number of DVTs identified per week of the 15-week study was recorded. In addition, the time from beginning anti-TB medication, to the ultrasound scan that confirmed the diagnosis of a DVT, was calculated in days. The number of days to identifying the DVT was analysed, and the median, variance, standard deviation, minimum, maximum, and inter-quartile range were calculated and expressed as descriptive statistics.

2.6.2 Sensitivity, specificity and the positive predictive value (PPV)

The enrolled population group were assessed each week by the study nurse for clinical signs of a DVT and a record was kept (i.e. each week). If a symptom was present, it was counted, therefore there could be more than 400 notations. The type of symptom encountered was also documented. Chi-squared tests were performed and the overall risks between the different clinical symptoms were compared between the DVT and non-DVT groups. The sensitivity, specificity and positive predictive value (PPV) were calculated from this data.

2.6.3 Logistic regression models and Kaplan-Meier curves

Logistic regression models were constructed for the independent variables: age, CD4 T-cell count, race, BMI, smoking, and ambulatory status. This allowed for the log odds for the dependent variable DVT to be calculated for each of the independent variables. The Wald chi-squared test was used to test the independent variables. Known probability distribution (chi-squared distribution) was used to test for a predictor in the logistic regression model. Alpha was 0.05 and the p-values that were less than Alpha were regarded as a statistically significant risk factor.

The Kaplan-Meier graphs were used to illustrate the DVT survival probability curve. DVT survival over the 15-week period was denoted with a diagnosis of a negative ultrasound scan. The Kaplan-Meier technique and Cox regression test were used to evaluate and construct the DVT detection probability curve; for the categorical variables, ambulatory status, the TB regimen, and the use of prophylactic anti-coagulants.

The participants were all being treated with TB regimen 1 or 2. Regimen 1 was for first-time TB sufferers and regimen 2 for participants who had previously been treated for a TB infection. The policy of the DP Marais Hospital was to administer prophylactic anticoagulants

when the mobility of the participant dropped by 50%. This was a judgement made by the medical staff responsible for the care of the participant. As there was very strong relationship between having received anti-coagulants and ambulatory status, and since all 61 DVT participants actually received anti-coagulants, it was felt that this variable should be excluded from this Cox logistic regression test. When included, all other variables become non-significant. As this curve will represent the DVT negative group, the changes in the contour represent the use of prophylactic anticoagulation.

2.6.4 Multivariate models

Generalised linear regression models were built to compare the multiple variables from the demographics, risk factors and clinical factors with the dependent variable DVT. Initially all the variables were included and compared. If the results showed a statistical significance that was close to the value of one they were excluded, as they were not deemed significant. The categorical variables included race, smoking, alcohol, and ambulatory status. For these calculations, the single Caucasian was included in the mixed-race group. The continuous variables were BMI and age. The Wald chi-squared test was used to test for a statistical difference between the variables.

The multivariate models were also performed to see if the use of ART and the different TB drug regimens were associated with the development of DVTs.

2.7 Ancillary study

The ancillary study included a single routine abdominal ultrasound that was performed at week 0. The 400 participants who were registered on the study had their abdominal ultrasound reports reviewed and expressed as descriptive statistics.

2.8 Ethical considerations

Ethics approval for the study was granted by the Faculty of Health and Wellness Sciences Research Ethics Committee of the Cape Peninsula University of Technology (CPUT), as well as by the University of Cape Town (UCT). (CPUT Registration Number NHREC: REC-230408-014. UCT Registration Number HREC REF: 449/2010.) The study was conducted according to the Code of Ethics of the World Medical Association (Declaration of Helsinki). All participants signed written informed consent. The informed consent was available in three languages: English, Afrikaans and isiXhosa (Appendix A). Approval was granted to do the study by the DP Marais Hospital, and the Western Cape Department of Health (Appendix D),

Confidentiality of the participants' information was upheld. The study nurse and principal researcher were responsible for the inventory and organisation of the data collection forms. The medical care team was kept informed of all ultrasound reports by copies of the reports placed in the participants' medical folders. The study folder was kept without personal identifying data. Participants were assigned a study number and this was used on all study paperwork. The princiapal researcher and study nurse maintained a confidential key of study numbers and patient names. All the data was kept in a locked room and the electronic database was also kept locked. Access to this data was restricted to the research team. The CRF forms were anonymous, and the relevant data was kept in a locked cupboard at the study site for the duration of the study. The data, with only the patient code visible, was accessible to the supervisors and statistician.

Evidence has shown that there are no known biological effects when diagnostic imaging ultrasound machines are used appropriately by trained sonographers (Fowlkes & Holland, 1998:52).

CHAPTER 3

The Results

The statistical analysis was performed using IBM SPSS statistical software version 19 and a Microsoft Excel 2007 package.

3.1 Enrolment

Enrolment for this study is as shown in Figure 3.1. In the 20-month time period, 1571 patients were admitted to the DP Marais TB Hospital. There were 8.9% (n = 141) patients that were not screened for the following reasons: re-admission, 1.9% (n = 31), and therefore previously screened; mentally confused and unable to sign informed consent, 1.8% (n = 29); and the patients whose documents were missing at the time of assessment, so there was no record of when the anti-TB drugs had begun, 0.25% (n = 4). The remaining 4.9% (n = 77) were not assessed for reasons unknown.

Of the 1430 patients who were screened, 59.4% (n = 933) did not meet the inclusion criteria described in Chapter 2, Section 2.3.1. The reasons for this were: they had been on TB treatment for more than 21 days, 41.5% (n = 653), had been diagnosed with MDR TB, 14.3% (n = 224), a known DVT diagnosed at another health facility, 2.9% (n = 46), planned short stay, that is, less than 15 weeks, 0.4% (n = 7), and unknown HIV status, 0.19% (n = 3).
For the study, 497 patients were eligible; however 6.1% (n = 97) were not enrolled. Of these, 2.9% (n = 46) did not want to participate in the study. Another 2.3% (n = 37) were transferred to another hospital and 0.4% (n = 7) absconded from the hospital prior to enrolment. Unfortunately, 0.4% (n = 7) died before they could be enrolled in the study.
Four hundred eligible participants enrolled in the study (Figure 3.1).

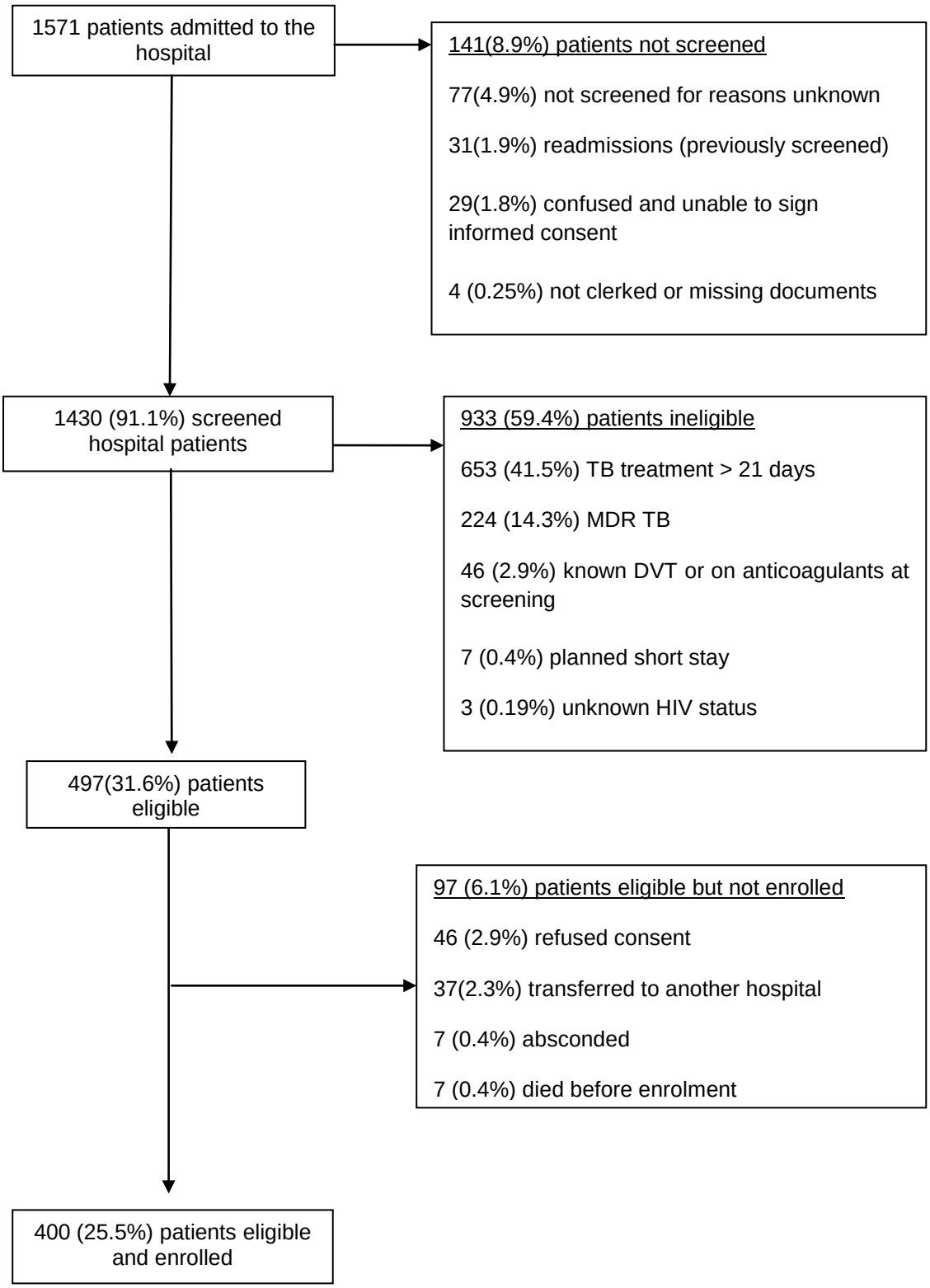


Figure 3.1 Enrolment flow chart showing all the admissions to the DP Marais Hospital

3.2 Study population

The enrolled sample of 400 participants represented 25.5% of the TB population at the DP Marais Hospital. The eligible patients who were not enrolled did not differ statistically from the 400 enrolled participants in terms of age (p = 0.26) or sex (p = 0.47) and these participants will not be discussed further.

The following results pertain only to the 400 that make up the enrolled sample.
In the enrolled sample there were 68% (n = 272) males and 32% (n = 128) females. The median age of this group was 38 years with an inter-quartile range (IQR) of 19 years (33 – 52 years).

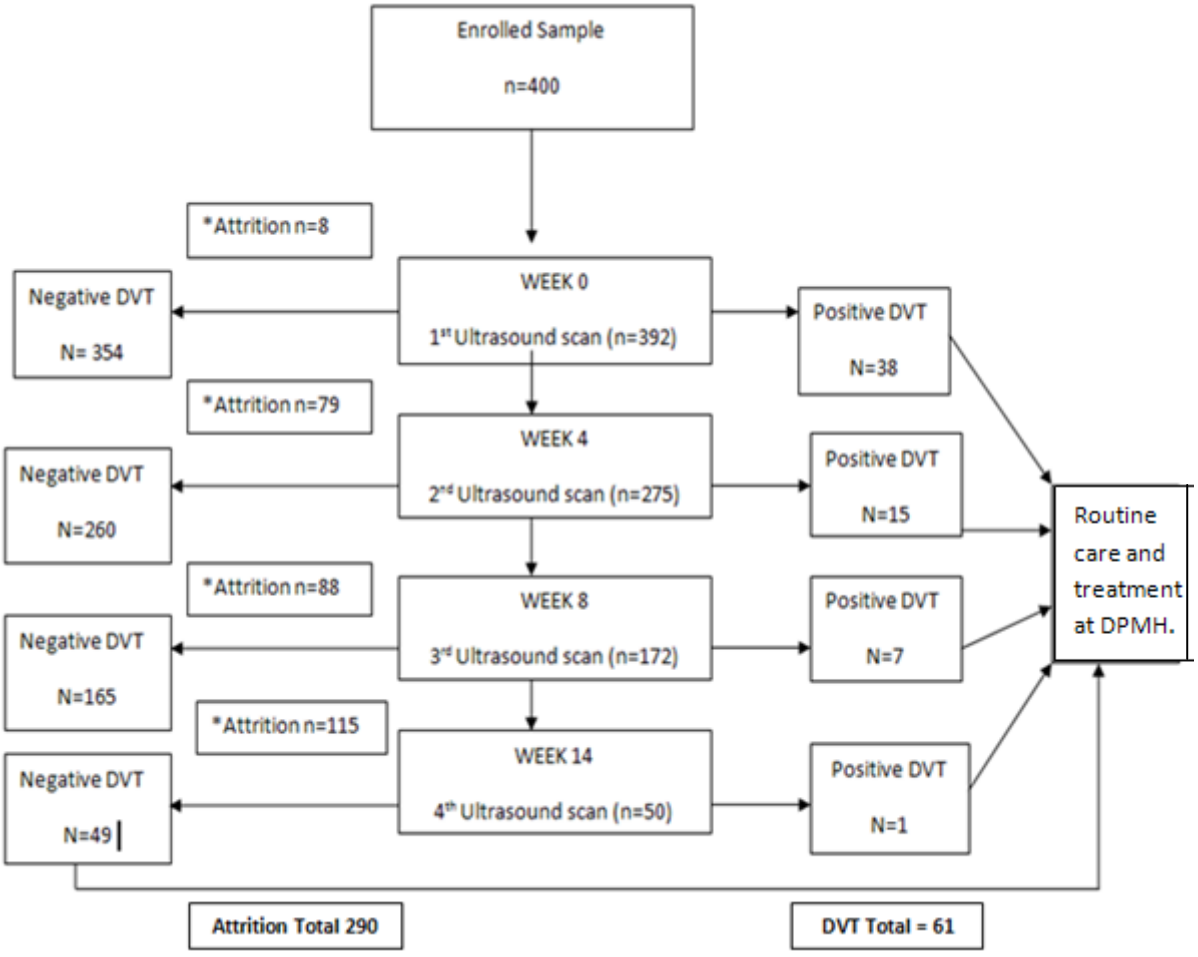
3.2.2 DVTs identified in the study population

In the enrolled group of 400 participants, ultrasound identified 15.3% (n = 61) DVTs.
Once participants were enrolled, they were booked for the first ultrasound scan and this was regarded as week '0'. This was within 21 days of starting TB treatment. Prior to the first ultrasound being performed, two participants died, four absconded and two had protocol violations (TB treatment for more than 21 days). The week '0' ultrasound results showed 38 DVTs identified. Once the ultrasound scan had identified the DVT, the medical staff members were informed and the participant received routine care and treatment for a DVT in the hospital ward. These participants were removed from the study as they were deemed to have reached the primary end-point.

The next routine scan was performed at week '4' (2^{nd} ultrasound examination), and by then 15 more DVTs had been identified. Between week '0' and week '4' there was an attrition of 79 participants. By the 3^{rd} routine ultrasound examination at week '8', a further 7 DVTs had been identified with an attrition of 88 participants. The final routine scan was performed at week 14 (4^{th} ultrasound examination), where a single DVT was identified and the attrition was 115 participants. Of the 400 enrolled participants, only 12.5% (n = 50) received all four routine scans. While the participants were involved in the study, they received routine care and treatment from the hospital (figure 3.2).

Attrition represented those participants who exited the study early. As the study progressed, the total attrition was 72.5% (n = 290) participants. This was further divided into: early discharge, 39.5% (n = 158), transferred out, 8.75% n = 35), absconded, 15% (n = 60) and death 9% (n = 36).

An early discharge was due to an improvement in the participant's condition and transfer to another hospital represented deterioration in their condition and the need to upscale their treatment.



*(*Attrition represents those participants who exited the study, e.g. early discharge, died, transferred or absconded).*

Figure 3.2 Study flow chart demonstrating the sequential attrition rate and positive DVT detection rate throughout the study

3.3 Demographics

For the assessment of association between the presence of DVT and demographic variables, chi-squared tests were performed for sex and race. An independent median test was used for age.

The study population comprised in-patients at the DP Marais TB Hospital. The study sample consisted of 32.3% females (n = 128) and 67.8% males (n = 270) (table 3.1). Most of the participants fell into the coloured (mixed race) group, 58.5% (n = 234), with African, 41% (n =

164), and Caucasian as the smallest group, 0.3% (n = 1) (table 3.1). For the multivariate statistical tests, this single Caucasian was included in the mixed race group.

The youngest participant was 19 years old and the oldest was 76 years. In the positive DVT group, the median age was 39 years (with a standard deviation of 11.7), and the IQR = 19 years (32.5 – 51.5 years) (table 3.1). In the negative DVT group the median was 37.6 years and the IQR = 17 years (29 – 46 years).

There was no statistical difference in the demographic characteristics, sex (p = 0.44), age (p = 0.36) and race (p = 0.09) between the positive DVT and the negative DVT groups.

Table 3.1 Demographics

Demographics	Positive DVT *(n = 61)	%	Negative DVT *(n = 339)	%	p value
Sex					
Male	44	72.1	226	66.6	
Female	17	27.8	111	33.3	0.44
Age (in years)					
Median	39		37.6		0.357
IQR	19 (32.5-51.5)		17 (29-46)		
Race					
Coloured	29	47.5	205	60.4	
White	1	1.6	0	0	
Black	31	50.1	133	39.4	0.09

(Percentages may not add up to 100% due to rounding off) * = n

3.4 Clinical characteristics

The clinical characteristics included whether or not the participant was having anticoagulants administered, Body Mass Index (BMI = mass in kilograms/height in metres^2), TB regimen, HIV status, baseline CD4 T cell count (recorded when the patient enrolled in the study) and whether or not the HIV-positive participants had begun ART. The clinical characteristics were compared for a difference between the positive DVT and negative DVT groups. Both BMI and CD4 T cell counts were tested with a student's t-test and the use of anticoagulants, TB regimen, HIV status and the use of ART used a chi^2 test for statistical significance between the two DVT groups.

Table 3.2 Clinical characteristics

Clinical Characteristics	Positive DVT Pop*(61)	%	Negative DVT Pop*(339)	%	p value
Anticoagulants					
Yes	61	100	54	15.9	
No	0	0	284	83.8	
Unknown	0	0	1	0.29	0.0001
BMI					
Median	17.2		17.4		
IQR	3.3 (15.4-18.7)		3.5 (15.8-19.3)		0.07
Unknown	2		14		
TB regimen					
Regimen 1	31	51.70%	96	28.30%	
Regimen 2	29	48.30%	236	69.90%	
Unknown/other	1	1.60%	6	1.80%	0.0005
HIV status					
Positive	40	65.60%	192	57.10%	
Negative	21	34.40%	144	42.90%	
Unknown	0	0	2	0.50%	0.23
ART					
Yes	29	73.30%	128	69.60%	
No	9	23.70%	66	30.40%	0.41
Unknown	2	4.80%	8	2.30%	
CD4 T cell count					
Median	72.5		69		0.1
IQR	133.2 (29-162.2)		127 (26-153)		

(Percentages may not add up to 100% due to rounding off) * = n

3.4.1 Anticoagulants

As the treatment for a DVT is with anticoagulants, all the 15.5% (n = 61) participants diagnosed with a DVT had anticoagulation therapy; an additional 13.7% (n = 54) participants had prophylactic anticoagulants, making a total of 29.2% (n = 115) (table 3.2). This was DP Marais Hospital policy: to administer prophylactic anticoagulants when the mobility of the participant had dropped by 50%.

For the survival plot calculations, the 61 positive DVT participants were excluded as they all received anticoagulants due to their DVT diagnosis, rather than for prophylactic use. The two groups (those who used anticoagulants and those who did not) were compared. This was statistically significant with p = 0.0001. The initiation of the anticoagulants in the DVT negative group is shown in the Kaplan-Meier curve below (figure 3.3). This illustrates the

likelihood of the participants in the negative DVT group receiving anticoagulants as prophylaxis.

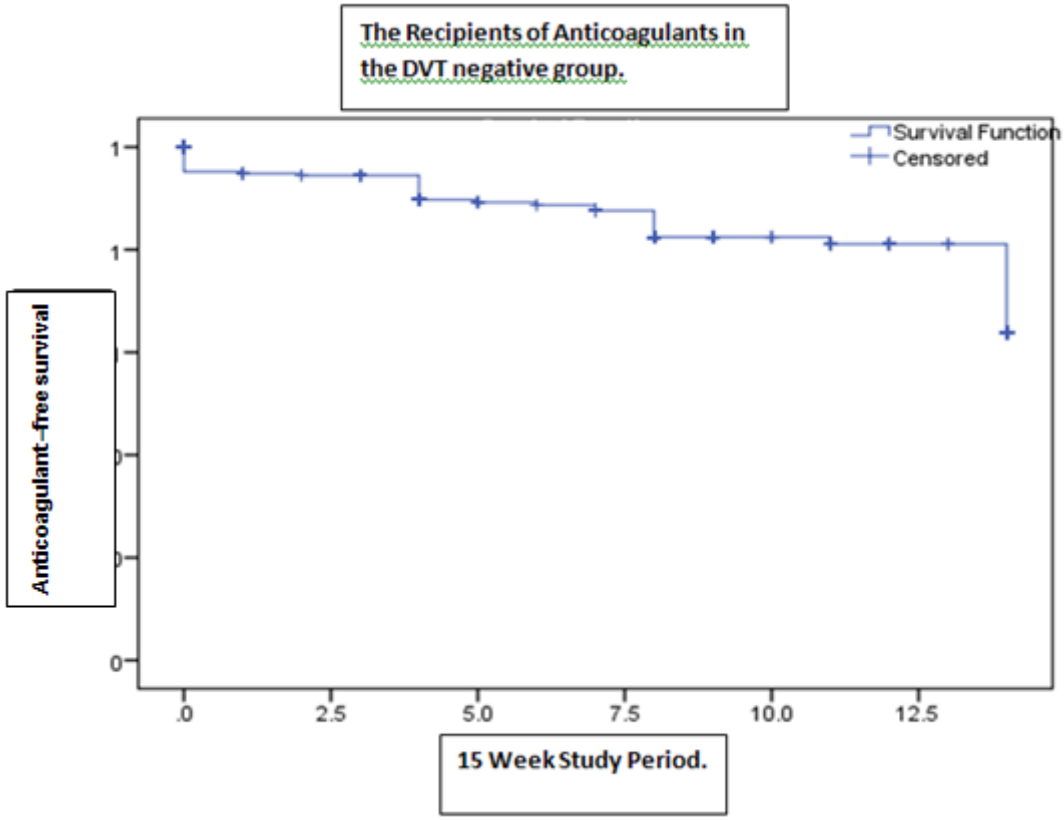


Figure 3.3 Kaplan-Meier curve showing the possibility of receiving anticoagulants during the study period

3.4.2 Body mass index (BMI)

More than half the participants had a low BMI 57% (n = 223) with only 2.9% (n = 11) of the group measuring an increased BMI. There were 39% (n = 152) who fell within the normal BMI range. Only 0.52% (n = 2) of participants had BMIs greater than 30, that is, obese. The minimum BMI recorded was 10.1 and the maximum 32.1. The median was 17.5, with a standard deviation of 2.95. This was not shown to be a statistically significant risk factor for a DVT (p = 0.07).

3.4.3 HIV, ART and CD4 T cell count

There were 58.1% (n = 232) of participants who were HIV positive and 41.3% (n = 165) whose HIV test was negative. There was no significant statistical difference between the DVTs identified between these groups (p = 0.23). Of the 58.1% (n = 232) of participants who were HIV positive, there were 67% (n = 157) who had begun ART at the time of the study

interview. This left 32.6% (n = 75) of participants who were not using ART. This was not statistical significant between the positive DVT and negative DVT groups who were using ART (p = 0.41). In the DVT group the median for the CD4 T cell count was 72.5 and the IQR =133.2 (29 – 162.2) and in the negative DVT group the median = 69 and the IQR= 127 (26 – 153). The difference between these two groups was not statistically different (p = 0.1) (table 3.3).

3.4.4 TB regimen

The TB regimens were either regimen 1, for first-time TB sufferers, or regimen 2 for participants who had previously been treated for a TB infection.

There were 32.4% (n = 127) of the participants on regimen 1 and 67.6% (n = 265) on regimen 2. The TB regimen was unknown in 1.7% (n = 7) of the participants. In this study population, 67.6% were treated with regimen 2 and 10.9% developed a DVT. The remaining 32.4% were on regimen 1 and 24.4% developed a DVT. The incidence of DVT in the regimen 1 group was more than double that of regimen 2. Regimen 1 was shown to be a statistically significant risk factor for a DVT (p = 0.0005) (table 3.3).

The logistic regression models were developed to assess the risk of a DVT depending on the TB regimen, and are illustrated in the Kaplan-Meier curve (figure 3.4). TB regimen 1 is shown as the blue curve, with many more DVTs being identified than in regimen 2, represented by the green curve.

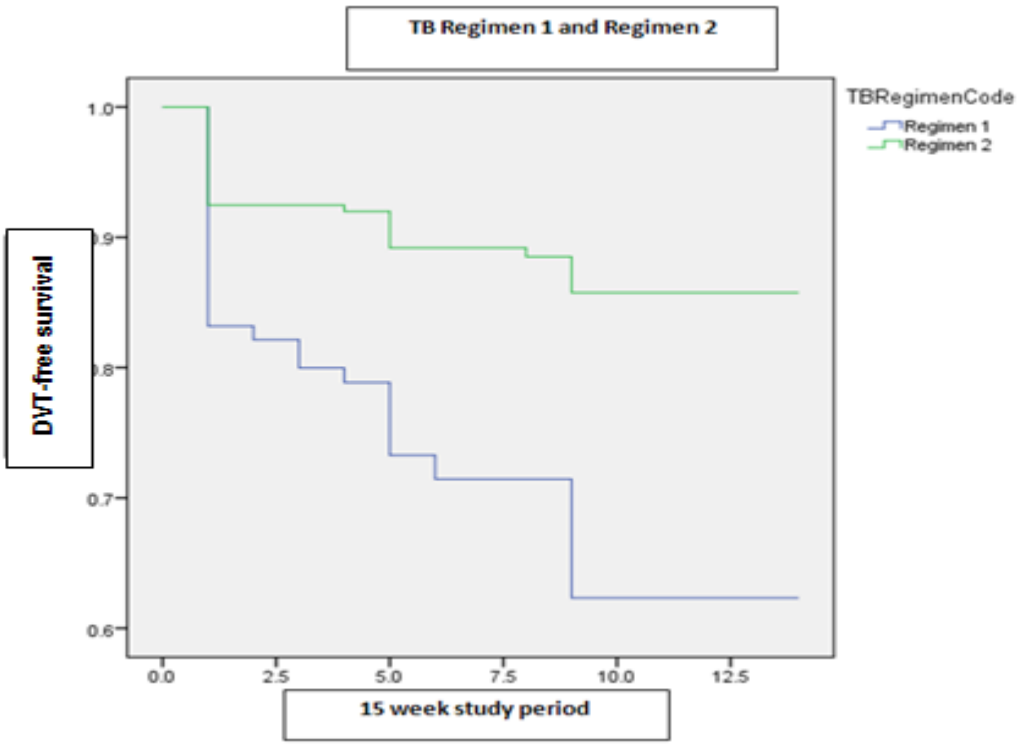


Figure 3.4 Risk of DVT according to TB regimen 1 or 2

3.4.4.1 TB regimen of positive DVT and negative DVT groups, the HIV status and ART usage

In the DVT positive group, there were the same number of HIV negative participants (10) on regimen 1 (32.2%) and regimen 2 (34.4%). Of the HIV-positive participants, 21 (67.7%) were on regimen 1 and 19 (65.5%) were on regimen 2. This group can further be divided into those who were on ART and those who were not. On regimen 1 there were 16 (76.1%), and on regimen 2, 14 (73.6%) who were using ART. In the group not using ART there were 3 (14.2%) on regimen 1 and 5 (25.3%) on regimen 2. There were 2 (9.5%) participants in the regimen 1 group who fell into the 'unknown ART' usage set.

The negative DVT group had 29.1% of participants on regimen 1 and 48.2% on regimen 2. Of the HIV positive participants, 70.8% were on regimen 1 and 51.2% were on regimen 2. This group was further being divided into those who were on ART and those who were not. On regimen 1 there were 63.2%, and on regimen 2, 66.1% who were using ART. In the group not using ART, there were 30.9% on regimen 1 and 31.4% on regimen 2. There were 5.9% of the participants in the regimen 1 group who fell into the 'unknown ART' usage group and 2.5% in the regimen 2 set (table 3.4).

Table 3.3 Table showing the DVT positive and negative groups and the comparison between the HIV statuses, the use of ART and the division between regimen 1 and regimen 2

DVT+	REG 1 (31)	%	REG 2 (29)	%
HIV-	10	32.2	10	34.4
HIV+	21	67.7	19	65.5
ART+	16	76.1	14	73.6
ART-	3	14.2	5	25.3
ART?	2	9.5	0	0
DVT-	REG 1 (96)	%	REG 2 (236)	%
HIV-	28	29.1	115	48.7
HIV+	68	70.8	121	51.2
ART+	43	63.2	80	66.1
ART-	21	30.9	38	31.4
ART$_{unknown}$	4	5.9	3	2.5

(Percentages may not add up to 100% due to rounding off) * = n

The multivariate models were built to see if the use of ART and the different TB drug regimens were associated with the development of DVTs. Generalised regression models were built to compare the multiple variables with the dependent variable DVT. The Wald chi-squared test was used and there was no statistical difference between the variables TB regimen, ART usage and CD4 T cell count. See table 3.5 below.

Table 3.4 Multivariate models were built to see if the use of ART and the different TB drug regimens were statistically significant.

Source	**Type III**		
	Wald Chi-square	**Df**	**p-value**
(Intercept)	28.946	1	.000
TB regimen Code	2.186	1	.139
ART code	.144	1	.704
CD4 count	.809	1	.368

Dependent Variable: DVT

Variables: (Intercept), TB regimen code, ART code, CD4 count

3.5 Risk factors

The potential DVT risk factors that were assessed were smoking, alcohol, recreational drugs, and ambulatory status.

Table 3.5 Risk factors

Risk Factors	Positive DVT n = 61	%	Negative DVT n = 339	%	p-value
Smoking					0.02
Status					
Current	16	26.2	142	41.9	
Ex-smoker	33	54.1	113	33.3	
Never smoked	12	19.7	82	24.2	
Unknown	0	0	2	0.6	
Smoking Frequency					0.13
<5 cigarettes	23	37.7	101	29.8	
5 – 10 cigarettes	4	6.6	58	17.1	
11 – 20 cigarettes	15	24.6	69	20.4	
> 20 cigarettes	5	8.2	18	5.3	
Unknown	2	3.2	11	3.2	
Alcohol					0.02
None	15	24.6	114	33.9	
Social	10	16.4	69	20.5	
Daily	11	18	44	13.1	
Binge	25	41	109	32.4	
Unknown	0	0	2	0.6	
Recreational drugs					0.70
Yes	20	32.3	120	35,7	
No	40	66.7	216	64.3	
Unknown	1	1.6	2	0.6	
Ambulatory status					
Only in bed at night	2	3.3	5	1.5	
Up in the day but may rest am/pm	2	3.3	58	17.1	
Up some of the day but with long rests	14	23	130	38.3	
Only out of bed for meals/bathroom visits	31	50.8	126	37.2	
Does not get out of bed	12	19.7	19	5.6	<0.0001
Unknown	0	0	1	3	

(Percentages may not add up to 100% due to rounding off) * = n

3.5.1 Smoking

When analysing the participants' smoking status, there were 0.6% (n = 2) participants with missing data. The current smokers category showed 39.5% (n = 158) participants, with 36.5% (n = 146) ex-smokers and 23.5% (n = 94) who had never smoked. When assessing the frequency of the participants' smoking habits, there were 23.5% (n = 94) participants who had never smoked, while 3.25% (n = 13) were missing entries. The remaining data showed 31% (n = 124) participants smoked fewer than 5 cigarettes a day, 16% (n = 62) smoked between 5 – 10 cigarettes, 20.8% (n = 84) smoked between 11 – 20 cigarettes and lastly 5.8% (n = 23) smoked more than 20 cigarettes a day (table 3.2). There was a statistical difference in the smoking status between the positive DVT and the negative DVT groups, with p = 0.02. Smoking was therefore a statistically significant risk factor for a DVT.

3.5.2. Alcohol and recreational drugs

The alcohol consumption was divided into four groups. There were 0.5% (n = 2) participants whose details were unknown. Those who did not take alcohol accounted for 32.3% (n = 129). There were 19.8% (n = 79) who described themselves as social drinkers, and 13.8% (n = 55) who took alcohol on a daily basis. The largest group of 33.8% (n = 134) admitted to binge drinking (table 3.2). There was a statistical difference in the alcohol consumption status between the positive DVT and the negative DVT groups with p =. 0.02. Therefore the consumption of alcohol was a statistically significant risk factor.

There were 64% (n = 256) participants who did not use recreational drugs, while 35.3% (n = 140) acknowledged that they used such drugs. There were 3 participants from whom this information was not obtained. There was no statistical difference in the use of recreational drugs between the positive DVT and the negative DVT groups (p = 0.7) (table 3.2).

3.5.3 Ambulatory status

The ambulatory status was documented and this was divided into five groups, the results of which are below:

1. Only in bed to sleep at night comprised 1.8% (n = 7) of the participants.
2. Up most of the day but may rest in bed morning or afternoon comprised 15% (n = 60) of the participants.
3. Up for some of the day but with long rests comprised 36% (n = 144) of the participants.
4. Only out of bed for meals or bathroom trips comprised 39.3% (n = 157) of the participants.
5. Does not get out of bed during the day and receives meals, medication, etc., at the bedside comprised 7.8% (n = 31) of the participants (table 3.2).

The majority of the participants, 75.3% (n = 301), fell into the ambulatory status 3 (36% n = 144) and 4 (39.3% n = 157).

Smoking, smoking frequency, alcohol, recreational drugs, and ambulatory status had chi-squared tests performed and the overall risks between these different categorical variables were compared. The univariate risk factors were compared for a difference between the positive DVT and negative DVT groups. The risk factors that were not statistically significant were smoking frequency, recreational drugs. The risk factor that proved to be the most statistically significant was the ambulatory sub-division ‘does not get out of bed’ where $p < 0.0001$. Two other risk factors that were significant were smoking and alcohol, $p = 0.02$ and $p = 0.01$ respectively (table 3.2).

The logistic regression models were developed to assess the risk of a DVT depending on the ambulatory status. The odds ratio or risk of developing a DVT for a person with ambulatory status 5 (does not get out of bed during day) is 1.26 times (95% confidence interval) that of a person with ambulatory status 1 (only in bed to sleep at night). The odds ratio is illustrated in the Kaplan-Meier curve in figure 3.3.The Kaplan Meier curve below shows the length of the study in weeks on the x-axis and the DVT-free survival on the y-axis. Each time the contour changes on the y-axis it represents the discovery of a DVT. The five coloured curves represent each of the ambulatory statuses.

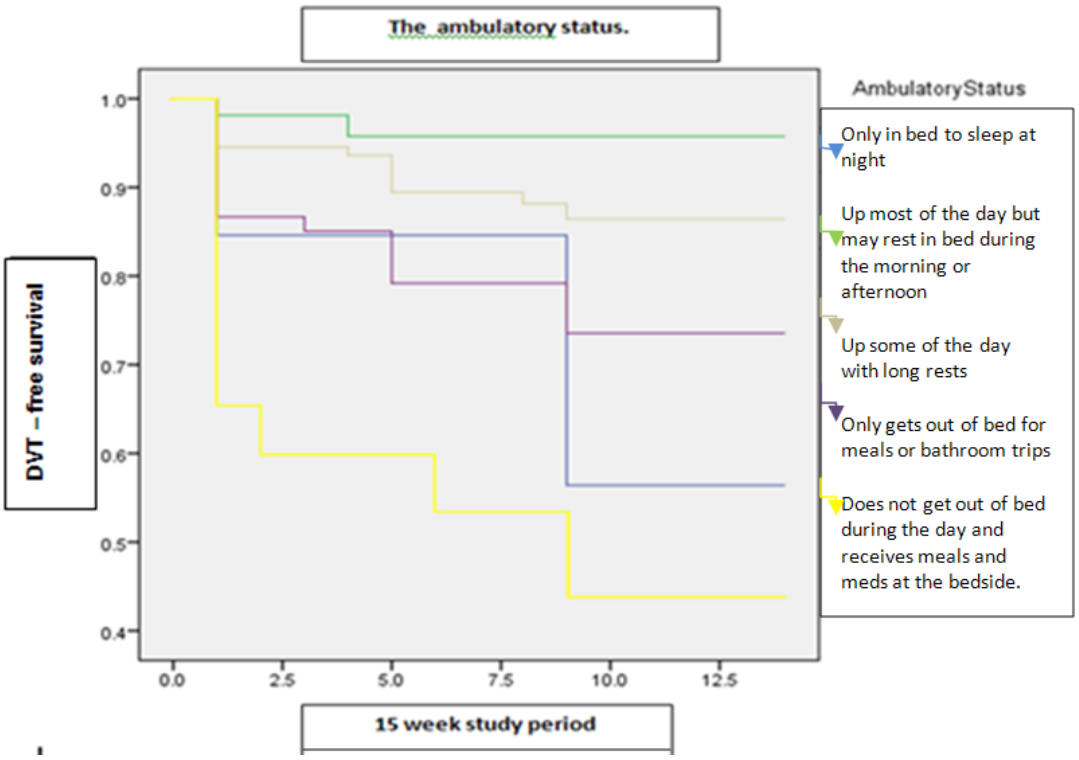


Figure 3.5 Risk of DVT according to ambulatory status

3.5.4 Logistic regression calculations for risk of a DVT

Logistic regression models were developed to identify factors associated with a DVT. The predictive value used was $\alpha = 0.05$. It was considered significant if $p < \alpha$.

The variables ambulatory status ($p = 0.003$), race ($p = 0.03$), and BMI ($p = 0.008$), were all significantly associated with a DVT.

- For the overall ambulatory status, the odds ratio was a 1.262 (95% CI) increased risk for developing a DVT for the person whose ambulatory status was 'does not get out of bed during day' as compared with those whose status was 'only in bed to sleep at night'.
- The BMI odds ratio showed for every one-unit increase in the BMI, there was a 0.104 (95%CI) predictive decrease in risk of a DVT in this study population.
- Race showed an increase in the odds ratio for a DVT between the mixed race and black groups. The mixed race has a 1.16 (95% CI) increased risk for developing a DVT

Those variables in this study population that were not significant were smoking (overall smoking status), $p = 0.098$, age $p = 0.057$, HIV $p = 0.396$ and the CD4 T cell count $p = 998$.

- The age calculations showed a difference of only 0.057 i.e. greater than alpha and therefore not significant. For every year older, there was a 0.022 (95% CI) expected increase in the odds ratio of a DVT.
- The odds ratio to develop a DVT for a person with HIV status was not significant. An HIV- positive person had a 1.313 (95% CI) expected increase in the risk of developing a DVT compared with a person with negative HIV status.
- The CD4 T cell count p = 0.998. This figure is very close to 1 (0.998), predicting little risk of a DVT as the CD4 count dropped or increased.

3.6. TB History of the enrolled population

Chi-squared tests were performed on the variables of previous TB episodes and number of TB episodes. The univariate factors were compared for a difference between the positive DVT and negative DVT groups.

The majority (90.5%) of the participants (n = 360) had a positive diagnosis of pulmonary TB and only 8.5% (n = 34) had a diagnosis of extra-pulmonary TB. There were 1% (n = 4) of the participants in which the differentiation between pulmonary or extra-pulmonary TB was not recorded. There was an increase in the number of DVTs seen in the group who were suffering from their first episode of TB compared with those who had had a previous episode or multiple episodes of TB. This difference was shown to be a statistically significant (p = 0.01 and p = 0.03) (table 7)

Table 3.6 TB History of enrolled population

	Positive DVT	%	Negative DVT	%	p value
Previous TB episode					
Yes	33	54.1%	241	71.3%	
No	28	45.9%	97	28.6%	
Unknown			1	0.3%	0.01
Number of previous TB episodes					
One episode	29	47.5%	142	41.9%	
Two episodes	3	4.9%	59	17.45%	
Three episodes	1	1.6%	17	5%	
Four episodes	0	0.0%	9	3%	
Five episodes	0	0.0%	6	1.8%	
Unknown/missing			9	2.7%	0.03

(Percentages may not add up to 100% due to rounding off)

3.7 Multivariate models: Demographics, risk factors and clinical factors

Generalised regression models were built to explore interactions between multiple variables and DVT risk. The multiple variables from the demographics, risk factors and clinical factors were used with the dependent variable DVT. Initially all the variables were included and compared. If the results showed a statistical significance that was close to the value of 1, they were excluded, as they were not deemed significant. The CD4 count and ART were not significant variables and were the first to be excluded. As the entire sample was not using ART, this meant the test excluded 42% of the sample. Once these two variables were excluded, the test sample included 96.2% of the sample. In the final sample there were 6 variables that were used and these are shown in table 3.7. The categorical variables included race, smoking, alcohol and ambulatory status. The continuous variables were BMI and age.

There were two variables that were statistically significant risk factors: ambulatory status (p = 0.003) and race (p = 0.03). This was similar to that found in the univariate analysis.

Table 3.7 Multivariate results using the variables race, smoking, alcohol, ambulatory status, age and BMI

Variable	Wald-Chi-square	Type III df	p value
Race	4.692	1	0.03
Smoking	2.911	2	0.233
Alcohol	3.182	3	0.364
Ambulatory status	16.057	4	0.003
Age	2.697	1	0.101
BMI	2.397	1	0.122

Dependent Variable: DVT

Model: Race code, smoking status code, alcohol consumption code, ambulatory status, Age, BMI

3.8. Clinical symptoms of a DVT

The types of DVT symptoms encountered were calf pain, Homan's sign, swelling and redness of the limb (table 3.8). The most frequent symptom was pain in the right calf, 71.7% (n = 281) and left calf, 69.4% (n = 272), and this was common to both the positive and negative DVT groups. Chi-squared tests were performed and the overall risks between the different clinical symptoms were compared between the positive DVT and negative DVT groups. The calculations showed that clinical symptoms were not significantly associated with a DVT (p = 0.66), as shown in table 3.8.

Table 3.8 Clinical symptoms of a DVT

Symptom	Positive DVT		Negative DVT	
	Right leg	Left leg	Right leg	Left leg
Calf pain	14 (18.2%)	17 (22%)	267 (24.3%)	255 (23.3%)
Homan's sign	13(16.9%)	15 (19.5%)	201 (18.3%)	190 (17.3%)
Swelling	9 (11.7%)	9 (11.7%)	91 (8.3%)	94 (8.6%)
Redness	0	0	0	0

(Percentages may not add up to 100% due to rounding off)

Within the positive DVT population, only 52.5% (n = 32) were positive for DVT clinical symptoms. Of this group, 47.5% (n = 29) did not have clinical symptoms of a DVT, that is, a silent DVT was present. This difference was shown to be statistically significant as $p<0.001$ (chi-squared test). The clinical evaluation for a DVT diagnosis in this study population had a sensitivity of 52.4% and a specificity of 65.3%. The positive predictive value (PPV) was 21.7%.

Table 3.9 Clinical symptoms of a DVT and ultrasound findings

	ULTRASOUND FINDINGS	
CLINICAL FINDINGS	Positive DVT (61)	Negative DVT(331)
Positive for symptoms	32	115
Negative for symptoms	29	216

Table 3.10 below illustrates the week the clinical symptoms presented. Most of the clinical symptoms were present in the first four weeks, with week 0 being the most common. As the study progressed, the clinical symptoms began to diminish.

Table 3.10 Week number in which the clinical symptoms appeared

Week	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	Totals
+DVT on u-sound	38	2	2	2	9	1	0	1	5	0	0	0	0	0	1	61
L calf pain	80	44	28	22	20	16	12	10	10	7	4	6	5	4	4	272
R calf pain	80	46	27	21	21	14	10	10	12	9	7	9	7	4	4	281
L dorsi-flex pain	58	35	21	17	14	12	10	9	8	5	3	4	3	3	3	205
R Dorsi-flex Pain	60	38	18	15	16	11	9	9	10	8	4	6	4	3	3	214
L swelling	38	15	7	7	10	6	2	5	6	2	1	2	1	0	1	103
R swelling	36	14	6	5	11	4	3	6	6	3	2	2	1	0	1	100
L redness	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
R redness	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

(Percentages may not add up to 100% due to rounding off)

3.9 DVT distribution in the lower limb

There was a similar distribution of DVTs between right, 39.3% (n = 24) and left, 37.7% (n = 23) legs. Of note was that 23% (n = 14) were bilateral. The most common position for a DVT was the right popliteal vein, 36% (n = 22), followed by the right posterior tibial vein, 34.4% (n = 21), the left popliteal vein, 31.1% (n = 19) and the left superficial femoral vein, 31.1% (n = 19). All the veins were counted if a DVT was found to involve the entire lower limb, accounting for numbers not adding up to the n = 61 DVTs discovered.

Table 3.11 Position of the DVT in the peripheral veins

	Bilateral	Right Leg	Left Leg
DVT	14 (23%)	24 (39.3%)	23 (37.7%)
Position in the vein			
CFV		10 (16%)	7 (11.4%)
SFV		12 (19.6)	19 (31.1%)
POP		22 (36%)	19 (31.1%)
PTV		21 (34.4%)	18 (29.5%)
PV		12 (19.6%)	8 (13.1%)
ATV		9 (14.7%)	5 (8.2%)

(Percentages may not add up to 100% due to rounding off)

Of the 61 DVTs identified, there were 6.5% (n = 4) where the thrombus extended up into the iliac veins with 4.9 % (n = 3) reaching the distal IVC. In 1.6% (n = 1), the subject showed thrombus up to the level of the hepatic veins.

Table 3.12 Table showing the four participants who had thrombus extending proximal to the common femoral vein, whether clinical symptoms were present, if they had an abnormal abdominal ultrasound, and their mobility status

4 Participants with extended DVTS	ONE	TWO	THREE	FOUR
DVT	Bilateral Iliacs and distal IVC[1]	Right Right iliac, distal and prox IVC[1]	Right R iliac	Left L iliac Distal IVC[1]
Clinical symptoms	Left	NIL	Left + Right	Left
Abdomen u-sound	Enlarged liver and splenic nodules	Enlarged liver	Normal	Normal
Mobility status[2]	5	3	4	3

1 – Inferior vena cava

2 – Mobility status

1 - only in bed at night

2 - up in the day but may rest am/pm

3 - up some of the day but with long rests

4 - only out of bed for meals/ bathroom visits

5 - does not get out of bed.

3.10 Onset of the DVT

The median day for the onset of a DVT was at day 11 with an IQR=7 (8 – 15 days). Week 0 was the most common time for identifying a DVT, with 62% (n = 38) of the DVTs discovered at this time. Week 4 was the next most frequent time, with 14.7% (n = 9) being identified, and this was followed by week 8 with 8.25% (n = 5) DVTs. There were two DVTs discovered in weeks 1, 2 and 3, and only one DVT found in weeks 5, 7 and 14. No DVTs were identified in weeks 6, 9, 10, 11, 12 and 13.

In the group of participants that were found to have a DVT at week 0 (n = 38). The most common days for identifying a DVT from starting TB medication were days 8, 10 and 11, with 8 DVTs discovered on each of these days. The median day was day 10 and IQR=5 (8 – 13 days).

Table 3.13 Positive DVT group identified at week 0 and the number of days from starting TB medication: the mean, median, inter-quartile range, standard deviation, minimum and maximum number of days

Days from starting TB medication (+DVT)	
Median	10
IQR	5 (8-13)
Std dev	4.69
Min	2
Max	20

The Kaplan-Meier curve (figure3. 8) illustrates the overall probability of a DVT during the 15-week study period. Logistic regression analyses were performed. The 15-week study period is represented on the x-axis and the DVT-free survival on the y-axis. Each change of contour represents a DVT diagnosis. Incidence = 15.3% (95%CI). The life table (table 3.14) is shown below figure 3 6.

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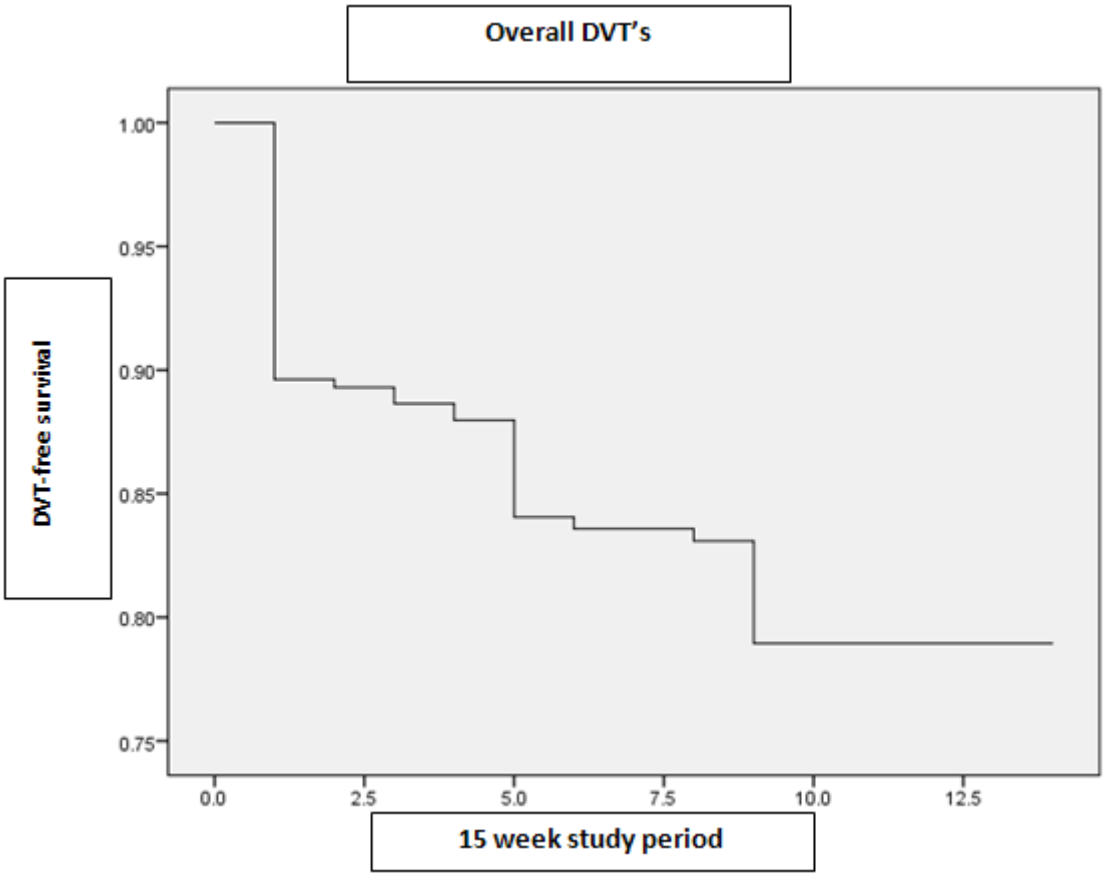

Figure 3.6 Kaplan-Meier probabilities of DVT over the 15-week study period

Table 3.14 Life table used for the Kaplan-Meier graph shown in Figure 3.6

Interval Start Time	Number Entering Interval	Number Withdrawing during Interval	Number Exposed to Risk	Number of Terminal Events	Proportion Terminating	Proportion Surviving	Cumulative Proportion Surviving at End of Interval	Std. Error of Cumulative Proportion Surviving at End of Interval	Probability Density	Std. Error of Probability Density	Hazard Rate	Std. Error of Hazard Rate
0	398	83	356.5	37	0.1	0.9	0.9	0.02	0.104	0.016	0.11	0.02
1	278	4	276	1	0	1	0.89	0.02	0.003	0.003	0	0
2	273	2	272	2	0.01	0.99	0.89	0.02	0.007	0.005	0.01	0.01
3	269	9	264.5	2	0.01	0.99	0.88	0.02	0.007	0.005	0.01	0.01
4	258	67	224.5	10	0.04	0.96	0.84	0.02	0.039	0.012	0.05	0.01
5	181	4	179	1	0.01	0.99	0.84	0.02	0.005	0.005	0.01	0.01
6	176	2	175	0	0	1	0.84	0.02	0	0	0	0
7	174	14	167	1	0.01	0.99	0.83	0.02	0.005	0.005	0.01	0.01
8	159	77	120.5	6	0.05	0.95	0.79	0.03	0.041	0.016	0.05	0.02
9	76	11	70.5	0	0	1	0.79	0.03	0	0	0	0
10	65	2	64	0	0	1	0.79	0.03	0	0	0	0
11	63	5	60.5	0	0	1	0.79	0.03	0	0	0	0
12	58	8	54	0	0	1	0.79	0.03	0	0	0	0
13	50	2	49	0	0	1	0.79	0.03	0	0	0	0
14	48	47	24.5	1	0.04	0.96	0.76	0.04	0	0	0	0

3.11 Mortality

Table 3.15 lists the number of deaths, 9% (n = 36), encountered in the study population, the number of days they were on the study, the cause of death recorded in the hospital folder (autopsy confirmation not obtained as none of these patients had a post mortem), whether or not a DVT had been identified and if the participant was having anticoagulants administered..

Over the 15-week period the total number of deaths within the study population was 36 (9%). Within this group there were 5 (13.8%) DVTs identified and a pulmonary embolus was recorded in two patients as cause of death. There were 2 (5.5%) participants who died prior to their first ultrasound scan. The average length of time on the study was 30 days, with the shortest time being 1 day and the longest 104 days. In this group 61.1% (n=22) were having prophylactic anticoagulants administered

Table 3.15 Mortality within the study population

PT ID	Days on Study	Reason		DVT *	Anti-coag*
1	6	PTB, bulla lung disease, substance abuse		Neg	
22	8	PTB		No u-s	
37	22	PTB		Neg	
33	11	PTB, probable lung CA		Neg	Yes
24	47	PTB. HIV positive stage IV, pneumonia, cryptococcal meningitis.		Neg	Yes
16	17	PTB, COAD, HIV positive, CA cervix stage 3b		Neg	
49	40	PTB, HIV positive stage IV, pneumothorax,		DVT	
61	1	PTB, HIV positive stage IV, septicaemia, hepatitis,		Neg	
107	44	PTB		Neg	
117	7	PTB with major haemoptysis.		Neg	
123	4	PTB, DTB, PCE, PE, RVD, pancytopaenia, substance abuse		Neg	Yes
131	104	PTB, DTB, RVD, DIH, sepsis, renal failure, thombosytopaenia	Neg		Yes
152	72	PTB		Neg	Yes
158	2	PTB, COAD, substance abuse, destroyed lung		DVT	Yes
167	64	PTB, DTB, TBM, RVD		Neg	
183	68	PTB, RVD		Neg	Yes
201	42	PTB, respiratory arrest		Neg	Yes
204	42	PTB, respiratory tract infection		Neg	Yes
210	25	DTB, RVD, pancytopaenia		No u-s	Yes
222	16	PTV, RVD, substance abuse		Neg	
229	14	PTB		Neg	
239	8	PTB, RVD, DTB		Neg	
292	17	PTB, RVD, pregnant		Neg	
293	8	PE, PTB		DVT	Yes
298	51	PTV, RVD		Neg	Yes
311	20	PTB, dehydration		Neg	Yes
313	27	PTB, RVD		Neg	Yes
326	98	PTB, RVD metabolic dysfunction		DVT	Yes
334	4	PTB, RVD		DVT	Yes
338	27	PTB, DTB, RVD and sepis		Neg	
340	1	PTB, PE		DVT	Yes
354	24	PTB, RVD		Neg	Yes
370	16	PTB, DTB, RVD, anaemia		Neg	Yes
372	10	PE, MI, PTB, anaemia, CA		Neg	Yes
387	71	PTB, RVD, thrombocytopaenia		Neg	Yes
394	46	DTB, HIV, sepsis, major depressive episode		Neg	Yes

*neg = negative for DVT on ultrasound

DVT = positive DVT finding on ultrasound

No u-s = participant demised prior to DVT scan

*Yes= anticoagulants were being administered

Key to table 3.15

KEY	
CA	Carcinoma
COAD	Chronic obstructive airways disease
DTB	Disseminated tuberculosis
MI	Myocardial infarction
PCE	Pericardial effusion
PE	Pulmonary embolism
PTB	Pulmonary tuberculosis
RVD	Retroviral disease
TBM	Tuberculosis miliary

3.12 Ancillary studies

The ancillary study included a single routine abdominal ultrasound that was performed at week 0. Of the 400 participants who were registered on the study, 382 abdominal ultrasound reports were reviewed. There were 75.5% (281) abnormal reports, 22.5% (n = 90) normal reports and 4.5% (n = 18) with no report. table 3.16 shows examples of the different types of abnormal abdominal organ pathology identified.

Table 3.16 Abnormal abdominal organs identified on the abdominal ultrasounds

Abnormal organ pathology	%
LIVER	32.9
RENAL	28.7
SPLEEN	25.4
LYMPH ADENOPATHY	20.2
PLEURAL EFFUSION	11.5
PERICARDIAL EFFUSION	10.2
BILIARY	5.4
FREE FLUID	11
PANCREAS	3.4
IVC	0.26

In the positive DVT group there were 18.3% (n = 11) participants that had normal abdominal reports. The remaining 81.9% (n = 50) had abnormal abdominal reports. The most common findings were echogenic kidneys, 31.1% (n = 19), and splenic nodules, 29.5% (n = 18). Lymphadenopathy was present in 24.5% (n = 15), and 21.3% (n = 13) had enlarged livers. Incidental pericardial effusions were seen in 9.8% (n = 6) of the subjects.

In the four participants where the thrombus extended into the iliac veins and the IVC, two had normal abdominal ultrasound reports. The remaining two abnormal abdominal reports both showed enlarged livers and one had accompanying splenic nodules.

The different pathologies in each of the abdominal organs are listed in the tables below.

The most common abnormality of the liver seen was an enlarged liver with 25.9% (n=99) being reported. This was followed by 12% (n=46) of the livers being determined as echogenic. 9.1% (n=35) were recorded as heterogenous and one 0.26% was considered hypoechoic. There were several focal liver lesions reported. 1.3% (n=5) noted single or multiple echogenic lesions within the liver, 0.78% (n=3) reported simple liver cysts and 0.78% (n=3) were seen as single or multiple hypoechoic lesions. A dilated portal vein was described 1.3% (n=5) and a single 0.26% report of a thrombosed portal vein with cavernous transformation was seen. A single, 0.26% account of multiple small nodules and a single subprenic collection was reported.

Table 3.17 Liver Abnormalities Identified on the Abdominal Ultrasounds

LIVER ABNORMALITIES	% (n)
Enlarged Liver	25.9% (n=99)
Echogenic liver	12% (n=46)
Heterogenous	9.1% (n=35)
Echogenic lesions	1.3% (n=5)
Dilated Portal Vein	1.3% (n=5)
Simple Liver cysts	0.78% (n=3)
Multiple small Hypoechoic lesions	0.52% (n=2)
Hypoechoic Liver	0.26% (n=1)
Thrombosed Portal vein with Cavernous Transformation	0.26% (n=1)
Multiple small nodules with dilated PV ?cirrohis	0.26% (n=1)
Dilated hepatic veins	0.26% (n=1)
Subprenic collection	0.26% (n=1)

The participants were not examined in a fasted state so the ultrasound scan showed the majority 86.4% (n=330) to have a contracted gall bladder. Cholelithiasis was seen in 2.9% (n=11), gall bladder sludge in 1.57% (n=6) and 1.52% (n=2) participants had pericholecystic

fluid. The main bile duct (MBD) was dialated 1.87% (n=7) : the MBD was deemed dilated if it was greater than 6mm. The normal diameter is 4-6mm and is age dependant (Saunders, 1991:300). The maximum MBD measurement was 27mm, the minimum 1.1mm and the mean MBD measurement was 3.1mm (Table 3.18)

Table 3.18 Billary Abnormalities Identified on the Abdominal Ultrasounds

GALL BLADDER AND MBD ABNORMALITIES	% (n)
Contracted	86.4% (n=330)
Calculi	2.9% (n=11)
Sludge	1.57% (6)
Peri-cholecystic fluid	0.52% (n=2)
MBD	
Dilated (> 6mm)	1.83% (n=7)
*max MBD diameter = 27mm	
*min MBD diameter 1.1mm	
*mean MBD diameter 3.1mm	

The most common abnormality seen within the urinary system were echogenic kidneys 29% (n=110). This was followed by enlarged kidneys 4.9% (n=19). 1.8% (n=7) were seen on the right and 3.1% (n=12) were seen on the left. 1.3% (n=5) of the kidneys were regarded as small: 0.52% (n=2) on the right and 0.78% (n=3) on the left. A kidney was recorded as enlarged if its length was greater than 130mm and small if the length measured less than 80mm (Saunders, 1991:300). Simple cortical cysts were seen in 3.4% (n=13), loss of corticomedullary differentiation in 1% (n=4), mild hydronephrosis in 0.78% (n=3) and renal calculi in 0.78% (n=3). A single 0.26% (n=1) hypoechoic mass and a single 0.26% (n=1) perinephric collection were also seen (Table 3.19)

Table 3.19 Renal Abnormalities Identified on the Abdominal Ultrasounds

RENAL ABNORMALITIES	% (n)
Enlarged Kidneys	4.9% (n=19)
* right	1.8%(n=7)
* max size - 150mm	
* min size -83mm	
* mean - 108.6mm	
* left	3.1% (n=12)
* max size - 150mm	
* min size -83mm	
* mean - 108.6mm	
Small kidneys	1.3% (n=5)
*right	0.52% (n=2)
* left	0.78%(n=3)
Echogenic Kidneys	29%(n-110)
Simple Cysts	3.4% (n=13)
Loss of corticomedullary differentiation	1% (n=4)
Mild Hydronephrosis	0.78% (n=3)
Calculi	0.78% (n=3)
Hypoechoic mass ?Renal Abscess	0.26% (n=1)
Perinephric collection	0.26% (n=1)

The pancreas was difficult to visualise as the patient was not kept nil per mouth. Enlargement was judged by the sonographer only if the ultrasound landmarks could be seen. 1.8% (n=7) were thought to be enlarged and 0.52 % (n=2) were heterogenous. A single finding of a dialated pancreatic duct 0.26% (n=1), calcifications with in the pancreas 0.26% (n=1) and a solid, focal mass 0.26% (n=1) (Table 3.20).

Table 3.20 Pancreatic Abnormalities Identified on the Abdominal Ultrasounds

PANCREAS ABNORMALITIES	% (n)
Enlarged	1.8% (n=7)
Heterogenous	0.52% (n=2)
Dilated duct	0.26% (n=1)
Calcifications	0.26% (n=1)
Focal mass	0.26% (n=1)

Many of the participants had an empty bladder 23.8% (n=91) and this precludes examination of the pelvic structures on ultrasound. Echogenic debre was seen within the bladder in 1.57% (n=6), a solid mass was seen 0.78% (n=3), simple ovarian cysts 0.52% (n=2), complex masses within the psoas muscle 0.52% (n=2) and early intrauterine pregnancy was identified 0.52% (n=2). A single occurrence of uterine fibroids 0.26% (n=1), thickened loops of bowel 0.26% (n=1) and an enlarged prostate 0.26% (n=1) (Table 3.21)

Table 3.21 Abnormalities Identified within the pelvis on the Abdominal Ultrasounds

PELVIC ABNORMALITIES	% (n)
Empty bladder	23.8% (n=91)
Echogenic bladder debre	1.57% (n=6)
Solid mass	0.78% (n=3)
Simple ovarian cyst	0.52% (n=2)
Mass within the psoas muscle	0.52% (n=2)
Early Pregnancy	0.52% (n=2)
Uterine Fibroids	0.26% (n=1)
Thickened Bowel	0.26% (n=1)
Enlarged prostate	0.26% (n=1)

There were three incidental findings recorded on the abdominal ultrasound reports. A single 0.26% (n=1) echogenic mass within the right ventrical of the heart, a single 0.26% (n=1) right adrenal mass and a 0.26% (n=1) left direct inguinal hernia that was easily reducable (Table 3.22).

Table 3.22 Incidental Abnormalities Identified on the Abdominal Ultrasounds

Incidental Findings	
Echogenic mass in RV of the heart	0.26% (n=1)
Right adrenal mass	0.26% (n=1)
Left inguinal hernia	0.26% (n=1)

CHAPTER 4

Discussion

4.1 Discussion

This thesis has shown that an effective ultrasound service, successfully administered by a trained sonographer, can be provided at a district-level hospital. This can also facilitate a screening service to diagnose both symptomatic and asymptomatic deep vein thromboses in newly diagnosed tuberculosis (TB) patients at primary health care level (PHC). In addition, this study has confirmed the high rate of deep vein thrombosis (DVT) in newly diagnosed TB patients and provides detail on additional risk factors. The study illustrates the poor performance of clinical symptoms and signs as a trigger for further investigation for confirmation of DVT. Given the frequency and impact of the embolic complications of DVT, this study provides a strong justification for further research into routine serial ultrasonic screening and/or prophylactic antithrombolytics in newly diagnosed TB patients.

4.2 Intervention

A part-time ultrasound service was successfully established over a 20-month period at the DP Marais TB Hospital in Cape Town, with the first study patient scanned on 30 March 2010 and the final follow-up ultrasound examination performed on 5 December 2011. During this time the ultrasound clinic was held once a week. A total of 889 DVT study scans and 382 abdominal ultrasound examinations were performed by trained sonographers among newly admitted TB patients. A DVT incidence of 15.3% within the study population was identified. Of these, just over half (52.5%) had clinical symptoms of a DVT, with 47.5% of the diagnosed DVTs occurring in asymptomatic patients. Most DVTs were diagnosed within two weeks of treatment commencement, with the more common days for developing a DVT being days 8, 10 and 11 after treatment commencement. Of the 61 DVTs identified, there were 4 (6.5%), where the thrombus extended up into the iliac veins, with 3 (4.9 %) reaching the distal IVC. One (1.6%) subject showed thrombus up to the level of the hepatic veins.

Besides the ultrasound DVT examination of the lower extremity, the service was extended to include other anatomical regions. Of the 382 abdominal ultrasounds performed, 281 (75%) were reported as abnormal. Many of the abnormal abdominal ultrasounds showed multiple pathologies, illustrating the complexities of both TB and the co-morbidity HIV. Examples of some of these pathologies that were very helpful for patient management were the imaging of pericardial effusions, liver abscesses, psoas abscesses, metastatic disease, renal disease and cysticercosis.

4.3 Ultrasound improves diagnosis

For many years it has been known that respiratory infections increase the risk of VTE (Ambrosetti et al., 2006:396), and in particular a DVT which is a known complication following the treatment of TB. Left untreated, there is the danger of a DVT's developing into a PE, which has a mortality rate of 30% (Picton & McCollum, 2007:36). Neil White states in his report of 1989 that "a DVT is difficult to recognise and clinical symptoms are an insensitive method of diagnosis" (1989:435). Today the modality of choice for diagnosing a DVT is a compression ultrasound examination (CUS). Ultrasound has a reported sensitivity of 88 – 100% and specificity of 92 – 100% for the diagnosis of a DVT (Dähnert, 2007:396). In this study, diagnosis based on clinical signs and symptoms had a sensitivity of 58% with a specificity of 65%.

Importantly, this study has shown that by screening for a DVT using regular routine ultrasound scans in this population, it is possible to detect a DVT with ultrasound prior to the onset of clinical symptoms ($p = 0.0000000005$). This allowed for the identification of the serious 'silent' DVT, the commencement of appropriate treatment, and the avoidance of sequelae and complications.

Of the study participants diagnosed with a DVT, 47.5% were considered 'silent', that is, no clinical symptoms were observed. Overall 37.7% of the study population had clinical symptoms, but of these just over half (52.5%) were proved positive for a DVT with ultrasound. The most common clinical symptom was found to be pain in the left calf (28%).

The silent DVT is important as there is potential morbidity attached to it. However, the false positive group (48%) should also be considered. This group was clinically positive for DVT symptoms but ultrasound ruled out the presence of thrombus. Without the ultrasound diagnosis, there is the potential for unnecessary treatment increasing cost, treatment risk and discomfort to the patient. The treatment for a DVT is with anticoagulants. All patients should be closely monitored when using anticoagulants, as although bleeding is rare, it can occur and there is also the possibility of developing heparin-induced thrombocytopaenia (HIT) (Franchini, 2005:14-18). This proposes two important advantages when using ultrasound examinations in this population group:

1. Ultrasound has the ability to diagnose the 'silent' DVT and so reduce morbidity and mortality.

2. Ultrasound can easily differentiate a false positive clinical suggestion of a DVT, therefore limiting the problem of over-diagnosis that increases cost to the state and discomfort to the patient.

4.4 Comparisons with other studies

There are four reported studies on DVTs in the setting of early TB treatment (table 4.1). Both the studies of White (1989:434) and Petersen et al. (2001) were retrospective, while the research of Ambrosetti et al. (2006:396) and this study were prospective studies. The DVT incidence (15.3%) in this study was almost five times more than that in the study done by White in 1989 (3.4%) and nearly double what Petersen et al. found in 2001 (8%). In all three of the previous studies the DVT was suspected clinically and then confirmed by imaging, either with contrast venography or CUS. This study used ultrasound as an imaging tool, regardless of whether the patient had clinical symptoms or not. It explored the utility and efficacy of using routine serial CUS as a screening diagnostic tool for DVT diagnosis. This was made possible by choosing the more economical imaging of sonographers' reporting ultrasound scans, rather than the more common, but expensive, 'radiologist-imaging' used in the past. In 2006 Ambrosetti et al. also looked at VTE in a TB setting in Italy, but found only an overall VTE incidence of 0.6% (DVT = 0.4% and PE = 0.2%) (Ambrosetti et al., 2006:396).

Table 4.1 Comparisons between other studies

	Prevalence %	**Median day to DVT**	**Male: Female**	**Median age (years)**	**New TB cases %**	**PTB %**	**Morbidity %**
WHITE	3.4	<14	01:01	37.7	-		10.80%
PETERSEN et al.	8	17	-	-	-		
AMROSETTI et al.	0.6	20	02:01	44	75	92	
THIS STUDY	***15.3***	***10***	***2.5:1***	***39***	***31.2***	***90.5***	**8.10%**

This study identified the most DVTs (62%) during the first or baseline ultrasound scan that was called week 0, and which occurred within 21 days of starting TB treatment with the eighth, tenth and eleventh day from commencing TB treatment the most common. This was much sooner than in the studies by Petersen et al. in 2001 and Abrosetti et al. in 2006 which showed that the DVT was clinically symptomatic at a median of 17 days and 20 days (+/- 15 days) respectively. The results from this study do concur with that reported by White (1989), who suggested that the DVT occurred in the first two weeks of treatment's commencing.

The studies of White (1989:434-435) and Petersen et al. (2001) were retrospective, and examined data extending over several years. This study was unique in that data collection was prospective and the study design allowed for active ultrasound screening. The CUS was not only used to confirm a DVT when clinically suspected, but also used to actively screen for a thrombus in participants with no clinical symptoms.

White's research (1989:434), that of Ambrosetti et al. (2006), and this study had a wide but similar age range. White's median age was equal to 37.7 years (15 – 86); the median age of Abrosetti et al. was 44 years (26 – 62), while this study had a median age of 39 years (32 – 51). There were 2.5-fold more men affected by DVTs in our study than women, which was very similar to the incidence reported by Abrosetti et al. (2:1), but different from that reported in White's study (1:1). However, in this study, sex was statistically not significant as an independent predictor for a DVT. TB admission was more common among men than women in this study, as shown by the total admissions to DP Marais Hospital over the study time period, which also showed a 2.5:1 male-to- female ratio.

In White's study (1989:434-435), 5 of the 46 (10.8%) DVT patients died, while in this study 5 (8.1%) of the 61 patients with a DVT died. There was an overall study mortality rate in this study of 9%. In all five cases the main cause of death was the primary disease of TB or HIV, and in two PE was included in the possible cause of death. Unfortunately this was not confirmed as none of the patients underwent autopsy.

There is a correlation between a PE and DVT with a DVT thought to be the main cause of a PE in 9 – 56% of cases (Dähnert, 2007:322). A DVT and a PE are usually thought to be part of the same disease process, but at different chronological stages (Brakenridge, et al., 2013:1231-1238). In reported literature, clinical symptoms of a DVT are only present in 30% of proven symptomatic PE (Pomero et al., 2011:405-411), raising once again the problem of the silent DVT. It is also thought that in 30% of angiographically diagnosed PE that are negative for a DVT that the entire thrombus may have embolised to the lung with no residual clot remaining in the lower extremity veins (Dähnert, 2007:322). A PE cannot be predicted on the findings of CUS of the lower limb (Pomero et al., 2011:405-411).

In both the study by Ambrosetti et al. (2006:396) (92%) and in this study (90.5%), most of the participants had pulmonary TB. However, in this study the majority of the cases were repeat TB infections (68.8%), which may reflect the patient population who are admitted to the DP Marais Hospital, many of whom are non-adherent and require injectable treatment. This was very different from the findings of Ambrosetti et al. (2006:396), which showed 75% were first-

time infections, compared with only 31.2% found in this study. The data of Abrosetti et al. (2006:396) was collected from 46 TB units in Italy, which is considered a low-incidence country. A sampled subset of 1237 patients was used. This was determined by the willingness of the centres to impartially state the incidences of the VTE events in consecutive patients.

4.5 Risk factors

This study considered four patient risk factors based on literature that may have influenced the development of DVTs, HIV status, BMI, smoking and the mobility of the patient. Lack of mobility had the greatest impact on DVT risk ($P<0.001$). This concurred with the literature that DVT and PE are well-described complications of hospitalisation and immobilisation (Ahuja et al., 2007:38).

A normal BMI is between 18 and 24.9. In this study an abnormal BMI was observed in more than half of the participants but in most of the cases it was lower than normal i.e below 18. A BMI greater than 30 is classified as obese and there were only 2 participants who fell into this catogory. The literature that quotes an abnormal BMI refers to increased BMI or obese patients that are predisposed to developing a DVT (Severinsen et al., 2009a:1850-1857). An obese patient may be less mobile, thereby contributing to the risk of a DVT, but in this TB population, most had a low BMI, possibly moderating the risk of further reduced mobility. BMI was found to be a significant independent moderator of risk for a DVT ($p = 0.008$). This suggests that in these patients a low BMI may have provided some reduction in the risk of a DVT.

In this population group, smoking status and alcohol consumption proved to be a mildly statistically significant risk factor for the development of a DVT. Smoking in particular is regarded as an acquired risk factor for DVT development (Goldhaber & Morrison, 2002:1437). However, other studies have shown that if the smoking ceases, former smokers will fall into the same risk category as one who has never smoked (Severinsen et al., 2009b:1297-1303), a further reason that stopping smoking should be encouraged!

Surprisingly in this study the HIV status did not significantly impact on the risk of developing a DVT. This differs from other studies that stated the HIV-infected patient had an increase in the odds ratio of 43% for developing a PE, a 10% increase of developing a DVT and a 40% increase of developing both a DVT and a PE (Malek et al., 2011:278-282). Current thinking is that co-infected individuals normally have more severe disease, may be less mobile, are more likely to be bed ridden and may have a greater inflammatory profile with increased risk

of thrombosis (Malek et al., 2011: 278-282). Of the 58% who were co-infected with TB and HIV in this study however, 67.7% were on antiretroviral therapy (ART). This is in keeping with current South African guidelines that make provision for patients with TB to commence ART regardless of CD4 T cell count. ART results in a reversal of the effects of the HIV infection with improved CD4 T cell counts' reduced viral load, enhanced well-being and consequently increased mobility and presumably reduced risk of DVT. ART may have mitigated any increased risk associated with HIV. Logistic regression in this study, however, showed that change in the CD4 T cell made little difference to DVT risk. Further studies in this area, particularly at the level of pathogenesis, would be useful.

4.6 Impact of the TB regimen

The association between a DVT and pulmonary TB is thought to be due to the alliance between haemostatic changes and the inflammation that results in a hypercoagulable state. Robson's study reported that fibrinogen levels in all patients were elevated in the first two weeks of TB treatment but returned to normal within 12 weeks. The DVT development was helped by the elevated plasma fibrinogen with impaired fibrinolysis, together with a reduction in antithrombin iii and reactive thrombocytosis (Robson et al., 1996,943-949).

Although regimen 2 in the South African TB programme has now been changed, at the time of this study, it was used in the treatment of patients undergoing a second or further bout of treatment. This included a daily injection of intra-muscular streptomycin added to the four-drug regimen of regimen 1 (ethambutol, isoniazid, rifampicin and pyrazinamide) administered orally. Patients with known repeat episodes were given regimen 2 empirically. In this study, the regimen that patients were taking was found to be an independent predictor of DVT risk ($p<0.05$). In this study population, 68.7% had had previous episodes of TB treated so were subsequently treated with regimen 2. Of this group, 10.9% developed a DVT. The remaining 31.3% of the population were on regimen 1. The DVT incidence in this group was more than double (24.4%) that of the regimen 2-group. One explanation for this is that the additional drug, streptomycin, present in regimen 2, protects against the formation of DVTs. This would correspond with the literature that proposes that some antibiotics (including streptomycin) have antithrombolytic properties and are a possible cause of an acquired factor V deficiency. Patients with an idiopathic factor V deficiency can suffer from bleeding disorders that can range from mild to severe (Colman, 2006:927). An alternative hypothesis would be that a DVT is a more common complication seen in the first M.tb infection rather than in repeat infections. (This needs further investigation.)

4.7 Barriers to a point care ultrasound service

While it would make good medical sense to have a more reliable diagnosis of a DVT and other abdominal conditions on site at the point of care, such as that provided by an ultrasound scan, there are a number of barriers to this provision, particularly in low- and middle-income countries such as South Africa.

4.7.1 Economics

In the time period that this study at the DP Marais Hospital was carried out, there was no on-site imaging service for the TB patients. If a DVT was suspected clinically, then the patient needed to be transported approximately 7km to a secondary hospital. Here the DVT ultrasound scan would be performed by the radiologist, a report written, and the patient finally returned to the DP Marais Hospital for management and treatment. This needed the time and resources of a medical specialist, created a bottleneck for this service and required a queue with a probable waiting list. Patient transportation had to be arranged, as well as staff supervision away from the primary facility. Added to this is the discomfort and distress to a sick, frail and often high-risk patient, with the accompanying additional potential morbidity and mortality.

In South Africa, ultrasound is often thought to be in the realm of the tertiary institute and has until recently fallen under the domain of the specialist such as a radiologist or vascular surgeon. Both are specialist doctors. The radiologist is a specialist physician with many years of professional training. This makes the ultrasound examination, when performed by a radiologist, an expensive imaging procedure. The hourly rate for a radiologist fluctuates but is approximately R371 – R430 (Western Cape Government, 2013). In private practice this can escalate to as much as R654 – R1134 p/h. A radiologist is a specialist with a medical degree, followed by years of specialisation in radiology.

Training of sonographers began in the Western Cape in the mid 1990s. With a sonographer both performing and reporting an ultrasound, the cost is considerably reduced. Training of these individuals is less costly, is goal directed and is achieved at a fraction of the time taken to train a medical specialist. The hourly rate for a sonographer is approximately R120 – R200. For this study, the qualified sonographer who assisted with the ultrasound scanning had an hourly rate of R140 p/h as a research assistant.

A factor not considered here is whether a radiologist may be able to perform many more DVT studies than an ultrasonographer. A radiologist also has an in-depth understanding of the disease process and extended knowledge that can be drawn on to trouble shoot with complicated cases. However, a point-of-care sonographer could save patient time, see

uncomplicated cases, and allow the more complex cases to be referred to the radiologist. In addition, not discussed in this study, is the use of digital distance reporting. In this scenario, the ability to consult real time with the radiology specialist would assist the sonographer with difficult cases and could add support when additional imaging or treatment might be required at a secondary or tertiary level.

Included in the cost of beginning an ultrasound clinic should be the initial outlay of the ultrasound machine; depending of the choice of machine this can vary from around R250 000 – R1 200 000. For this study, a Toshiba Eccocee machine was provided by the Desmond Tutu HIV foundation (DTHIVF). As this study was primarily a vascular project, it was important to include both special probes and software for Doppler ultrasound, as well as what was needed for routine abdominal ultrasound. The present day equivalent of such a machine would cost approximately R250 000– R300 000, and this would include both the abdominal and vascular probes. An ultrasound machine, if used by trained sonographers, is a robust, reliable machine. It is required to be serviced annually and general daily care and cleaning can be performed by the sonographers. As with all imaging equipment, the technology advances very rapidly and new machines soon become outdated. In a situation such as this study, a new ultrasound machine should have a lifespan of between 5 – 10 years. It could be a lot longer; however if the imaging needs of the institution become more sophisticated, upgrading the ultrasound machine would have to be considered.

When compared with other vascular imaging, such as the conventional venogram or a CT venongram, ultrasound is the most economical (table 1.3, Chapter 1). Other advantages include mobility, the lack of ionising radiation and introduction of contrast media, as well as the versatility of the ultrasound machine. With the simple addition of one ultrasound probe and software, the same machine was used for imaging the abdomen. (Imaging the abdomen was part of the additional service that was offered by this researcher for this project.)

The objective of this thesis was to create a rationale for point-of-care screening for DVT in TB patients, using a sonographer-led ultrasound service. While cost effectiveness is beyond the scope of this thesis, a cost-effective study would further strengthen the rationale for this much needed point-of-care service.

4.7.2 Logistics and support

The public sector medical environment in South Africa currently has not considered the routine deployment of sonographers to primary health care settings such as TB clinics and hospitals to perform activities such as the ultrasound diagnosis of a DVT.

This study has shown that it is both feasible and useful for a sonographer to perform and report DVT scans in a TB hospital setting. A significant incidence of DVTs was discovered. The data from this study also shows that a significant number of DVTs were discovered prior to clinical symptoms. While not proved, it may be assumed that a significant number of sequelae known to occur with undiagnosed and untreated DVT may have been averted by this intervention. In addition, ancillary services such as the abdominal ultrasound screens provided a useful abdominal ultrasound scanning resource.

However, establishing a future ultrasound service such as this one does have a number of challenges to overcome. The most problematical would be engaging the sonographer. Currently, only a few sonographers (approximately eight) graduate each year in the Western Cape. Following community service, most sonographers are lost to the better working conditions of private practice and medical facilities abroad. This may reflect on public sector demand. Given the lack of opportunities and dearth of sonographers at TB clinics/hospitals, the community service sonographer may struggle with both confidence and insight regarding this high-risk, specialised scanning situation and population group. However, a solution to this could be overcome by allowing a tertiary teaching hospital to supervise the community service sonographer. This would give sonographers access to a forum for discussion, advice and help regarding these difficult ultrasound cases. It would be important to ensure careful quality control both regarding the use of the ultrasound machine and the scan performed. Careful documentation that can be assessed by more senior and experienced sonographers would ensure strict quality control. In addition, greater demand may encourage a more supportive mentorship environment with the possibility of digital distance reporting as back-up and real-time specialist support from a tertiary radiology department.

As this study situation only required a weekly ultrasound clinic, several primary health care situations could be serviced together. Of note, and certainly encouraging, is the fact that a sonographer-led antenatal care service has already been successfully established within the midwife obstetric unit (MOU) service within the Western Cape.

This project had the use of a suitable ultrasound machine that was funded by the Desmond Tutu HIV Foundation, alleviating the main capital outlay for such a service. DP Marais Hospital management made the necessary arrangements to house, store and safeguard the machine.

While the practicalities of an ultrasound clinic are simple, they should be addressed and can be difficult in clinics with minimal space. For this study, a clinic room provided by the hospital was allocated and set up with the use of an examination couch for the ultrasound scans. As this service was provided only once a week, it was reasonable to share space within the clinic. If the regular clinic times were changed, this created logistic challenges. Once established within the clinic, the ultrasound service proved invaluable to the medical staff, as the sonographers were easily accessible to the medical team and patients. Additional staff included a nurse and porter. Many of the study participants were weak and very frail at the commencement of their treatment. The assistance of both the study sister and the porter in the movement and transportation of these ill patients was essential.

4.7.3 Other benefits of the service

As well as the DVT ultrasound scans, there was the ancillary service offered by the research sonographers that included an abdominal scan that detected abdominal pathology in 75% of the scans performed.

Unfortunately, since the routine abdominal ultrasounds were requested by the medical staff, these patients were not kept nil per mouth (npm). This is a requirement for optimal visualisation of the abdominal organs on ultrasound. For this study, the medical/nursing team attending to these patients felt it would be too disruptive to the management of the wards to keep the participants in a fasted state. In spite of this, multiple abdominal pathologies were identified. The scope of the sonographer is to identify and describe ultrasound findings. This was done by reporting any change in the structure, echogenicity, or size of the abdominal organs. Some of the abnormal reports might not have had a direct influence on patient management (e.g. single kidney, asymptomatic gall stones); others had a more direct influence (e.g. the presence of an abscess, a thrombosed portal vein or a pericardial effusion). Many of the participants had multiple abdominal pathologies illustrating the complexity of their disease.

An ultrasound scan is not pathognomonic but it does provide significant insight to the extent of some of the abdominal pathologies. HIV is a common TB co-morbidity and this too can show changes in the abdominal organs that can be visualised in the routine abdominal ultrasound (Kawooya et al., 2008:62).

In this study, ultrasound showed an abnormal ultrasound appearance most commonly in the liver, followed by the kidneys and spleen. In Africa, a change in the liver echo-texture is most commonly due to TB, and since this study was exclusively performed on TB patients, this would account for the high rate of abnormalities. Hepatomegaly is a common finding seen in HIV and focal liver changes may be due to TB, lymphoma, hepatocellular carcinoma (HCC), or regeneration nodules/focal nodular hyperplasia (FNH). With focal, echogenic masses (commonly seen in the liver and thought to represent benign haemangiomas), in this population group, Kaposi's sarcoma should also be considered (Kawooya et al., 2008:62). In this study approximately 1.3% of the liver lesions described were focal echogenic masses.

The most common abnormal renal ultrasound recorded was an increased echogenicity, and this is commonly seen in HIV nephropathy. Abnormal ultrasounds of the spleen were almost exclusively the presence of hypoechoic nodules of varying size. Most times this is due to TB infections or lymphoma, however, if the nodule has a 'bull's-eye' appearance on ultrasound, it usually represents small abscesses due to *Candida albicans* infections.The presence of lymph nodes within the abdomen was also common and is a frequent finding in abdominal TB (Kawooya et al., 2008:62). The incidental finding of an echogenic mass within the right ventrical of the heart might have represented clot as thrombosis can appear echogenic on the ultrasound image. This was important information for the medical staff as the patient had also been confirmed with DVTs present in both lower limbs.

The ultrasound machine, with the assistance of the sonographers, was also available to offer guidance to the medical officers with interventional procedures such as fine-needle aspiration or biopsies. Specimens gained from these procedures were sent for cytological or histological diagnosis. Assistance with therapeutic drainage of abscesses or collections was also done.

While the abdominal ultrasound was not a primary aim of this thesis, it does indicate another area of ultrasound medicine where further research is warranted.

4.8 Strengths and weaknesses of the study

The main strength of this study was its prospective active screening approach to the ultrasound investigations, proving that some DVTs are present prior to clinical symptoms developing, and demonstrating a remarkable rate of DVTs in new TB patients. This is unlike the previous studies that waited for the clinical symptoms to manifest before imaging confirmed the presence of a DVT (White, 1989; Petersen et al., 2001). This is probably the

main reason for the increased number of DVTs identified when compared with the retrospective studies cited in this thesis. In this study, 38% of the DVTs discovered were clinically silent. In addition, both the patients' legs were routinely assessed, regardless of whether one or both legs were symptomatic.

It is also important to note that the weekly interview and assessment performed by the study sister specifically around DVT and its symptoms may have increased the clinical awareness of the frequently subtle clinical symptoms of a DVT. This confounder would have reduced the impact of the number of 'silent' DVTs detected.

CUS with duplex Doppler ultrasound imaging is the modality of choice for differentiating between other differential diagnoses that may mimic a DVT, such as a ruptured Baker's cyst, superficial thrombophlebitis, calf haematoma or muscle tear (Picton & McCollum 2007:36). In a TB population there are further maladies that may mimic the symptoms of a DVT. Pain in the lower limb can be attributed to peripheral neuropathy that is common with the treatment for TB. The actual cause of the neuropathy is contentious, and includes an immune mediated neuropathy, direct invasion of nerves, vasculitic neuropathy, compressive neuropathy, a meningitic reaction and the toxic effects of the antituberculous medicine (Orrell et al., 2002 769-771). In HIV patients there is polymyositis, and while uncommon, it shares a similar clinical manifestation, thus adding to the difficulty of a clinical diagnosis of a DVT (Farham, 2003). Once again this illustrates the difficulty of a correct clinical diagnosis of a DVT.

There were several weaknesses that were identified in this study. Primary was the observational nature of the study and the fact that it was carried out within the service provision of this busy TB hospital. Empirical medical policies were beyond the control of the research team. One of these included the use of prophylactic anticoagulation in patients thought to be at particular risk of DVT. The use of routine prophylaxis anticoagulation therapy almost certainly affected the number of DVTs identified. Within the group of study participants who were not identified with a DVT, 15.9% received prophylactic anticoagulants. This was found to be statistically significant for the prophylactic use of anticoagulants ($p<0.05$). As the overall positive DVT incidence was 15.3%, and in the negative DVT group 15.9% received prophylactic anticoagulants, it could be postulated that without the use of prophylactic anticoagulants the DVT incidence might have been significantly increased.

This confounder of prophylactic anticoagulation could not be addressed within this study's design of an observational study. However, if further studies are to be considered, then the use of anticoagulants as prophylaxis should be controlled by the study and therefore a more objective incidence of DVTs might be observed. The DP Marais Hospital policy was to

administer anticoagulants to the participants if their medical condition was very poor or had deteriorated, regardless of whether a DVT or PE was identified. This was decided by the medical staff caring for the patient, and occurred when the patient's mobility had decreased by 50%. Prophylactic treatment for VTE is generally encouraged as it has been shown to improve patient care and outcome by reducing the number of PEs and DVTs (Nutescu, 2007:S5-S13). This was a significant confounder the impact of which could not be controlled, owing to the study design.

Unfortunatly none of the participants who died had a post mortum therefore the cause of death is unproven and the impact of the number of PEs as a cause of death is unknown. What has also not been identified is if the any of the deaths were due to haemorrhage linked to the propherlactic use of anticoagulation.

In an attempt to keep selection bias to a minimum, an effort was made to try to include all the patients who were admitted to the TB hospital if eligibility criteria were met. The reason for failing admission to the study was reviewed and the results assessed (figure 3.1, Chapter 3). Overall, of the patients admitted were not enrolled half these could be adequately accounted for in readmissions and those previously screened. A small number were mentally deficient and could not be included. Unfortunately there was missing documentation, which included the lack of a start date for the TB medication. A small group of the total admissions were not enrolled for reasons unknown, and this group has become a potential for selection bias. The group did not differ from the study population by sex or age.

A more comprehensive control group, with a detailed record of the clinical symptoms of the non-enrolled population group, would have provided a greater understanding of the role the clinical symptoms played within the enrolled participants. Additionally, the risk factors, length of time on TB drugs and demographics of the non-enrolled TB population may have helped appreciate the makeup of the enrolled group. As MDR TB patients were excluded from this study, this needs to be addressed in further studies to assess their increased or decreased risk for a DVT.

The ultrasounds for this study were performed by two sonographers, and there was no validation of the results. This was due to the need to maintain a more likely clinical service arrangement.

This study had a very high attrition rate of participants who exited the study early. As this study was observational, the length of stay at the hospital was not governed by the study. The majority of the attrition was due to the participants' improved medical health; they were

then referred ‘down’ to ambulatory care supervised by an outpatient clinic close to the participants’ homes (39.5%). As many of them lived a considerable distance from the hospital, it was impossible for them to return for follow-up ultrasound scans. Previous data and our assessment, however, suggest that a DVT is an early phenomenon in treatment and so we believe this confounder made less of an impact in the study findings than would have been the case if events had occurred sporadically throughout the intended study period.

A number of participants, 15% (n = 60), absconded from the institution before completing their treatment. This probably reflects the patient population, who are in many cases selected for admission by medical staff owing to previously demonstrated non-adherence to TB management. A number of the study participants’ disease worsened, which required the participant to be referred ‘up’ to more specialised care (8.75%), thus removing them from the study domain. Finally, there was a mortality rate of 9%.

4.9 The way forward

There are a number of recommendations that emanate from this original research:

1. This thesis describes original research that shows the feasibility of a point-of-care, sonographer-led, ultrasound service to screen proactively for DVT in tuberculosis patients. The research proposes that the service model may be replicable for similar clinics in comparable settings.

2. This research also showed the efficacy of and benefit accruing from prophylactic CUS screening of TB patients for a DVT, whether symptomatic or not, for diagnosis. It is recommended that a prospective, randomised controlled trial be conducted to more exactly quantify the benefit derived from this intervention.

3. This research also suggests a high rate of undiagnosed DVT in patients commencing TB treatment. It is recommended that a randomised controlled study be conducted to investigate the potential efficacy and benefit of prophylactic antithrombolytics in this setting.

4. It is recommended that both legs of a TB patient undergoing prophylactic scan for DVT be examined by ultrasound. The research showed that the most common position for the DVT to develop was the left popliteal vein. However, it is important to note that this study also showed that the DVTs were identified to a similar extent in both the right and the left leg. Of the DVTs identified, 37.7% were on the left, 39.3 % on the right, and 14% were bilateral. This is thought to be due to compression of the left common iliac vein by the left common iliac artery. The continuous arterial pulsations can form a chronic endothelial injury, which in turn

leads to the formation of intraluminal spurs (Dähnert, 2007:396). The data emanating from this research is important information for a sonographer who is going to assess a TB patient for a DVT.

5. In this study, 22.9% of the DVTs were identified in one or more of the calf veins. Thus, it confirms that high-risk patients, regardless of symptoms, benefit from CUS and duplex Doppler screening that includes the calf area (Gaitini, 2006:289-297).

6. If this type of population group were to be offered a single ultrasound scan to assess for DVTs, it should include both legs, regardless of the presence or lack of symptoms, and the sonographer should make every attempt to include the calf veins. Ideally it should occur within 21 days of starting the TB medication as the most common days for identifying a DVT were on days 8, 10 and 11. If this were the only scan we did in this study, we would have identified 62% of the DVTS. By adding a second scan after a four-week interval, a further 24% would have become known. A total of 86% of the DVTs would have been discovered with two ultrasound scans.

4.10 Conclusion

TB in South Africa is increasing and it has one of the highest notifications in the world, with about 1% of the population developing TB annually (Bekker & Maartens, 2011:397). It is one of the most common co-morbidity of the HIV patient in developing countries (Kawooya, et al., 2008:62).

This study indentified TB patients have a higher incidence of DVTs than has been previously shown and clinical symptoms are an insensitive diagnostic tool for identifying a DVT. Ultrasound is non-invasive, quick, and potentially cost saving when performed by sonographers. It can easily confirm or refute the clinical diagnosis and identify silent DVTs that have the potential to influence morbidity and contribute to mortality. Well suited to the PHC situation, its versatility allows other examinations such as the abdominal ultrasound to be included with little discomfort to the patient or cost to the clinic.

It is hoped that the results from this study will better equip the medical team in the non-tertiary setting to be vigilant for the presence of a DVT, as well as foreground the usefulness of the ultrasound scan.

REFERENCES

Ahuja, A.T., Griffith, J.F., Wong, K.T., Antonio, G.E., Chu, W.C.W., Ho, S.S.Y., Lolge, S.J., Paunipagar, B.K., Kennedy, A., Zwiebel, W.T., Sohaey, R., Ho, S.S.M. & Woodward, P. 2007. *Diagnostic imagery: ultrasound.* Salt Lake City, UT: AMIRSYS.

Ahmed, I., Majeed, A. & Powell, R. 2007. Heparin induced thrombocytopenia: diagnosis and management update. *Postgrad Med J*, 83(983):575-582, September.

Algahtani, F., Aseri, Z.A., Aldiab, A. & Aleem, A. 2013. Hospital versus home treatment of deep vein thrombosis in a tertiary care hospital in Saudi Arabia: are we ready? *Saudi Pharm J*, 21(2):165-168, April.

Ambrosetti M, Ferrarese M, Codecasa LR, Besozzi G, Sarassi A, Viggiani P, Migliori GB; AIPO/SMIRA TB Study Group. 2004. Incidence of venous thromboembolism in tuberculosis patients. Respiration,73(3):396. May 28.

Anderson, D.R., Kovacs, M.J., Kovacs, G., Stiell, I., Mitchell, M., Khoury, V., Dryer, J., Ward, J. & Wells, P.S. 2003. Combined use of clinical assessment and D-dimer to improve the management of patients presenting to the emergency department with suspected deep vein thrombosis (the EDITED study). *J Thromb Haemost*, 1(4):645-651, April.

Andrews, E.J. Jr & Fleischer, A.C. 2005. Sonography for deep venous thrombosis: current and future applications. *Ultrasound Q*, 21(4):213-225, December.

Badri, M., Wilson, D & Wood, R. 2002. Effect of highly active antiretroviral therapy on incidence of tuberculosis in South Africa: a cohort study. *Lancet*, 359(9323):2059-2064, June 15.

Bekker, L-G. & Maartens, G. 2011. Guest editorial: HIV/TB. *CME*, 29(10):397, October.

Bekker, L-G. & Wood, R. 2011. TB and HIV co-infection: when to start antiretroviral therapy. *CME*, 29(10):420-426, October.

Bellosta, R., Ferrari, P., Luzzani, L., Carugati, C., Cossu, L., Talarico, M. & Sarcina, A. 2007. Home therapy with LMWH in deep vein thrombosis: randomized study comparing single and double daily administrations. *Angiology*, 58(3):316-322, June – July.

Binder, B., Lackner, H.K., Salmhofer, W. & Hofmann-Wellenhof, R. 2009. Risk factors for deep vein thrombosis in women aged 18 to 50: a retrospective analysis. *Dermatol Surg*, 35(3):451-456, March.

Brackenridge, S.C., Henley, S.S., Kashner, T.M., Golden, R.M., Paik, D.H., Phelan, H.A., Cohen, M.J., Sperry, J.L., Moore, E.E., Minei, J.P., Maier, R.V. & Cushieri, J. 2013. Comparing clinical predictors of deep venous thrombosis versus pulmonary embolus after severe injury: a new paradigm for posttraumatic venous thromboembolism? *J Trauma Acute Care Surg*, 74(5):1231-1238, May.

British Medical Ultrasound Society. 2011. About ultrasound. http://www.bmus.org/about-ultrasound/au-home.asp [12 August 2011].

Chakraborty P.P, Bandyopadhyay D. 2009. Utility of Abdominal Ultrasonography in HIV patients. *Singapore Med J,* 50(7):7 10-4. July.

Chan, V.L., So, L.K., Lam, J.Y., Lau, K.Y., Chan, C.S., Lin, A.W. & Chu, C.M. 2009. Major haemoptysis in Hong Kong: aetiologies, angiographic findings and outcomes of bronchial artery embolisation. *Int J Tuberc Lung Dis*, 13(9):1167-1173, September.

CLOTS. 2009. The stroke. Diagram showing formation of clots in a leg vein. http://www.dcn.ed.ac.uk/clots/clots_patient_area/stroke.html [21 August 2012].

Colman, R.W. 2006. Factor V (labile factor, Proaccelerin, Accelerator or Globulin). In Colman, R.W, Marder, V.J., Clowes, A.W., George, J.N. & Goldharber, S.Z. (eds). *Hemostasis and thrombosis: basic principles and clinical practice.* 5th ed. Philadeophia, PA: Lippincott, Williams & Wilkins: 924-927.

Corr, P.D. 2003. Life threatening haemoptysis: a clinical and radiological study. Unpublished DMed thesis, University of Natal, Durban, South Africa.

Cundiff, D.K., Agutter, P.S., Malone, P.C. & Pezzullo, J.C. 2010. Diet as prophylaxis and treatment for venous thromboembolism? *Theor Biol Med Model*, 7:31, August 11.

Dähnert, W. 2003. *Radiology review manual.* 5th ed. Philadelphia, PA: Lippincott, Williams & Wilkins.

Dähnert, W. 2007. *Radiology review manual.* 6th ed. Philadelphia, PA: Lippincott, Williams & Wilkins.

De Azevedo Prazeres, G. 2009. Deep vein thrombosis: internal medicine. http://www.medstudents.com.br/medint/medint5.htm [2 January 2011].

Del Rios, M., Lewiss, R.E. & Saul, T. 2009. Focus on: Emergency ultrasound for deep vein thrombosis. *ACEP News*, March. http://www.acep.org/content.aspx?id=44490 [3 September 2012].

Diedrich, C.R. & Flynn, J.L. 2011. HIV-1/*Mycobacterium* tuberculosis coinfection immunology: how does HIV-1 exacerbate tuberculosis? *Infect Immun*, 79(4):1407-1417, April.

Farham, B. 2003. Musculoskeletal manifestations of the HIV infection. *CME*, 21(6):342, June.

Fowlkes, J.B. & Holland, C.K. 1998. Biologic effects and safety. In Rumack, C.M., Wilson, S.R. & Charboneau, J.W. *Diagnostic ultrasound.* 2nd ed. St Louis, MI: Mosby, vol. 1, pp. 34-52.

Franchini, M. 2005. Heparin-induced thrombocytopenia: an update. *Thrombosis Journal*, 3:14-18. http://www.thrombosisjournal.com/content/pdf/1477-9560-3-14.pdf [8 October 2013].

Fraser, J.D. & Anderson, D.R. 2004. Venous protocols, techniques, and interpretations of the upper and lower extremities. *Radiol Clin North Am*, 42(2):279-296, March.

Fraser, R.S., Colman, M.I., Muller, N.L. & Paré, P.D.1998. *Synopsis of diseases of the chest.* 3rd ed. Philadelphia, PA: Saunders.

Gaitini, D. 2006. Current approaches and controversial issues in the diagnosis of deep vein thrombosis via duplex Doppler ultrasound. *J Clin Ultrasound*, 34(6):289-297, July – August.

Goldhaber, S.Z. & Morrison, R.B. 2002. Pulmonary embolism and deep vein thrombosis. *Circulation*, 106:1436-1438.

Goodacre, S., Sampson, F., Stevenson, M. Wailoo, A., Sutton, A., Thomas, S., Locker, T., Ryan, A. 2006. Measurement of the clinical and cost-effectiveness of non-invasive diagnostic testing strategies for deep vein thrombosis. *Health Technol Assess*, 10(15):1-168, iii-v, May.

Grimm, L. & Manson, W.C. 2011. Bedside ultrasonography in deep vein thrombosis: images. Medscape, August.

Habib, A.G. 2009. A clinical and epidemiologic update on the interaction between tuberculosis and human immunodeficiency virus infection in adults. *Ann Afr Med*, 8(3):147-155, July – September.

Havlir, D.V., Getahun, H., Sanne, I. & Nunn, P. 2008. Opportunities and challenges for HIV care in overlapping HIV and TB epidemics. *JAMA*, 300(4):423-430, July.

Hirsch, J., Anand, S., Halperin, J.L. & Fuster, V. 2001. Guide to anticoagulant therapy: heparin. A statement for healthcare professionals from the American Heart Association. *Circulation*, 103:2994-3018.

Hoffmann, M., Limmer, S., Schloericke, E., Bruch, H. & Kujath, P. 2010. Pulmonary embolism secondary to para-inflammatory thrombosis of the iliac veins. *Internet Journal of Orthopedic Surgery*, 17(2). DOI: 10.5580/1dd http://ispub.com/IJOS/17/2/3504 [21 August 2012].

Howard, A.A. & El-Sadr, W.M. 2010. Integration of tuberculosis and HIV services in sub-Saharan Africa: lessons learned. *Clin Infect Dis*, 50(Suppl. 3):S238-S244, May.

Hunter, R.L., Olsen, M.R., Jagannath, C & Actor, J.K. 2006. Multiple roles of cord factor in the pathogenesis of primary, secondary, and cavitary tuberculosis, including a revised description of the pathology of secondary disease. *Ann Clin Lab Sci*,36(4):371-386, Autumn.

Johnson, L.F. 2012. Access to antiretroviral treatment in South Africa, 2004 – 2011. *Southern African Journal of HIV Medicine*, 13(1):22-27.

Kawooya, M.G., Muyinda, Z., Byanyima, R. & Malwadde, E.K. 2008. Abdominal ultrasound findings in HIV patients: a pictorial review. *Ultrasound*, 16(2):62-72, May.

Krafts, K. 2009. Virchow's triad. *Pathology Student*. May. http://www.pathologystudent.com/?p=400 [20 July 2013].

Kranzer, K. 2011. Intensified tuberculosis case finding among HIV infected individuals. *CME*, 29(10):418-419, October.

Krüger, K., Wildberger, J., Haage, P. & Landwehr, P. 2008. Diagnostic imaging of venous disease: Part 1: methods in diagnosis of veins and thrombosis. *Radiologe*, 48(10):977-992, October.

Kumar, A. Farhana, A., Guidry, L., Saini, V., Hondalus, M. & Steyn, A.J.C. 2011. Redox homeostasis in mycobacteria: the key to tuberculosis control? *Expert Rev Mol Med*, 13:e39. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3241215/ [20 July 2013].

Kumar, P.J. & Clark, M.L. 2009. *Kumar & Clark's clinical medicine*. 7th ed. Edinburgh: Elsevier/Saunders.

Lazarus, A.A. & Thilagar, B. 2007. Abdominal tuberculosis. *Dis Mon*, 53(1):32-38, January.

Legge, A. 2006. Deep vein thrombosis risk increases as HIV disease worsens. NAM Aidsmap, 7 August. http://www.aidsmap.com/Our-name/page/1563890/ [10 January 2013].

Lewis, B.D. 2005. The peripheral veins. In Rumack, C., Wilson, S. & Charboneau, J. *Diagnostic ultrasound.* 3rd ed. MI: Elsevier Mosby: 939-948.

Line, B.R. 2001. Pathophysiology and diagnosis of deep venous thrombosis. *Semin Nucl Med*, 31(2):90-101, April.

Madhusudhana, S., Moore, A. & Moormeier, J.A. 2009. Current issues in the diagnosis and management of deep vein thrombosis. *Mo Med*, 106(1):43-49, January – February.

Malek, J., Rogers, R., Kufera, J. & Hirshon, J.M. 2011. Venous thromboembolic diseases in the HIV-infected patient. *Am J Emerg Med*, 29(3):278-282, March.

Mark, P.L., Ashok, P.P., Deshpande, R.B & Mahashur, A.A. 2009. A patient with hypercoagulable state due to tuberculosis. *Indian Journal of Chest Diseases & Allied Sciences*, 51:49-51.

Masotti, L., Ray, P., Righini, M., Le Gal, G., Antonelli, F., Landini, G., Cappelli, R., Prisco, D. & Rottoli, P. 2008. Pulmonary embolism in the elderly: a review on clinical, instrumental and laboratory presentation. *Vasc Health Risk Manag*, 4(3):629-636.

McManus, R.J., Fitzmaurice, D.A., Murray, E. & Taylor, C. 2011. Thromboembolism. *Clin Evid*: ii, March.
http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3217723/#__ffn_sectitle
[10 April 2911].

Meetoo, D. 2010. In too deep: understanding, detecting and managing DVT. *Br J Nurs*, 19(16):1021-1027, September 9 – 22.

Middelkoop K. 2011. TB epidemiology in HIV-prevalent settings. *CME*, 29(10):428-429, October.

National Institute for Health and Care Excellence. 2011. NICE clinical guidelines: Tuberculosis: CG 117. Clinical diagnosis of management of tuberculosis and measures for its prevention and control.
http://publications.nice.org.uk/tuberculosis-cg117
[8 October 2013].

NICE *see* National Institute for Health and Care Excellence.

Norman, R., Bradshaw, D. Schneider, M., Pieterse, D. & Groenewald, P. 2000. Frequently asked questions. What are the causes of death due to cardiovascular disease in SA? Burden of Disease Research Unit, Medical Research Council.
http://www.mrc.ac.za//bod/faqcardio.htm [1 October 2013].

Nutescu, E.A. 2007. Assessing, preventing, and treating venous thromboembolism: evidence-based approaches. *Am J Health Syst Pharm*, 64(11, Suppl. 7):S5-S13, June.

Orrell, R.W., King, R.H.M., Bowler, J.V & Ginsberg, L. 2002. Peripheral nerve granuloma in a patient with tuberculosis. *J Neurol Neurosurg Psychiatry*, 73:769-771.

PAWC *see* Provincial Government of the Western Cape.

Pennell, R.C., Mantese, V.A. & Westfall, S.G. 2008. Duplex scan for deep vein thrombosis – defining who needs an examination of the contralateral asymptomatic leg. *Journal of Vascular Surgery*, 48(2):413-416, August.

Peter, J. & Theron, G. 2011. The progression of TB diagnosis in the HIV era: from microscopes to molecules and back to the bedside. *CME*, 29(10):404-408, October.

Petersen, S., Badri, M. & Bekker, L.G. 2001. Morbidity and mortality of DVT during the inpatient treatment of TB. Poster presented at the South African Infectious Diseases Conference, Cape Town, 28 November – 1 December 2001.

Picton, A. & McCollum, C. 2007 Improving access to vascular ultrasound. *Ultrasound*, 15(1):35-37, February.

Pineo, G.F. & Hull, R.D. 2009. Economic and practical aspects of thromboprophylaxis with unfractionated and low-molecular-weight heparins in hospitalized medical patients. *Clin Appl Thromb Hemost*, 15(5):489-500, October.

Pomero, F., Brignone, C., Serraino, C., Panzone, S., Bracco, C. Migliore, E., Dalmasso, P., Perin, P.C. & Fenoglio, L.M. 2011. Venous lower-limb evaluation in patients with acute pulmonary embolism. *South Med J*, 104(6):405-411, June.

Provincial Administration of the Western Cape. 2004. Cape Town TB control. Progress report: 1997 – 2003. Cape Town: PAWC Metropole Region: City of Cape Town. http://www.capetown.gov.za/en/CityHealth/Documents/Guidelines,%20Specifications/TB%20Progress%20Report%201997%20-%202003.pdf
[18 April 2009].

Robson, S.C., White, N.W., Aronson, I., Woollgar, R., Goodman, H. & Jacobs, P. 1996. Acute-phase response and the hypercoagulable state in pulmonary tuberculosis. *British Journal of Haematology*, 93(4):943-949, June.

Sampson, F.C., Goodacre, S.W., Thomas, S.M. & Van Beek, E.J.R. 2007. The accuracy of MRI in diagnosis of suspected deep vein thrombosis: systematic review and meta-analysis. *Eur Radiol*, 17(1):175-181, January.

Sanders R.C.1991. 2009. *Clinical Sonography A Practical Guide.2*nd ed. USA: Little, Brown and Company.

Sasindran, S.A. & Torrrelles, J.B. 2011. *Mycobacterium tuberculosis* infection and inflammation: what is beneficial for the host and for the bacterium? http://www.frontiersin.org/cellular_and_infection_microbiology/10.3389/fmicb.2011.00002/abstract [18 August 2012].
Severinsen, M.T., Kristensen, S.R., Johnsen, S.P., Dethlefsen, C., Tjønneland, A. & Overvad, K. 2009a. Anthropometry, body fat, and venous thromboembolism: a Danish follow-up study. Circulation,120(19):1850-1857.

Severinsen, M.T., Kristensen, S.R., Johnsen, S.P., Dethlefsen, C., Tjønneland, A. & Overvad, K. 2009b. Smoking and venous thromboembolism: a Danish follow-up study. *J Thromb Haemost*, 7(8):1297-1303, August.

Själander, A., Jansson, J.H., Bergqvist, D., Eriksson, H., Carlberg, B. & Svensson, P. 2008. Efficacy and safety of anticoagulant prophylaxis to prevent venous thrombosis in acutely ill medical inpatients: a meta-analysis. *J Intern Med*, 263(1):52-60, January.

Smith, I. 2003. Mycobacterium tuberculosis pathogenesis and molecular determinants of

virulence. *Clin Microbiol Rev*, 16(3):463-496, July.

Society for Vascular Surgery. 2012. Deep vein thrombosis.
http://www.vascularweb.org/vascularhealth/pages/deep-vein-thrombosis-(-dvt-)-.aspx
[2 September 2012].

Sonnenberg, P., Glynn, J.R., Fielding, K., Murray, J., Godfrey-Faussett, P. & Shearer, S. 2005. How soon after infection with HIV does the risk of tuberculosis start to increase? A retrospective cohort study in South African gold miners. *J Infect Dis*, 191(2):150-158.

Thomas, S.M., Goodacre, S.W., Sampson, F.C. & Van Beek, E.J.R. 2008. Diagnostic value of CT for deep vein thrombosis: results of a systematic review and meta-analysis. *Clin Radiol*, 63(3):299-304, March.

THRIFT. 1992. Summary of DVT risk assessment. *BMJ*, 305:567-574.
http://www.gp-training.net/protocol/cardiovascular/dvt.htm
[31 October 2010].

Toll, D.B., Oudega, R., Vergouwe, Y., Moons, K.G. & Hoes, A.W. 2008. A new diagnostic rule for deep vein thrombosis: safety and efficiency in clinically relevant subgroups. *Fam Prac*, 25(1):3-8. February.

Ultrasound Image Gallery. 2012. A free gallery of high-resolution, ultrasound, color Doppler and 3D images.
http://www.ultrasound-images.com
[17 August 2012].

Van der Heuvel, M.M., Els, Z., Koegelenberg, C.F., Naidu, K.M., Bolliger, C.T. & Diacon, A.H. 2007. Risk factors for recurrence of haemoptysis following bronchial artery embolisation for life-threatening haemoptysis. *Int J Tuberc Lung Dis*, 11(8):909-914, August.

Veller, M. & Pillai, J. 2009. Lower limb venous thrombosis. *CME*, 27(7):306-311, July.
Venkatesh, K.K., Swaminathan, S., Andrews, J.R. & Mayer, K.H. 2011. Tuberculosis and HIV co-infection: screening and treatment strategies. *Drugs*, 71(9):1133-1152, June.

Wells, P.S., Anderson, D.R., Rodger, M., Forgie, M., Kearon, C., Dreyer, J., Kovacs, G., Mitchell, M., Lewandowski, B. & Kovacs, M. 2003. Evaluation of D-dimer in the diagnosis of suspected deep-vein thrombosis. *N Engl J Med*, 349:1227-1235.

Western Cape Government. 2013. Chief Director: General specialist and emergency services: Government Department Western Cape. January 2013.
http://southafricajobsvacancies.com/medical-specialist-grade-1-to-3-radiology-17736.html
[19 January 2013].

Western Cape Government. Department of Health. 2004. The new TB control programme drug regimens of the Western Cape. D.P. Marais Hospital, Cape Town, South Africa.

White, N.W. 1989. Venous thrombosis and rifampicin. *Lancet*, 344(8660):434-435, August 19.

WHO *see* World Health Organization.

Wilbur, K., Lynd, L.D. & Sadatsafavi, M. 2011. Low-molecular-weight heparin versus unfractionated heparin for prophylaxis of venous thromboembolism in medicine patients – a pharmacoeconomic analysis. *Clin Appl Thromb Hemost*, 17(5):454-465, October.

Wood, R. 2007. The case for integrating tuberculosis and HIV treatment services in South

Africa. *J Infect Dis*, 196(Suppl. 3):S497-S499.

Wood, R., Lawn, S.D., Johnstone-Robertson, S. & Bekker, L.G. 2011. Tuberculosis control has failed in South Africa – time to reappraise strategy. *S Afr Med J*, 101(2):111-114, February.

World Health Organization. 2005. WHO declares TB an emergency in Africa. 26 August. http://www.who.int/mediacentre/news/releases/2005/africa_emergency/en/ [20 July 2013].

World Health Organization. 2009a. Antiretroviral therapy. http://www.who.int/hiv/topics/treatment/en/index.html [30 July 2011].

World Health Organization. 2009b. Tuberculosis: The 5 elements of DOTS. http://www.who.int/tb/dots/whatisdots/en/ [13 April 2009].

World Health Organization. 2012. Tuberculosis: WHO fact sheet no. 104. http://www.who.int/tb/publications/factsheets/en/ [27 October 2012].

World Health Organization. Media Centre. 2009. HIV-related TB deaths higher than past estimates. 24 March. http://www.who.int/mediacentre/news/releases/2009/tuberculosis_report_20090324/en/ [4 April 2009].

APPENDIX A

Cape Peninsula University of Technology

Deep Vein Thrombosis - ULTRASOUND STUDY.

Informed Consent

Investigators Statement:

We are asking you to be part of this research study. The purpose of this consent form is to give you the information you will need to help you decide whether or not to join this study. Please read it carefully. You may ask questions about the purpose of the research, what you would need to do, the possible risks and benefits, your rights as a volunteer and anything else about the research. Please ask if you do not understand any part of this form. When your questions have been answered you can decide if you want to join this study. This process is called 'informed consent'.

Voluntary Participation

You may choose not to be part of this study. If this is the case no health care will be withheld and you will continue to receive the standard medical care at this hospital. You have the right to withdraw from this study at any time. There will be no penalty or loss of benefits to which you are entitled.

Background

It has been shown from previous research that patients who start treatment for their TB infection may develop a blood clot in the veins of their legs. This is called a DVT or a deep vein thrombosis. A DVT may cause pain, swelling or other problems. The most important complication with a clot is that a piece may break off and travel to other parts of the body such as the lungs. Large clots in the lungs can be very dangerous and can be fatal. DVT's are usually treated for up to three months (and sometimes longer) with anticoagulation therapy to thin the blood.

An ultrasound machine uses sound waves to image parts of the body. It is very accurate for identifying DVT's in blood vessels. This study will use such a machine to look at the blood vessels of the lower legs for clot formation.

Purpose of the Study

The purpose of this study is to use Ultrasound to investigate the presence of a DVT in the lower limb of patients being treated for TB and to determine the time period for the development of DVT in such patients. Furthermore, this study aims to investigate whether other factors such as HIV status, smoking, body mass index and mobility contribute to the development of DVT's.

Entrance into the Study

We are asking the patients who are admitted to this hospital to participate. Our study nurse will ask you some questions to determine if you can participate. Depending on your answers we will ask you to join the study.

As part of the study we need to know if you are infected with HIV or not. This is to try and decide if HIV increases the risk of developing a DVT. Your HIV status will be kept confidential and if you need to talk to someone about this the study nurse will be able to help you. The nurse will also ask you if you smoke what you weigh and how mobile you are.

Ultrasound Examination

This study will require the patients to undergo four (4) ultrasound examinations of the lower limbs. This test takes about 30-40 minutes to carry out. It is a painless examination and requires the patients to lie on their backs while a small instrument called a probe is moved across the skin. A water based gel is first applied to the skin so the probe has good contact and can move smoothly. Some patients find this test relaxing and fall asleep during the test.

Risks and Benefits

There are no known risks to an ultrasound examination. The most important benefit for this group of patients is that if a DVT develops it will be identified and confirmed on ultrasound. This will probably be before there are any clinical symptoms. This in turn will allow treatment to begin early. This examination will be carried out at this hospital so there will be little disruption to the patient's stay.

Other Information

Joining this study is voluntary. You can stop at any time. If you choose to join the study or not it will not affect your health care. Information about you is confidential. We will code the study records. The link between your name and the code will be kept separate in a secure location. Only the study investigators will have access to that information. The link between your name and the code will be kept for 10 years and then destroyed. We will need access to your medical records and we have an agreement with your hospital to allow us access to the information.

Subject's statement:

This study has been explained to me. I volunteer to take part in this research. I have had a chance to ask questions. If I have further questions about the research I can ask the study nurse or one of the research assistants. If I have questions about my rights as a research subject I can contact the ethics committee at CPUT or the principal researcher at 0827746266. I give my permission for the study investigator to access my medical records for the purposes described above. I will receive a leaflet explaining this study to take away with me.

_____

Signature of subject Date Printed name of subject.

_____

Signature of witness Date Printed name of witness.

Cape Peninsula University of Technology

Deep Vein ThrombosiS– Ultrasound Study

Patient Information Leaflet

Study Purpose.

This study is to look at DTV's, one of the complications that patients can develop while on treatment for TB. Several ultrasound examinations of the lower legs will be done to recognise the presence of clots in the lower legs. We want to establish when the clot is liable to develop, where in the legs it is most likely to form and if problems such a HIV, smoking, mobility or being very thin are risk factors for clot development.

Deep Vein Thrombosis

A DVT is a blood clot that can form in the patient's legs. The clot can break off and travel to the lungs and this can be very dangerous. It is dangerous because in the lungs the clot can block important blood vessels causing shortness of breath, chest pain and in severe cases loss of consciousness and death. If a DVT develops it is common for the patient to be unaware of any change but sometimes there is pain and swelling of the lower legs. Often there are no signs or symptoms of a DVT for the doctor to identify making it very difficult to diagnose. Ultrasound imaging can accurately identify the presence of a DVT in patient's legs. DVT's are treated for between 3-6 months with special blood thinning agents.

Ultrasound

An ultrasound machine uses sound waves to build an image for the operator to see. It is safe and has no known side effects. In order to visualise the veins in the lower legs the patient will lie on their back on a bed and a small instrument called a probe will be moved over the skin. A water based jelly will be applied to the skin so the probe moves easily.

General

As a patient in a clinical study you have the right to ask questions and have any concerns you have about this study addressed. You have the right to confidentiality of your medical information. You have the right to withdraw yourself from this trial at any time. Please speak to any member of the study staff with your question which they will endeavour to answer. Alternatively they will put you in contact with the person who will be able to answer your questions. You can contact the Research Ethics Committee at CPUT (021 9596917) or the principal researcher Sheila Brock at 082 7746266 if you are unhappy with the answers to your questio

Cape Peninsula University of Technology

Ifomu yemvumelwano

Uphando-sifundo lwase-CPUT olumalunga ngokoma kwegazi kwimithambo yegazi esemilenzeni (deep vein thrombosis; DVT)

Inkcaza yomphandi:

Uyamenywa ukuba uthathe inkxaxheba kolu phando-sifundo. Injongo yale fomu yemvumelwano kukukunika iinkcukacha ezizakunceda ukuba uthabathe isigqibo malunga nokuthatha inkxaxheba kolu phando-sifundo. Nceda thatha ixesha ufunde ulwazi oluvezwe apha, oluzakuthi luchaze ngolu phando-sifundo. Uvumelekile ukubuza imibuzo malunga neenjongo zokwenza oluphando, ngezinto ekuzakufuneka uzenze, iingozi kwakunye neenzuzo ezibandakanyekayo ekuthatheni kwakho inkxaxheba kolu phando, namalungelo akho ekukhetheni ukuba uthathe inkxaxheba kolu phando ngokunganyanzelekanga. Uvumelekilo ukuba ungabuza nayiphi na imibuzo ngezinto ongaziqondiyo ezibhalwe kule fomu. Xa wanelisekile ziimpendulo ungasithatha isigqibo malunga nokuthabatha inkxaxheba kolu phando-sifundo.

Intatho-nkxaxheba engenasinyanzeliso

Uvumelekile ukuba ungala ukuthabatha inkxaxheba kolu phando-sifundo. Oku akuthethi ukuba impilo yakho ingangafumani nkathalelo esibhedlele. Kwakhona, ukuthatha kwakho inkxaxheba **kungentando yakho ngokupheleleyo** kwaye ukhululekile ukuba ungarhoxa nangaliphi na ithuba, nkqu nokuba ubuvumile ekuqaleni. Ukuba uthi hayi, oku akusayi kukuchaphazela nangayiphi na indlela. Ukwakhululekile ukuba uyeke kwesi sifundo nangaliphi ixesha.

Iinkcukacha ngophando-sifundo

Kubonakalisiwe kuphando lwezifundo zangaphambili ukuba abantu abahlaselwe yi-TB kwaye bethatha amayeza okunyanga esi sigulo bomelwa ligazi (blood clot) emilenzeni. Ngokolwimi lesilungu oku kubizwa ngokuba yi-deep vein thrombosis (DVT). Oku kungabangela iintlungu, ukudumba okanye ezinye iingkxaki. Eyona ngkaxi ebalulekileyo exhalabisayo yeyokuba eligazi lomileyo lingafikelela kwamanye amalungu omzimba afana nemiphunga, ntoleyo ingabangela ukuba umntu ophathekileyo aphulukana nobomi bakhe. Ukoma kwengazi okanye iDVT kuyanyangeka ngeyeza lokunyibilikisa igazi elisetyenziswa inyanga ezintathu. Igazi elomileyo kwimithambo yegazi libonwa okanye likhangelwa ngomashini owenzelwe (ultrasound machine) oko. Lo mashini uzakusetyenziswa kolu phando ukukhangela igazi elomileyo emilenzeni.

Iinjongo zophando-sifundo

Iinjongo yoluphando kukujonga indlela i-ultrasound esebenza ngayo ukukhangela igazi elomileyo emilenzeni yezigulane ezinyangwa isifo se-TB, nokujonga ukuba iDVT ithatha ixesha elingakanani ukuvela emzimbeni. Esi sifundo sizakuphinde siphande ukuba ingaba ingkculazi, ukutshaya, kwakunye nokutyeba komzimba kunenkxaxheba ezinayo kusinina ekwenzeni iDVT.

Ukuthatha inkxaxheba kolu phando-sifundo

Zonke izigulane kwesi sibhedlela ziyacela ukuba zithathe inkxaxheba kolu phando-sifundo. Umongikazi ojongene nolu phando uzakubuza imibuzo ethile malunga nokuthatha kwakho inkxaxheba kolu phando. Ukuthatha kwakho inkxaxheba kolu phando kuxhomekeke kwimpendulo ozakuthi uzinike.

Olunye ulwazi olubalulekileyo oluzakusetyenziswa kwesi sifundo lumalunga nesimo sakho sokuhlaselwa yintsholongwane yengkculazi. Oku kufunelwa ukuqonda ukuba ubukho bale ntsholongwane emzimbini bunayo kusini na inkxaxheba obuyithathayo ekuvelani kwe-DVT. Isimo sakho sengkculazi sizakuhlala siyimfihlelo kwaye ukuba ufuna ukuthetha ngaso, ungakwenza oko

kumongikazi ojongene nolu phando. Umongikazi uzakuphinde akubuze ukuba uyatshaya kusini na, ubungakanani bomzimba wakho, kwakunye nendlela ohamba ngayo (ukuba usebenzisa isithuthi kusini na).

Ukuhlolwa nge-ultrasound

Umthathi-nkxaxheba uzakuvavanywa imilenze nge-ultrasound izihlandlo ezine. Olu vavanyo luthatha ixesha elingangemizuzu engamashumi amathathu ukuya kwamane. Ayinabuhlungu kwaye ifuna nje ukuba isigulane silale ngomqolo ebhedini ukuze kuhanjiswe into ekuthiwa yi-probe esikhumbeni esithanjiswe ijeli ukuze iprobe ihambe lula. Ezinye izigulane ziyifumana i-ultrasound ikhulula umzimba de zibiwe bubuthongo zilale xa isenziwa.

Ubungozi

Akukho bungozi obaziwayo obunokwenzaka xa isenziwa i-ultrasound. Inzuzo efunyanwa ngumthathi-nkxaxheba yeyokubonwa kwe-DVT ukuze ikwazi ukunyangwa ngokukhawuleza. Olu phando-sifundo luzakwenzelwa esibhedlela ukuze kungabikho kuphazamiseka kwisigulane.

Enye inkcazelo

Ukuthabatha inkxaxheba kolu phando akunyanzelekanga. Uvumelekile ukuba ungayeka nangaliphi na ixesha ukuba ufuna ukwenza oko. Isigqibo sakho ngokuthatha inkxaxheba asisayi kuchaphezela ukujongwa kwempilo yakho nangayiphi na indlela. Nayiphi na ingxelo ngawe izakugcinwa iyimfihlo, kusetyenziswe amanani endaweni yegama nefani yakho. Ngumphandi-sifundo kuphela ozakuba nelungelo lokubona iinkcukacha zakho. Iinkcukacha zakho zizakugcinwa kangangeminyaka elishumi, emva koko zitshatyalaliswe. Sizakucela imvume kwisibhedlela sakho ukuba sibone inkcukacha zempilo yakho, kodwa kuphela ukuba uyavuma sikwenze oko.

Inkcaza yomthathi-nkxaxheba:

Ndicaciselwe ngokwanelisekayo ngolu phando-sifundo. Ndiyavuma ukubandakanyeka kolu phando-sifundo ngokunganyenzelekanga. Bendinalo ithuba lokubuza imibuzo ngezinto endingaziqondiyo ngolu phando, kwaye ukuba ikhona enye into endifuna ukuyiqonda ndakuyibuza kumongikazi okanye umntu ojongene nolu phando. Ukuba ndinemibuzo ngamalungelo am njengomntu othabatha inkxaxheba kolu phando, ndakuqhakamshelana nabantu bekomiti yophando-zifundo besikolo esiphakamileyo i-CPUT okanye umphandi oyintloko kule nombolo yomnxeba 0827746266. Ndinika umphandi imvume yokujonga iinkcukacha ngesimo sam sempilo ezimalunga nokuchazwe ngasentla. Ndithenjiswe ngokunikwa ifomu yemvumelwano ngolu phando-sifundo.

Utyikityo lomtahthi-nkxaxheba	Umhla	Igama lomtahthi-nkxaxheba

Utyikityo lomngqini	Umhla	Igama lomngqini

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Iinkcukacha ezilungiselelwe isigulane

Iinjongo zesifundo

Injongo yesisifundo kukuphanda ngegazi elomileyo kwimithambo yegazi (DVT). Le yenye yeengxaki ezifunyanwa ngabantu ebanyangwa isifo se-TB. Uvavanyo lwemilenze luzakwenziwa nge-ultrasound ukukhangela ukuba igazi elomileyo likhona kusini na. Sifuna ukujonga ukuba eli gazi lomileyo lithatha ixesha elingakanani ukubakhona emithanjeni, libakhona kweyiphi indawo yomlenze, ingaba ingkculazi, ukutshaya, ubungakanani bomzimba, kwakunye nendlela yokuhamba kunenkxaxheba ezinayo ekwenzeni iDVT kusinina.

Deep Vein Thrombosis (DVT)

I-DVT ligazi elomileyo elithi lifunyanwe emilenzeni yesigulane asinyangwa isifo se-TB. Eyona ngkaxi ebalulekileyo exhalabisayo yeyokuba eligazi lomileyo lingafikelela kwamanye amalungu omzimba afana nemiphunga, ntoleyo ingabangela ukuba umntu ophathekileyo aphefumle nzima, kubebuhlungu isifuba de aphulukana nobomi bakhe xa esisimo sithe sanobuzaza. Kuyinto eqhelekileyo ukuba umntu ophathekileyo angazazi ukuba kukho igazi elomileyo emilenzeni yakhe kodwa ngamanye amaxesha uva iintlungu okanye adumbe imilenze. Kumaxesha amaninzi akukho mpawu zibonakalayo kumntu ohlaselwe yi-DVT ezinokuthi zibonwe ngugqirha. I-ultrasound ingakwazi ukukhupha umboniso obonakalisa ubukho be-DVT emlenzeni. Ukunyanga i-DVT kuthatha ixesha elingangenyanga ezintathu ukuya kwezintandathu ngamayeza anyibilikisa igazi ukuze lihambe kakuhle emithanjeni yegazi.

I-ultrasound

Umashini we-ultrasound usebenzisa amaza ukwenza umfanekiso wento engaphakathi emzimbeni. Ikhuselekile kwaye ayinabungozi obusecaleni. Xa isenziwa lento, isigulane kufuneka silale ngomqolo ebhedini ukuze kuhanjiswe into ekuthiwa yi-probe esikhumbeni esithanjiswe ijeli ukuze iprobe ihambe lula.

Inkcaza yesiqhelo

Uvumelekile ukuba ungabuza nayiphi na imibuzo okanye izinto ongaziqondiyo ngolu phando-sifundo kubantu abanjongene naso okanye abantu abanokwazi ukuyiphendula. Unelungelo lokugcina isimo sakho sempilo siyimfihlo. Ukwanalo nelungelo lokuyeka kolu phando ukuba uwusafuni kuqhubeka kulo. Unelungelo lokuqhakamshelana nabantu bekomiti yophando-zifundo besikolo esiphakamileyo i-CPUT okanye umphandi oyintloko kule nombolo yomnxeba 0827746266.

Informed Consent in Afrikaans.

Cape Peninsula University of Technology

DIEP VENEUSE TROMBOSE – ULTRAKLANK STUDIE.

Ingeligte Toestemming

Ondersoeker (navorser) verslag.
Ons versoek jou uit om deel te neem aan hierdie navorsings studie. Die doel van die toestemmingsvorm is om aan jou die nodige inligting te verskaf om te besluit of jy wil deel vorm van die navorsing of nie.
Lees die volgende asseblief deeglik.
Jy mag vrae aangaande die doel van die navorsing vra, wat jy sal moet doen, die moontlike risiko's en voordele, jou regte as 'n vrywillige en enigeiets anders aangaande die navorsing. Vra asseblief as jy enige deel van die vorm nie verstaan nie. As jou vrae beantwoord is, kan jy besluit of jy wil deel vorm van die studie. Hierdie proses word "ingeligte toestemming" genoem.

Vrywillige deelname
Jy mag kies om nie deel te vorm van die studie nie. Indien dit die geval is sal geen gesongheidsorg van jou weerhou word nie en jy sal voortgaan om die standard mediese sorg by die hospital te ontvang. Jy het die reg om ter enige tyd van die ondersoek te ontrek. Daar sal geen verlies van voordele waarop jy geregtig is weees nie.

Agtergrond
Vorige studies het daarop gedui dat pasiënte wat behandeling vir hul TB infeksie begin, 'n bloedklont in die venes van hul bene mag ontwikkel. Dit word 'n DVT genoem of 'n diep veneuse trombose.

'n DVT mag pyn, swelling of ander probleme veroorsaak. Die belangrikste komplikasie met 'n bloedklont is dat 'n deel mag afbreek en na ander dele van die liggaam versprei word soos byvoorbeeld die longe. Groot klonte in die longe kan baie gevaarlik en noodlottig wees. DVT's word gewoonlik behandel met antistollings terapie vir ongeveer 3 maande (of soms langer) om die bloed te verdun.

'n Ultraklank masjien maak gebruik van klankgolwe om dele van die liggaam uit te beeld. Dit is baie akkuraat om DVT's in bloedvate te identifiseer. Die studie sal van so 'n masjien gebruik maak om die bloedvate van die onderbene te ondersoek vir klontvormasie.

Doel van die studie
Die doel van die studie is om Ultraklank te gebruik om die teenwoordigheid van 'n DVT in die onderste ledemate, van pasiënte wat behandeling vir TB ontvang, te ondersoek en om vas te stel wat die tydsperiode vir die ontwikkeling van 'n DVT in sulke pasiente is. Verder is die doelstelling van die studie om vas te stel of ander faktore soos MIV status, rook, liggaam mass indeks (body mass index) en beweeglikheid bydra tot die ontwikkeling van DVT's.

Toetrede tot ondersoek
Ons vra die pasiënte wat in hierdie hospital opgeneem word om deel te neem aan die ondersoek. Ons studie??? verpleegster sal 'n paar vrae aan jou stel om vas te stel of jy kan deelvorm. Afhangende van jou antwoorde sal ons jou vra om deel te neem.

As deel van die studie moet ons weet of jy met die MIV virus besmet is of nie. Dit is om te probeer bepaal of die MIV virus die risiko om DVT's te ontwikkel verhoog. Jou MIV status sal vertroulik gehou word en indien jy nodig het om met iemand hieroor te praat sal die studie??? verpleegster jou kan help. Die verpleegster sal jou ook vra of jy rook, wat jou gewig is en hoe beweeglik jy is.

Ultraklank Ondersoek.
Die studies sal vereis dat pasiente vier(4) ultraklank ondersoeke van onderste ledemate moet ondergaan. Die toets neem omtrent 30-40 minute om uit te voer. Die ondersoek is pynloos en vereis

dat die pasiënte om hul rug moet lê terwyl ‘n klein instrument, genoem ‘n klankkop, oor die vel beweeg word. ‘n Gel, met ‘n waterbasis, word eers op die vel aangewend sodat die klankkop goeie kontak kan maak en maklik kan beweeg. Sommige pasiënte ondervind die toets ontspannend en raak aan die slaap.

Risiko’s en Voordele

Daar is geen risiko’s verbonde aan die ultraklank ondersoek nie. Die mees belangrike voordeel vir hierdie groep pasiënte is dat as ‘n DVT ontwikkel, dit geïdentifiseer en bevestig word met ultraklank. Dit sal waarskynlik wees voor enige kliniese simptome verskyn. Die ondersoek sal by hierdie hospitaal uitgevoer word met die minimum
ongerief tot die pasiënt se verblyf.

Ander informasie.

Deelname aan die studie is vrywillig. Jy kan ter enige tyd onttrek. Indien jy kies om deel te vorm van die studie of nie sal dit nie jou gesondheidsorg affekteer nie. Informasie aangaande jou is vertroulik. Ons sal die uitslae van die studie kodeer. Die verband tussen jou naam en die kode sal apart in ‘n veilige plek bewaar word. Slegs die studie ondersoekers sal toegang tot die inligting hê. Die verband tussen jou naam en kode sal vir 10 jaar gehou word en dan vernietig word. Ons sal toegang tot jou mediese rekords moet hê en ons het met die hospital ooreengekom om toelating tot dit te verkry.

Deelnemer verklaring

Hierdie studie is aan my verduidelik. Ek bide aan om deel te neem aan die studie. Ek het ‘n kans gehad om vrae te vra. Indien ek verdere vrae aangaande die navorsing het, kan ek die studie verpleegster of een van die navorsing assistente vra. Indien ek vrae het oor my regte as navorsings deelnemer kan ek die etiek komitee by KPUT (021 959 6917) of die hoof ondersoeker Sheila Brock kontak by 0827746266. Ek gee my toestemming vir die studie ondersoeker om toegang tot my mediese rekords te hê vir die doel wat beskryf is. Ek sal ‘n afskrif van die toestemmingsvorm ontvang.

_____

Handtekening van deelnemer Datum Gedrukte naam van deelnemer

_____

Handtekening van getuie Datum Gedrukte naam van getuie

Cape Peninsula University of Technology

DIEP VENEUSE TROMBOSE – ULTRAKLANK STUDIE.

Pasient Informasie blad

Doel van Studie

Die studie is om na DVT's te soek wat een van die komplikasies is wat pasiënte kan ontwikkel tydens die behandeling van TB. Verskeie ultraklank ondersoeke van die onderste ledemate sal gedoen word om die teenwoordigheid van klonte in die onderste ledemate te erken. Ons wil vasstel wanneer die klont moontlik kan begin vorm, waar in die bene dit moontlik vorm en of probleme soos MIV, rook, beweeglikheid of om baie maer te wees risiko faktore is vir klontformasie.

Diep Veneuse Trombose

'n DVT is a bloedklont wat in 'n pasiënt se bene kan vorm. Die klont kan opbreek en na die longe vervoer word wat baie gevaarlik kan wees. Dit is gevaarlik omdat die klont belangrike bloedvate kan blokkeer wat kortasem, borskas pyn en in ernstige gevalle verlies aan bewussyn en dood tot die gevolg kan hê. Indien 'n DVT ontwikkel is dit algemeen dat die pasiënt onbewus van enige verandering is, maar pyn en swelling van die bene kan soms teenwoordig wees. Dikwels is daar geen tekens of simptome van 'n DVT identifiseerbaar vir die dokter nie wat dit baie moeilik maak om te diagnoseer. Ultraklank beelding kan die teenwoordigheid van DVT's in die bene van die pasiënt baie akkuraat vasstel. DVT's word vir 3-6 maande met spesiale bloedverdunnings middels behandel.

Ultraklank

'n Ultraklank masjien maak gebruik van klankgolwe om 'n sigbare beeld vir die operateur op te bou. Dit is veilig en het geen erkende newe effekte nie. Om die venes in die onderste ledemate te visualiseer moet die pasient op die rug op 'n bed lê en 'n klein instrument, genoem 'n klankkop, sal oor die vel beweeg word. 'n Gel met 'n waterbasis word op die vel aangewend sodat die klankkop maklik kan beweeg.

Algemeen

As 'n pasiënt van 'n kliniese studie het jy die reg om vrae te vra en enige bekommernisse aangaande die studie moet aangespreek word. Jy het die reg tot vertroulikheid op jou mediese inligting. Jy het die reg om ter enige tyd aan die studie te onttrek. Praat asseblief met enige lid van die studie personeel wat jou vrae sal aanspreek. Andersins sal hulle jou in kontak laat tree met die persoon wat die vrae kan beantwoord. Jy kan die etiek komitee by KPUT of die hoof navorser Sheila Brock kontak by 0827746266 as jy nie gelukkig is met die antwoorde op jou vrae nie

APPENDIX B: The Clinical Reference Form (CRF)

DVT Study: Patient Data Collection Form

Consent:

Date signed:

Mental state of patient:

Consent explained to patient in:

Copy given to patient in:

Demographics:

D.O.B.:_____ Racial group:

Gender: M / F Highest education level:

Work history: Employed – Yes: occupation:

No, pensioner No ☐ ability grant No, unemp ☐ d ☐

If unemployment <3/12, occupation prior to unemployment:

Medical history:

TB History

Current TB history:

Current TB episode diagnosed on (date):

Number of TB treatment defaults for current episode:_____

Current TB treatment start date:

Number of treatment days to 1st u/s:

Type of TB: Pulmonary TB ☐ ra Pulmonary TB ☐

Current TB episode investigations:

AFB – sample 1(date):_____Pos / Neg

sample 2 (date):_____Pos / Neg

_____

Culture (date):_____ Pos / Neg

Chest X-ray: Yes / No Date:_____

_____

_____

Current TB drug treatment:

- Regimen 1 (rifampicin, isoniazid, pyrazinamide) ☐
- Regimen 2 (rifampicin, isoniazid, pyrazinamide, streptomycin) ☐
- Other TB medications ☐

Warfin treatment:

Yes / No

If yes, 1st INR result:_____ Date: _____

Surgical treatment of current episode: Yes / No

Details:

Past TB history:

Previous TB episode/s: Yes / No How many episodes: ☐

Outcome episode 1:

- Treatment completed: Yes / No
- Cured: Yes / No
- Defaulted treatment: Yes / No

Outcome episode 2:

- Treatment completed: Yes / No
- Cured: Yes / No
- Defaulted treatment: Yes / No

Outcome episode 3:

- Treatment completed: Yes / No
- Cured: Yes / No
- Defaulted treatment: Yes / No

HIV Status:

Pos / Neg

If Pos, CD4 count:_____ Date:

Relevant past medical history

Previous Surgery: Yes / No

Previous DVT: Yes / No

Previous Pulmonary Embolism: Yes / No

Previous Bleeding Disorder: Yes / No

Relevant social history:

Smoking history:

Non-smoker ☐ Ex-smoker ☐ Current smoker ☐

- <5 cigarettes per day ☐
- 5-10 cigarettes per day ☐
- 11-20 cigarettes per day ☐
- >20 cigarettes per day ☐

Duration of smoking (years/months):

Alcohol consumption: Yes / No

Daily Binge Social

Recreational drugs: Yes / No

Ambulatory Status on Admission:

- Only in bed to sleep at night ☐
- Up most of the day, but may rest in bed during morning or afternoon ☐
- Up for some of the day, but with long rests ☐
- Only out of bed for meals or bathroom trips ☐
- Does not get out of bed during day and receives meals, medication etc. at the bedside ☐

Physical examination:

Date:_____

Height (cm):_____Weight (kg):_____

If Female: LMP:_____Pregnosticon Pos / Neg

Enrollment:

Inclusion criteria:

Age 18 to 90 Yes / No

Diagnosis of TB Yes / No

Less than 3 weeks TB treatment Yes / No

HIV status known Yes / No

Estimated admission > 14 weeks Yes / No

Exclusion criteria:

Unable/refuses to give consent	Yes / No	
HIV consent not given/HIV status unknown	Yes / No	
Confirmed DVT or PE		Yes / No
Concurrent participation in another study		Yes / No
TB treatment longer than 3 weeks		Yes / No

Date enrolled:_____

Enrolled by:_____

Study number identification:_____

Week 0 review date:

Weekly review done: Yes / No If No, reason:

Action:

Scan done: Yes / No If No, reason:

Action:

Signs/symptoms of DVT: Yes / No

Left leg		***Right leg***	
Painful calf	☐	Painful calf	☐
Dorsiflexion pain	☐	Dorsiflexion pain	☐
Swelling	☐	Swelling	☐
Redness	☐	Redness	☐

Ambulatory status of patient:

Change in ambulation? Yes / No

- Only in bed to sleep at night ☐
- Up most of the day, but may rest in bed during morning or afternoon ☐
- Up for some of the day, but with long rests ☐
- Only out of bed for meals or bathroom trips ☐
- Does not get out of bed during day and receives meals, medication, etc. at the bedside ☐

Signs/symptoms of adverse events: bleeding, CVA, death, pulmonary embolism:

Diagnosis/description:_____

Date:_____

Action:_____

Week 0 ultrasound review:

Time of ultrasound scan:_____

Ultrasound findings:

DVT: Yes / No

Location of DVT: Left leg Right leg

Further action needed? Yes / No

_____

_____

_____

Week 1 review date:

Weekly review done: Yes / No If No, reason:

Action:

Scan done: Yes / No If Yes, reason:

Scan outcome:

Action:

Signs/symptoms of DVT: Yes / No

Left leg		***Right leg***	
Painful calf	☐	Painful calf	☐
Dorsiflexion pain	☐	Dorsiflexion pain	☐
Swelling	☐	Swelling	☐
Redness	☐	Redness	☐

Ambulatory status of patient:

Change in ambulation? Yes / No

- Only in bed to sleep at night ☐
- Up most of the day, but may rest in bed during morning or afternoon ☐
- Up for some of the day, but with long rests ☐
- Only out of bed for meals or bathroom trips ☐
- Does not get out of bed during day and receives meals, medication, etc. at the bedside ☐

Signs/symptoms of adverse events: bleeding, CVA, death, pulmonary embolism:

Diagnosis/description:_____

Date:_____

Action:_____

Week 2 review date:

Weekly review done: Yes / No If No, reason:

Action:

Scan done: Yes / No If Yes, reason:

Scan outcome:

Action:

Signs/symptoms of DVT: Yes / No

Left leg		*Right leg*	
Painful calf	☐	Painful calf	☐
Dorsiflexion pain	☐	Dorsiflexion pain	☐
Swelling	☐	Swelling	☐
Redness	☐	Redness	☐

Ambulatory status of patient:

Change in ambulation? Yes / No

- Only in bed to sleep at night ☐
- Up most of the day but may rest in bed during morning or afternoon ☐
- Up for some of the day, but with long rests ☐
- Only out of bed for meals or bathroom trips ☐
- Does not get out of bed during day and receives meals, medication, etc. at the bedside ☐

Signs/symptoms of adverse events: bleeding, CVA, death, pulmonary embolism:

Diagnosis/description:_____

Date:_____

Action:_____

Week 3 review date:

Weekly review done: Yes / No If No, reason:

Action:

Scan done: Yes / No If Yes, reason:

Scan outcome:

Action:

Signs/symptoms of DVT: Yes / No

Left leg		***Right leg***	
Painful calf	☐	Painful calf	☐
Dorsiflexion pain	☐	Dorsiflexion pain	☐
Swelling	☐	Swelling	☐
Redness	☐	Redness	☐

Ambulatory status of patient:

Change in ambulation? Yes / No

- Only in bed to sleep at night ☐
- Up most of the day, but may rest in bed during morning or afternoon ☐
- Up for some of the day, but with long rests ☐
- Only out of bed for meals or bathroom trips ☐
- Does not get out of bed during day and receives meals, medication, etc. at the bedside ☐

Signs/symptoms of adverse events: bleeding, CVA, death, pulmonary embolism:

Diagnosis/description:_____

Date:_____

Action:_____

Week 4 review date:

Weekly review done: Yes / No If No, reason:

Action:

Scan done: Yes / No If No, reason:

Action:

Signs/symptoms of DVT: Yes / No

Left leg		***Right leg***	
Painful calf	☐	Painful calf	☐
Dorsiflexion pain	☐	Dorsiflexion pain	☐
Swelling	☐	Swelling	☐
Redness	☐	Redness	☐

Ambulatory status of patient:

Change in ambulation? Yes / No

- Only in bed to sleep at night ☐
- Up most of the day, but may rest in bed during morning or afternoon ☐
- Up for some of the day, but with long rests ☐
- Only out of bed for meals or bathroom trips ☐
- Does not get out of bed during day and receives meals, medication, etc. at the bedside ☐

Signs/symptoms of adverse events: bleeding, CVA, death, pulmonary embolism:

Diagnosis/description:_____

Date:_____

Action:_____

Week 4 ultrasound review:

Time of ultrasound scan:_____

Ultrasound findings:

DVT: Yes / No

Location of DVT: Left leg Right leg

Further action needed? Yes / No

_____

_____

_____

Week 5 review date:

Weekly review done: Yes / No If No, reason:

Action:

Scan done: Yes / No If Yes, reason:

Scan outcome:

Action:

Signs/symptoms of DVT: Yes / No

Left leg		***Right leg***	
Painful calf	☐	Painful calf	☐
Dorsiflexion pain	☐	Dorsiflexion pain	☐
Swelling	☐	Swelling	☐
Redness	☐	Redness	☐

Ambulatory status of patient:

Change in ambulation? Yes / No

- Only in bed to sleep at night ☐
- Up most of the day, but may rest in bed during morning or afternoon ☐
- Up for some of the day, but with long rests ☐
- Only out of bed for meals or bathroom trips ☐
- Does not get out of bed during day and receives meals, medication, etc. at the bedside ☐

Signs/symptoms of adverse events: bleeding, CVA, death, pulmonary embolism:

Diagnosis/description:_____

Date:_____

Action:_____

Week 6 review date:

Weekly review done: Yes / No If No, reason:

Action:

Scan done: Yes / No If Yes, reason:

Scan outcome:

Action:

Signs/symptoms of DVT: Yes / No

Left leg		***Right leg***	
Painful calf	☐	Painful calf	☐
Dorsiflexion pain	☐	Dorsiflexion pain	☐
Swelling	☐	Swelling	☐

Redness ☐ Redness ☐

Ambulatory status of patient:

Change in ambulation? Yes / No

- Only in bed to sleep at night ☐
- Up most of the day, but may rest in bed during morning or afternoon ☐
- Up for some of the day, but with long rests ☐
- Only out of bed for meals or bathroom trips ☐
- Does not get out of bed during day and receives meals, medication, etc. at the bedside ☐

Signs/symptoms of adverse events: bleeding, CVA, death, pulmonary embolism:

Diagnosis/description:_____

Date:_____

Action:_____

Week 7 review date:

Weekly review done: Yes / No If No, reason:

Action:

Scan done: Yes / No If Yes, reason:

Scan outcome:

Action:

Signs/symptoms of DVT: Yes / No

Left leg		***Right leg***	
Painful calf	☐	Painful calf	☐
Dorsiflexion pain	☐	Dorsiflexion pain	☐
Swelling	☐	Swelling	☐
Redness	☐	Redness	☐

Ambulatory status of patient:

Change in ambulation? Yes / No

- Only in bed to sleep at night ☐
- Up most of the day, but may rest in bed during morning or afternoon ☐
- Up for some of the day, but with long rests ☐
- Only out of bed for meals or bathroom trips ☐
- Does not get out of bed during day and receives meals, medication, etc. at the bedside ☐

Signs/symptoms of adverse events: bleeding, CVA, death, pulmonary embolism:

Diagnosis/description:_____

Date:_____

Action:_____

Week 8 review date:

Weekly review done: Yes / No If No, reason:

Action:

Scan done: Yes / No If No, reason:

Action:

Signs/symptoms of DVT: Yes / No

Left leg		***Right leg***	
Painful calf	☐	Painful calf	☐
Dorsiflexion pain	☐	Dorsiflexion pain	☐
Swelling	☐	Swelling	☐
Redness	☐	Redness	☐

Ambulatory status of patient:

Change in ambulation? Yes / No

- Only in bed to sleep at night ☐
- Up most of the day, but may rest in bed during morning or afternoon ☐
- Up for some of the day, but with long rests ☐
- Only out of bed for meals or bathroom trips ☐
- Does not get out of bed during day and receives meals, medication, etc. at the bedside ☐

Signs/symptoms of adverse events: bleeding, CVA, death, pulmonary embolism:

Diagnosis/description:_____

Date:_____

Action:_____

Week 8 ultrasound review:

Time of ultrasound scan:_____

Ultrasound findings:

DVT: Yes / No

Location of DVT: Left leg Right leg

Further action needed? Yes / No

_____

_____

_____

Week 9 review date:

Weekly review done: Yes / No If No, reason:

Action:

Scan done: Yes / No If Yes, reason:

Scan outcome:

Action:

Signs/symptoms of DVT: Yes / No

Left leg		***Right leg***	
Painful calf	☐	Painful calf	☐
Dorsiflexion pain	☐	Dorsiflexion pain	☐
Swelling	☐	Swelling	☐
Redness	☐	Redness	☐

Ambulatory status of patient:

Change in ambulation? Yes / No

- Only in bed to sleep at night ☐
- Up most of the day, but may rest in bed during morning or afternoon ☐
- Up for some of the day, but with long rests ☐
- Only out of bed for meals or bathroom trips ☐
- Does not get out of bed during day and receives meals, medication, etc. at the bedside ☐

Signs/symptoms of adverse events: bleeding, CVA, death, pulmonary embolism:

Diagnosis/description:_____

Date:_____

Action:_____

Week 10 review date:

Weekly review done: Yes / No If No, reason:

Action:

Scan done: Yes / No If Yes, reason:

Scan outcome:

Action:

Signs/symptoms of DVT: Yes / No

Left leg		***Right leg***	
Painful calf	☐	Painful calf	☐
Dorsiflexion pain	☐	Dorsiflexion pain	☐
Swelling	☐	Swelling	☐
Redness	☐	Redness	☐

Ambulatory status of patient:

Change in ambulation? Yes / No

- Only in bed to sleep at night ☐
- Up most of the day, but may rest in bed during morning or afternoon ☐
- Up for some of the day, but with long rests ☐
- Only out of bed for meals or bathroom trips ☐
- Does not get out of bed during day and receives meals, medication, etc. at the bedside ☐

Signs/symptoms of adverse events: bleeding, CVA, death, pulmonary embolism:

Diagnosis/description:_____

Date:_____

Action:_____

Week 11 review date:

Weekly review done: Yes / No If No, reason:

Action:

Scan done: Yes / No If Yes, reason:

Scan outcome:

Action:

Signs/symptoms of DVT: Yes / No

Left leg		***Right leg***	
Painful calf	☐	Painful calf	☐

Dorsiflexion pain	☐	Dorsiflexion pain	☐
Swelling	☐	Swelling	☐
Redness	☐	Redness	☐

Ambulatory status of patient:

Change in ambulation? Yes / No

- Only in bed to sleep at night ☐
- Up most of the day, but may rest in bed during morning or afternoon ☐
- Up for some of the day, but with long rests ☐
- Only out of bed for meals or bathroom trips ☐
- Does not get out of bed during day and receives meals, medication, etc. at the bedside ☐

Signs/symptoms of adverse events: bleeding, CVA, death, pulmonary embolism:

Diagnosis/description:_____

Date:_____

Action:_____

Week 12 review date:

Weekly review done: Yes / No If No, reason:

Action:

Scan done: Yes / No If Yes, reason:

Scan outcome:

Action:

Signs/symptoms of DVT: Yes / No

Left leg		***Right leg***	
Painful calf	☐	Painful calf	☐
Dorsiflexion pain	☐	Dorsiflexion pain	☐
Swelling	☐	Swelling	☐
Redness	☐	Redness	☐

Ambulatory status of patient:

Change in ambulation? Yes / No

- Only in bed to sleep at night ☐
- Up most of the day, but may rest in bed during morning or afternoon ☐
- Up for some of the day, but with long rests ☐

- Only out of bed for meals or bathroom trips ☐
- Does not get out of bed during day and receives meals, medication, etc. at the bedside ☐

Signs/symptoms of adverse events: bleeding, CVA, death, pulmonary embolism:

Diagnosis/description:_____

Date:_____

Action:_____

Week 13 review date:

Weekly review done: Yes / No If No, reason:

Action:

Scan done: Yes / No If Yes, reason:

Scan outcome:

Action:

Signs/symptoms of DVT: Yes / No

Left leg		***Right leg***	
Painful calf	☐	Painful calf	☐
Dorsiflexion pain	☐	Dorsiflexion pain	☐
Swelling	☐	Swelling	☐
Redness	☐	Redness	☐

Ambulatory status of patient:

Change in ambulation? Yes / No

- Only in bed to sleep at night ☐
- Up most of the day, but may rest in bed during morning or afternoon ☐
- Up for some of the day, but with long rests ☐
- Only out of bed for meals or bathroom trips ☐
- Does not get out of bed during day and receives meals, medication, etc. at the bedside ☐

Signs/symptoms of adverse events: bleeding, CVA, death, pulmonary embolism:

Diagnosis/description:_____

Date:_____

Action:_____

Week 14 review date:

Weekly review done: Yes / No If No, reason:

Action:

Scan done: Yes / No If No, reason:

Action:

Signs/symptoms of DVT: Yes / No

Left leg		***Right leg***	
Painful calf	☐	Painful calf	☐
Dorsiflexion pain	☐	Dorsiflexion pain	☐
Swelling	☐	Swelling	☐
Redness	☐	Redness	☐

Ambulatory status of patient:

Change in ambulation? Yes / No

- Only in bed to sleep at night ☐
- Up most of the day, but may rest in bed during morning or afternoon ☐
- Up for some of the day, but with long rests ☐
- Only out of bed for meals or bathroom trips ☐
- Does not get out of bed during day and receives meals, medication, etc. at the bedside ☐

Signs/symptoms of adverse events: bleeding, CVA, death, pulmonary embolism:

Diagnosis/description:_____

Date:_____

Action:_____

Week 14 ultrasound review:

Time of ultrasound scan:_____

Ultrasound findings:

DVT: Yes / No

Location of DVT: Left leg Right leg

Further action needed? Yes / No

_____

_____

_____

APPENDIX C: DVT Ultrasound Report Form

Cape Peninsula University of Technology
Deep Vein Thrombosis – Ultrasound Study
Ultrasound Report

Week: 0 / 4 / 8 / 14

PATIENT No. _____ DATE: _____

A compression ultrasound with Doppler was performed on the lower extremities of the above patient.

☐ no DVT identified

☐ positive DVT identified in the LEFT / RIGHT leg

In the RIGHT / LEFT leg the DVT is identified in the: -

- CFV
- SFV
- POP V
- ATV
- PTV
- PV

Comment: Signature:

2 Abdominal Ultrasound Report Form.

Cape Peninsula University of Technology
Deep Vein Thrombosis – Ultrasound Study

Abdomen Ultrasound REPORT

Ref. Number: _____
Date: _____

Aorta and IVC:

Pancreas:

Liver and Gall Bladder:

Right Kidney :

Left Kidney :

Spleen:

Pelvis:

Pleural effusion:

Lymph adenopathy:

Free fluid:

Pericardial effusion:

Comment:

Sonographer: _____

Date: _____

Appendix D: Letter from DP Marais Hospital granting consent to perform the study.

Verwysing / Reference Isalathiso

Departement van Gesondheid / Department of Health /ISebe IezeMpilo
Navrae / Enquiries / Imibuzo Dr JB Mobbs
DP Marais Hospital
PO Box 30360
TOKAI, 7966
Telefoon / Telephone / Ifowuni (021) 712-7491

Fax / Ifaksi (021) 712-4435 / 713-0335

13 August 2008

Sheila Brock
UCT Desmond Tutu Centre

Dear Sheila
RESEARCH: DVT AND TUBERCULOSIS

Please be informed that you are welcome to undertake your research study at DP Marais Hospital as your submission comply to all protocols.

Kindly inform us on what your research will commence

Regards

John

Appendix E: Ethics

Cape Peninsula
University of Technology

1 March 2010
CPUT/HW-REC 2010/H02

P.O. Box 1906 • Bellville 7535 South Africa •Tel: +27 21 442 6162 • Fax +27 21 447 2963
Symphony Road Bellville 7535

OFFICE OF THE CHAIRPERSON:
HEALTH AND WELLNESS SCIENCES RESEARCH ETHICS COMMITTEE (HW-REC)
Registration Number NHREC: REC- 230408-014

At the meeting of the Health and Wellness Sciences-REC on 9 October 2009 approval was granted to Sheila Brock, pending minor amendments now received. This approval is for research activities related to an D Tech: Radiography at this institution.

TITLE:
Compression and Doppler ultrasound of deep vein thrombosis in patients on tuberculosis treatment.

INTERNAL SUPERVISOR: Dr T Maisha

INTERNAL CO-SUPERVISOR: Ms F Isaacs

Comment:
Research activities are restricted to those detailed in the proposal and application submitted for this meeting in October 2009.

Approval will not extend beyond 28 February 2011. An extension must be applied for should data collection for this study continue beyond this date.

Prof PENELOPE ENGEL-HILLS
CHAIR: HEALTH AND WELLNESS SCIENCES RESEARCH ETHICS COMMITTEE

e-mail: *engelhillsp@cput.ac.za*

UNIVERSITY OF CAPE TOWN

Health Sciences Faculty
Research Ethics Committee
Room E52-24 Groote Schuur Hospital Old Main Building
Observatory 7925
Telephone [021] 406 6626 • **Facsimile** [021] 406 6411
e-mail: lamees.emjedi@uct.ac.za

27 September 2010

HREC REF: 449/2010

Prof LG Bekker
Desmond Tutu HIV Foundation
IIDMM
Medical School

Dear Prof Bekker

PROJECT TITLE: OBSERVATIONAL STUDY TO EXAMINE THE INCIDENCE OF AND THE UTILITY OF ULTRASONOGRAM SCREENING IN THE DIAGNOSIS OF ASYMPTOMATIC DVT IN TUBERCULOSIS PATIENTS COMMENCING ANTITUBERCULOSIS THERAPY

Thank you for submitting your new study to the Faculty of Health Sciences Human Research Ethics Committee.

It is a pleasure to inform you that the FHS HREC has **formally approved** the above-mentioned study.

Approval is granted for one year until 28 September 2011.

Study 322/2002 is now closed.

Please send us an annual progress report (website form FHS 016) if your research continues beyond the approval period. Alternatively, please send us a brief summary of your findings so that we can close the research file.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Please quote the REC. REF in all your correspondence.